Stereoselective Cyclopropanations via Gold(I)-Catalyzed Retro-Buchner Reactions

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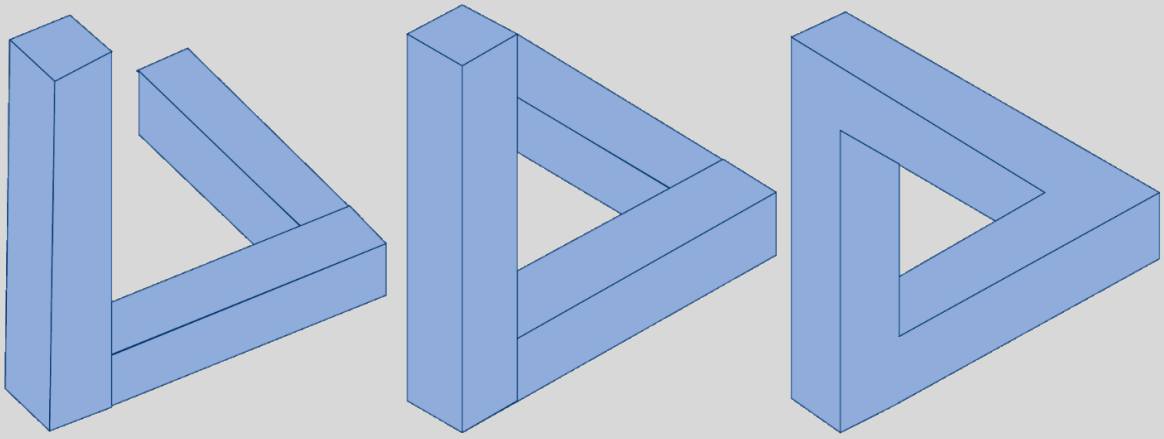

DOCTORAL THESIS
2017

Bart Herlé

Stereoselective Cyclopropanations via Gold(I)-Catalyzed Retro-Buchner Reactions

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

ICIQ – Institut Català d'Investigació Química

Tarragona 2017

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d'Investigació
Química

I STATE that the present study, entitled 'Stereoselective Cyclopropanations via Gold(I)-Catalyzed Retro-Buchner Reactions', presented by Bart Herlé to receive the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, May 16th, 2017

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren Pablos

*First and foremost, I would like to express my deepest gratitude to my PhD supervisor **Prof. Dr. Antonio M. Echavarren**, who has let me be part of his research group for over four years. I am grateful for the opportunity he has given me, for his patience and his trust in me during these years, for inspiring me to always improve, and for his invaluable advice and guiding. Thank you.*

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*I would also like to thank **Dr. Jan Streuff** and **Prof. Dr. Yahui Wang** for accepting to take part as external reviewers.*

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en boulderen, klimmen, hiken, Marató Barcelona 2014, ***Topillos Atomicos****, kiwi-detox, enzovoorts.*

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List of publications

At the time of printing this manuscript, the results herein have been published in the following journals:

"Stereoselective *cis*-Vinylcyclopropanation via a Gold(I)-Catalyzed Retro-Buchner Reaction under Mild Conditions"
B. Herlé, P. M. Holstein, A. M. Echavarren
ACS Catal., **2017**, *7*, 3668-3675.
doi: 10.1021/acscatal.7b00737

"Gold(I) Carbenes by Retro-Buchner Reaction: Generation and Fate"
Y. Wang, P. R. McGonigal, B. Herlé, M. Besora, A. M. Echavarren
J. Am. Chem. Soc., **2014**, *136*, 801-809.
doi: 10.1021/ja411626v

Table of Contents

Prologue

The manuscript of this Doctoral Thesis has been divided into five main parts: a general introduction to transition-metal catalyzed alkene cyclopropanation reactions, followed by four research chapters. Each chapter consists of five sections: an introduction on the research topic, the objectives, and a discussion on the obtained results, ending with the conclusions and an experimental part.

The *General Introduction* describes the properties and the applications of cyclopropanes, followed by general synthetic strategies for their formation. Methods for stereo- and enantioselective cyclopropanation reactions are reviewed focusing on the transition-metal catalyzed alkene cyclopropanation. The reactivity of gold carbenes is compared to other transition metals. Finally, safe and versatile methods for the formation of metal carbenes, and specifically the gold-catalyzed retro-Buchner reaction of 7-substituted cycloheptatrienes are treated in detail. Part of this work has been published in *J. Am. Chem. Soc.*, **2014**, *136*, 801-809, and has been performed in collaboration with **Dr. Yahui Wang**.

The first chapter, called "*Dibenzonorcaradiene Derivatives as Carbene Precursors for Gold(I)*", describes the efforts towards finding a more reactive carbene precursor that is easier to functionalize and diversify.

The second chapter, "*Stereoselective cis-Vinylcyclopropanation via a Gold(I)-Catalyzed Retro-Buchner Reaction under Mild Conditions*", describes the formation of vinyl gold(I) carbenes from 7-alkenyl cycloheptatriene derivatives and their subsequent use in alkene cyclopropanation reactions. A Julia-Kocienski reagent was developed for the formation of alkenyl cycloheptatrienes from aldehydes and ketones in a single step. A large scope of vinylcyclopropanes with excellent *cis*-selectivity and vinyl-aminocyclopropanes exhibiting moderate to good *cis*-selectivity was prepared. Part of this work has been described in *ACS Catal.,* **2017**, *7*, 3668-3675. This work was performed in collaboration with **Dr. Philipp M. Holstein**.

In the third chapter, "*Mechanistic Investigations and the Origin of Diastereoselectivity*", the mechanism of the gold(I)-catalyzed

vinylcyclopropanation reaction, described in *chapter 2*, is studied experimentally and computationally. Based on the obtained results, an advanced stereochemical model was developed for gold(I)-catalyzed cyclopropanations. At the same time, the mechanism of an unprecedented gold(I)-mediated vinylcyclopropane isomerization reaction was elucidated. Part of this work has also been described in *ACS Catal.,* **2017**, *7*, 3668-3675. This work was performed in collaboration with **Dr. Philipp M. Holstein**.

The fourth and last chapter, "*New Cycloheptatriene Derivatives for the Room-Temperature Retro-Buchner Reaction*", describes the synthesis of new functionalized cycloheptatriene derivatives. The activation barrier for carbene formation is greatly lowered by these reagents, which allows the retro-Buchner reaction to take place at ambient temperature. The results described in this chapter should be considered preliminary but were highly relevant to the topic of this manuscript and are thus included herein. This work has been performed in collaboration with **Evaristo Villaseco Arribas**, whom I co-supervised as a La Caixa – ICIQ summer fellow.

List of Abbreviations and Acronyms

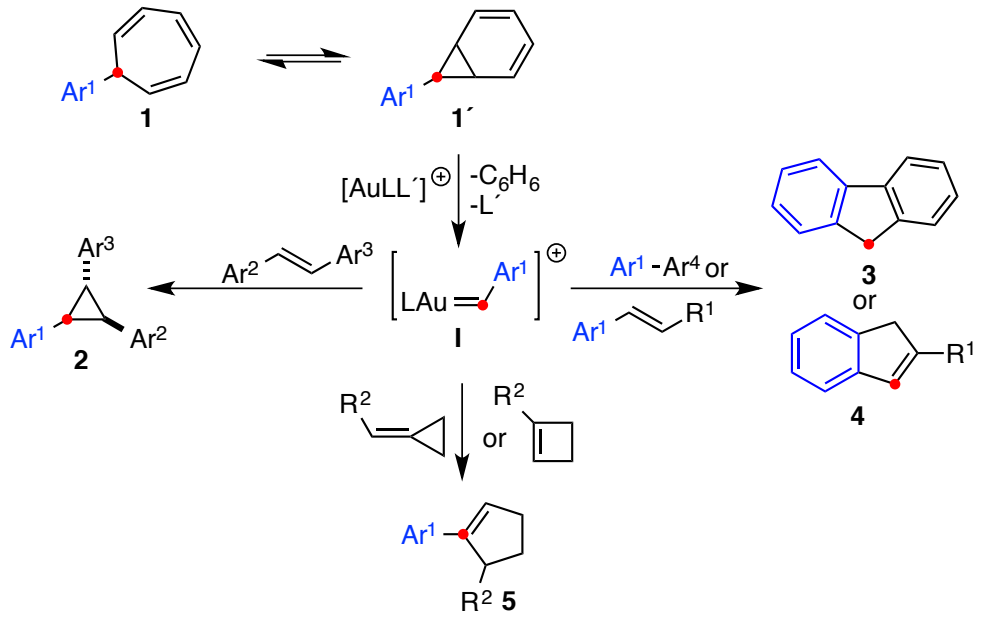
In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations from "Guidelines for authors" of The Journal of Organic Chemistry. Abbreviations and acronyms used in this manuscript are referenced in the list below:

A-	Acceptor moiety-
adam	Adamantyl
$BAr^F{}_4^-$	Tetrakis[3,5-bis(trifluoromethyl)phenylborate]
BOX	Bisoxazoline
calc.	Calculated
cat.	Catalyst
COD	1,4-Cyclooctadiene
D-	Donor moiety-
d	Day/days
dba	Dibenzylideneacetone
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIC	*N*,*N*'-Diisopropylcarbodiimide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
(*R*)-DTBM-SEGPHOS	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)-phosphino]-4,4′-bi-1,3-benzodioxole
DMAP	4-Dimethylaminopyridine
S-DOSP	[(*S*)-(-)-*N*-(*p*-Dodecylphenylsulfonyl)prolinate]
E	Electrophile
ESI	Electron spray ionization
equiv	Equivalents
EWG	Electron withdrawing group
gem	Geminal

GOESY	Gradient enhanced nuclear Overhauser effect spectroscopy
h	Hour / hours
IPr	1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
IS	Internal standard
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L	Ligand
M	Metal
MIDA	*N*-Methyl imino diacetic acid
min	Minutes
MIRC	Michael Assisted Ring Closure
MS	Molecular sieves
n.d.	Not determined
Nu	Nucleophile
Ox.	Oxidant
pin	Pinacol
Pheox	Phenyloxazoline
Phth	Phthalimide
S-PTTL	*N*-phthaloyl-(*S*)-*tert*-leucinato
RDG	Reduced density gradient
Salen	2,2′-Ethylenebis(nitrilomethylidene)diphenol
(*S,S,S*)-SKP	(-)-1,13-Bis(diphenyl)phosphino-(5a*S*,8a*S*,14a*S*)-5a,6,7,8,8a,9-Hexahydro-5*H*-[1]benzopyrano[3,2-d]xanthene
T.	Temperature
TBAF	Tetra-*n*-butylammonium fluoride
temp	Temperature
TMP	Tetramethylpiperidide
TPP	Tetraphenylporphyrine
TS	Transition state
vdW	Van der Waals
XPhos	2-Dicyclohexylphosphino-2´,4´,6´-triisopropylbiphenyl

Synopsis

The formation of gold(I) carbenes via the retro-Buchner reaction of 7-substituted-1,3,5-cycloheptatriene derivatives **1** has recently emerged as a versatile and safe alternative to, for example, the decomposition of diazo compounds with transition metals.[1] The formation of aryl gold(I) carbenes and the subsequent cyclopropanation of stilbenes in moderate to good yields with varying diastereoselectivity,[2] and several applications of this chemistry in intramolecular Friedel-Crafts-type reactions,[3] and [4+1] cycloadditions with methylenecyclopropanes and cyclobutenes have been reported.[4] A considerable drawback is the high temperature at which the retro-Buchner reaction takes place (120 °C), which puts limitations on the scope and applicability of this transformation.



Scheme 1. Formation of aryl gold(I) carbenes from 7-aryl cycloheptatrienes and subsequent transformations.

1 Jia, M.; Ma, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9134-9166.

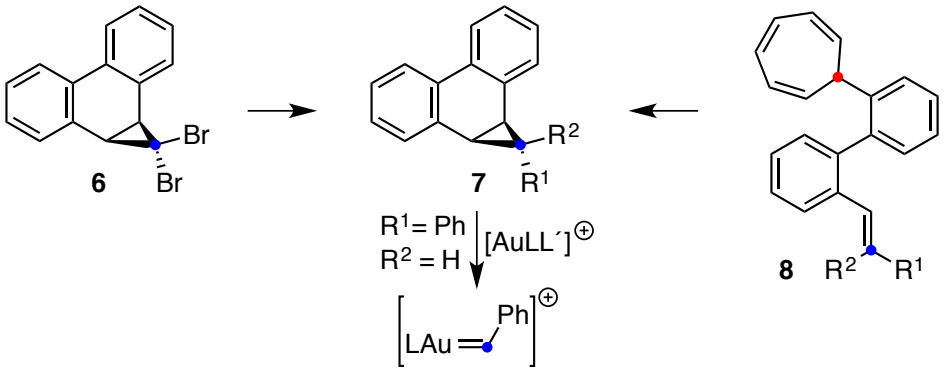
2 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**,

2 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

3 Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801-809.

4 Wang, Y.; Muratore, M. E.; Rong, Z.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 14022-14026.

In order to lower the activation energy for the formation gold(I) carbenes, 1-substituted dibenzonorcaradiene derivatives **7** instead of cycloheptatrienes were considered as carbene precursors because of their structural resemblance to norcaradiene **1´**, and their known predisposition to produce carbenes upon irradiation with light. Several derivatives were synthesized bearing distinct functional groups either through a common 1,1-dibromo intermediate **6,** or through an intramolecular gold(I)-catalyzed cyclopropanation of a biaryl compound with an appending alkene **8**. Unfortunately, the dibenzonorcaradiene derivatives did not offer an improvement over the existing cycloheptatrienes, although the prepared compounds might still find application in the light-mediated carbene formation.



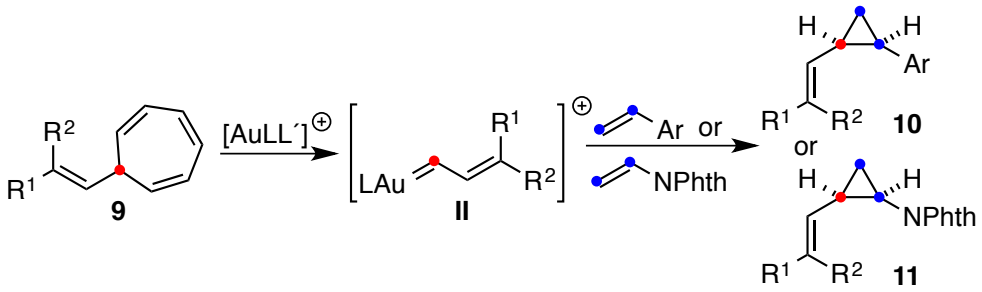
Scheme 2. Synthesis of 1-substituted dibenzonorcaradiene derivatives from a dihalo intermediate **6** or via a gold(I)-catalyzed intramolecular cyclopropanation reaction of **8**.

Vinylcyclopropanes **10** are important motifs in biologic and synthetic compounds, or can be used as synthetic intermediates because of their ability to undergo a plethora of rearrangement and cycloaddition reactions.

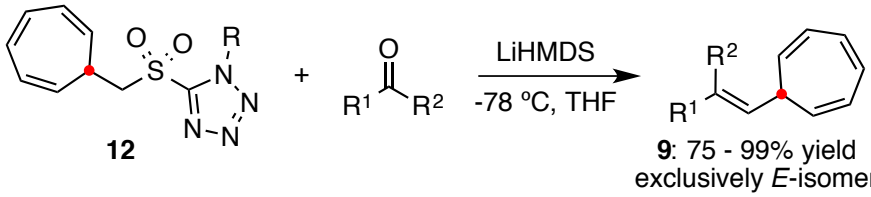
The formation of vinyl gold(I) carbenes **II** via the retro-Buchner reaction of 7-alkenyl cycloheptatriene derivatives takes place at considerably lower temperatures (75 °C).[5] A large series of vinylcyclopropanes **10** and vinyl-aminocyclopropanes **11** was prepared via the gold(I)-catalyzed retro-Buchner/alkene cyclopropanation reaction. Excellent *cis*-selectivity was achieved for aryl alkenes, while the cyclopropanation of *N*-vinylphthalimide was slightly less selective. Novel Julia-Kocienski reagents **12** were developed for the

5 Herlé, B.; Holstein, P. M.; Echavarren, A. M. *ACS Catal.* **2017**, 3668-3675.

formation of the desired 7-alkenyl-1,3,5-cycloheptatriene **9** from readily available aldehydes and ketones in one step. The applicability of the retro-Buchner reaction was greatly enhanced by the improved reaction conditions and the easy access to the cycloheptatriene derivatives.



Scheme 3. The formation of vinyl gold(I) carbenes **II** via the retro-Buchner reaction of 7-alkenyl cycloheptatriene derivatives **9** and subsequent alkene cyclopropanation reaction.



Scheme 4. Formation of 7-alkenyl cycloheptatriene derivatives **9** from readily available aldehydes and ketones in one step.

The diminished *cis*-selectivity for the vinyl-aminocyclopropanes **11** and the bis- and tris-arylcyclopropanes **2** from our group´s previous work, prompted us to investigate the reaction pathway with greater detail. Combined experimental and computational studies demonstrated the excellent intrinsic *cis*-selectivity for the cyclopropanation. Based on DFT calculations, a refined stereochemical model for the *cis*-selectivity in gold-catalyzed cyclopropanation reactions could be proposed. In addition, the mechanism of an unprecedented gold(I)-mediated isomerization of cyclopropanes was elucidated, where the cyclopropane is opened by gold(I) to form a complex with a linear carbocationic structure where the positive charge is stabilized as an allylic carbocation **III**.

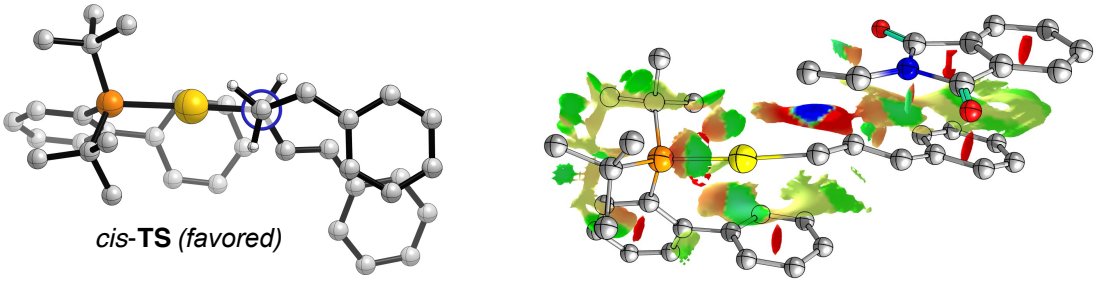
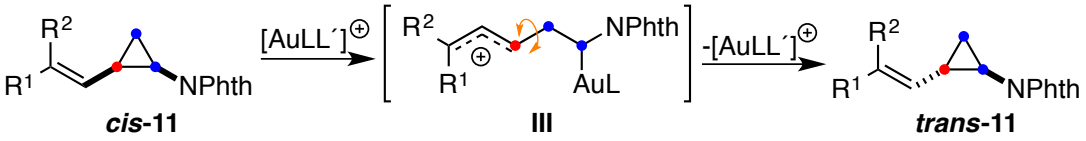
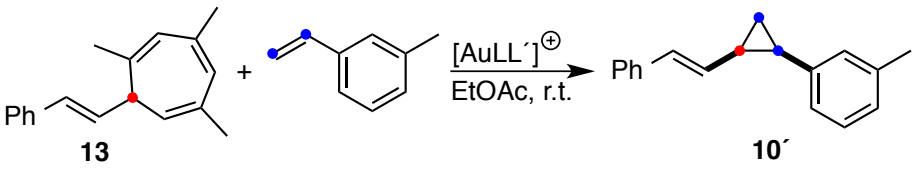


Figure 1. Transition state structure leading to *cis*-vinylcyclopropanes (left) and RGD isosurface representation of attractive non-covalent interaction in the *cis*-transition state.



Scheme 5. The mechanism of an unprecedented gold(I)-mediated cyclopropane isomerization.

By combining the knowledge obtained during the investigations on both the scope and mechanism with the alkenylation approach to form the cycloheptatriene reagents, a novel class of cycloheptatriene derivatives **13** was developed. In the case of the substituted cycloheptatriene, the energy barrier for the retro-Buchner reaction was overcome at room temperature, opening the door to the development of enantioselective gold(I)-catalyzed cyclopropanation reactions.



Scheme 6. The gold(I)-catalyzed retro-Buchner reaction taking place at room temperature using new cycloheptatriene derivatives **13**.

General Introduction

1. Cyclopropane

1.1. Properties of cyclopropane

The cyclopropane ring is the smallest cycloalkane, bearing the molecular formula C_3R_6, and is a structural isomer of propene.[6] The triangular structure forces the carbon-carbon bond angles to be 60°, instead of the usual 109.5° for sp^3 hybridized orbitals of carbon atoms. As such, there is a significant amount of ring strain within the molecule, which consists mainly of 1) angular (Baeyer) strain originating from the less than ideal C-C bond angles; 2) torsional (Pitzer) strain due to the coplanar arrangement of the carbon atoms, which force the hydrogen atoms to adopt a staggered conformation; 3) van der Waals strain due to the repulsion of the contiguous hydrogen atoms (Figure 2).[7]

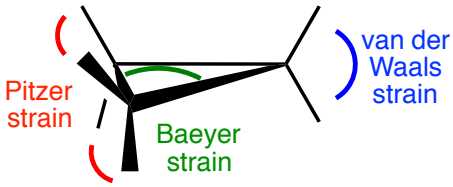


Figure 2 The three forms of strain contributing to the strong ring strain of cyclopropane.

The high reactivity of cyclopropanes and their propensity to react with electrophiles are generally accredited to the release of ring strain. The strain energy of cyclopropane is 27.6 kcal·mol^{-1}, which is not that different from the 26.2 kcal·mol^{-1} for cyclobutane.[8] In addition, the energies required for the homolytic C-C bond cleavage are very similar: 61.0 kcal·mol^{-1} for cyclopropane and 62.5 kcal·mol^{-1} for cyclobutane (Scheme 7),[9] as compared to 88.0 kcal·mol^{-1} for *n*-butane.[10] Yet, the reactivity of cyclopropanes resembles that of C-C double bonds, while the chemistry of cyclobutanes is comparable to alkanes. Therefore,

6 Kulinkovich, O. G. *Cyclopropanes in Organic Synthesis*; John Wiley & Sons, Inc, 2015.

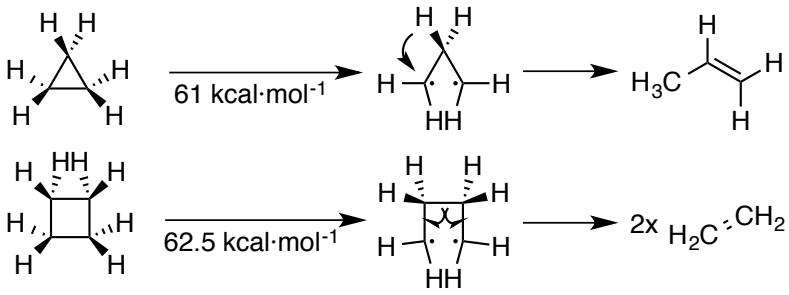
7 a) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165-198. b) de Meijere, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7836-7840. c) Walsh, A. D. *Nature* **1947**, *159*, 712.

8 Geiseler, G. *Ber. Bunsenges. Phys. Chemie* **1970**, *74*, 727-727.

9 a) Berson, J. A.; Pedersen, L. D.; Carpenter, B. K. *J. Am. Chem. Soc.* **1976**, *98*, 122-143. b) Ackermann, T. *Ber. Bunsenges. Phys. Chemie* **1969**, *73*, 241-241.

10 Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255-263.

the thermodynamic properties alone cannot explain the chemistry of cyclopropanes. Three models have been proposed that help describing the unique properties of this cycloalkane.



Scheme 7. Comparison of the energy required for the homolytic bond cleavage of cyclopropane and cyclobutane.

1.2. Coulson-Moffitt model

The *Coulson-Moffitt model* describes the cyclopropane as constructed by three sp^3-hybridized carbon centers where the bonding orbitals are angled outward by about 22° (Figure 3).[11] Because of the angle, the overlap is about 20% less effective, which is cited as the source of angular strain. Because the bonds are angled they are sometimes called "bent bonds", or even receive the honorary title of "banana bonds".

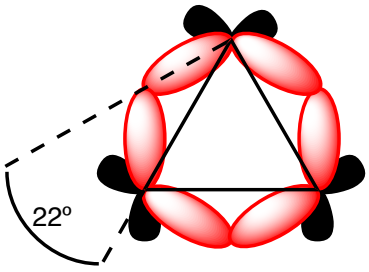


Figure 3. Representation of the Coulson-Moffitt model.

For normal carbon atoms, one *s* orbital and three *p* orbitals are hybridized to give four equivalent sp^3 orbitals, which all have about 25% *s* character.[12] For cyclopropanes, the orbitals are far from equivalent. The orbitals directed outwards have about 33% *s* character (~sp^2), while the ones involved in ring

11 a) Coulson, C. A.; Moffitt, W. E. *J. Chem. Phys.* **1947**, *15*, 151-151. b) Coulson, C. A.; Moffitt, W. E. *Philos. Mag.* **1949**, *40*, 1. b) Flygare, W. H. *Science* **1963**, *140*, 1179-1185. c) Peters, D. *Tetrahedron* **1963**, *19*, 1539-1546.

12 de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809-826.

bonding have only 17% *s* character (~sp^5) and resemble much more the *p* orbitals.[13] The preferred angle of 90°C for the *p* orbital helps to relieve some of the strain.[14] The increased *p* character of the C-C bonds is also responsible for the alkene-like reactivity.

1.3. Walsh model

According to the *Walsh model*, which was developed at the same time, the cyclopropane is constructed by the intra-annular overlap of the sp^2-hybridized orbitals of each carbon atom and three *p* orbitals of which one is anti-bonding (Figure 4).[15] In this model, too, the angular strain is attributed to decreased overlap. The bonds formed by overlap of the *p* orbitals can be viewed as distorted π-bonds, explaining the alkene-like reactivity.[16]

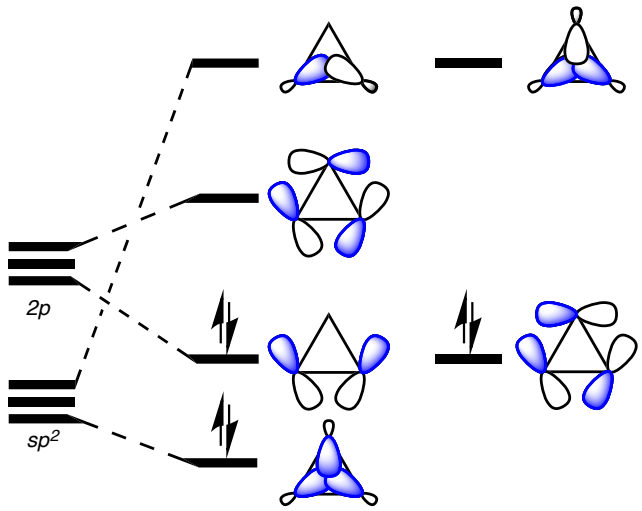


Figure 4. Representation of the Walsh model.

1.4. σ-Aromaticity

The *σ-aromaticity model* proposed by Dewar treats the cyclopropane as a 3-center 6-electron cyclic array that follows the *4n+2* rule.[17] A minor modification proposed by Cremer two years later, merges it with the Walsh model and views

13 Keese, R. *Angew. Chem.* **1980**, *92*, 73-73.
14 de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809-826.
15 a) Walsh, A. D. *Nature* **1947**, *159*, 712. b) Sugden, T. N. *Nature (London)* **1947**, *160*, 367. c) Walsh, A. D. *Trans. Faraday Soc.* **1949**, *45*, 179.
16 Bernett, W. A. *J. Chem. Educ.* **1967**, *44*, 17.
17 Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669-682.

the set of sp^2 orbitals as a 3-center 2-electron bond.[18] The *σ-aromaticity model* explains many characteristics of cyclopropane, such as the relatively low ring strain compared to cyclobutane, the NMR characteristics, and its reactivity towards electrophiles because aromaticity can be maintained in the transition state.[19] Yet, the *σ-aromaticity model* has not gone without controversy as no evidence has been found and alternative explanations for the observed effect have been proposed.[20]

1.5. Vinylcyclopropane

Analysis by UV spectroscopy,[21] NMR spectroscopy,[22] and X-ray diffraction has demonstrated the conjugation between cyclopropanes and an adjacent double bond.[23] The σ-bond between the alkene and the cyclopropane has 13-15% double-bond character and is significantly shorter than a normal σ-bond.[24] The partial double bond character can be explained by either one of the models as the orbitals with *p* character conjugate with the π-bond (Figure 5).[25]

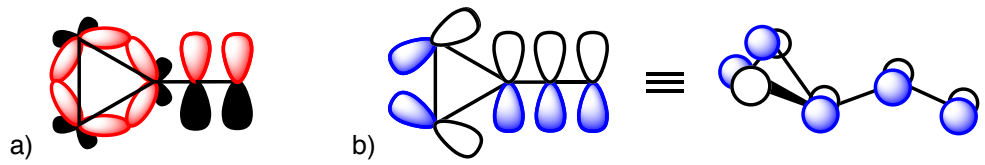


Figure 5. Conjugation of the cyclopropane bonds that have significant *p*-character with the vinylic π-bond for a) Coulson-Moffitt model and b) Walsh model.

18 Cremer, D.; Gauss, J. *J. Am. Chem. Soc.* **1986**, *108*, 7467-7477.
19 a) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165-198. b) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669-682.
20 a) Pelloni, S.; Lazzeretti, P.; Zanasi, R. *J. Phys. Chem. A* **2007**, *111*, 8163-8169. b) Wu, W.; Ma, B.; I-Chia Wu, J.; Schleyer, P. v. R.; Mo, Y. *Chem. - Eur. J.* **2009**, *15*, 9730-9736.
21 Cromwell, N. H.; Hudson, G. V. *J. Am. Chem. Soc.* **1953**, *75*, 872-874.
22 Noe, E. A.; Young, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 6218-6220.
23 Drumright, R. E.; Mas, R. H.; Merola, J. S.; Tanko, J. M. *J. Org. Chem.* **1990**, *55*, 4098-4102.
24 Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*; John Wiley & Sons, Inc.: 2006, p 136-233.
25 Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117-3179.

1.6. Cyclopropane motif

Cyclopropanes have attracted much attention from synthetic chemists because of the energy that can be harnessed by releasing the ring strain.[26] As such, cyclopropanes have been widely used as synthetic intermediates. On the other hand, its electronic properties and strained structure have attracted the attention of the physical organic community. Cyclopropanes have very pronounced steric, stereoelectronic and directing effects, which make them versatile probes for the study of regio-, diastereo- and enantioselectivity.

The cyclopropane subunit can be found in many biologically important natural products, such as terpenes, pheromones, fatty acids, and unusual amino acids (Figure 6).[27] The cyclopropane moiety can also be found in many synthetic compounds that exhibit biological properties,[28] such as enzyme inhibition,[29] insecticidal, [30] antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor, and antiviral activities.

26 Kulinkovich, O. G. *Cyclopropanes in Organic Synthesis*; John Wiley & Sons, Inc, 2015.

27 a) Salaün, J. In *Small Ring Compounds in Organic Synthesis VI*; de Meijere, A., Ed.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2000, p 1-67. b) Faust, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2251-2253. c) Salaün, J.; Baird, M. S. In *Current Medicinal Chemistry*; Atta-ur-Rahman, Ed.; Bentham Science Publishers B.V.: Schiphol, 1995; Vol. 2, p 511-542.

28 Kulinkovich, O. G. *Cyclopropanes in Organic Synthesis*; John Wiley & Sons, Inc, 2015.

29 Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537-552.

30 Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703-722.

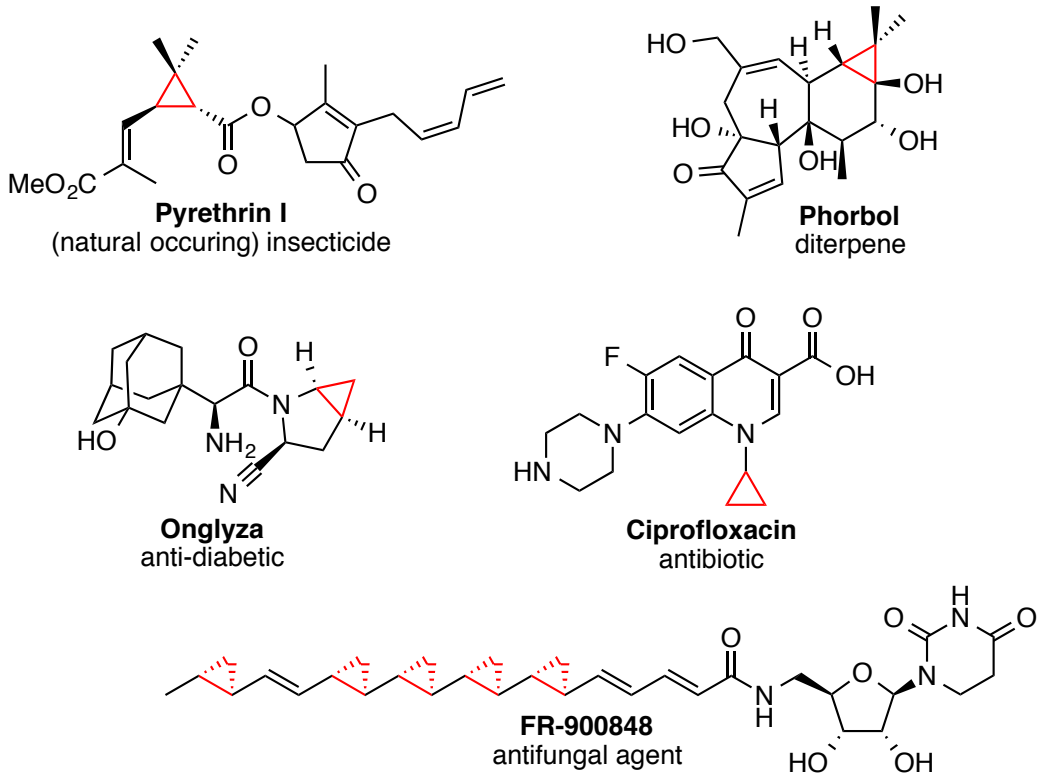
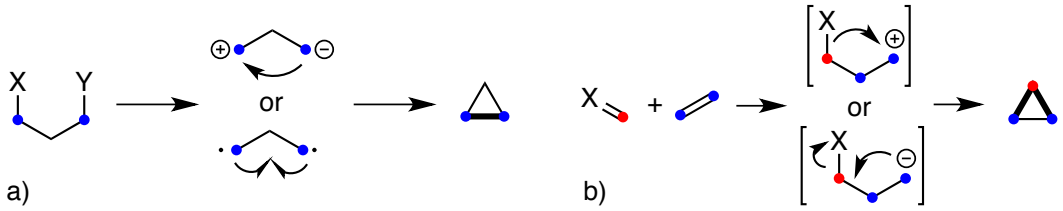


Figure 6. Examples of cyclopropane bearing natural or synthetic biologically-important compounds.

2. Cyclopropanation reactions

The synthesis of cyclopropanes can be divided into two main pathways; 1,3-Cyclization reactions when the cyclopropane is made by the formation of a single C-C bond (Scheme 8a), or [2+1] cyclization reactions when two C-C bonds are formed in a single step (Scheme 8b). For 1,3-cyclization reactions, precursors to 1,3-zwitterionic or 1,3-diradical compounds undergo a cyclization reaction to form cyclopropanes,[31] while in the [2+1] cyclization reaction, carbenes or their chemical equivalents, carbenoids, undergo a cyclization reaction with alkenes. In biological systems, formation of cyclopropanes can proceed through either one of the two pathways.[32]



Scheme 8. General representation of the 1,3-cyclization or [2+1] cyclization reactions.

2.1. 1,3-Cyclization reactions

The first synthesis of cyclopropane was achieved in 1882 by treatment of 1,3-dibromopropane with sodium (Scheme 9a).[33] Nowadays, the 1,3-cyclization reaction is still employed for the preparation of simple cyclopropane derivatives on multi-gram or even industrial scale (Scheme 9b and 9c).[34] Diastereoselective[35] and catalytic enantioselective transformations have been achieved for 1,3-cyclization reactions (Scheme 9d).[36]

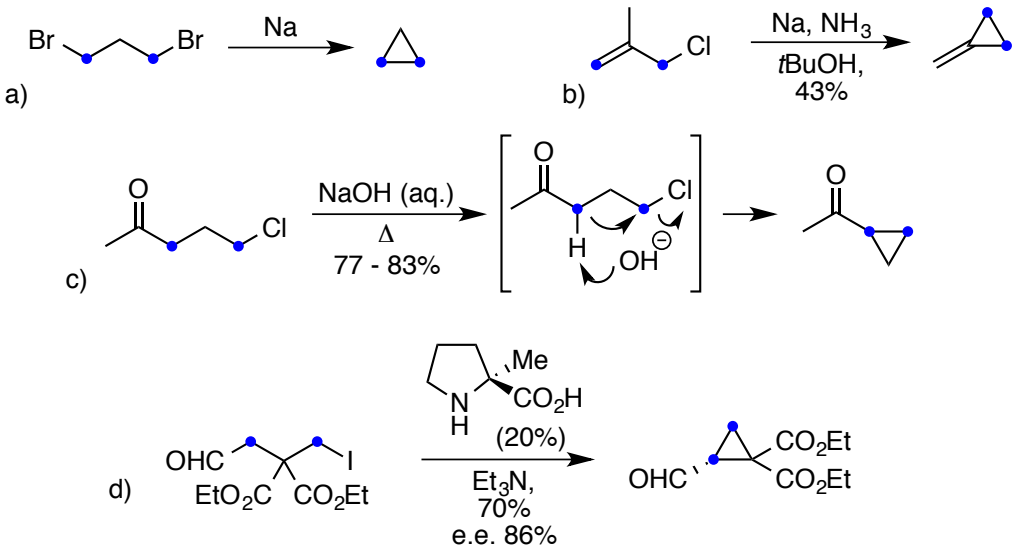
31 Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383-7423.

32 a) Law, J. H. *Acc. Chem. Res.* **1971**, *4*, 199-203. b) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625-1648. c) Liu, H. U.; Walsh, C. T. In *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons, Ltd: New York, 1987; Vol. 1, p 959–1025. d) Thibodeaux, C. J.; Chang, W.-c.; Liu, H.-w. *Chem. Rev.* **2012**, *112*, 1681-1709.

33 Freund, A. *J. Prakt. Chem.* **1882**, *26*, 367-377.

34 a) Cannon, G. W.; Ellis, R. C.; Leal, J. R. *Org. Synth.* **1951**, *31*, 74-77. b) Salaün, J. R.; Champion, J.; Conia, J. M. *Org. Synth.* **1977**, *57*, 36-40.

35 a) Inoue, T.; Kitagawa, O.; Ochiai, O.; Taguchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 691-692. b) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J.*



Scheme 9. a) Synthesis of cyclopropane by Freund, 1882.[37] b and c) Large-scale syntheses of simple cyclopropane derivatives.[38] d) Catalytic enantioselective 1,3-cyclization reaction.[39]

2.2. [2+1] Cyclization reactions

2.2.1. Kizhner cyclopropane synthesis

The oldest example of the [2+1] cyclization reaction to form cyclopropanes is known as the *Kizhner (Kischner) cyclopropane synthesis*, discovered in 1911.[40] However, in the original discovery a cyclopropane was formed by addition of hydrazine to α,β-unsaturated carbonyl compounds, which decomposes with the release of nitrogen to form a diradical species that cyclizes. Therefore, this reaction can also be categorized as a 1,3-cyclization for some cases. In others, a pyrazoline is formed by the 1,3-dipolar addition of a diazo compound to an alkene, which decomposes to form a cyclopropane and the reaction can be considered a [2+1] cyclization reaction (Scheme 10).

Am. Chem. Soc. **2001**, *123*, 2964-2969. c) Nakamura, E.; Sekiya, K.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 337-340.

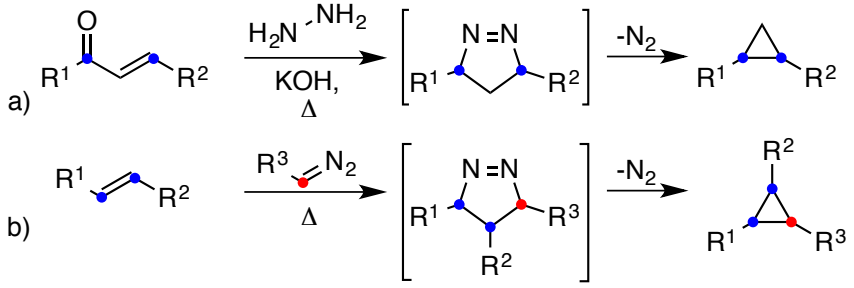
36 Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450-451.

37 Freund, A. *J. Prakt. Chem.* **1882**, *26*, 367-377.

38 a) Cannon, G. W.; Ellis, R. C.; Leal, J. R. *Org. Synth.* **1951**, *31*, 74-77. b) Salaün, J. R.; Champion, J.; Conia, J. M. *Org. Synth.* **1977**, *57*, 36-40.

39 Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450-451.

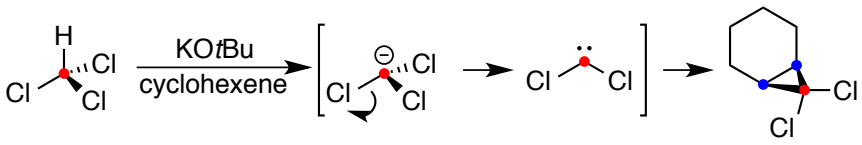
40 a) Kishner, N. M.; Zavadovskii, A. *J. Russ. Phys. Chem. Soc.* **1911**, *43*, 1132. b) Wang, Z. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: 2010.



Scheme 10. General representation of the Kizhner cyclopropane synthesis by the reaction of a) α,β -unsaturated carbonyl compound with hydrazine, or b) diazo compounds with alkenes.

2.2.2. Free dihalocarbenes

In 1954, von E. Doering and Hoffmann reported the use of *free dihalocarbenes* in the cyclopropanation of cyclohexene with dichlorocarbene (Scheme 11).[41] During the reaction, haloform is deprotonated by a strong base and a free carbene is formed after α-elimination. The reaction is limited to the formation of dihalocarbenes.[42]

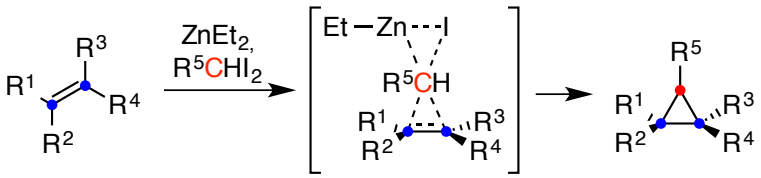


Scheme 11. The formation of dichlorocarbene and trapping with cyclohexene.

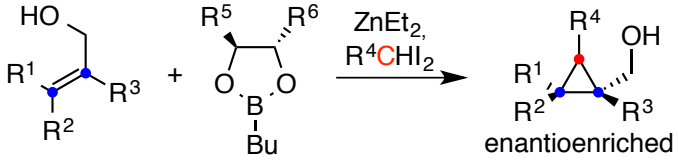
2.2.3. Simmons-Smith reaction

The *Simmons-Smith reaction*, discovered in 1958,[43] is likely the most powerful method for the generation of cyclopropanes (Scheme 12). The reaction owes its popularity to the generality and stereospecificity. A wide range of alkenes can be selectively functionalized, while the reaction displays a large functional-group tolerance. The mechanism has been well studied and several modifications have been reported, which make the reaction more reproducible, user friendly, and even asymmetric cyclopropanations have been achieved (Scheme 13).[44]

41 von E. Doering, W.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162-6165.
42 Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099-1132.
43 Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323-5324.
44 Kürti, L. s.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier, 2005.



Scheme 12. General representation of the stereospecific Simmons-Smith reaction.[45]



Scheme 13. Enantioselective cyclopropanation using the Charette modification of the Simmons-Smith reaction.[46]

2.2.4. Johnson-Corey-Chaykovsky cyclopropanation

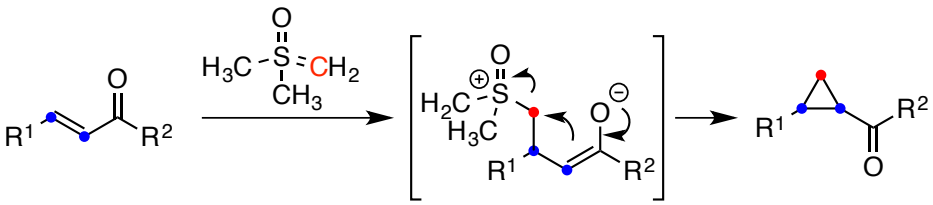
In 1961, Johnson discovered that the reaction between a sulfur ylid and benzaldehyde did not produce the anticipated Wittig product but instead an epoxide was formed.[47] The reaction was further developed by Corey and Chaykovsky, who used dimethylsulfoxonium methylid for the epoxidation of aldehydes and ketones.[48] A cyclopropane was formed instead of an epoxide when α,β-unsaturated carbonyls were used as substrates (Scheme 14). Modifications allow the use of many Michael acceptors, although the reaction is generally limited to the transfer of methylene. Yet, substituted methylene units have been transferred.[49]

2.2.5. Michael Induced Ring Closure

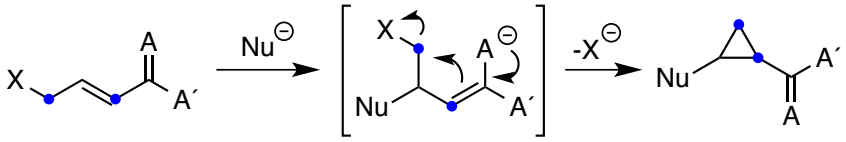
The *Michael Induced Ring Closure* (*MIRC*) leads to the formation of three-, four-, five-, six-, and seven-membered ring systems.[50] Mechanistically, this

45 Charette, A. B.; Beauchemin, A. In *Organic Reactions*; John Wiley & Sons, Inc.: 2004.
46 Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829-11832.
47 Johnson, A. W.; LaCount, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 417-423.
48 a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867-868. b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.
49 Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341-347.
50 a) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609-2612. b) Prempree, P.; Radviroongit, S.; Thebtaranonth, Y. *J. Org. Chem.* **1983**, *48*, 3553-3556.

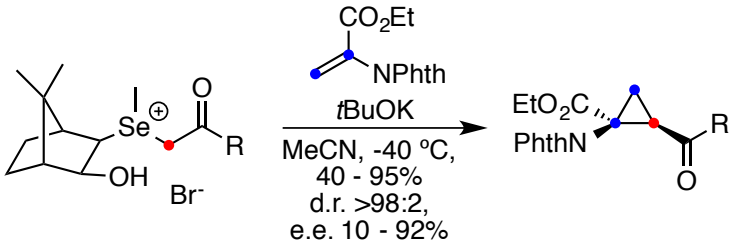
transformation is similar to the Johnson-Corey-Chaykovsky reaction, however it is not limited to the use of ylids. The reaction can be performed as either a 1,3-cyclization (Scheme 15), or [2+1] cyclization (Scheme 16). Excellent stereoselectivity has been achieved and this transformation plays an important role in the synthesis of 1-aminocyclopropanes-1-carboxylic acids (Scheme 16).[51]



Scheme 14. General representation of the Johnson-Corey-Chaykovsky reaction.



Scheme 15. MIRC used in a 1,3-cyclization reaction.



Scheme 16. The enantioselective MIRC reaction using chiral selenium ylids.[52]

2.2.6. Kulinkovich reaction

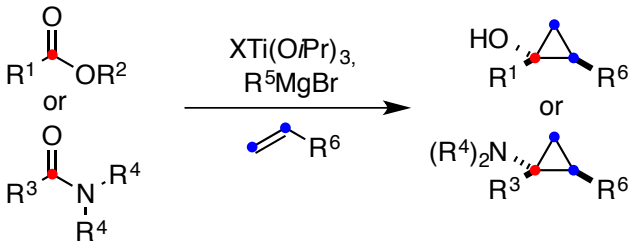
The *Kulinkovich* reaction uses a titanium catalyst for the formation of cyclopropanols from esters and Grignard reagents (Scheme 17).[53] Later modifications allow the use of carboxamides and cyano groups instead of esters (Scheme 17). More complex Grignard reagents can be used to obtain *cis*-

51 a) Wang, H.-Y.; Yang, F.; Li, X.-L.; Yan, X.-M.; Huang, Z.-Z. *Chem. - Eur. J.* **2009**, *15*, 3784-3789. b) Joucla, M.; El Goumzili, M.; Fouchet, B. *Tetrahedron Lett.* **1986**, *27*, 1677-1680. c) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979-1029.

52 Zhou, R.; Deng, X.; Zheng, J.; Sheng, Q.; Sun, X.; Tang, Y. *Chin. J. Chem .* **2011**, *29*, 995-1000.

53 Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244-2245.

cyclopropanols but because of the their high reactivity, the functional group tolerance can be somewhat limited.[54]



Scheme 17. General representation of a catalytic Kulinkovich reaction.

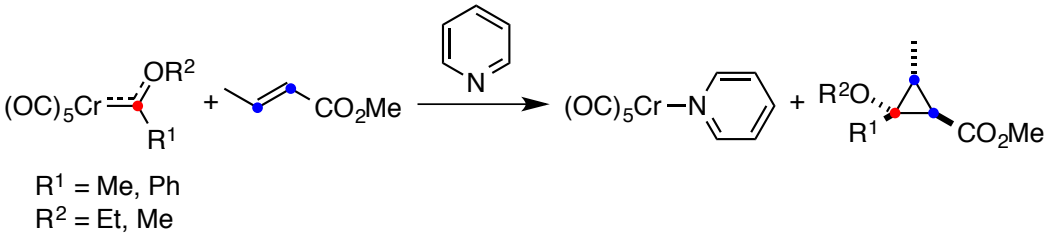
2.2.6. Transition-metal catalyzed cyclopropanations

The *carbene transfer from* a *transition-metal-carbene complex* to an alkene was already postulated in 1966 by Jolly and Pettit.[55] It was not until 1970 when Fischer reopened the field and demonstrated that carbene complexes could be used as practical carbene transfer reagents (Scheme 18).[56] Initially, the scope was limited to nucleophilic alkenes, the reactions suffered from low selectivity and the scope was also limited in terms of the carbenes. Formation of the metal-carbene complexes was difficult, so only simple, yet highly stabilized carbenes could be used. Although the direct reaction of diazo compounds with alkenes can be induced thermally or photochemically, carbene complexes can be formed by their transition-metal mediated decomposition under mild conditions. The *decomposition of diazo compounds by transition-metal complexes* to form metal-carbene complexes for carbene-transfer reactions has grown to one of the most extensively studied fields within organic chemistry. The rapid development includes the use of more stable diazo compounds, broad substrate scope, mild reaction conditions, and diastereo- and enantioselective versions (Scheme 19).

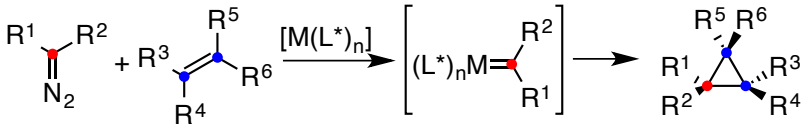
54 a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597-2632. b) Meijere, A. d.; Kozhushkov, S. I.; Savchenko, A. I. *J. Organomet. Chem.* **2004**, *689*, 2033-2055.

55 Jolly, P. W.; Pettit, R. *J. Am. Chem. Soc.* **1966**, *88*, 5044-5045.

56 Fischer, E. O.; Heinz Dötz, K. *Chem. Ber.* **1970**, *103*, 1273-1278.



Scheme 18. The first reported use of metal complexes as carbene transfer reagents.[56]

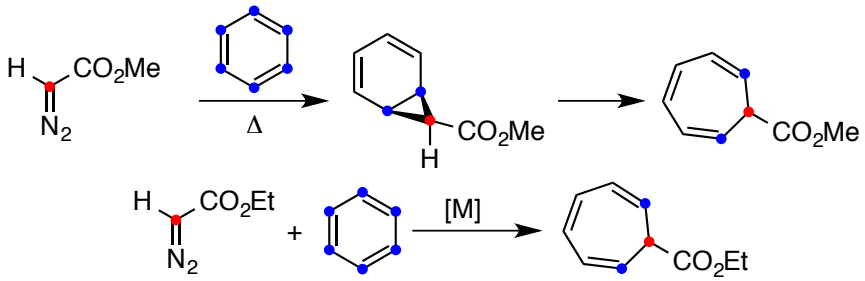


Scheme 19. General representation of the formation of carbene complexes and cyclopropanation by the decomposition of diazo compounds.

2.2.7 Buchner reaction

The reaction of diazo compounds with arenes to form cycloheptatrienes, nowadays known as the *Buchner reaction*, was reported in 1885 by E. Buchner and T. Curtius and would actually predate the *Kizhner reaction* as the first cyclopropanation reaction.[57] A cycloheptatriene is formed in two steps. In the first step, one of the aromatic bonds is cyclopropanated to form a norcaradiene, which then undergoes a 6-electron disrotatory electrocyclic opening.[58] The cycloheptatriene-norcaradiene equilibrium is influenced by steric and electronic effects, with electron withdrawing substituents on the C7 favoring the norcaradiene tautomer. In the original report, diazo compounds were heated to reflux in aromatic solvents but later several transition-metal catalysts have been found that efficiently catalyze the *Buchner reaction*.[59]

57 Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2377-2379.
58 McNamara, O. A.; Maguire, A. R. *Tetrahedron* **2011**, *67*, 9-40.
59 Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873-876.



Scheme 20. General representation of the Buchner reaction as invented (top), and transition-metal catalyzed (bottom).

2.2.7.2 E. Buchner or E. Büchner?

Some authors believe that the inventor of the *Buchner reaction* and the Büchner funnel are one and the same person.[60] However, one should take care not to confuse the biochemist Eduard Buchner (20 May 1860 – 13 August 1917) with the chemist Ernst Büchner (18 March 1850 – 25 April 1924). Apart from living at the same time, they both published their work as "E. Buchner" or "E. Büchner" as neither had more initials. To make matters more confusing, for both the year 1888 marked an important date; Eduard Buchner received his PhD and went on to publish his Nobel-prize-winning work on fermentation, and Ernst Büchner filed his patents for the Büchner funnel and Büchner flask.[61]

60 a) Lovely, C. J.; Browning, R. G.; Badarinarayana, V.; Dias, H. V. R. *Tetrahedron Lett.* **2005**, *46*, 2453-2455. b) Wang, Z. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons, Inc.: 2010. c) Komine, N.; Flores, J. A.; Pal, K.; Caulton, K. G.; Mindiola, D. J. *Organometallics* **2013**, *32*, 3185-3191.

61 Jensen, W. B. *J. Chem. Educ.* **2006**, *83*, 1283.

3. Stereo- and enantioselective cyclopropanation reactions

Nearly all biological compounds are chiral and cyclopropane motifs are not exempt of this rule. In the past two decennia great progress has been made in the development of synthetic methods to obtain enantiopure cyclopropanes. In the next section the major advances in the asymmetric Simmons-Smith reaction, transition-metal-catalyzed decomposition of diazo compounds, and several other methods will be briefly reviewed.

3.1. Asymmetric Simmons-Smith reaction

One of the key aspects of the *Simmons-Smith reaction* is the influence of proximal groups. The reaction is susceptible to steric effects and usually takes place from the least hindered site. However, a proximal hydroxy group can influence the reaction in a more specific way. Not only does it enhance the rate of the reaction, but it also works as a directing group. The coordination of zinc to the hydroxy group directs the cyclopropanation to the face of the alcohol. This diastereoselectivity had previously been exploited for the synthesis of asymmetric cyclopropanes, starting from chiral alcohols (Scheme 21).[62] In recent years, this strategy has been expanded by the use of chiral auxiliaries that can be cleaved after the reaction (Scheme 22).[63]

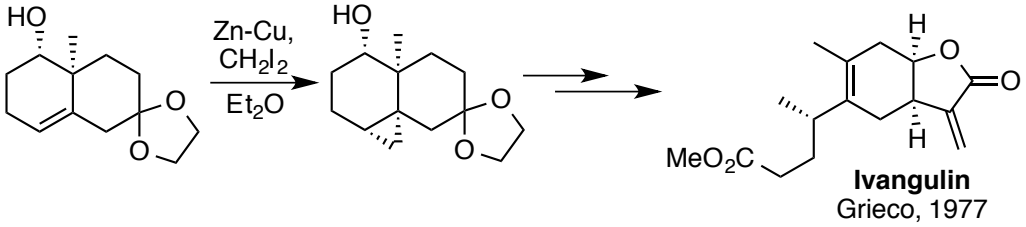
The first example of an enantioselective Simmons-Smith reaction was reported in 1992 (Scheme 23).[64] This strategy also uses the proximity of the hydroxy group in combination with a chiral ligand to direct the cyclopropanation. With the development of the *Charette modification*, excellent stereo- and enantioselectivity can be obtained (Scheme 24).[65]

62 Grieco, P. A.; Oguri, T.; Wang, C.-L. J.; Williams, E. *J. Org. Chem.* **1977**, *42*, 4113-4118.

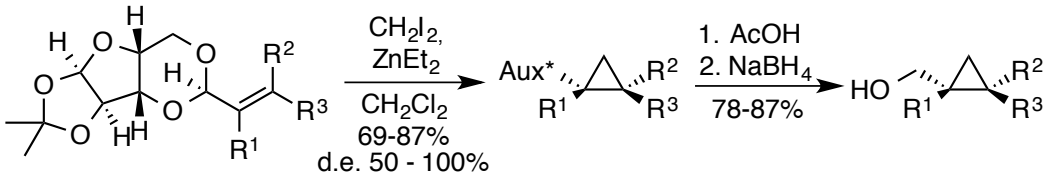
63 Vega-Pérez, J. M.; Periñán, I.; Vega, M.; Iglesias-Guerra, F. *Tetrahedron: Asymmetry* **2008**, *19*, 1720-1729.

64 Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575-2578.

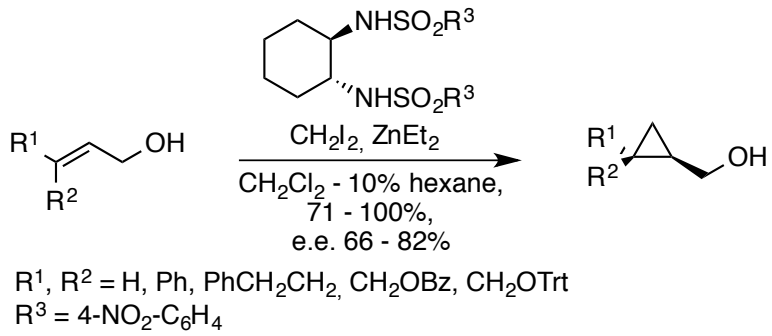
65 Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829-11832.



Scheme 21. The use of a diastereoselective Simmons-Smith reaction in the synthesis of Ivangulin.[66]



Scheme 22. The use of D-xylofuranose as chiral auxiliary for the Simmons-Smith reaction.[67]

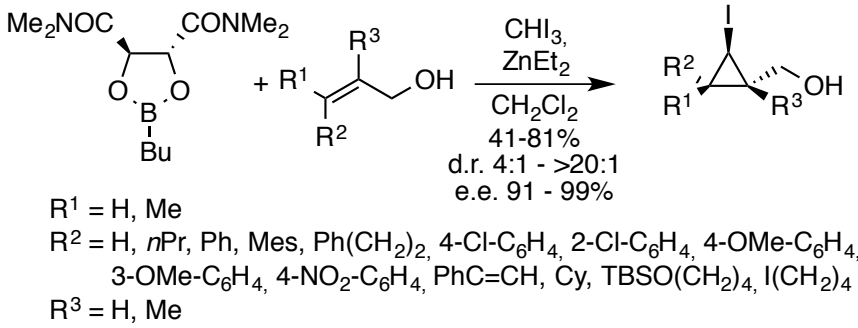


Scheme 23. First example of the enantioselective Simmons-Smith reaction.[68]

66 Grieco, P. A.; Oguri, T.; Wang, C.-L. J.; Williams, E. *J. Org. Chem.* **1977**, *42*, 4113-4118.

67 Vega-Pérez, J. M.; Periñán, I.; Vega, M.; Iglesias-Guerra, F. *Tetrahedron: Asymmetry* **2008**, *19*, 1720-1729.

68 Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575-2578.



Scheme 24. Excellent diastereo- and enantioselectivity obtained using the Charette modification.[69]

3.2. Asymmetric transition-metal catalyzed cyclopropanation

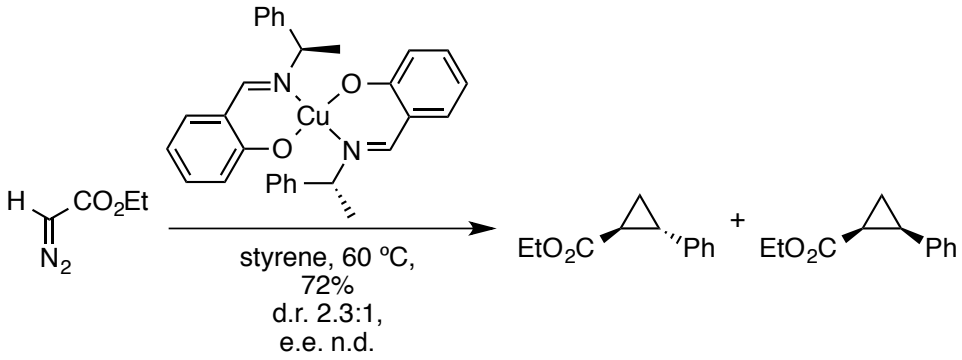
As early as 1966, groundbreaking work by Noyori and co-workers demonstrated the application of *transition-metal-catalyzed decomposition of diazo compounds* for the asymmetric formation of cyclopropanes (Scheme 25).[70] Rapid development in this field now makes it one of the most efficient routes to optically active cyclopropanes. By clever catalyst design, excellent yields and diastereo- and enantioselectivity can be obtained. Some recent examples include cobalt-porphyrine (Scheme 26),[71] copper-BOX (Scheme 27), rhodium carboxylates (Scheme 28), ruthenium-PheOX, and iridium-salen complexes.[72]

69 Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829-11832.

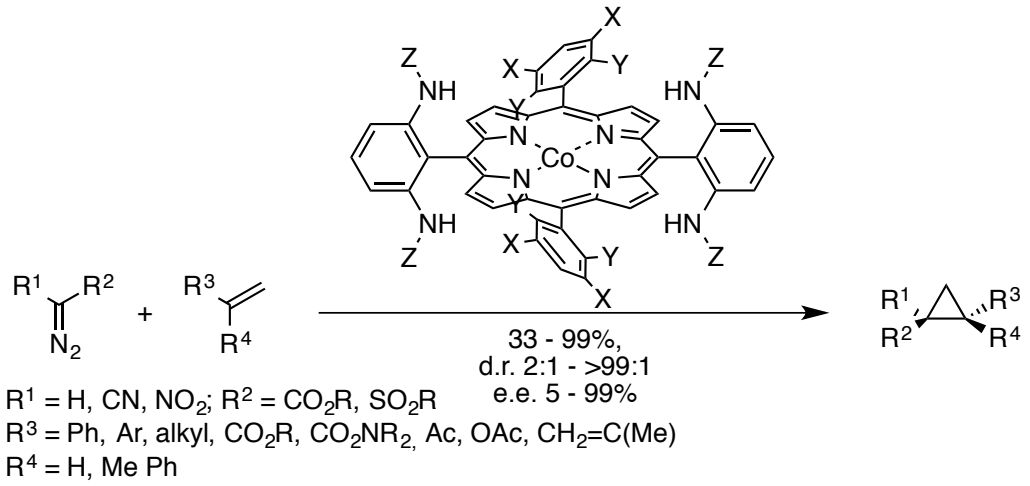
70 Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *7*, 5239-5244.

71 a) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8460-8463. b) Ruppel, J. V.; Gauthier, T. J.; Snyder, N. L.; Perman, J. A.; Zhang, X. P. *Org. Lett.* **2009**, *11*, 2273-2276. c) Zhu, S.; Ruppel, J. V.; Lu, H.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2008**, *130*, 5042-5043. d) Zhu, S.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc.* **2010**, *132*, 12796-12799. e) Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; Lopez de Mesa, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 15292-15295.

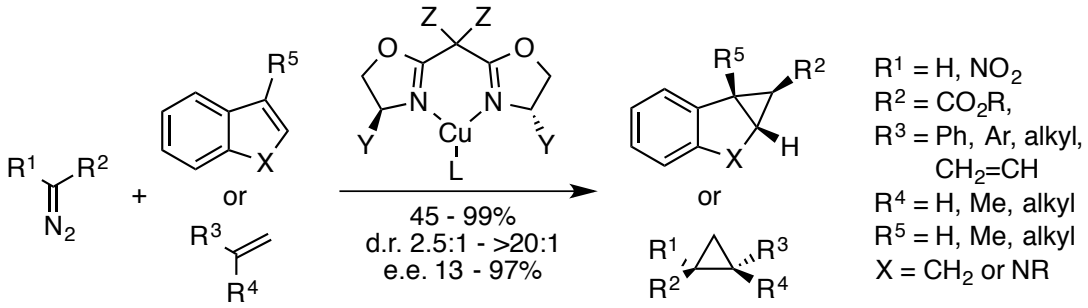
72 a) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979-1029. b) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041-7095. c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050.



Scheme 25. First example of enantioselective transition-metal catalyzed cyclopropanation.[73]

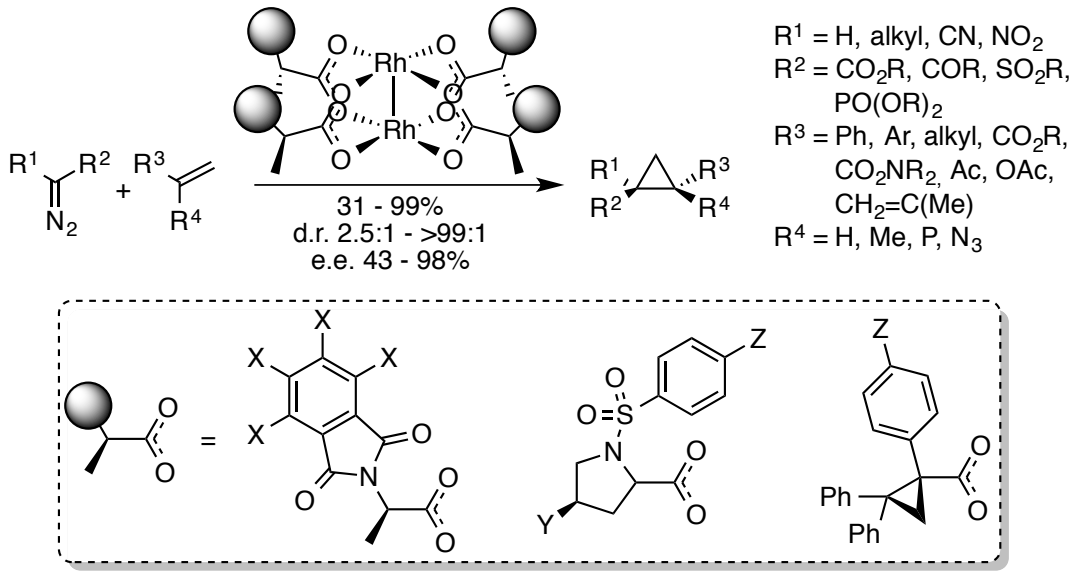


Scheme 26. Highly selective cyclopropanation using cobalt-porphyrine complexes.

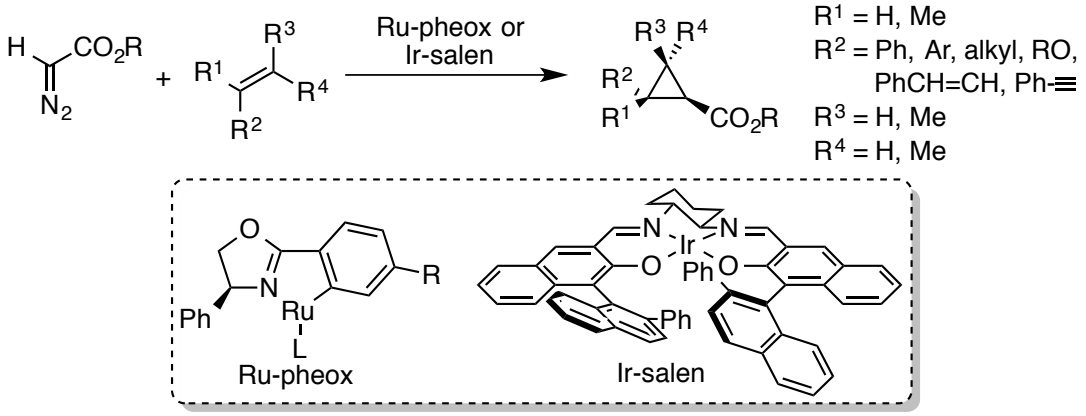


Scheme 27. Good diastereo- and enantioselectivity was obtained in the alkene cyclopropanation with copper-BOX complexes.

73 Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *7*, 5239-5244.



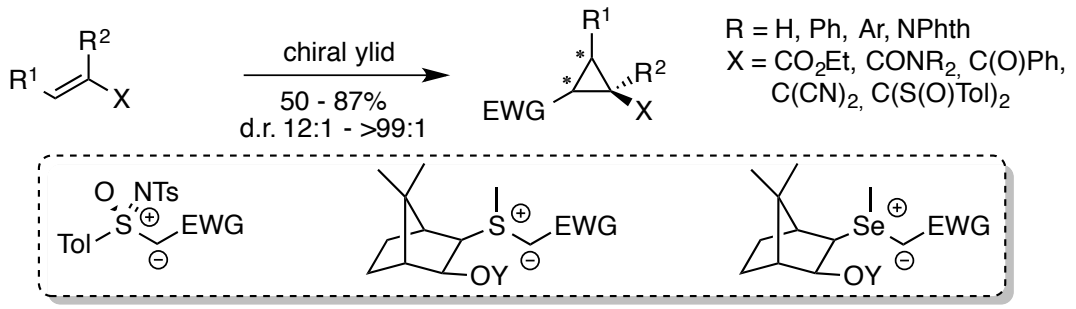
Scheme 28. Different rhodium complexes with acetate derived ligands for alkene cyclopropanation reactions.



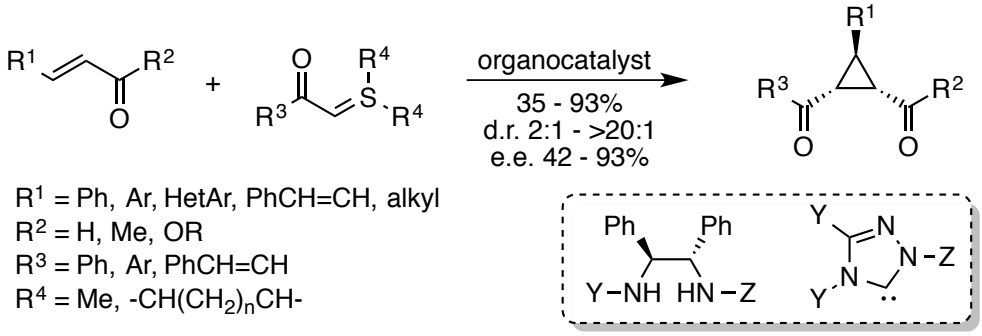
Scheme 29. Ruthenium-PheOX or iridium-salen complexes for the asymmetric alkene cyclopropanation.

3.3. Other asymmetric methods

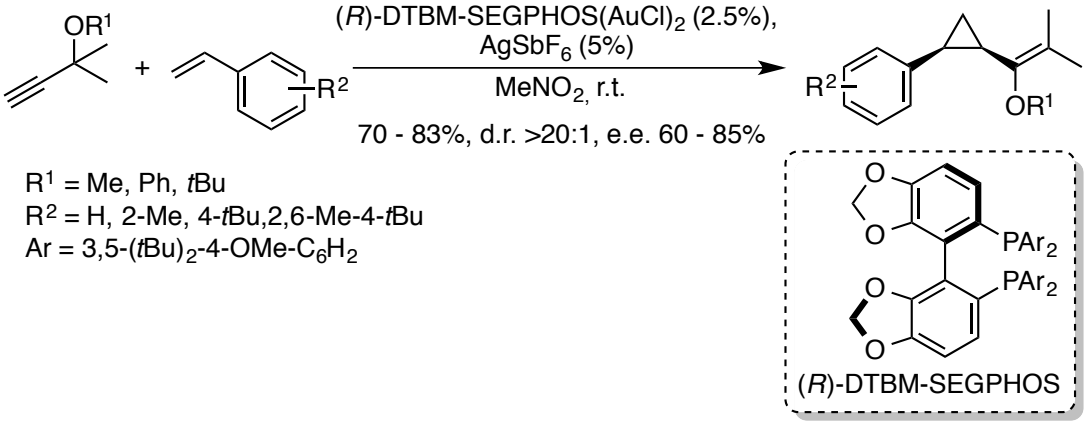
Several other methods have been developed for the formation of asymmetric cyclopropanes. One broadly employed strategy is that of the *Michael-initiated ring closure*. This method relies on chiral auxiliaries (Scheme 30), organocatalysts (Scheme 31), or metal catalysts to induce chirality. Other notable examples include C-H insertion, nucleophilic ring closure, and, the recently more explored, reaction of propargylic carboxylates (Scheme 32).[72]



Scheme 30. MIRC reaction using chiral ylids.[72]



Scheme 31. MIRC using organocatalysts.[72]



Scheme 32. Gold(I)-catalyzed alkene cyclopropanation from propargylic carboxylates.[74]

74 Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

4. Carbenes

Carbenes can exist in either a singlet or triplet state, depending on the electronic spin they possess.[75] In a singlet carbene, the two electrons are spin paired occupying the same orbital so the total spin (ħ) is zero (Figure 7a). Triplet carbenes have two unpaired electrons occupying different orbitals and their total spin is one (Figure 7b). For simple carbenes, the triplet state is usually more stable by about 8 kcal·mol^{-1}. Singlet carbenes usually exist as the excited state.[76] Substituents that donate electron pairs can stabilize singlet carbenes by delocalizing the electron pair to an empty *p*-orbital of the carbene center. With sufficient stabilization the singlet carbene can become the ground state (Figure 7c).[77]

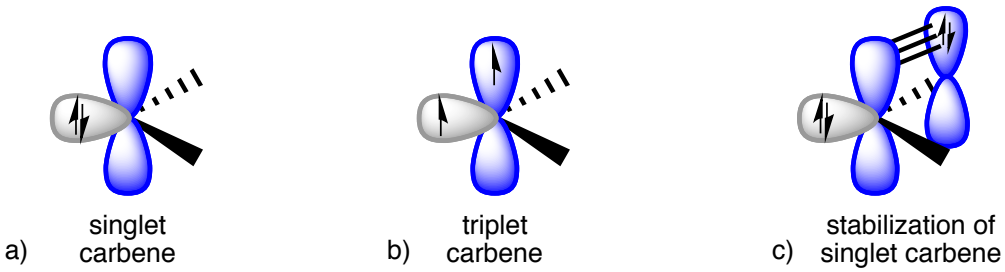


Figure 7. Depiction of a singlet carbene on the left, triplet carbene in the middle, and a stabilized singlet carbene on the right.

Metal-coordinated carbenes can be further divided into two groups: The singlet-carbene like *Fischer carbenes*, and the triplet carbene derived *Schrock carbenes*.[78] A third classification, the so-called *carbenoids*, is a class of compounds that display the reactivity of carbenes but are structurally different. A famous example of a carbenoid intermediate would be the Zn-iodine complex in the *Simmons-Smith reaction*.[79]

75 Skell, P. S.; Woodworth, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 4496-4497.
76 Mueller, P. H.; Rondan, N. G.; Houk, K. N.; Harrison, J. F.; Hooper, D.; Willen, B. H.; Liebman, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 5049-5052.
77 Nemirowski, A.; Schreiner, P. R. *J. Org. Chem.* **2007**, *72*, 9533-9540.
78 Crabtree, R. H. In *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons, Inc.: 2005, p 309-341.
79 Charette, A. B.; Beauchemin, A. In *Organic Reactions*; John Wiley & Sons, Inc.: 2004.

Fischer carbenes commonly are complexes of middle and late transition metals in low oxidation states with π-acceptor ligands. On the level of molecular orbitals, the lone pair of the singlet carbene is donated to an empty *d*-orbital of the metal, while a lone pair from the metal is back donated to an empty *p*-orbital on the carbon (Figure 8). *Fischer carbenes* are often stabilized by π-donating substituents on the carbon. This leads to competition for the vacant *p*-orbital on the carbon, reducing the back donation from the metal. Much like carbon monoxide, the carbene is considered a neutral ligand while the carbon has an electrophilic character.[80]

Schrock carbenes complexes are complementary in every aspect to *Fischer carbenes* and usually consist of early to middle transition metals in high oxidation states. This type of complex is usually electron deficient and/or has strong π-donating ligands. The carbon-metal bond is polarized, giving the carbon a nucleophilic character (Figure 8).

There are several complexes for which the lines are blurred, for example high oxidation-state complexes with heteroatom-alkylidene that do not react like carbenes, [81] or carbene complexes that react as both nucleophile and electrophile.[82]

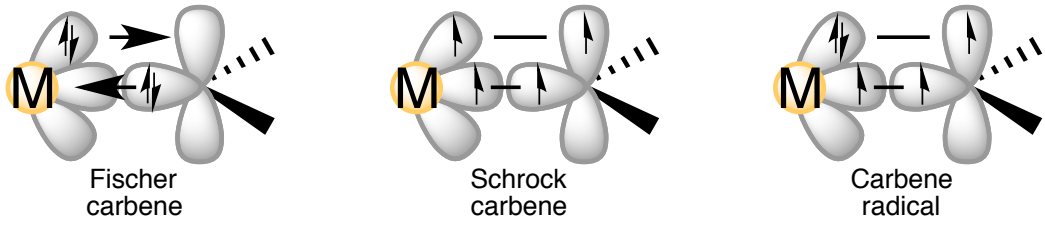


Figure 8. Depiction of a Fischer carbene, Schrock carbene and carbene radical.

The mechanism of cyclopropanation reactions of alkenes with carbenes is dependent on the nature of the carbene. Triplet and *Schrock carbenes* can be

80 Crabtree, R. H. In *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons, Inc.: 2005, p 309-341.

81 a) LaPointe, A. M.; Schrock, R. R. *Organometallics* **1995**, *14*, 1875-1884. b) Toreki, R.; Vaughan, G. A.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc.* **1993**, *115*, 127-137. c) Flatt, B. T.; Grubbs, R. H.; Blanski, R. L.; Calabrese, J. C.; Feldman, J. *Organometallics* **1994**, *13*, 2728-2732.

82 Casey, C. P.; Czerwinski, C. J.; Powell, D. R.; Hayashi, R. K. *J. Am. Chem. Soc.* **1997**, *119*, 5750-5751.

considered to react as diradicals with alkenes. During the cyclopropanation reaction, one bond is formed before the other, leading to an intermediate with two unpaired electrons, which allows rotation around the former olefinic C-C bond, therefore allowing the possibility for the reaction to take place in a stereoselective manner (Scheme 33).

Singlet and *Fischer carbenes* react as electrophiles in cheletropic reactions; a type of pericyclic reaction in which two new bonds are formed to the same atom. Due to the nature of the singlet carbene, both bonds are formed at the same time and the reaction is therefore stereospecific (Scheme 33). The cyclopropanation mechanism for *Fischer carbenes* can be divided in two groups: First an indirect mechanism in which a metallobutane is formed first, followed by the formation of the second C-C bond to give the cyclopropane (Scheme 34). The other option is a direct cyclopropanation, in which the cyclopropane is formed in a single step, which can be highly asynchronous, or step-wise through a linear organometallic species (Scheme 35). The indirect mechanism is commonly proposed for palladium,[83] rhodium(I),[84] rhodium(III),[85] and some example for copper(I),[86] while the direct mechanism is postulated for chromium(III),[87] platinum(II),[88] rhodium(II),[89] ruthenium(II),[90] and other examples for copper(I),[91] and some

83 a) Straub, B. F. *J. Am. Chem. Soc.* **2002**, *124*, 14195-14201. b) Berthon-Gelloz, G.; Marchant, M.; Straub, B. F.; Marko, I. E. *Chem. - Eur. J.* **2009**, *15*, 2923-2931. c) Bernardi, F.; Bottoni, A.; Miscione, G. P. *Organometallics* **2001**, *20*, 2751-2758.

84 Rosenberg, M. L.; Krapp, A.; Tilset, M. *Organometallics* **2011**, *30*, 6562-6571.

85 Deng, J.; Wen, X.; Qiu, Z.; Li, J. *Tetrahedron* **2016**, *72*, 8456-8462.

86 a) Straub, B. F.; Gruber, I.; Rominger, F.; Hofmann, P. *J. Organomet. Chem.* **2003**, *684*, 124-143. b) Kefalidis, C. E.; Kanakis, A. A.; Gallos, J. K.; Tsipis, C. A. *J. Organomet. Chem.* **2010**, *695*, 2030-2038.

87 Concellón, J. M.; Rodríguez-Solla, H.; Méjica, C.; Blanco, E. G.; García-Granda, S.; Rosario Díaz, M. *J. Org. Chem.* **2008**, *73*, 3828-3836.

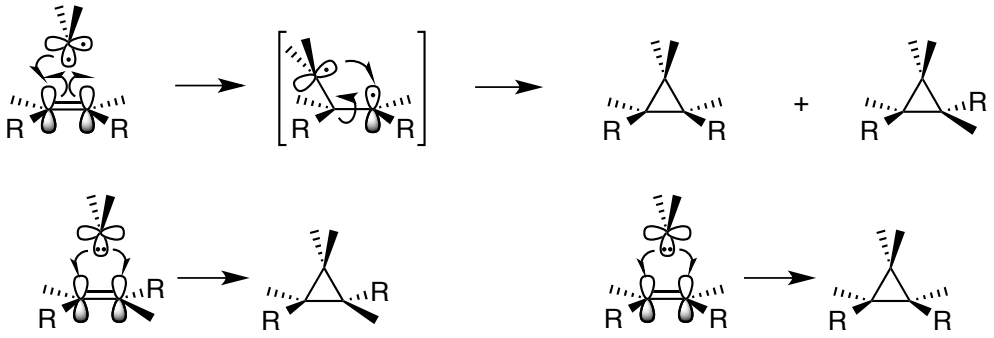
88 Marco-Contelles, J.; Soriano, E. *J. Mol. Struct.: THEOCHEM* **2006**, *761*, 45-51.

89 a) Intrieri, D.; Caselli, A.; Gallo, E. *Eur. J. Inorg. Chem.* **2011**, *2011*, 5071-5081. b) Xue, Y.-S.; Cai, Y.-P.; Chen, Z.-X. *RSC Advances* **2015**, *5*, 57781-57791. c) Bonge, H. T.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 2309-2320.

90 a) Basato, M.; Tubaro, C.; Biffis, A.; Bonato, M.; Buscemi, G.; Lighezzolo, F.; Lunardi, P.; Vianini, C.; Benetollo, F.; Del Zotto, A. *Chem. - Eur. J.* **2009**, *15*, 1516-1526. b) Xu, Z.-J.; Fang, R.; Zhao, C.; Huang, J.-S.; Li, G.-Y.; Zhu, N.; Che, C.-M. *J. Am. Chem. Soc.* **2009**, *131*, 4405-4417. c) Cornejo, A.; Fraile, J. M.;

other metals.[92] It has been shown that subtle differences in ligand, alkene and carbene can favor one mechanism or another (Scheme 36).[93]

Some transition-metal carbene complexes generate metalloradical carbenes, which are stabilized like Fischer carbenes but react as triplet carbenes (Figure 8),[94] which can be seen in some cobalt(III)-,[95] iron(II)-,[96] or nickel(II)-catalyzed cyclopropanation[97] reactions (Scheme 37).



Scheme 33. Top: Reaction of a Schrock carbene with an alkene, diradical intermediate and products. Bottom: stereospecific reaction of Fischer carbene with alkene.

García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Organometallics* **2005**, *24*, 3448-3457.

91 a) Rasmussen, T.; Jensen, J. F.; Østergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P.-O. *Chem. - Eur. J.* **2002**, *8*, 177-184. b) Garcia, J. I.; Jimenez-Oses, G.; Lopez-Sanchez, B.; Mayoral, J. A.; Velez, A. *Dalton Transactions* **2010**, *39*, 2098-2107. c) Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616-7625.

92 a) Wang, Q.; Försterling, F. H.; Hossain, M. M. *J. Organomet. Chem.* **2005**, *690*, 6238-6246. b) Harrold, N. D.; Corcos, A. R.; Hillhouse, G. L. *J. Organomet. Chem.* **2016**, *813*, 46-54. c) Zhang, X.; Geng, Z.-Y.; Wang, Y.-C.; Li, W.-Q.; Wang, Z.; Liu, F.-X. *J. Mol. Struct.: THEOCHEM* **2009**, *893*, 56-66.

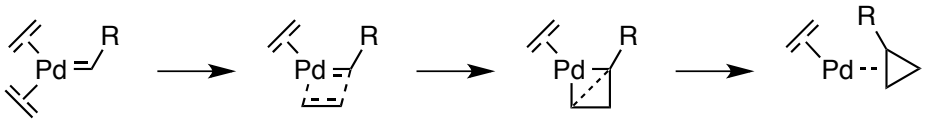
93 a) Meng, Q.; Li, M.; Tang, D.; Shen, W.; Zhang, J. *J. Mol. Struct.: THEOCHEM* **2004**, *711*, 193-199. b) Özen, C.; Tüzün, N. S. *Organometallics* **2008**, *27*, 4600-4610. c) García, J. I.; Jiménez-Osés, G.; Mayoral, J. A. *Chem. - Eur. J.* **2011**, *17*, 529-539.

94 a) Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. *J. Am. Chem. Soc.* **2010**, *132*, 10891-10902. b) Lu, H.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 8518-8521. c) Fantauzzi, S.; Gallo, E.; Rose, E.; Raoul, N.; Caselli, A.; Issa, S.; Ragaini, F.; Cenini, S. *Organometallics* **2008**, *27*, 6143-6151. d) Belof, J. L.; Cioce, C. R.; Xu, X.; Zhang, X. P.; Space, B.; Woodcock, H. L. *Organometallics* **2011**, *30*, 2739-2746.

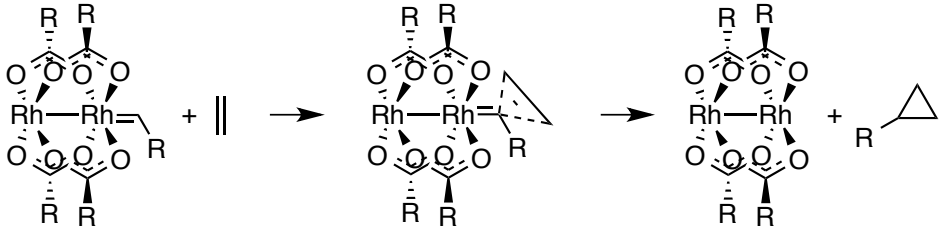
95 a) Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. *J. Am. Chem. Soc.* **2010**, *132*, 10891-10902. b) Das, B. G.; Chirila, A.; Tromp, M.; Reek, J. N. H.; Bruin, B. d. *J. Am. Chem. Soc.* **2016**, *138*, 8968-8975.

96 Tagliatesta, P.; Pastorini, A. *J. Mol. Catal. A: Chem.* **2003**, *198*, 57-61.

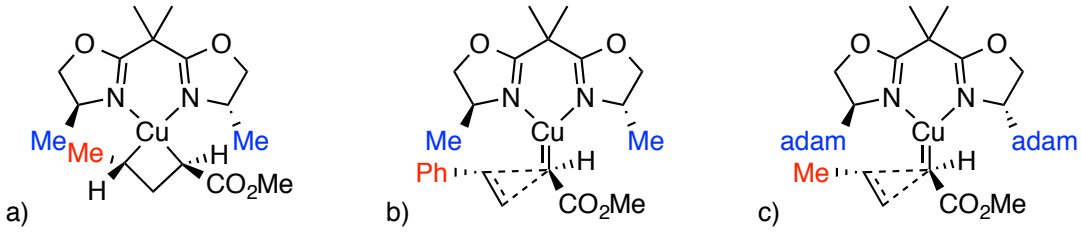
97 Guo, J.; Liu, Y.; Li, X.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2016**, *7*, 2717-2721.



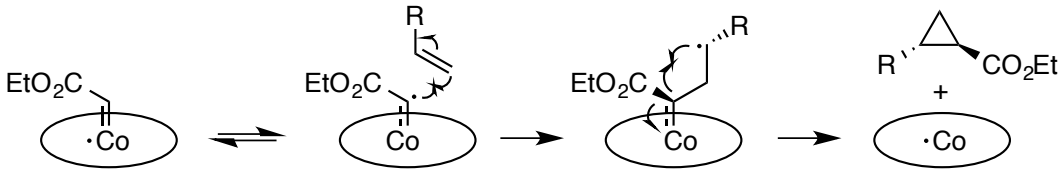
Scheme 34. Palladium(0)-catalyzed cyclopropanation with metallocyclobutane intermediate..[98]



Scheme 35. Rhodium(II)-catalyzed cyclopropanation following a concerted mechanism.[99]



Scheme 36. Subtle changes in substrate (a & b), or in ligand (a & c) can favor one mechanism or another.[100]



Scheme 37. Stereoselective cyclopropanation by carbene radicals.

98 Straub, B. F. *J. Am. Chem. Soc.* **2002**, *124*, 14195-14201.

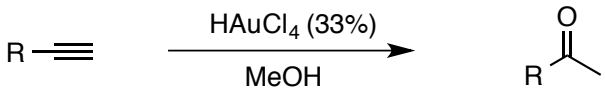
99 a) Intrieri, D.; Caselli, A.; Gallo, E. *Eur. J. Inorg. Chem.* **2011**, *2011*, 5071-5081. b) Xue, Y.-S.; Cai, Y.-P.; Chen, Z.-X. *RSC Advances* **2015**, *5*, 57781-57791. c) Bonge, H. T.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 2309-2320.

100 a) Meng, Q.; Li, M.; Tang, D.; Shen, W.; Zhang, J. *J. Mol. Struct.: THEOCHEM* **2004**, *711*, 193-199. b) Özen, C.; Tüzün, N. S. *Organometallics* **2008**, *27*, 4600-4610. c) García, J. I.; Jiménez-Osés, G.; Mayoral, J. A. *Chem. - Eur. J.* **2011**, *17*, 529-539.

5. Gold(I) in catalysis

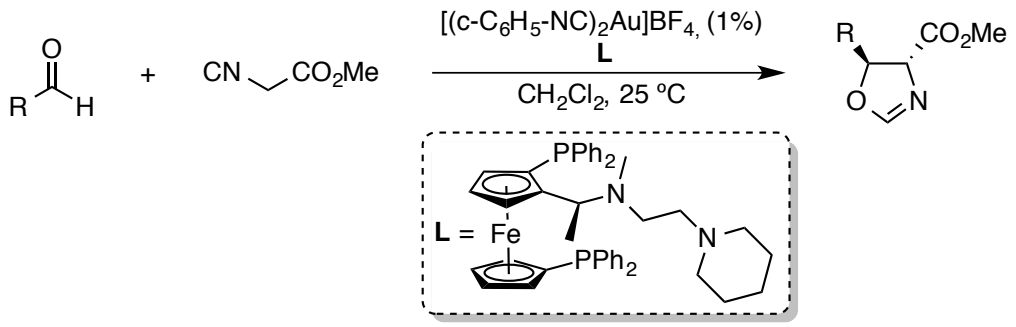
Gold, a precious and inert metal, that has been used since eons for decorative purposes as it proved unreactive towards hydrogen, carbon, and oxygen. It is not surprising that gold catalysis was already pronounced dead –"*catalytically dead*"– before it was even conceived.[101]

It was not until 1976 when Thomas and co-workers reported the first example of gold catalysis for the transformation of acetylenes into ketones (Scheme 38). In 1986, Ito and Hayashi published their ground-breaking work in which they reported the gold(I)-catalyzed asymmetric aldol reaction of aldehydes with isocyanides (Scheme 39).[102] The first use of gold(I) complexes in the activation of alkynes was reported by Teles as improvement over mercury(II) complexes in the addition of alcohols to alkynes in 1998 (Scheme 40).[103] Since then, the field has sprung to life and gold(I) has been used to catalyze many transformations, such as nucleophilic addition to alkynes, reactions of alkenes with alkynes, reactions of propargylic carboxylates, hydroarylation of alkynes, and oxidative reactions of alkynes.[104] Gold(I) catalysis is an ideal method for the rapid construction of complex molecular scaffolds, which can be witnessed by the increasing use of gold in total synthesis (Scheme 41).[105]

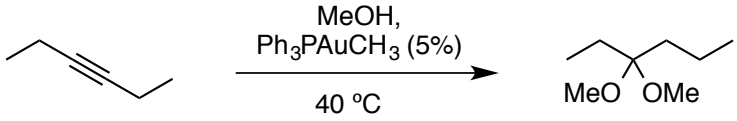


Scheme 38. The first example of gold in catalysis.[106]

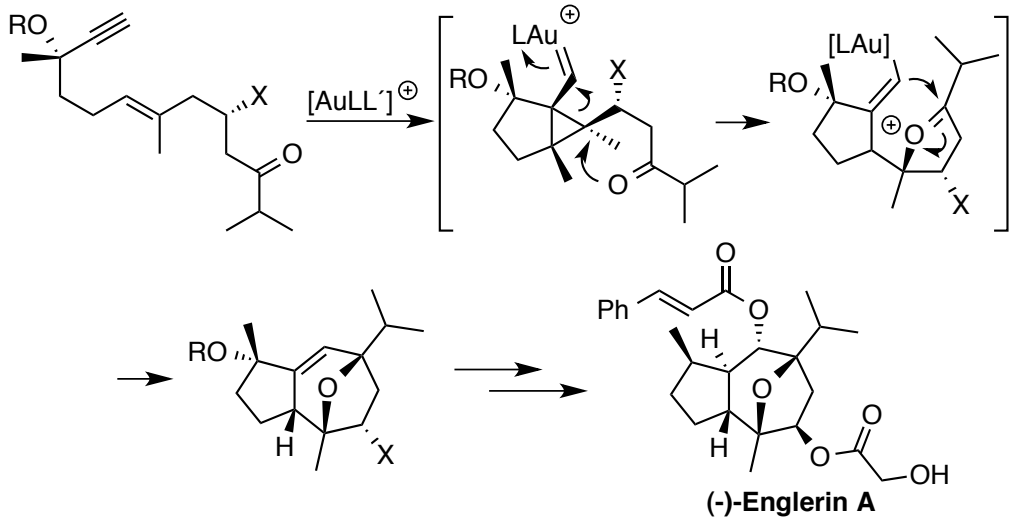
101 Schmidbaur, H. *Naturwiss. Rundsch.* **1995**, *48*, 443-451.
102 Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.
103 Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.
104 Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028-9072.
105 Pflasterer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331-1367.
106 Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983-1987.



Scheme 39. Asymmetric synthesis of oxazolines using gold(I).[107]



Scheme 40. First use of gold(I) in the activation of alkynes.[108]



Scheme 41. Enantioselective total synthesis of englerin A, using a gold(I)-catalyzed 1,6-enyne cyclization as key step.[109]

Gold is unique in several features: The gold-gold interaction (aurophilic interaction) is in the order of strength of hydrogen bonds. Gold(I) tends to adopt a linear coordination. Gold(I) complexes are not particularly nucleophilic and do not tend to undergo oxidative addition. In addition, the tendency of gold(III) to undergo reductive elimination is relatively low too, meaning that gold(I) and

107 Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.
108 Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.
109 Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.

gold(III) do not readily cycle between oxidation states. These properties, and even its color, are a consequence of the strong relativistic effects in gold.[110] The *6s* orbital is highly contracted, which leads to an expansion of the *5p* orbitals lowering the repulsive interactions between the electrons. Upon complexation with phosphine ligands, rehybridization of the orbitals greatly increases occupation of the *6s* orbital, which leaves the electron-accepting *6p* orbitals nearly unoccupied, giving gold(I) its remarkably soft Lewis acid character.

6. Gold(I)-carbene complexes

Gold carbenes can be considered as a class of Fischer carbenes. Toste and Goddard have developed a bonding model for gold carbenes, in which the L-Au-C bonding network is described by three sets of orbital interactions: A three-center, 4-electron σ-hyperbond involving donation of electron density from filled sp^x orbitals on the supporting ligand and carbene carbon atom to the empty *6s* orbital on gold, and two orthogonal π-bonds involving donation of electron density from filled metal *5d* orbitals to *p*-acceptor orbitals on the ligand and carbene carbon atom (Figure 9).[111] Despite their orthogonality, the two π-bonding components compete for electron density. Similarly, due to the hyperbonding character, the σ-components influence each other directly due to the trans influence. In other words, the more σ-donating the supporting ligand is, the weaker the σ-Au-C bond-order is, while increased π-acidity of the supporting ligand reduces the π-back-bonding from gold to the carbon.

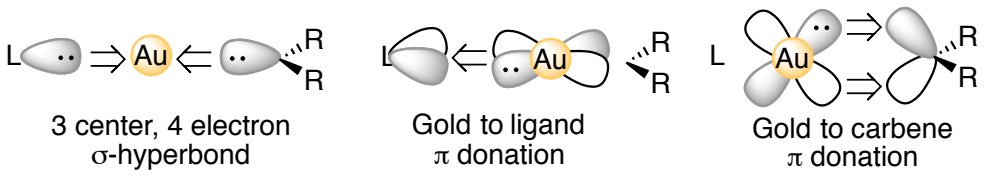


Figure 9. Bonding model for gold(I) carbene complexes as developed by Toste and Goddard.[111]

In the past years, there has been some controversy about the nature of gold carbenes and according to some authors the terms carbenoid or gold-stabilized

110 Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403.
111 Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482-486.

carbocation is a better description.[112] Theoretical and experimental work has demonstrated that the nature of the gold carbene can best be described as a continuum, ranging from a metal-stabilized singlet carbene to a metal-coordinated carbocation (Figure 10).[113] The position is mainly determined by the substituents of the carbene and the supporting ligand. A truly carbocationic structure can be evoked by using strongly electron donating substituents on the carbon with a strongly π-acidic ligand,[114] while in absence of highly stabilizing substituents, a carbene-like structure prevails.[115] Even though the Au-C bond-order is usually less than 1, the bond is best described by Au=C to account for both the σ- and π-character of the bond.

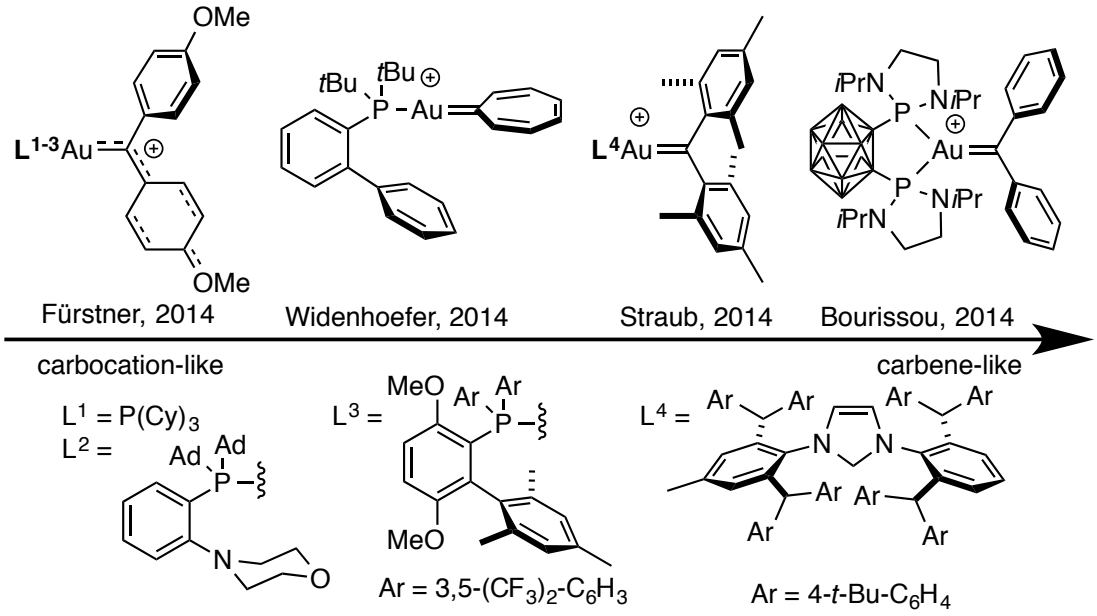


Figure 10. Isolated gold(I) complexes spanning a continuum from metal-coordinated cation to metal-stabilized carbene.[114]

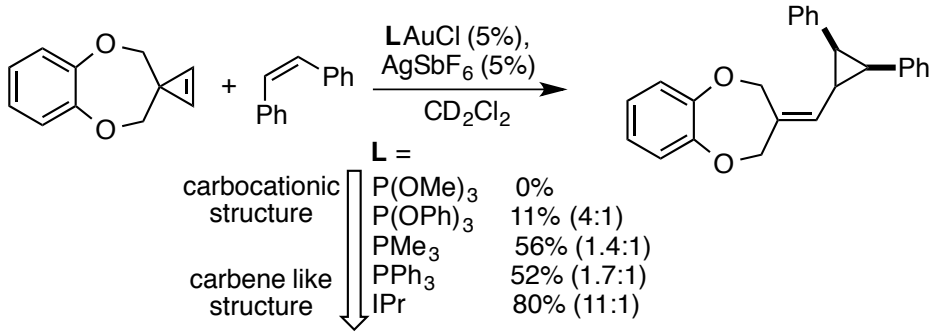
112 a) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033. b) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2510-2513.

113 Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482-486.

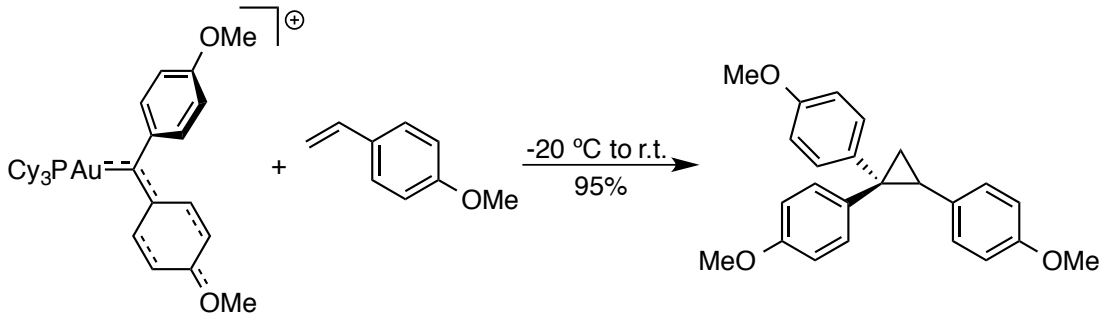
114 a) Seidel, G.; Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 4807-4811. b) Werlé, C.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 15452-15456.

115 a) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. - Eur. J.* **2015**, *21*, 7332-7339. b) Harris, R. J.; Widenhoefer, R. A. *Chem. Soc. Rev.* **2016**, *45*, 4533-4551.

The influence of the ancillary ligand was demonstrated by Toste, revealing that a more carbene like structure led to improved results in the cyclopropanation of *cis*-stilbene, while a truly carbocationic structure did not lead to any product formation (Scheme 42).[113] However, a strong Au=C bond character is not a prerequisite for carbene-like reactivity, as demonstrated by Fürstner (Scheme 43).[114a]



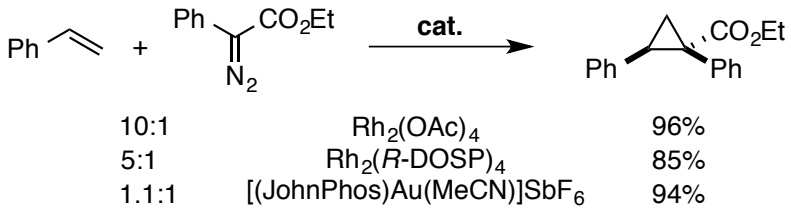
Scheme 42. Influence of the ancillary ligand on the carbene/carbocationic character of gold complexes demonstrated by the ability to catalyze a cyclopropanation reaction.



Scheme 43. Carbene-like cyclopropanation by a gold(I) complex with relatively strong cationic character.

7. Gold(I) as a carbene transfer catalyst

Gold has been used for the decomposition of diazo compounds and the subsequent carbene transfer reactions only since the past decade.[116] Gold possesses a unique character compared to other transition metals. For example, C-H insertion can be preferred over X-H insertion or cyclopropanation, it displays exceptionally high turn-over frequencies, and excellent diastereoselectivity can be achieved.[117] Gold-carbene complexes are highly electrophilic, but have a low oxophilicity, which makes them effective catalysts that do not require to be used under a protective atmosphere. Another important feature is that generally no carbene dimerization is observed, which is a notorious side reaction for other metal complexes. In order to achieve good conversions, large excesses (10:1) of alkene are added to compete with the dimerization. For gold, only a slight excess (1.1:1) of the alkene is enough to achieve full conversion without dimerization (Scheme 44). Finally, the nature of the carbene is directly influenced by the ancillary ligand because of the linear coordination of gold(I) complexes. Thus, the properties and reactivity of the carbene can be tuned precisely (Scheme 45).[118]



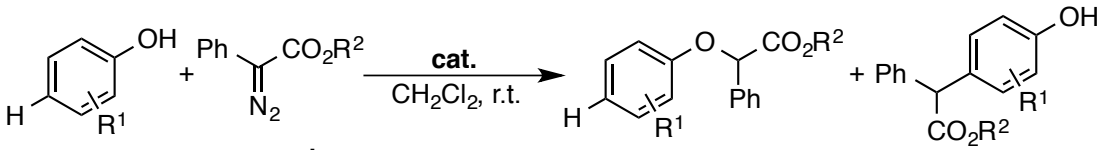
Scheme 44. Excellent yields for the gold(I)-catalyzed cyclopropanation can be obtained with just a slight excess of alkene.[119]

116 Fructos, M. R.; Belderrain, T. R.; de Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5284-5288.

117 Prieto, A.; Fructos, M. R.; Mar Díaz-Requejo, M.; Pérez, P. J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 1790-1793.

118 Liu, L.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 506-516.

119 a) Starmans, W. A. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 629-636. b) Chepiga, K. M.; Qin, C.; Alford, J. S.; Chennamadhavuni, S.; Gregg, T. M.; Olson, J. P.; Davies, H. M. L. *Tetrahedron* **2013**, *69*, 5765-5771. c) Prieto, A.; Fructos, M. R.; Mar Díaz-Requejo, M.; Pérez, P. J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 1790-1793.



cat.		
(S_a,S,S)-spiroBOXCuCl, $NaBAr^F{}_4$	71%	-
Ph_3PAuCl, $AgSbF_6$	46%	32%
(CyJohnPhos)AuCl, $AgSbF_6$	49%	39%
(2,4-*t*Bu-$C_6H_3O)_3AuCl$, $AgSbF_6$	-	100%

Scheme 45. Complementary reactivity to copper,[120] and strong effect of the ligand on the reactivity of the carbene.[121]

120 Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 12616-12617.

121 Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904-6907.

8. Alternatives to diazo compounds

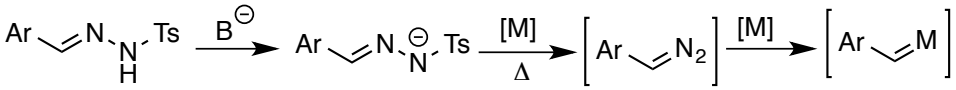
In terms of atom efficiency, it is hard to improve on diazo compounds. During the formation of the metal carbene, molecular nitrogen is released as the sole byproduct. However, these compounds engender several important safety risks. Many diazo compounds pose a direct threat as explosives. A notorious example is that of diazomethane: this compound is known to explode on contact with sharp edges, scratches in glassware, exposure to heat or intense light, alkali metals or calcium sulfate.[122] Furthermore, it is suspected to be carcinogenic, which is however overshadowed by its acute toxicity.

The risks can be reduced by placing electron-withdrawing groups on the carbon adjacent to the diazo moiety.[123] Compounds like ethyl diazoacetate are considerably more stable and are applied in industry.[124] However, the stabilizing substituents are transferred with the carbene during the reaction, and are therefore incorporated in the product. Some advancement has been made in the generation of unstable diazo compounds in a continuous production and consumption process.[125] Yet, versatile alternatives are invaluable.

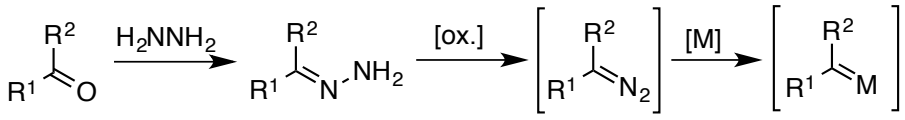
In the past few years, significant progress has been made to find alternatives to diazo compounds.[126] One strategy is to generate diazo compounds *in situ*, generating such small amounts that it is immediately consumed. Notable examples are the Bamford-Stevens reaction of tosylhydrazones under basic conditions (Scheme 46),[127] oxidation of hydrazones (Scheme 47),[128]

122 de Boer, T. J.; Backer, H. J. *Org. Synth.* **1956**, *36*, 16.
123 Maas, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 8186-8195.
124 Clark, J. D.; Shah, A. S.; Peterson, J. C.; Patelis, L.; Kersten, R. J. A.; Heemskerk, A. H. *Thermochim. Acta* **2002**, *386*, 73-79.
125 Proctor, L. D.; Warr, A. J. *Org. Process Res. Dev.* **2002**, *6*, 884-892.
126 Jia, M.; Ma, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9134-9166.
127 a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785-2788. b) Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433-9440. c) Zhang, J.-L.; Hong Chan, P. W.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 8733-8737.
128 a) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625-2628. b) Roda, N. M.; Tran, D. N.; Battilocchio, C.; Labes, R.; Ingham, R. J.; Hawkins, J. M.; Ley, S. V. *Org. Biomol. Chem.* **2015**, *13*, 2550-2554. c) Liu, H.; Wei, Y.; Cai, C. *New J. Chem.* **2016**, *40*, 674-678.

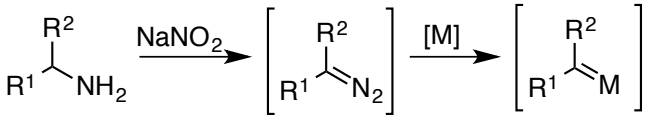
diazotization of amines with sodium nitrite (Scheme 48),[129] or thermolysis of triazoles (Scheme 49).[130]



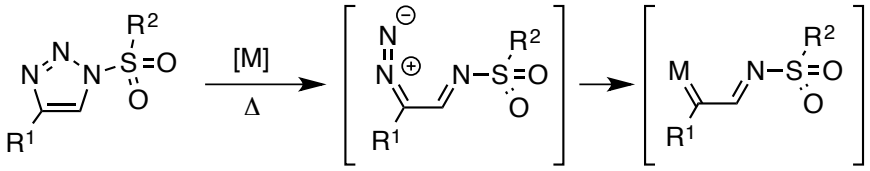
Scheme 46. General depiction of carbene formation by the Bamford-Stevens reaction of tosylhydrazones.



Scheme 47. General depiction of carbene formation by oxidation of hydrazines.



Scheme 48. General depiction of carbene formation from amines by with sodium nitrite.



Scheme 49. General depiction of carbene formation by thermolysis of triazoles.

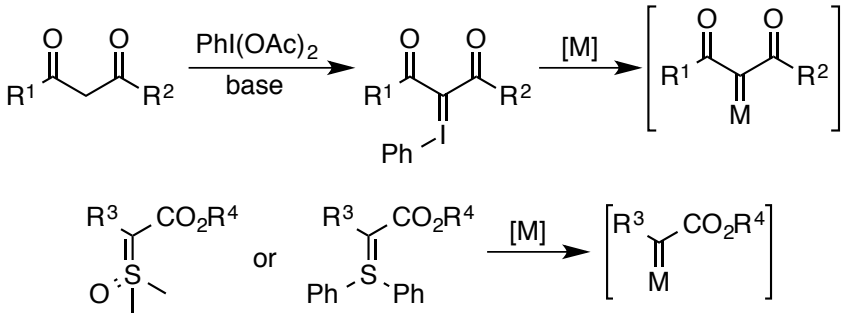
Phenyliodonium or sulfonium ylids can be viable substitutes for compounds that have an acidic methylene unit (Scheme 50).[131] Furthermore, carbenes have been

129 a) Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem.* **2001**, *66*, 8260-8263. b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2002**, *4*, 4531-4533. c) Morandi, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 938-941. d) Morandi, B.; Carreira, E. M. *Science* **2012**, *335*, 1471-1474. e) Liu, C.-B.; Meng, W.; Li, F.; Wang, S.; Nie, J.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6227-6230.

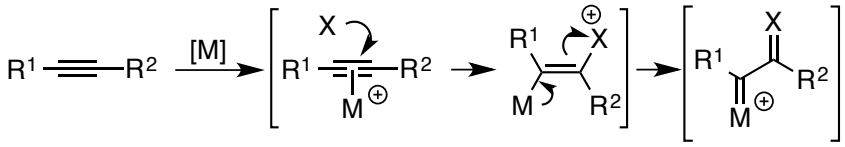
130 a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 862-872. b) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151-5162. c) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 1371-1373.

131 a) Müller, P.; Fernandez, D.; Nury, P.; Rossier, J.-C. *J. Phys. Org. Chem.* **1998**, *11*, 321-333. b) Müller, P. *Acc. Chem. Res.* **2004**, *37*, 243-251.

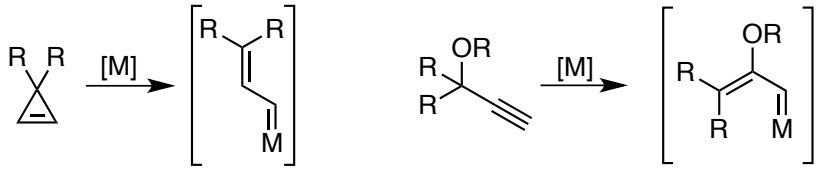
generated from alkynes through oxidation or nucleophilic attack (Scheme 51), cyclopropenes (Scheme 52),[132], propargyl ethers or esters (Scheme 52).[133,134]



Scheme 50. General depiction of phenyliodonium (top) or sulfonium (bottom) ylids for the formation of carbenes.



Scheme 51. General depiction of carbene formation by activation of alkyne towards nucleophilic attack or oxidation.



Scheme 52. Formation of carbenes by activation of cyclopropenes (left) and propargyl carboxylates (right).

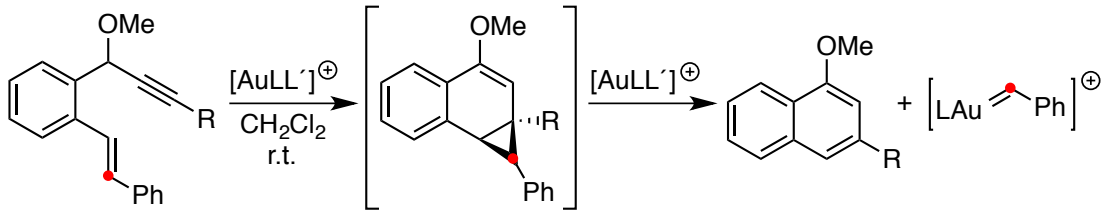
In 2010 it was discovered that 3-methoxy-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene can spontaneously undergo a retro-cyclopropanation

132 a) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2008**, 6405-6407. b) González, M. J.; González, J.; López, L. A.; Vicente, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 12139-12143. c) Archambeau, A.; Miege, F. d. r.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* **2015**, *48*, 1021-1031. d) Qian, D.; Zhang, J. *Chem. Soc. Rev.* **2015**, *44*, 677-698.

133 a) Sogo, H.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 10057-10060. b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513. c) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

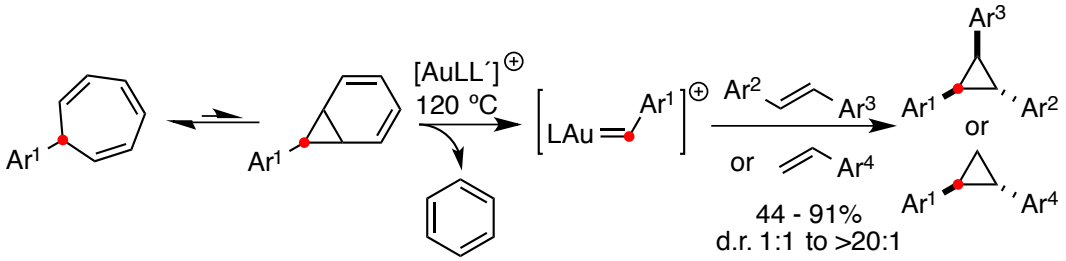
134 Iqbal, N.; Sperger, C. A.; Fiksdahl, A. *Eur. J. Org. Chem.* **2013**, *2013*, 907-914.

in the presence of a gold catalyst (Scheme 53).[135] The possibility of a gold-catalyzed retro-cyclopropanation had previously been observed in the gas phase but this was the first catalytic example of such a transformation.[136]



Scheme 53. Formation of gold(I)-carbenes via a cyclization/retro-cyclopropanation cascade.

Based on this concept, 7-aryl-1,3,5-cycloheptatrienes were developed as an alternative to diazo compounds, not much later (Scheme 53).[137] The cycloheptatriene is in equilibrium with its norcaradiene isomer, which can undergo a retro-cyclopropanation, or rather *retro-Buchner reaction*, to release benzene and generate a gold(I) carbene. The carbene was used in the cyclopropanation reaction of *E*-stilbenes and styrenes, leading to moderate to good yields with poor to excellent diastereoselectivity (Scheme 54). The major isomer was determined to be the *trans*-isomer in most cases.

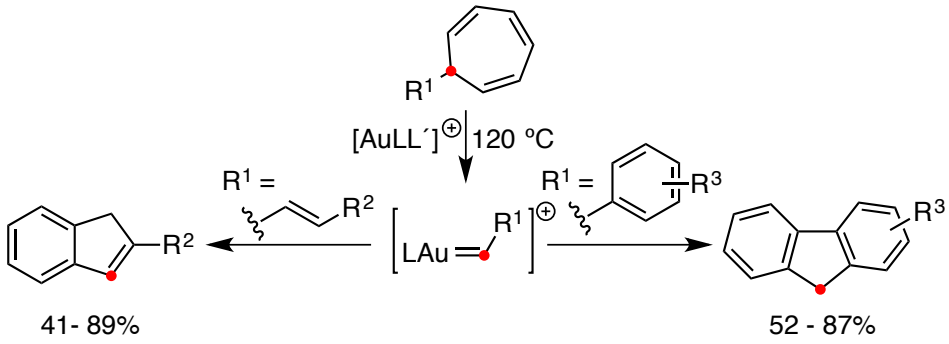


Scheme 54. Formation of gold(I) carbenes via the retro-Buchner reaction of 7-substituted cycloheptatriene derivatives, and subsequent alkene cyclopropanation.

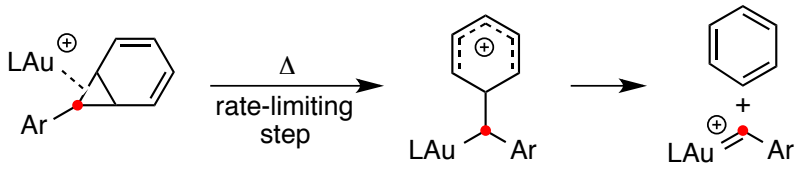
This work was succeeded by an in-depth study on the generation and fate of the gold carbenes formed in this reaction.[138] The cyclization of *ortho*-aryl or *ortho*-

135 Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881-11883.
136 Batiste, L.; Fedorov, A.; Chen, P. *Chem. Commun.* **2010**, *46*, 3899-3901.
137 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.
138 Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801-809.

styrenyl substituted aryl-cycloheptatrienes gave fluorenes and indenes, respectively (Scheme 55). The mechanism of the retro-Buchner reaction was investigated by DFT calculations, identifying the rate-limiting step of the reaction to be the first C-C bond cleavage of norcaradiene to form a Wheland-type intermediate. The second C-C bond cleavage passes over a smaller energy barrier before forming the carbene complex (Scheme 56).



Scheme 55. Formation of gold(I) carbenes via the retro-Buchner reaction for the intramolecular formation of indenes and fluorenes.

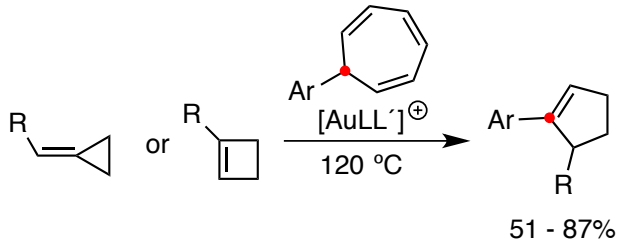


Scheme 56. Mechanism of the gold(I)-catalyzed retro-Buchner reaction: cleavage of the first C-C bond leads to a Wheland-type intermediate. A carbene is formed after the second C-C bond cleavage.

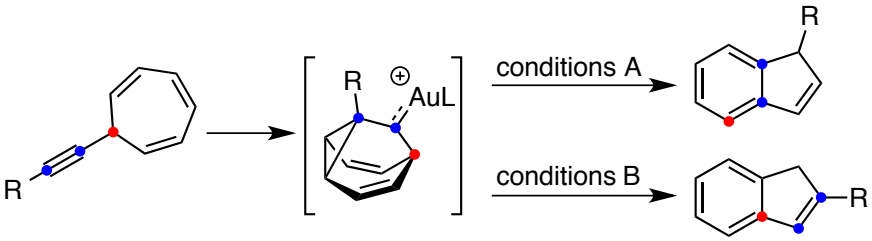
Afterwards, another application for cycloheptatrienes was demonstrated in the formal [4+1] addition of gold carbenes with methylenecyclopropanes or cyclobutenes (Scheme 57).[139] However, if alkyne-substituted cycloheptatrienes are used, the activation of the triple bond is preferred and fluxional barbaralyl gold(I)-carbene cations are formed instead, which ultimately lead to indenes (Scheme 58).[140]

139 Wang, Y.; Muratore, M. E.; Rong, Z.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 14022-14026.

140 McGonigal, P. R.; de León, C.; Wang, Y.; Homs, A.; Solorio-Alvarado, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 13093-13096.



Scheme 57. Formal (4+1) reaction of methylenecyclopropanes or cyclobutenes with gold(I) carbenes.



Scheme 58. Formation a barbaralyl cations by cyclization of 7-alkyne cycloheptatriene derivatives.

Despite the great results obtained, the retro-Buchner reaction requires substantial heating, 120 °C, and the transformation is limited to a few privileged complexes, which limits the applicability of the subsequent transformations. Therefore, further development of the gold(I)-catalyzed retro-cyclopropanation for the formation of gold(I) carbenes, and exploration and understanding of their subsequent transformations are desired.

General Objectives

The gold(I)-catalyzed retro-Buchner reaction has recently emerged as a safe and versatile alternative for the formation of transition-metal carbene complexes. However, the reaction takes place at high temperatures, which puts limitations on its applicability. The scope is limited to 7-aryl-1,3,5-cycloheptatriene derivatives, with the single exception of an example with 7-styrenyl cycloheptatriene. Moreover, only a limited number of synthetic strategies for the formation of cycloheptatriene derivatives have been developed.

The general objective of the work presented in this manuscript is to further develop de gold(I)-catalyzed retro-Buchner reaction, in terms of scope, applicability and mechanistic understanding.

The first main objective is to improve the applicability by lowering the reaction temperature (activation barrier) of the retro-Buchner reaction, which will increase the substrate tolerance, allow other ligands to be used in this transformation, and improve the selectivity. These modifications will increase the scope of the reaction.

In order to lower the activation barrier, other carbene precursors will be investigated. More constrained molecules could be less prone to decomposition reactions. Furthermore, the use of another molecular scaffold could allow for new synthetic strategies to obtain other derivatives for the carbene transfer.

The formation of vinyl gold(I) carbenes and further reactivity will be investigated.

Other (coinage) metals will be investigated for their ability to catalyze the retro-Buchner reaction of cycloheptatriene derivatives as their non-linear coordination might allow the development of highly diastereo- and enantioselective transformations.

The second main objective is to increase our mechanistic understanding of the retro-Buchner reaction and subsequent gold(I)-catalyzed carbene transfer reactions. Hence, further mechanistic studies on the retro-Buchner reaction and gold(I)-catalyzed cyclopropanation reaction will provide more insight in the

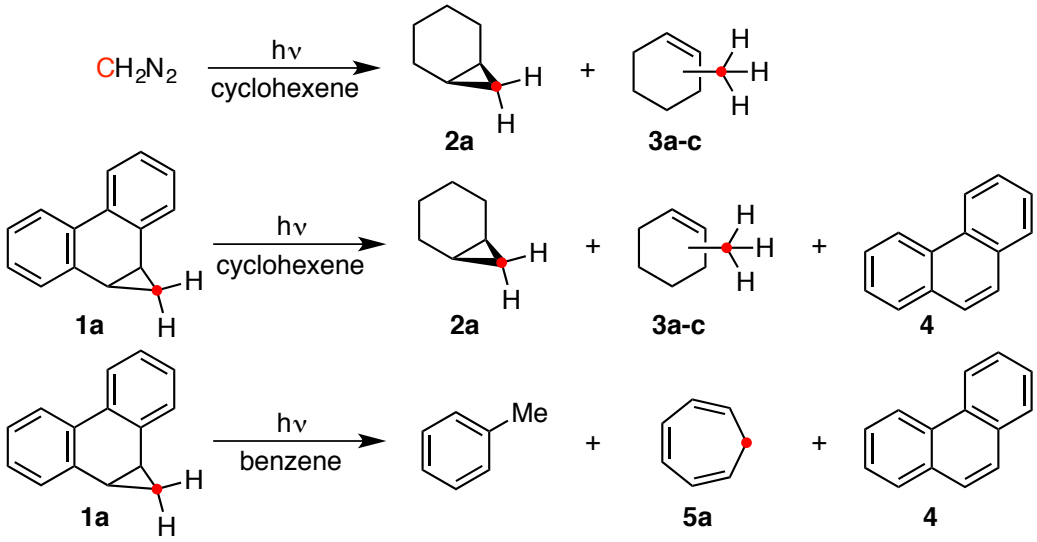
selectivity determining factors. This knowledge can be applied in the design of enantioselective cyclopropanations or other transformations.

1.

Dibenzonorcaradiene Derivatives as Carbene Precursors for Gold(I)

Introduction

It was discovered in 1965 that 9,10-dihydro-9,10-methanophenanthrene (**1a**) can be photolyzed in the presence of cyclohexene to produce 4-, 3-, and 1-methylcyclohexene (**3a-c**) and norcarane (**2a**) in the same ratio as was observed for diazomethane under similar conditions (10:25:25:40; Scheme 59).[141] This provided the first, yet indirect, evidence of the formation of methylene from 9,10-dihydro-cyclopropa[*l*]phenanthrene derivatives. In the presence of benzene, both toluene and cycloheptatriene (**5a**) are formed. The ratio of toluene is higher compared to when diazomethane is used as carbene precursor in this experiment due to the subsequent photolysis of cycloheptatriene to toluene.[142]



Scheme 59. Formation of methylene by photolysis of diazomethane (top),[143] and 9,10-dihydro-9,10-methanophenanthrene (bottom two).[144]

In the same work, the possibility of generating methylene from phenylcyclopropane (**6**) and cycloheptatriene (**5a**) was investigated (Scheme 60). The formation of methylene via photolysis of phenylcyclopropane was

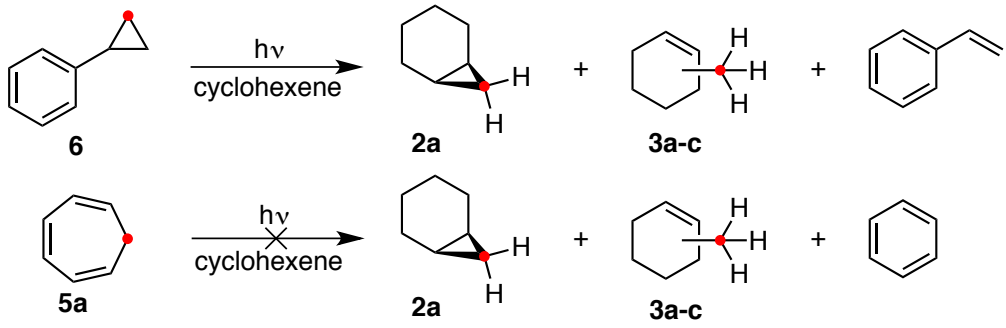
141 a) Richardson, D. B.; Durrett, L. R.; Martin, J. M.; Putnam, W. E.; Slaymaker, S. C.; Dvoretzky, I. *J. Am. Chem. Soc.* **1965**, *87*, 2763-2765. b) von E. Doering, W.; Buttery, R. G.; Laughlin, R. G.; Chaudhuri, N. *J. Am. Chem. Soc.* **1956**, *78*, 3224-3224.

142 a) Lemmon, R. M.; Strohmeier, W. *J. Am. Chem. Soc.* **1959**, *81*, 106-108. b) Dauben, W. G.; Cargill, R. L. *Tetrahedron* **1961**, *12*, 186-189.

143 von E. Doering, W.; Buttery, R. G.; Laughlin, R. G.; Chaudhuri, N. *J. Am. Chem. Soc.* **1956**, *78*, 3224-3224.

144 Richardson, D. B.; Durrett, L. R.; Martin, J. M.; Putnam, W. E.; Slaymaker, S. C.; Dvoretzky, I. *J. Am. Chem. Soc.* **1965**, *87*, 2763-2765.

demonstrated by the formation of norcarane and methylcyclohexene. No evidence for the generation of methylene was observed for the photolysis of cycloheptatriene, however.



Scheme 60. Formation of methylene from phenylcyclopropane and its attempted formation from cycloheptatriene.

Already in 1965 it was noted that the analytical data for their 9,10-dihydro-9,10-methanophenanthrene (**1a**) were to *"agree in detail with those since reported for this hydrocarbon ("dibenzonorcaradiene")"*.[144] Structurally, the cyclopropa-phenanthrenes bear great resemblance with cycloheptatrienes where the equilibrium leans completely towards the norcaradiene tautomer (Figure 11).

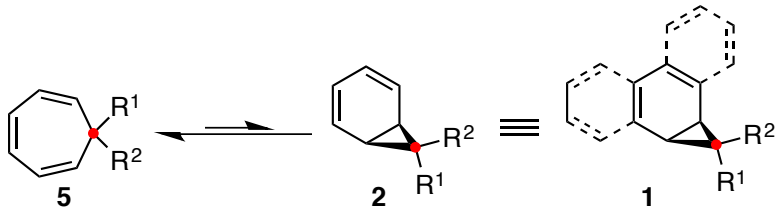
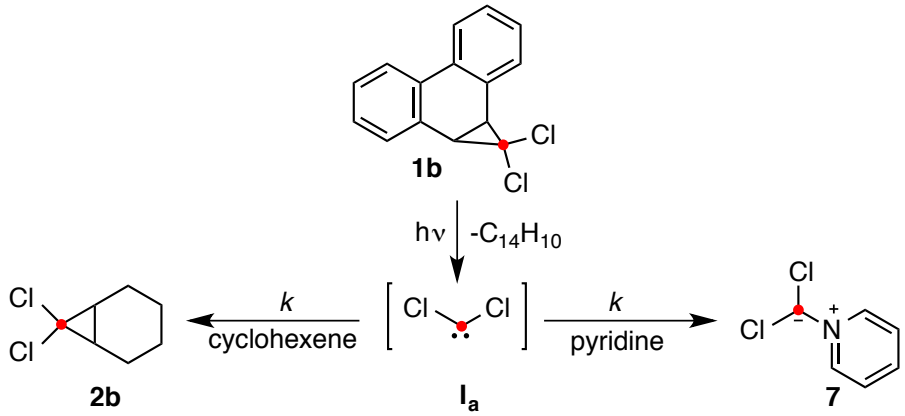


Figure 11. Structural resemblance of cycloheptatriene and 9,10-dihyrdo-1*H*-cyclopropa[*l*]phenanthrene derivatives.

Carbene formation from dibenzonorcaradiene derivatives lay dormant until 1990 when the groups of Chateauneuf and Johnson used the photolysis of 1,1-dichloro-dibenzonorcaradiene (**1b**) to determine the first absolute rate kinetics for the reaction of dichloromethylene ($\mathbf{I_a}$) with alkenes in solution (Scheme 61).[145] In the following years, the work was succeeded by many reports describing the variation of the cyclopropane substituents, in order to generate

145 Chateauneuf, J. E.; Johnson, R. P.; Kirchhoff, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 3217-3218.

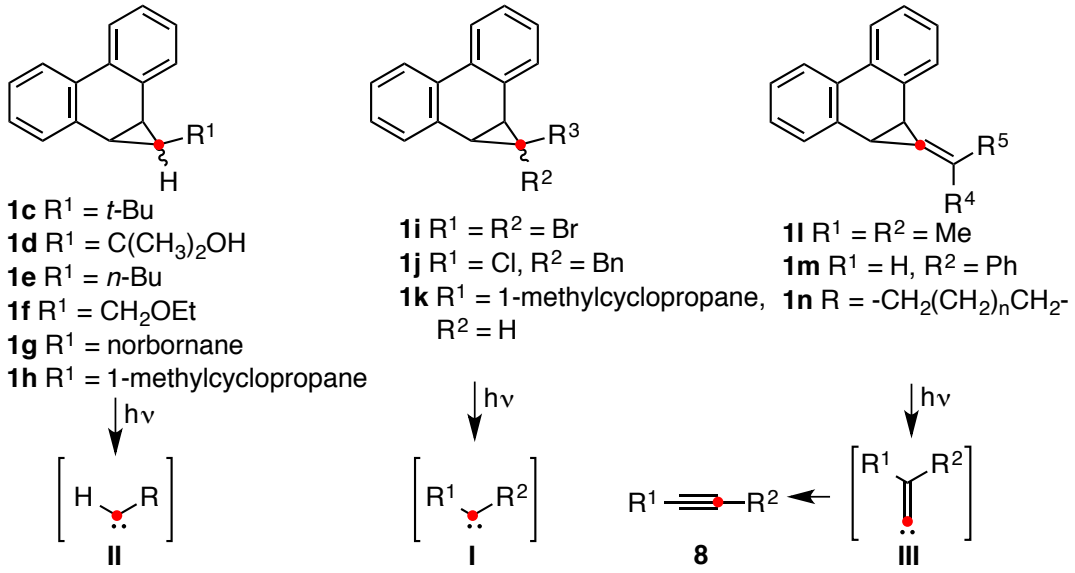
and study the behavior of different carbenes (Scheme 62),[146] and improvements for the synthesis of these motifs.[147]



Scheme 61. Formation of dichloromethylene and rate kinetic studies.[145]

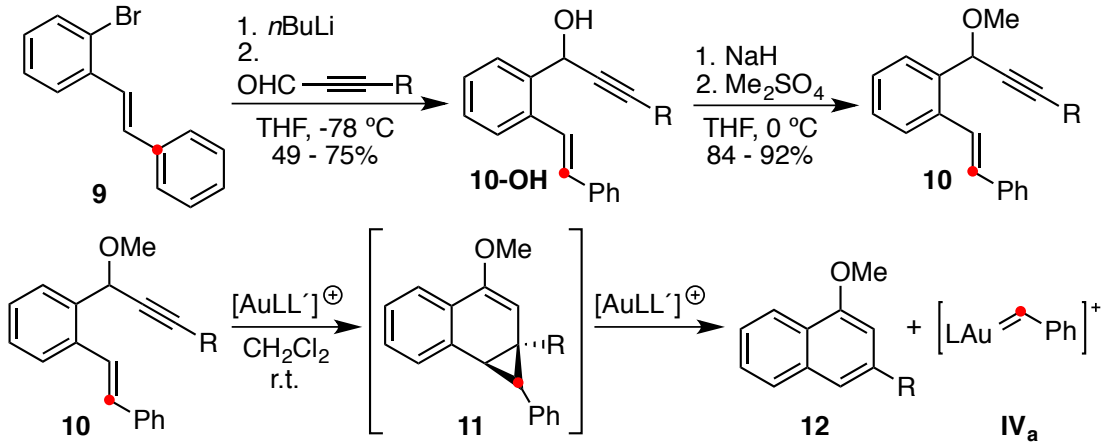
146 a) Glick, H. C.; Likhotvorik, I. R.; Jones Jr, M. *Tetrahedron Lett.* **1995**, *36*, 5715-5718. b) Nigam, M.; Platz, M. S.; Showalter, B. M.; Toscano, J. P.; Johnson, R.; Abbot, S. C.; Kirchhoff, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 8055-8059. c) Robert, M.; Likhotvorik, I.; Platz, M. S.; Abbot, S. C.; Johnson, R. *J. Phys. Chem. A* **1998**, *102*, 1507-1513. d) Ruck, R. T.; Jones Jr, M. *Tetrahedron Lett.* **1998**, *39*, 2277-2280. e) Ruck, R. T.; Jones Jr, M. *Tetrahedron Lett.* **1998**, *39*, 4433-4436. f) Thamattoor, D. M.; Snoonian, J. R.; Sulzbach, H. M.; Hadad, C. M. *J. Org. Chem.* **1999**, *64*, 5886-5895. g) Farlow, R. A.; Thamattoor, D. M.; Sunoj, R. B.; Hadad, C. M. *J. Org. Chem.* **2002**, *67*, 3257-3265. h) Graves, K. S.; Thamattoor, D. M.; Rablen, P. R. *J. Org. Chem.* **2011**, *76*, 1584-1591. i) Moore, K. A.; Vidaurri-Martinez, J. S.; Thamattoor, D. M. *J. Am. Chem. Soc.* **2012**, *134*, 20037-20040. j) Hardikar, T. S.; Warren, M. A.; Thamattoor, D. M. *Tetrahedron Lett.* **2015**, *56*, 6751-6753. k) Maurer, D. P.; Fan, R.; Thamattoor, D. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 4499-4501.

147 Nguyen, J. M.; Thamattoor, D. M. *Synthesis* **2007**, *2007*, 2093-2094.



Scheme 62. Formation of various carbene species via photolysis of dihydro-1*H*-cyclopropa[*l*]phenanthrene derivatives.[146]

The rate-limiting step in the gold(I)-catalyzed retro-Buchner reaction is the double C-C bond cleavage of the norcaradiene derivative, which requires significant heating.[148] The retro-cyclopropanation from the related 3-methoxy-dihydro-1*H*-cyclopropa[*a*]naphthalene derivatives **11** occurs at room temperature but the application is limited by the synthetic approach for the 1,5-enyne substrates **10** (Scheme 63).[149]



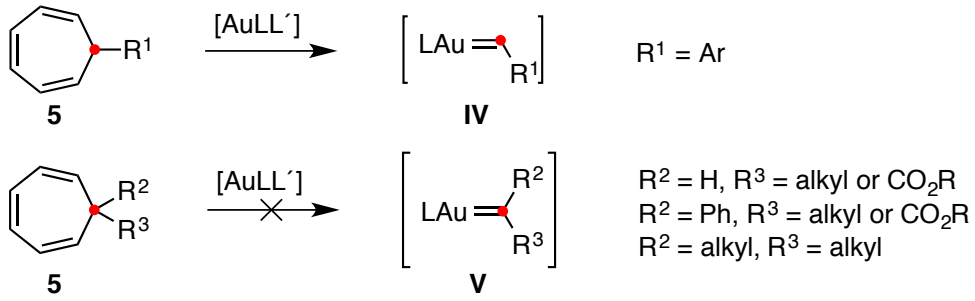
Scheme 63. Synthesis of 3-methoxy-dihydro-1*H*-cyclopropa[*a*]naphthalenes and formation of gold(I) carbenes by cyclization/retro-cyclopropanation.

148 Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801-809.

149 Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881-11883.

Dibenzonorcaradiene derivatives **1** bearing structural similarities could offer an interesting alternative as carbene precursors for gold(I) chemistry. The synthesis of versatile intermediates is well reported,[150] while the propensity to generate free carbenes by irradiation with light is strong. In addition, the fixed norcaradiene structure, where the double bonds are part of the aromatic system of the benzo moieties, could eliminate the unwanted [1,5]-H shift, which competes with the retro-Buchner reaction.[151]

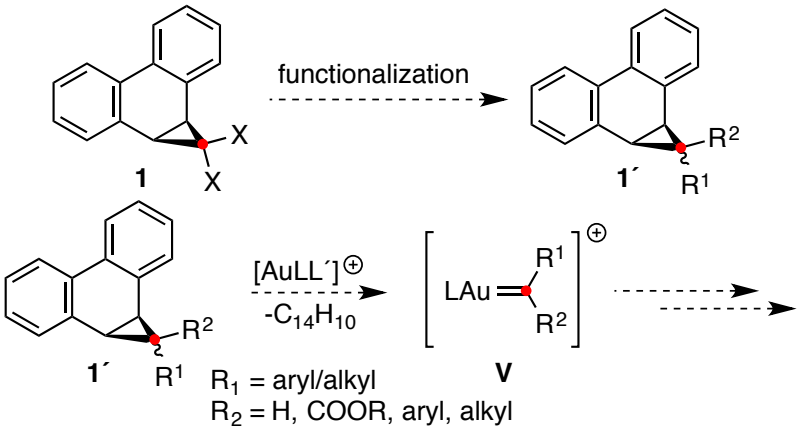
A major limitation of the cycloheptatriene derived carbene formation is that only mono-substituted stabilized carbenes, such as aryl-carbenes, can be formed (Scheme 64).[152]



Scheme 64. Scope and limitations for the retro-Buchner reaction from cycloheptatriene derivatives.

With a more reactive carbene precursor, the generation of disubstituted and possibly alkyl-substituted carbenes and via the gold(I)-catalyzed retro-Buchner reaction can be investigated (Scheme 65).

150 Nguyen, J. M.; Thamattoor, D. M. *Synthesis* **2007**, *2007*, 2093-2094.
151 de Dobbelaere, J. R.; van Zeeventer, E. L.; de Haan, J. W.; Buck, H. M. *Theor. Chim. Acta* **1975**, *38*, 241-244.
152 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.



Scheme 65. Prospected formation of disubstituted gold(I) carbenes from dibenzonorcaradiene derivatives.

Therefore, the divergent synthesis of 1-substituted dibenzonorcaradiene derivatives from a common intermediate will be investigated. The carbene precursors can then be tested for their ability to undergo the gold(I)-catalyzed retro-cyclopropanation to form carbene complexes that can undergo further transformations.

Objectives

1,1-Disubstituted dibenzonorcaradiene (1a,9b-dihydro-1*H*-cyclopropa[*l*]-phenanthrenes) have been used for light-induced formation of free carbenes. It is expected that these compounds could also be used for the gold-mediated formation of gold(I) carbenes because of their structural resemblance to norcaradienes.

The objective of the work summarized in this chapter was to investigate the formation of gold(I) carbenes from 1-substituted dibenzonorcaradiene derivatives.

The dibenzonorcaradiene derivatives are highly crystalline and the efficient syntheses of versatile intermediates have been reported. Opposed to the limited synthetic options for cycloheptatrienes, the objective is to exploit the synthetic strategies towards phenanthrene derivatives for the divergent synthesis of different mono- and disubstituted carbene precursors. The propensity of the phenanthrene derivatives to generate carbenes under mild conditions might allow the formation of gold carbenes at relatively mild conditions, as well.

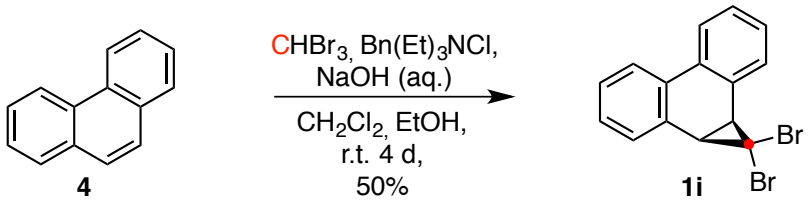
With ready access to a library of carbene precursors from which carbenes can be generated under mild conditions, the effect of different carbene substituents on the gold(I)-catalyzed retro-Buchner and cyclopropanation reaction could be investigated.

The mild conditions and the increased accessibility of the derivatives could enable the cyclopropanation of a broad and functional-group tolerant scope of substrates. Furthermore, the formation of gold carbenes from phenanthrenes might provide new mechanistic insights.

Results and discussion

Synthesis of dibenzonorcaradiene derivatives.

The synthesis of simple alkyl substituted dibenzonorcaradiene derivatives has been reported for the study of mono- and di-alkyl carbenes.[146] These methods conveniently start from the 1,1-dibromo derivative **1i**, which therefore became the starting point for this investigation. The *in situ* generation of dibromomethylene and addition to phenanthrene (**4**) gave 1,1-dibromo-dibenzonorcaradiene (**1i**) in 50% yield on a several-grams scale (Scheme 66).[153] Employing a similar strategy, [154] the 1,1-diiodo-dibenzonorcaradiene could not be obtained.



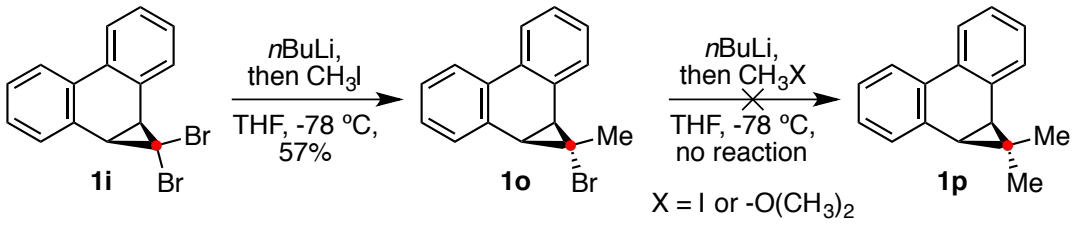
Scheme 66. Synthesis of 1,1-dibromo intermediate **1i**.

Treatment of 1,1-dibromo compound **1i** with *n*-butyl lithium at low temperature to perform a lithium-halogen exchange,[155] followed by quenching with methyl iodide led to the formation of 1-bromo-1-methyl derivative **1o** as a single stereoisomer (Scheme 67). The configuration of **1o** was demonstrated by X-ray diffraction (Figure 12).

153 Nguyen, J. M.; Thamattoor, D. M. *Synthesis* **2007**, *2007*, 2093-2094.

154 a) Baird, M. S. *J. Chem. Soc., Chem. Commun.* **1974**, 196-197. b) Baird, M. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 54-56. c) Mathias, R.; Weyerstahl, P. *Angew. Chem.* **1974**, *86*, 42-43.

155 a) Hässig, R.; Siegel, H.; Seebach, D. *Chem. Ber.* **1982**, *115*, 1990-1997. b) Moore, K. A.; Vidaurri-Martinez, J. S.; Thamattoor, D. M. *J. Am. Chem. Soc.* **2012**, *134*, 20037-20040. c) Fox, M. A.; Chen, C. C.; Campbell, K. A. *J. Org. Chem.* **1983**, *48*, 321-326.



Scheme 67. Alkylation through lithium-halogen exchange to form **1o.**

Treatment of **1o** with a second equivalent of *n*-butyl lithium and quenching with methyl iodide did not yield 1,1-dimethyl derivative **1p** (Scheme 67). Neither treating **1o** with an excess of methyl lithium, nor treatment with *n*-butyl lithium followed by trimethyloxonium tetrafluoroborate led to the desired 1,1-dimethyl derivative **1p**, and mainly starting material was recovered.

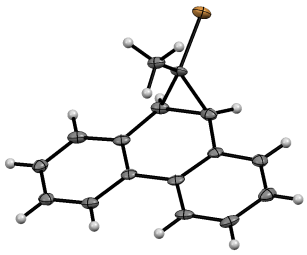
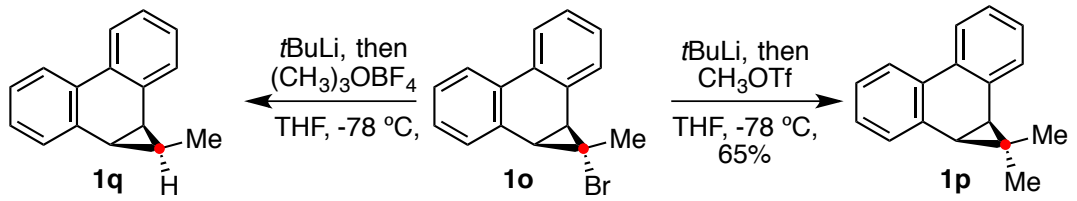
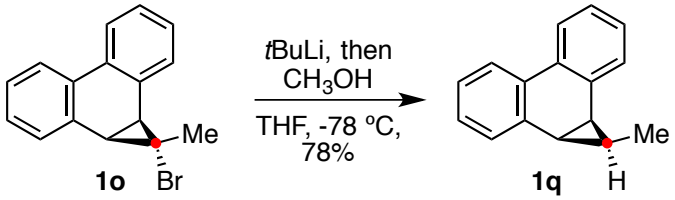


Figure 12. CYLview depiction of the X-ray crystal cluster of **1o** with 50% probability of the thermal ellipsoids.

The fact that the starting material was recovered, instead of the reduced compound, implied that no lithium-halogen exchange had taken place. When *tert*-butyl lithium was used in combination with trimethyloxonium tetrafluoroborate, the reduced compound **1q** was isolated instead of the starting material. Surprisingly, when switching to methyltriflate, the desired 1,1-dimethyl derivative **1p** was formed in 65% yield (Scheme 68). The synthesis of the 1-methyl derivative **1q** was optimized by performing the lithium-halogen exchange on **1o** with *tert*-butyl lithium followed by quenching with methanol (Scheme 69).

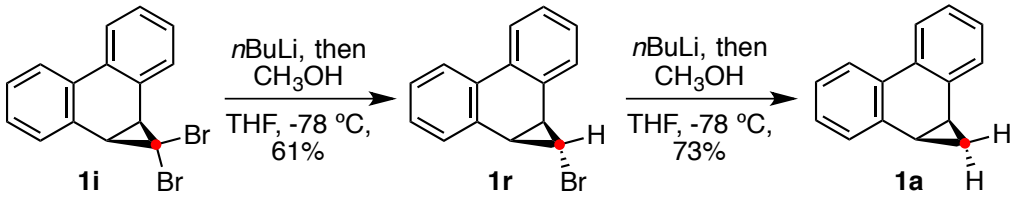


Scheme 68. Second lithium-halogen exchange requiring the use of *t*-BuLi to form **1p**.



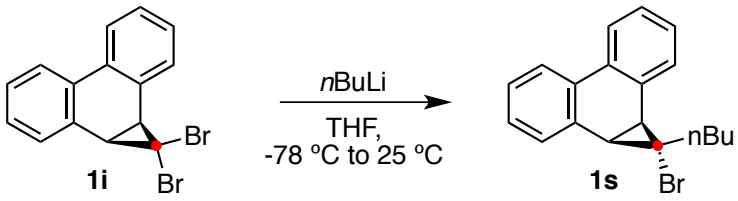
Scheme 69. The synthesis of **1q**.

The simplest substrate, 9,10-dihydro-9,10-methanophenanthrene (**1a**) was obtained by performing a lithium halogen exchange and quenching with methanol, twice (Scheme 70). The intermediate 1-bromo derivative **1r** can be used to access the isomer of **1q** and other alkyl derivatives, or can be used directly to obtain other derivatives.



Scheme 70. Synthesis of 9,10-dihydro-9,10-methanophenanthrene (**1a**).

The 1-bromo-1-butyl derivative **1s** was unintentionally prepared by warming 1-bromo-1-lithium intermediate in the absence of a suitable electrophile, as no alpha-elimination occurs on the cyclopropane (Scheme 71).[156]



Scheme 71. Formation of 1-bromo-1-butyl derivative **1s**.

156 a) Jones, W. M. *J. Am. Chem. Soc.* **1960**, *82*, 6200-6202. b) Eccles, W.; Jasinski, M.; Kaszynski, P.; Zienkiewicz, K.; Stulgies, B.; Jankowiak, A. *J. Org. Chem.* **2008**, *73*, 5732-5744.

1-Aryl substituted dibenzonorcaradiene derivatives

Thus far, no convenient methods exist for the formation of 1-aryl substituted dibenzonorcaradiene derivatives.[157] In fact, only very few methods exist for the arylation of *gem*-dihalocyclopropanes in general,[158] which is surprising considering the abundance and accessibility of these compounds. The aryl- and related derivatives are an indispensable class of carbene precursors, as stabilized carbenes can be generated from these reagents. Besides, the aryl derivatives are closely related to the 7-aryl cycloheptatriene derivatives and necessary for the side-by-side comparison of the two systems.

A C-C-bond formation for aryl groups as described in the section above for sp^3 carbon atoms would be unlikely to succeed.[159] Therefore, cross-coupling chemistry would be the method of choice for these compounds. Functionalization of secondary and especially tertiary carbons has proven a challenge for organic chemists.[160] Judging by the lack of suitable methods, the functionalization of secondary or tertiary cyclopropanes is even more challenging. Most examples of cross-coupling reactions with cyclopropanes require a specific directing group, such as an adjacent ester moiety,[161] or are performed on unfunctionalized cyclopropanes (Scheme 72).[162]

157 a) Nozaki, H.; Yamabe, M.; Noyori, R. *Tetrahedron* **1965**, *21*, 1657-1663. b) Bestmann, H. J.; Morper, H. *Angew. Chem.* **1967**, *79*, 578-579.

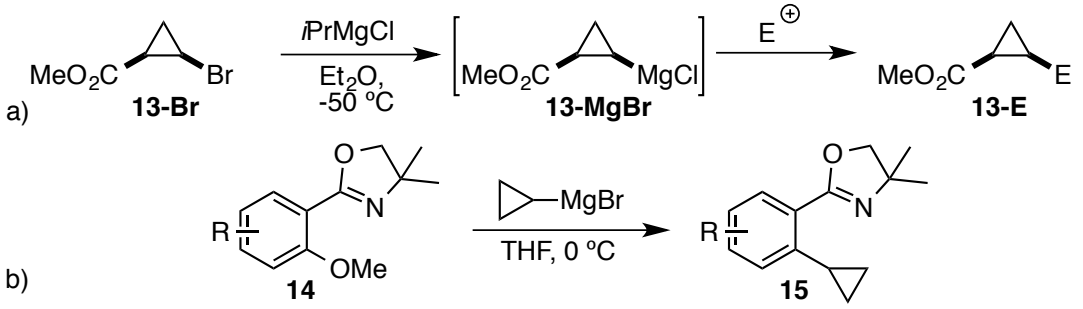
158 a) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958-2965. b) Eccles, W.; Jasinski, M.; Kaszynski, P.; Zienkiewicz, K.; Stulgies, B.; Jankowiak, A. *J. Org. Chem.* **2008**, *73*, 5732-5744. c) Keglevich, G.; Janke, F.; Petneházy, I.; Szöllösy, Á.; Miklós, P.; Tóth, G.; Töke, L. *Phosphorus Sulfur Relat. Elem.* **1988**, *36*, 61-68.

159 Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.

160 a) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937-4947. b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492. c) Rudolph, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670.

161 a) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 351-352. b) Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829-11832. c) Beaulieu, L.-P. B.; Zimmer, L. E.; Gagnon, A.; Charette, A. B. *Chem. - Eur. J.* **2012**, *18*, 14784-14791. d) Johnson, P. S.; Underwood, T. J.; Wheeler, S. *Tetrahedron Lett.* **2011**, *52*, 3226-3227.

162 a) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267-1269. b) Gagnon, A.; Amad, M. a. H.; Bonneau, P. R.; Coulombe, R.; DeRoy, P. L.; Doyon, L.; Duan, J.; Garneau, M.; Guse, I.; Jakalian, A.; Jolicoeur, E.; Landry,



Scheme 72. Examples of a) directed functionalization.[163] b) directed substitution with unfunctionalized cyclopropanes.[164]

When the experimental work was performed, only a few selected examples existed for a general cyclopropane-arene bond forming reaction,[165] which did not rely on generating a cyclopropane nucleophile for the reaction with the appropriate electrophile.[166] Fortunately, at the time of writing this manuscript, more examples have been reported,[167] such as for the Suzuki-Miyaura coupling,[168] Negishi coupling,[169] metalphotoredox catalysis,[170] and an expansion of the Murahashi-Feringa coupling (Scheme 73).[171]

S.; Malenfant, E.; Simoneau, B.; Yoakim, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4437-4441. c) Campbell, J. B.; Firor, J. W.; Davenport, T. V. *Synth. Commun.* **1989**, *19*, 2265-2272.

163 Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 351-352.

164 Fish, P. V.; Ryckmans, T.; Stobie, A.; Wakenhut, F.; Pfizer, Ed. 2006; Vol. WO2006064336 (A2).

165 a) Hohn, E.; Pietruszka, J. *Adv. Synth. Catal.* **2004**, *346*, 863-866. b) Ty, N.; Pontikis, R.; Chabot, G. G.; Devillers, E.; Quentin, L.; Bourg, S.; Florent, J.-C. *Bioorg. Med. Chem.* **2013**, *21*, 1357-1366. c) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718-8719. d) Martin, S. F.; Dwyer, M. P. *Tetrahedron Lett.* **1998**, *39*, 1521-1524. e) Piers, E.; Coish, P. D. G. *Synthesis* **2001**, *2001*, 0251-0261. f) Cai, S.; Dimitroff, M.; McKennon, T.; Reider, M.; Robarge, L.; Ryckman, D.; Shang, X.; Therrien, J. *Org. Process Res. Dev.* **2004**, *8*, 353-359.

166 a) Merkel, D.; Köbrich, G. *Chem. Ber.* **1973**, *106*, 2040-2048. b) Rauhut, C. B.; Cervino, C.; Krasovskiy, A.; Knochel, P. *Synlett* **2009**, *2009*, 67-70.

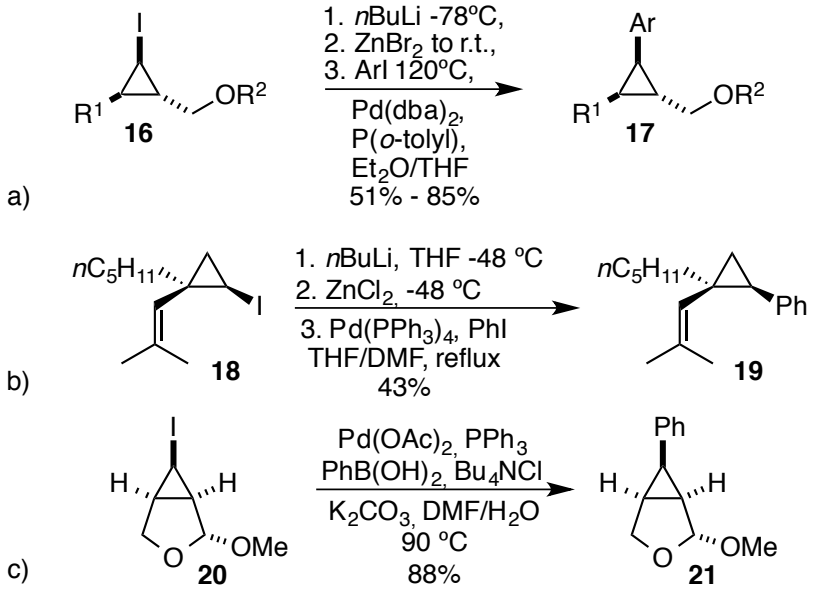
167 Daichi, S.; Kenta, Y.; Kazuya, S.; Yoshinori, N. *Chem. Lett.* **2015**, *44*, 818-820.

168 Yotsuji, K.; Hoshiya, N.; Kobayashi, T.; Fukuda, H.; Abe, H.; Arisawa, M.; Shuto, S. *Adv. Synth. Catal.* **2015**, *357*, 1022-1028.

169 Müller, D. S.; Marek, I. *J. Am. Chem. Soc.* **2015**, *137*, 15414-15417.

170 Zhang, P.; Le, C. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 8084-8087.

171 Giannerini, M.; Vila, C.; Hornillos, V.; Feringa, B. L. *Chem. Commun.* **2016**, *52*, 1206-1209.

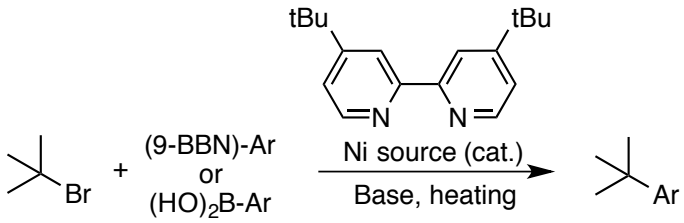


Scheme 73. Some examples of general cross-coupling methodologies for cyclopropanes. a) Negishi coupling of iodocyclopropanes.[172] b) Negishi coupling of vinylcyclopropanes.[173] c) Suzuki coupling of an *endo*-cyclopropane.[174]

The Suzuki-Miyaura coupling is a well-established coupling reaction known for its broad functional-group tolerance and scope.[175] Therefore, this transformation was chosen as a starting point for the studies towards 1-aryl derivatives. However, the palladium-catalyzed reaction of 1-bromo-1-methyl derivative **1o** and phenylboronoic acid did not produce any product.[176] The 1-bromo-1-methyl compound **1o** was recovered indicating that no oxidative addition had taken place, presumably because of the unactivated tertiary bromide that is also partially shielded by the large phenanthrene substituents.

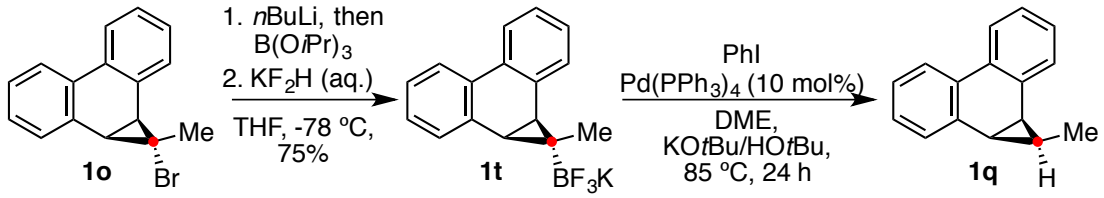
By the time of writing this manuscript, several methods for the Suzuki-Miyaura for tertiary bromides have been added to the literature,[177] and especially the field for secondary bromides has bloomed (Scheme 74).

172 Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829-11832.
173 Piers, E.; Coish, P. D. G. *Synthesis* **2001**, *2001*, 0251-0261.
174 Martin, S. F.; Dwyer, M. P. *Tetrahedron Lett.* **1998**, *39*, 1521-1524.
175 Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168.
176 Wallace, D. J.; Chen, C.-y. *Tetrahedron Lett.* **2002**, *43*, 6987-6990.
177 a) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624-627. b) Zhang, X.; Yang, C. *Adv. Synth. Catal.* **2015**, *357*, 2721-2727. c) Khan, R. I.; Pitchumani, K. *Green Chem.* **2016**, *18*, 5518-5528.



Scheme 74. General conditions for the Suzuki-Miyaura coupling as reported by Fu[178] and Yang.[179]

For the Suzuki-Miyaura coupling, the oxidative addition is often considered the rate-limiting step and can be detrimental for unreactive substrates. Specifically to overcome these issues, bulky electron-rich ligands have been developed, which enable transformations that are otherwise unachievable.[180] However, another approach was followed where the halide and the organoboron species were inverted in the hope to overcome the difficult oxidative addition step. In this approach, iodobenzene rather than the cyclopropane derivative has to undergo oxidative addition. The Suzuki precursor **1t** was synthesized from 1-bromo-1-methyl derivative **1o** by lithium-halogen exchange followed by the addition of triisopropyl borate and immediate treatment with potassium bifluoride (Scheme 75).[181]



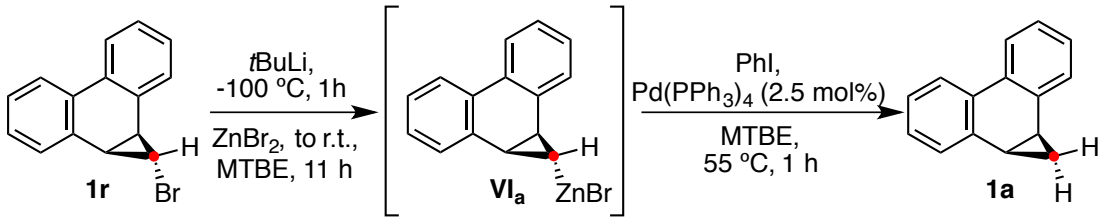
Scheme 75. Formation of potassium trifluoroborate salt **1t** and attempted Suzuki coupling.

The Suzuki coupling was performed with both iodobenzene and iodomethane.[182] Unfortunately, only the reduced compound **1q** was isolated (Scheme 75). Iodobenzene is a widely-used substrate in the Suzuki-Miyaura coupling generally

178 Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624-627.
179 Zhang, X.; Yang, C. *Adv. Synth. Catal.* **2015**, *357*, 2721-2727.
180 Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.
181 Molander, G. A.; Sandrock, D. L. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 811-823.
182 de Meijere, A.; Khlebnikov, A. F.; Sünnemann, H. W.; Frank, D.; Rauch, K.; Yufit, D. S. *Eur. J. Org. Chem.* **2010**, *2010*, 3295-3301.

leading to good results for the oxidative addition, it is therefore more likely that the transmetallation of the boronic acid species is the problematic step, instead. The formation of compound **1q** could be due to the protonolysis of the boronic acid formed during the reaction.

As discussed in some of the examples above, the Negishi coupling was used successfully in cyclopropane arylations before,[183] and was used in another attempt to facilitate the transmetallation step.[184] At the same time, the substrate was changed to the secondary bromide **1r** rather than the even more challenging tertiary bromide **1o**. The organo-zinc bromide **VI$_a$** was generated according to a modified literature procedure and reacted with iodobenzene using tetrakis(triphenylphosphine)palladium(0) as the catalyst.[185] However, this strategy led exclusively to the isolation of the reduced cyclopropane derivative **1a**, as well. It is again presumable that the transmetallation step of the zinc species did not proceed, and the isolated compound is the product of quenching during the work-up (Scheme 76).



Scheme 76. Formation of the organo-zinc reagent **VI$_a$** and attempted Negishi coupling.

The Murahashi-Feringa coupling uses highly-activated lithium species in the transmetallation step.[186] The more activated lithium dibenzonorcaradiene **VI$_b$** was used in an attempt to facilitate the transmetallation step in the reaction with

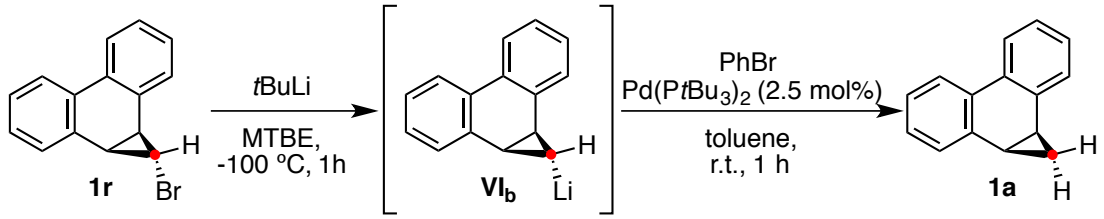
183 a) Piers, E.; Coish, P. D. G. *Synthesis* **2001**, *2001*, 0251-0261. b) Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829-11832. c) Beaulieu, L.-P. B.; Zimmer, L. E.; Gagnon, A.; Charette, A. B. *Chem. - Eur. J.* **2012**, *18*, 14784-14791.

184 Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958-2965.

185 Coleridge, B. M.; Bello, C. S.; Leitner, A. *Tetrahedron Lett.* **2009**, *50*, 4475-4477.

186 Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Nat. Chem.* **2013**, *5*, 667-672.

bromobenzene and bis(tri-*tert*-butylphosphine)palladium as catalyst, which again solely led to the isolation of the reduced compound **1a** (Scheme 77).



Scheme 77. Formation of the lithium species **VI$_b$** and attempted Murahashi-Feringa coupling.

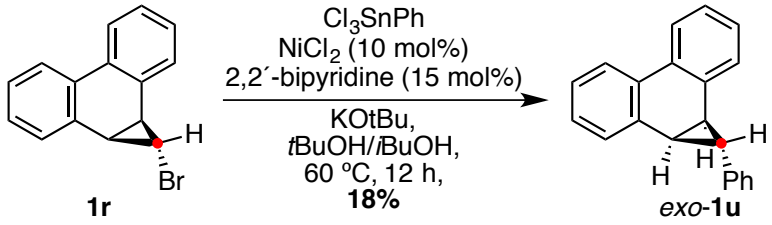
The arylation of dibenzonorcaradienes could not be achieved employing the reported procedure for cross-coupling with cyclopropane moieties. Therefore, the approach to this challenge had to be changed. Several groups have reported the coupling reactions of unactivated secondary and tertiary alkyl halides with aryl derivatives.[187] In contrast to the classical palladium-catalyzed cross-coupling approaches, which usually proceed through two-electron transfer chemistry, these new methods use nickel as catalyst, which are capable of undergoing one-electron transfer processes, could form an intermediate nickel-alkyl complex via a single-electron transfer reaction.

The nickel-catalyzed Stille coupling of 1-bromo derivative **1r** with trichloro(phenyl)stannane was performed and modest amounts of 1-phenyl derivative **1u** were obtained (Scheme 78).[188] Unfortunately, when the more challenging substrates 1,1-dibromo derivative **1i** or the tertiary bromide **1o** were treated under similar conditions, no reaction took place (Scheme 79). Despite the many recent advancements, especially in the field of nickel-catalyzed

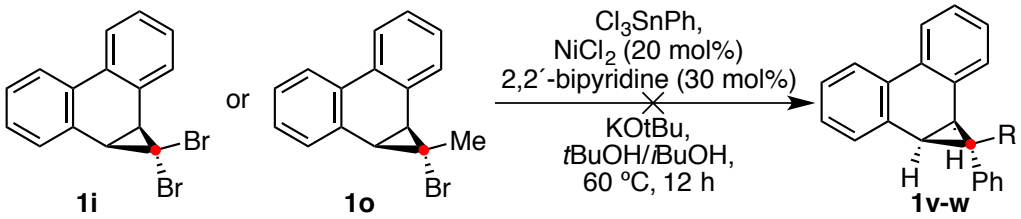
187 a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727. b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341. c) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788-7789. d) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G. r.; van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61-69. e) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137-4139. f) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686-3687. g) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297-1299. h) Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955-3957.

188 Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510-511.

cross-coupling reactions,[189] the functionalization of tertiary bromides remains a challenge.[190]



Scheme 78. Ni-catalyzed Stille coupling to form **1u**.



Scheme 79. Attempted Stille coupling for tertiary bromides.

Compound **1u** was formed as the single *exo*-isomer, bearing the same configuration as the parent compound. However, it is hard to determine whether the selectivity originates from the starting material or if it is the result of the methodology chosen, as the reaction proceeds through radical intermediates. The configuration was corroborated by X-ray analysis (Figure 13).

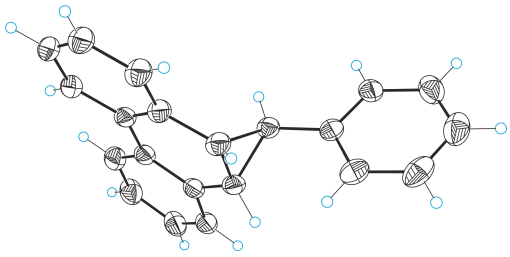
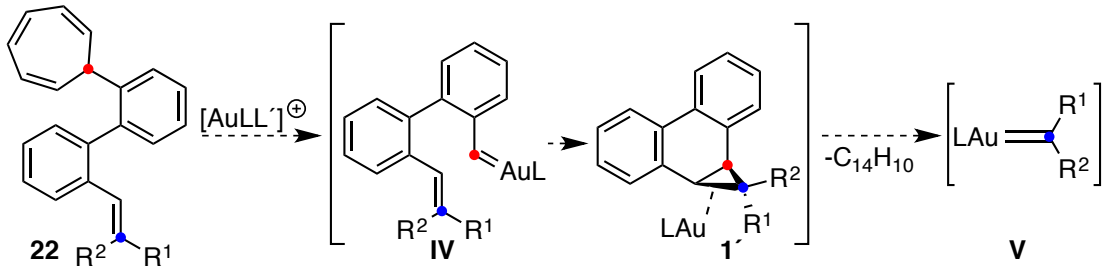


Figure 13. ORTEP drawing of the X-ray crystal cluster of *exo*-**1u** with 50% probability of the thermal ellipsoids.

189 Gu, J.; Wang, X.; Xue, W.; Gong, H. *Org. Chem. Front.* **2015**, *2*, 1411-1421.
190 Wang, X.; Wang, S.; Xue, W.; Gong, H. *J. Am. Chem. Soc.* **2015**, *137*, 11562-11565.

In-situ generation of dibenzonorcaradiene derivatives

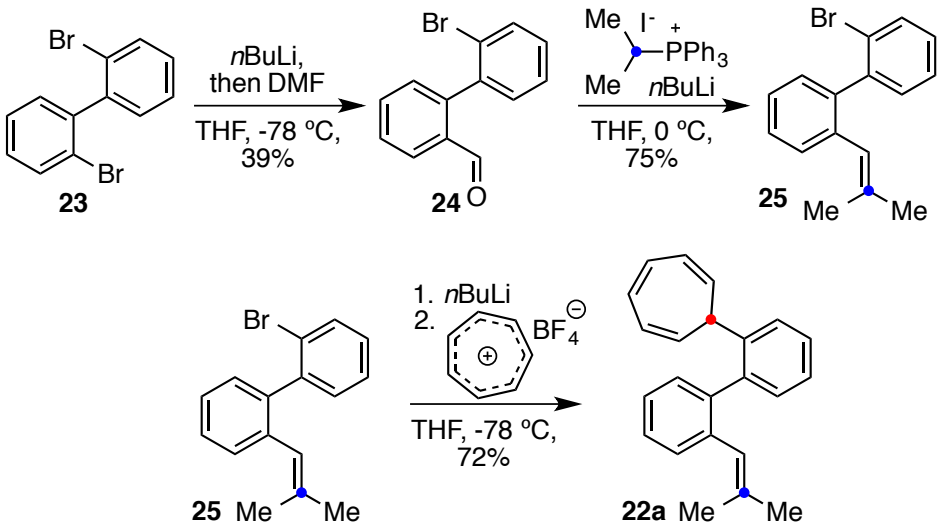
In parallel to the direct synthesis of the dibenzonorcaradiene from a common intermediate, the *in situ* generation of these carbene precursors was investigated to find a highly versatile alternative. The 1-substituted dibenzonorcaradiene derivatives **1** can be formed by an intramolecular gold(I)-catalyzed cyclopropanation, which can then undergo the retro-cyclopropanation to form a free gold(I)-carbene complex (Scheme 80). The first gold(I) carbene species **IV** can be formed by the retro-Buchner reaction of a biaryl cycloheptatriene derivative with a pendant alkene.



Scheme 80. The *in-situ* generation of 1-substituted dibenzonorcaradiene derivatives **1** from **22** and subsequent retro-cyclopropanation reaction to form free gold(I) carbenes.

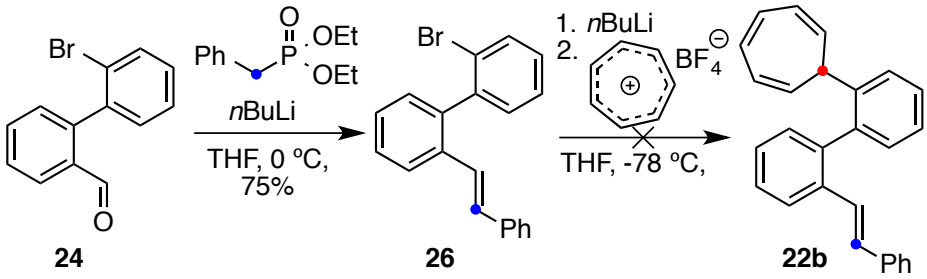
The synthesis started with the Bouveault reaction of 2,2´-dibromo-biphenyl (**23**) to give the necessary aldehyde **24**, which was reacted with isopropyl-triphenylphosphonium iodide to produce the isocrotyl derivative **25**.[191] A second lithium-halogen exchange, followed by the addition of tropylium tetrafluoroborate afforded the dimethyl derivative **22a** (Scheme 81).

191 Ebner, C.; Müller, C. A.; Markert, C.; Pfaltz, A. *J. Am. Chem. Soc.* **2011**, *133*, 4710-4713.



Scheme 81. Synthesis of biaryl derivative **22a**.

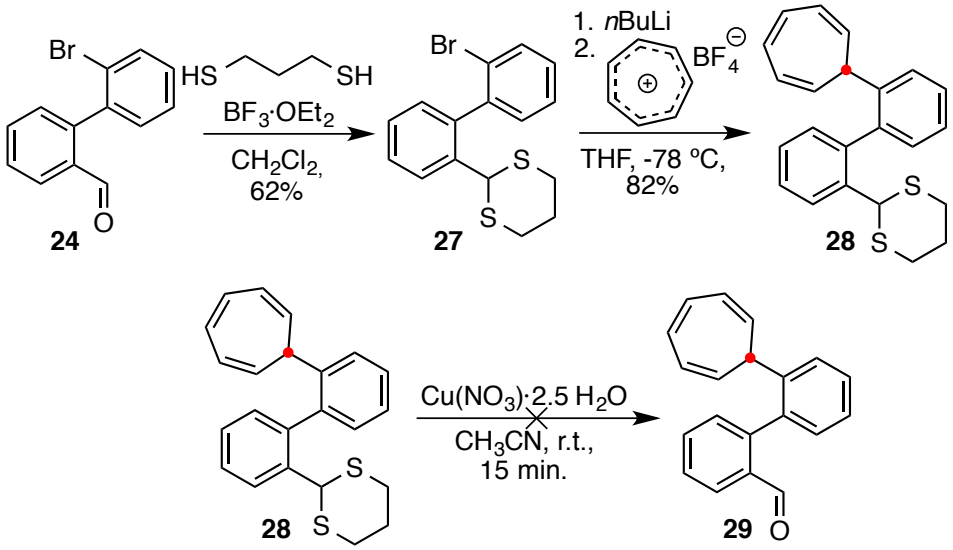
A similar route was used in an attempt to form the phenyl derivative. The Horner-Wadsworth-Emmons reaction with benzylphosphonate transformed the aldehyde into the styrenyl derivative **26**. Unfortunately, the lithium-halogen exchange reaction of **26** did not proceed as expected and two unidentified compounds were isolated instead (Scheme 82). By protecting the aldehyde as the dithiolane it was possible to install the cycloheptatriene (Scheme 83).[192] However, the compound decomposed during the deprotection.[193]



Scheme 82. Attempted formation of styrenyl-biphenyl derivative **22b**.

192 Solladie, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreno, M. C.; Garcia Ruano, J. L. *J. Org. Chem.* **1991**, *56*, 2317-2322.

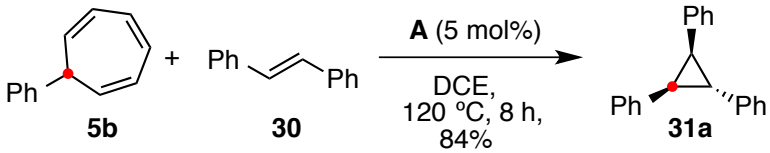
193 Oksdath-Mansilla, G.; Peñéñory, A. B. *Tetrahedron Lett.* **2007**, *48*, 6150-6154.



Scheme 83. Second attempt to synthesize cycloheptatrienyl-biphenyl derivative **22b**.

Formation of gold(I) carbenes from dibenzonorcaradiene derivatives

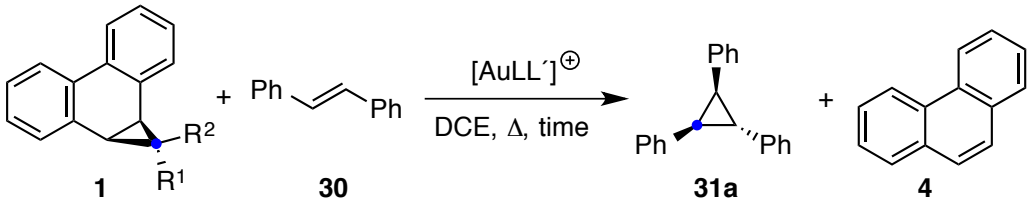
Having obtained several dibenzonorcaradiene derivatives **1a, 1g, 1i, 1o, 1p** and isocrotyl-biphenyl derivative **22a**, the formation of gold(I) carbenes from these precursors was investigated (Table 1). During the cyclopropanation with gold(I) carbenes from cycloheptatriene derivatives previously reported by our group, *E*-stilbene was used as the alkene and [(JohnPhos)Au(MeCN)]SbF_6 (**A**) as catalyst (Scheme 84). [194] In order to relate the results obtained for the dibenzonorcaradiene derivatives to the previously results, stilbene was used in these experiments as well. The disadvantage of this approach is that the ^{1}H NMR spectra for the starting material and the product are highly similar (Figure 14). In order to get a clearer picture of the conversion the formation of phenanthrene was monitored instead, which can easily be identified by a singlet at 7.75 ppm and a double doublet at 8.71 ppm.



Scheme 84. Formation of trisphenylcyclopropane from cycloheptatriene and stilbene under standard conditions.

194 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

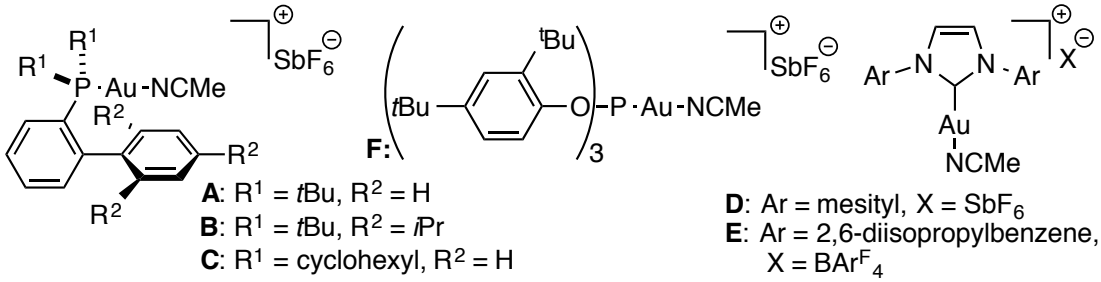
Table 1. Screening of conditions for the retro-Buchner reaction of dibenzonorcaradiene derivatives.



1 **30** **31a** **4**

	R¹	R²	Cat. (mol%)	T. (°C)	Time (h)	Conversion (%)[a]
1	Ph	H	**A** (5)	120	8	21
2	Ph	H	**A** (10)	100	14	19
3	Ph	H	**A** (100)	100	8	20
4	Ph	H	**B** (10)	100	14	18
5	Ph	H	**D** (10)	100	14	20
6	Ph	H	**F** (10)	100	14	n.r.
7	Ph	H	**A** (5)	80	8	5
8	Ph	H	**A** (5)	60	8	n.r.
9	Ph	H	**A** (5)	40	8	n.r.
10	Ph	H	**A** (5)	r.t.	8	n.r.
11	Ph	H	**A** (100)	60	24	n.r.
12	Br	Me	**A** (5)	120	2	n.r.
13	Br	Br	**A** (5)	120	2	n.r.
14	Br	Br	**A** (5)	120	8	n.r.
15	H	Me	**A** (5)	120	14	n.r.
16	H	H	**A** (5)	120	14	n.r.
17	Me	Me	**A** (5)	120	14	n.r.

Dibenzonorcaradiene **1** (0.1 mmol), *E*-stilbene (**30**) (0.1 mmol), catalyst **A**-**F** (5 mol%) in DCE (0.4 mL) for given time at given temperature. [a] determined by ^{1}H NMR relative to diphenylmethane as internal standard.



A: R¹ = *t*Bu, R² = H
B: R¹ = *t*Bu, R² = *i*Pr
C: R¹ = cyclohexyl, R² = H

D: Ar = mesityl, X = SbF_6
E: Ar = 2,6-diisopropylbenzene, X = $BAr^F{}_4$

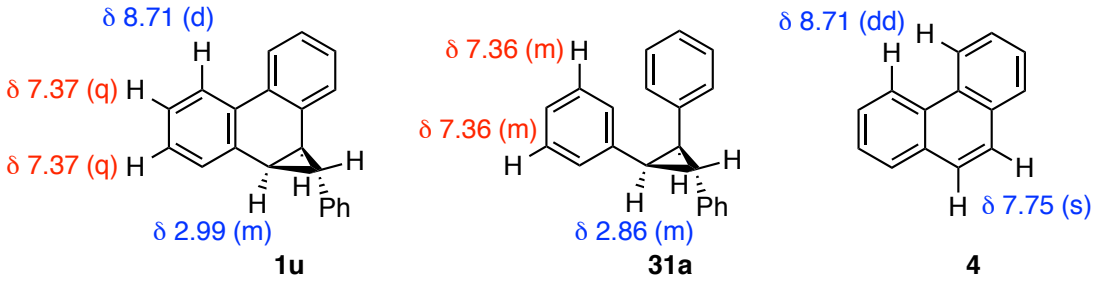


Figure 14. Phenanthrene with the protons easily identified by ^{1}H NMR analysis.

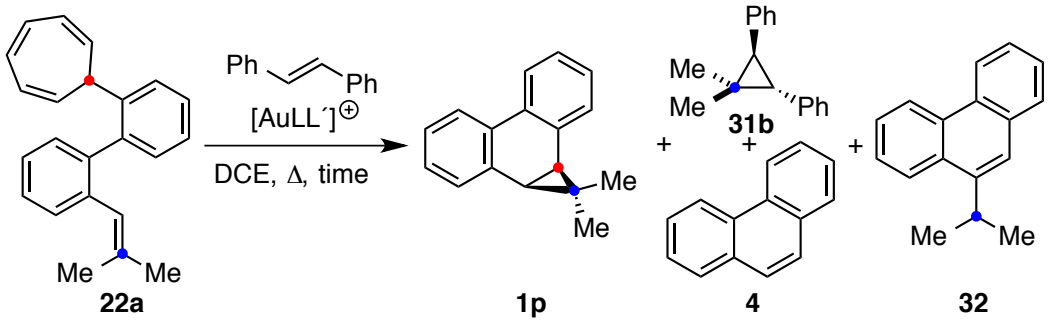
When the 1-phenyl dibenzonorcaradiene derivative **1u** is subjected to the reaction conditions optimized for cycloheptatriene derivatives, a modest conversion of 21% to the cyclopropane is observed (Table 1, entry 1). Increasing the catalyst loading and lowering the reaction temperature to 100 °C had little effect on the reaction outcome (Table 1, entry 2 and 3).

Several other catalysts were tested, leading to comparable results for tBuXPhos-**B** and IPr-gold complexes **D** (Table 1, entry 4 and 5). The phosphite complex **F** did not catalyze the reaction, probably because it is not stable under the reaction conditions (Table 1, entry 6). At 80 °C the reaction is significantly slower and at lower temperatures there is no observable reactivity (entries 7 to 10). Even with a stoichiometric amount of catalyst and prolonged reaction times, no liberated phenanthrene was observed at 60 °C (Table 1, entry 11). When other halo or alkyl substituted dibenzonorcaradiene derivatives were used, no conversion was observed at all (Table 1, entries 12 to 17).

The *in situ* generation of dibenzonorcaradiene derivatives, and the subsequent retro-cyclopropanation was investigated at the same time. During the reaction, its progress was monitored by formation of the dibenzonorcaradiene derivative **1p**, liberated phenanthrene **4**, and the thermal decomposition byproduct **32** (Table 2). Under the standard conditions, isocrotyl-biphenyl derivative **22a** quickly forms 1,1-dimethyl-dibenzonorcaradiene **1p** (Table 2, entry 1). Already within eight hours, the biphenyl derivative is fully converted to the dibenzonorcaradiene **1p** (Table 2, entry 2). However, no free phenanthrene was observed, meaning that the second retro-cyclopropanation reaction does not take place. When the tBuXPhos-gold complex **B** was used, the reaction was significantly slower and a substantial amount of byproduct was formed (entry 3).

No cyclization product was observed when the IPr-gold complex **E** was used, leading to decomposition (entry 4). In an attempt to force the retro-cyclopropanation from **1p** by employing higher temperatures, more product from the thermal rearrangement of dimethyl-dibenzonorcaradiene **32** was formed but phenanthrene (**4**) was never observed (entries 5 and 6).

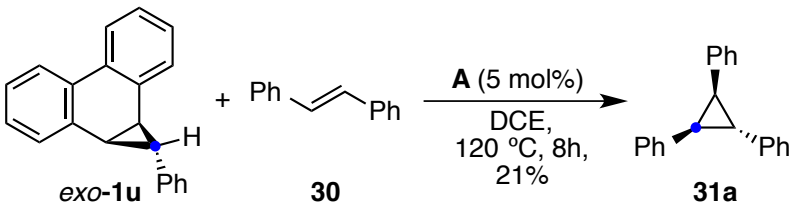
Table 2. Screening of conditions for the generation of phenanthrene derivatives and retro-Buchner reaction.



	Cat. (mol%)	T. (°C)	time (h)	1p (%)[a]	4 (%)[a]	32 (%)[a]
1	**A** (5)	120	1	89	-	-
2	**A** (5)	120	8	100	-	-
3	**B** (5)	120	14	19	-	21
4	**E** (5)	120	14	-	-	n.d.
5	**A** (5)	150	24	86	-	16
6	**A** (5)	180	8	31	-	14

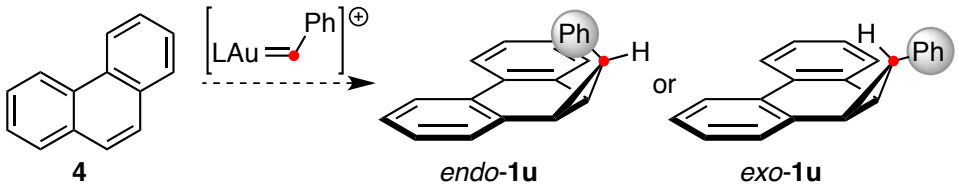
22a (0.1 mmol), stilbene (0.1 mmol), catalyst **A, B** or **E** (5 mol%) in DCE (0.4 mL) for given time at given temperature. [a] determined by ^{1}H NMR relative to diphenylmethane as internal standard.

The retro-Buchner reaction of 1-phenyl derivative **1u** in the presence of *E*-stilbene only gave moderate results (Scheme 85), which surprisingly did not change when reaction temperature, time and catalyst loading were varied (Table 1, entries 1 to 3). In order to gain more insight at the underlying cause of these results, some additional experiments were performed. The inhibition of the catalyst by phenanthrene can be ruled out, as the results were independent on the catalyst loading.



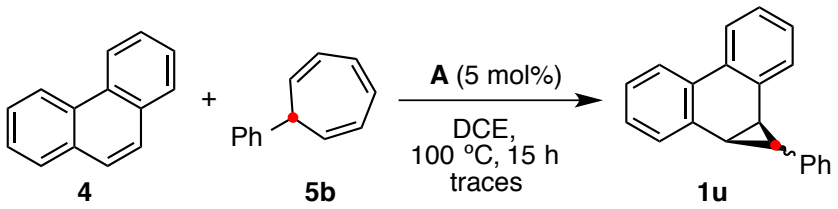
Scheme 85. Results obtained for the cyclopropanation of *E*-stilbene with gold carbenes generated from **1u**.

Another suggestion is the poor accessibility of the cyclopropane as both faces of *exo*-**1u** are shielded, hindering the approach of the catalyst. If the cyclopropanation using a aryl gold(I) carbene with phenanthrene would be able to produce the inverse isomer *endo*-**1u**, it too could be tested in the subsequent cyclopropanation reaction (Scheme 86). However, if the formation of *exo*-**1u** is also observed, it is unlikely that sterics play an important role it the poor reactivity of the retro-cyclopropanation.

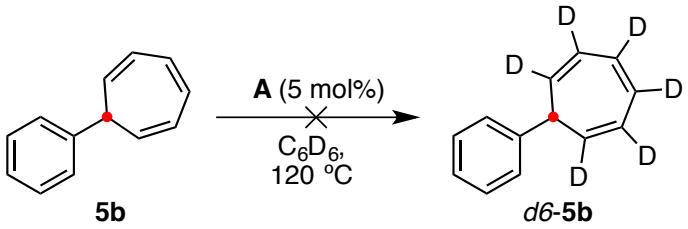


Scheme 86. Cyclopropanation of phenanthrene with a aryl gold(I) carbene.

When phenyl-cycloheptatriene **5b** and phenanthrene were subjected to the standard reaction conditions, traces of the 1-phenyl derivative **1u** were observed by GC-MS spectrometry but not enough was formed to isolate the compound for full characterization (Scheme 87). The formation of the cyclopropane derivative is by itself an interesting result, as *Z*-stilbene was found to be unreactive using cycloheptatriene derivatives.[194] When a comparable experiment was performed for the cycloheptatriene derivatives using deuterated benzene as solvent, no evidence for the gold(I)-catalyzed Buchner reaction was found (Scheme 88).

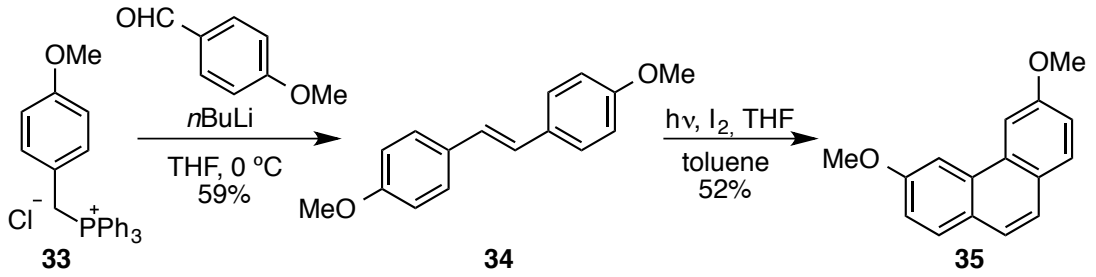


Scheme 87. Synthesis of **1u** by cyclopropanation of phenanthrene via the retro-Buchner reaction of **5b**.

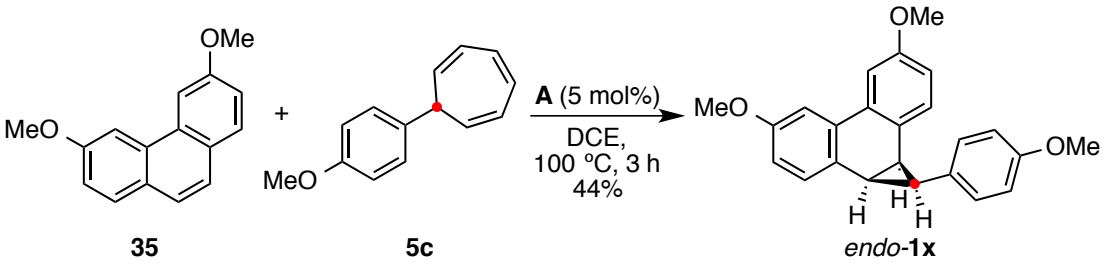


Scheme 88. Investigation on the gold(I)-catalyzed Buchner reaction of *d6*-benzene.

The electron-rich 3,6-dimethoxyphenanthrene (**35**) was prepared to provide a more reactive carbene acceptor (Scheme 89).[195] The cyclopropanation of 3,6-dimethoxy phenanthrene was performed using 7-(4-methoxyphenyl)-1,3,5-cycloheptatriene (**5c**) using the JohnPhos-gold complex at 100 °C for 15 h. A small amount of the corresponding dibenzonorcaradiene derivative **1x** could be isolated and characterized. Further optimization of the reaction conditions led to the isolation of **1x** in 44% yield (Scheme 90).



Scheme 89. Synthesis of 3,6-dimethoxy phenanthrene **35**.



Scheme 90. Cyclopropanation of 3,6-dimethoxyphenanthrene with aryl gold(I) carbenes.

Comparison of the ^{1}H NMR data revealed that exclusively the opposite (*endo*) isomer was formed during the cyclopropanation of phenanthrene. A clear distiniction between the shift for the hydrogens of the cyclopropane plus the

195 R., T. H.; J., G. M.; V., B. A. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1182-1186.

typical *trans*-coupling constants could be observed for *exo*-**1u**, whereas only a single singlet is observed for *endo*-**1x** (Figure 15).

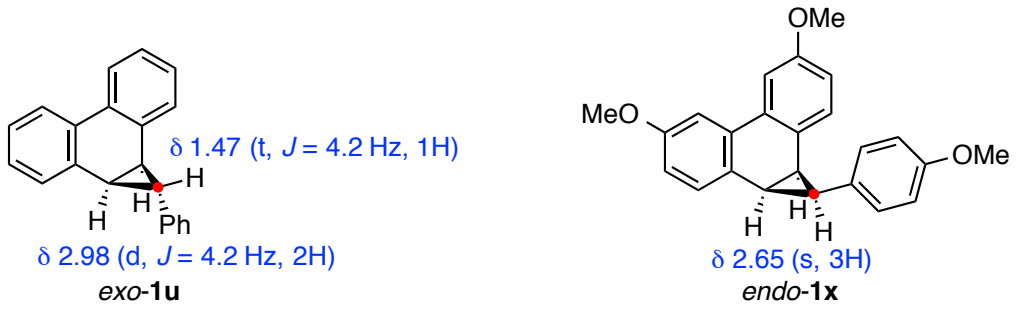


Figure 15. ^{1}H NMR analysis revealed distinct differences between the two isomers.

Only one stereoisomer is observed for the cyclopropanation of phenanthrene derivatives. It is therefore likely that the *exo*-isomer of the 1-substituted dibenzonorcaradiene derivatives is not accessible enough. The poor reactivity of di-alkyl substituted cycloheptatriene derivatives has also been ascribed to steric hindrance.[196] The *endo*-isomer might prove to be a better carbene precursor as the cyclopropane is shielded only in one direction, leaving the other face completely exposed.

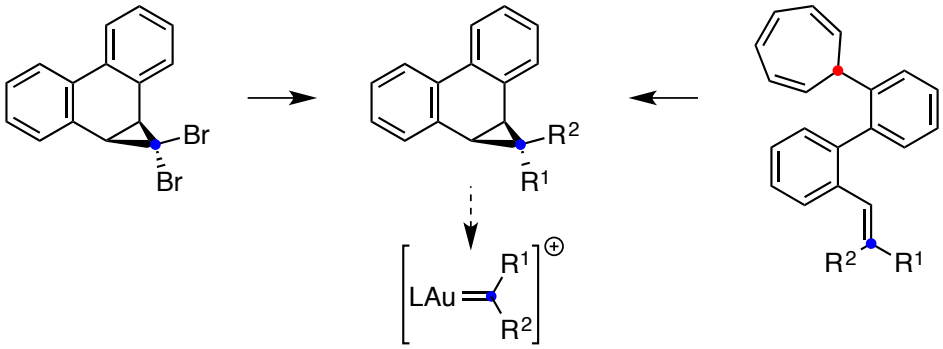
Unfortunately, in the method developed for the synthesis of 1-aryl derivatives, the configuration of the product is likely independent of the configuration of the starting material. Therefore, the stereoselectivity cannot be controlled by the substrate using this method. Thanks to the rapid development of new cross-coupling methods for hindered unactivated alkyl bromides, new strategies have appeared that might make the selective formation of the *endo*-isomer possible.

The formation carbenes from 1-alkyl dibenzonorcaradienes does not occur due to the lack of stabilizing α-substituents on the carbene, which has been observed for gold complexes with this ligand type. Using other gold complexes these carbene types might be generated. However, for now the retro-cyclopropanation remains limited to privileged gold(I) complexes and high temperatures.

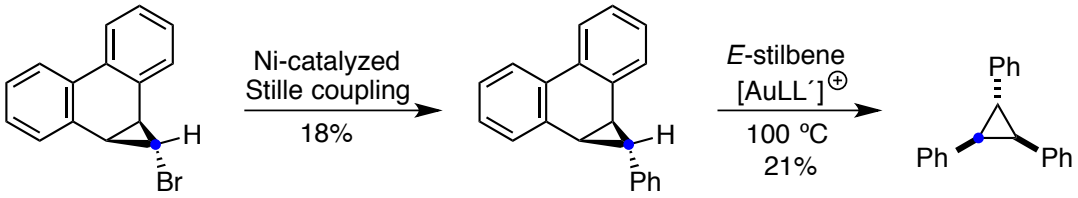
196 Wang, Y. PhD. Dissertation, ICIQ/Universitat Rovira i Virgili, 2014.

Conclusion

Two synthetic strategies have been used to obtain several dibenzonorcaradiene derivatives. The compounds can be synthesized by functionalization of a common 1,1-dihalo-dibenzonorcaradiene intermediate, or through a gold(I)-catalyzed intramolecular cyclopropanation reaction of a biaryl derivative with an appending alkene moiety. Both strategies can be used to conveniently vary the alkyl substituents that would be transferred to the carbene.



The functionalization of 1-bromo dibenzonorcaradiene with an aryl moiety proved challenging but was overcome using a nickel-catalyzed Stille coupling, which exclusively afforded the *exo*-isomer. As the field of transition-metal catalyzed coupling reactions has been rapidly evolving, it is likely that improved methods could lead to both *exo*- and *endo*-isomers with better yield.



Unfortunately, the prepared examples did not offer an improvement over the existing cycloheptatriene derivatives in the gold(I)-catalyzed retro-cyclopropanation reactions. The use of *exo*-1-phenyl dibenzonorcaradiene led poor yields for the cyclopropanation of stilbenes, which is likely caused by the sterical congestion. The *endo*-isomer could be more reactive towards gold(I) complexes, as the cyclopropane is exposed from one face. Further investigations in this direction would be required to confirm this hypothesis.

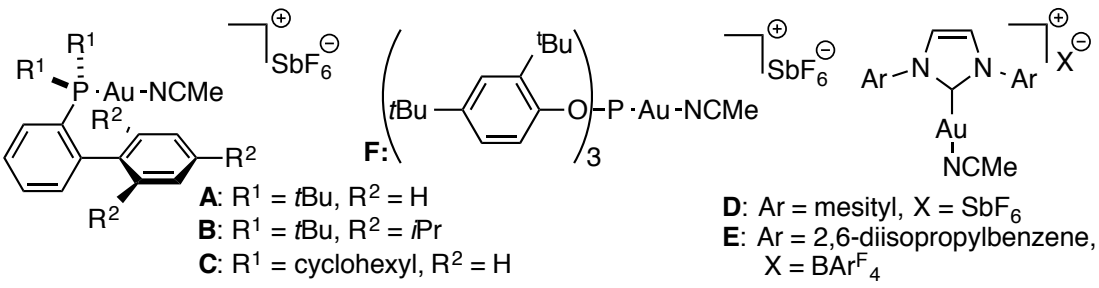
Although, the norcaradiene derivatives described herein, and the synthetic strategies towards, did not lead to further development of the gold(I)-catalyzed retro-Buchner reaction, the compounds could make an interesting entry in photolytic carbene formation. One might even envision the light-induced formation of free carbenes from dibenzonorcaradiene derivatives, which can be trapped by transition-metal complexes and used for subsequent transformations.

Experimental section

General information

All reactions were carried out under argon in anhydrous solvents obtained by passing them through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA), unless noted otherwise. All gold-catalyzed reactions were performed in HPLC-grade solvents, without a protective atmosphere. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck Gf234). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 °C on Bruker Avance 300, 400 and 500 Ultrashield apparatus. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (*J*) are reported in hertz (Hz). Mass spectra were recorded on a Waters LCT Premier Spectrometer (ESI and APCI) or on an Autoflex Bruker Daltonics (MALDI and LDI). Melting points were determined using a Büchi melting point apparatus.

The following gold complexes were synthesized according to literature procedures.[197]



197 Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.

1a,9b-Dihydro-1*H*-cyclopropa[*l*]phenanthrene (1a)

To a cooled solution of 1,1-dibromo-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (**1i**) (1.73 g, 5 mmol, 1 equiv) in THF (20 mL) at -78 °C is added *n*-butyl lithium (2.2 mL, 2.5 M, 5.5 mmol, 1.1 equiv) and the mixture is stirred for 1 h. Methanol (0.4 mL, 10 mmol, 2 equiv) is added and the cooling is removed. Once the mixture reaches ambient temperature, it is poured into a separatory funnel with water and extracted with dichloromethane. Flash chromatography (c-hexane) yields 701 mg (73%) of a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.92 (m, 2H), 7.42 (dd, *J* = 5.9, 3.1 Hz, 2H), 7.30 – 7.20 (m, 4H), 2.55 (dd, *J* = 8.9, 4.9 Hz, 2H), 1.55 (td, *J* = 8.9, 3.9 Hz, 1H), -0.09 (td, *J* = 4.9, 3.9 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.3, 129.3, 129.1, 127.6, 125.9, 123.2, 19.6, 12.7.

1,1-Dibromo-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (1i)

This compound was synthesized according to a literature procedure.[198] Spectroscopic data matched the reported.

1-Bromo-1-methyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (1o)

This compound was synthesized following a modified literature procedure.[199]

To a solution of phenanthrene (1.0 g, 2.81 mmol, 1 equiv) in dry THF (15 mL) under an argon atmosphere at -78 °C, was added *n*-butyl lithium (1.43 mL, 2.5 M, 3.57 mmol, 1.25 equiv) over 1 minute and stirring was continued for another 20 minutes. Next, iodomethane (267 µL, 4.29 mmol, 1.5 equiv) is added at once over the glass wall and stirring is continued over night, while the mixture is allowed to slowly warm to room temperature. The reaction is carefully quenched by the addition of water and the mixture is extracted with diethyl ether (20 mL) and washed with water (2 x 30 mL) and brine (30 mL), before being dried over

198 Nguyen, J. M.; Thamattoor, D. M. *Synthesis* **2007**, *2007*, 2093-2094.
199 Moore, K. A.; Vidaurri-Martinez, J. S.; Thamattoor, D. M. *J. Am. Chem. Soc.* **2012**, *134*, 20037-20040.

anhydrous sodium sulfate. Flash chromatography (c-hexane) yields 464 mg (57%) of white crystals.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 – 7.92 (m, 2H), 7.50 – 7.44 (m, 2H), 7.30 (ddd, *J* = 6.6, 4.3, 1.8 Hz, 4H), 3.19 (s, 2H), 1.22 (s, 3H).

^{13}C NMR (75 MHz, Chloroform-*d*) δ 130.9, 130.8, 130.1, 128.1, 127.2, 122.9, 34.7, 33.9, 19.1.

HRMS-APCI: calculated for $C_{16}H_{13}$ $[M+H]^+$: 205.1012; found: 205.1014.

Suitable crystals for X-ray spectroscopy were obtained by slow evaporation of c-hexane.

1,1-Dimethyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (1p)

1-bromo-1-methyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (568 mg, 2 mmol) is dissolved in MTBE (8 mL) and cooled to -100 °C, before *tert*-butyl lithium (4.0 mL, 1.5M, 6 mmol, 3 equiv) is added. After stirring at this temperature for 1 h, methyltriflate (905 µL, 8 mmol, 2 equiv) is added over the glass wall and the reaction is stirred for another 30 minutes. The reaction is quenched with water (10 mL) after it was stirred over night while slowly warming to room temperature, and extracted with dichloromethane Flash chromatography (c-hexane) yields 400 mg (91%) of a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.91 (m, 2H), 7.34 – 7.31 (m, 2H), 7.26 – 7.19 (m, 4H), 2.33 (s, 2H), 1.37 (s, 3H), 0.49 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.8, 131.1, 130.2, 127.4, 125.9, 122.5, 31.6, 27.6, 23.4, 14.2, 14.1.

GC-MS (ESI)**:** R.T: 8.011 min. MS: calculated: 220.4, found 220.1.

1-Methyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (1q)

1-bromo-1-methyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (71 mg, 0.25 mmol) is dissolved in THF (2.5 mL) and cooled to -78 °C. A solution of *n*-butyl lithium (110 µL, 2.5M, 0.28 mmol, 1.1 equiv) is slowly added and the reaction is stirred for 40 minutes. The reaction is then quenched by the addition of methanol (1.25 mL) and the cooling is removed. When the mixture reaches room

temperature, the solvents are evaporated and flash chromatography (c-hexane) yields a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.94 (m, 2H), 7.38 – 7.33 (m, 2H), 7.27 – 7.23 (m, 4H), 2.59 (d, *J* = 9.0 Hz, 2H), 1.53 (q, *J* = 3.0 Hz, 1H), 0.44 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.0, 131.7, 130.2, 127.5, 126.0, 122.4, 23.4, 8.9, 6.9.

GC-MS (ESI)**:** R.T: 8.077 min. MS: calculated: 206.1, found 206.1.

1-Bromo-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (1r)

A solution of 1,1-dibromo-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (3.50 g, 10 mmol) in THF (40 mL) is cooled to -78 °C and *n*-butyl lithium (9.6 mL, 2.5 M, 24 mmol, 2.4 equiv) is slowly added before the reaction is stirred for 1 h. Methanol (2 mL, 50 mmol, 5 equiv) is then added and the reaction is allowed to warm to room temperature. Dichloromethane (30 mL) and water (60 mL) are added mixture is extracted, washed with water (30 mL) and brine (30 mL) and is concentrated. Flash chromatography (c-hexane) yields 1.73 g (61%) of a white powder.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.91 (m, 3H), 7.48 (dd, *J* = 5.4, 1.9 Hz, 2H), 7.31 – 7.26 (m, 4H), 3.00 (d, *J* = 3.2 Hz, 2H), 2.41 (t, *J* = 3.2 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 131.9, 129.8, 129.3, 128.1, 127.2, 123.3, 29.9, 27.7.

1-Bromo-1-butyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (1s)

A solution of 1,1-dibromo-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (1.75 g, 5 mmol) in THF (20 mL) is cooled to -78 °C and *n*-butyl lithium (2.2 mL, 2.5 M, 5.5 mmol, 1.1 equiv) is slowly added before the reaction is stirred for 1 h. The reaction is then allowed to warm to room temperature. The reaction is quench by pouring the mixture into a separatory funnel with dichloromethane (10 mL) and water (20 mL). The mixture is extracted, washed with water (20 mL) and

brine (10 mL), and concentrated. Flash chromatography (c-hexane) yields a white solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.99 – 7.93 (m, 1H), 7.53 – 7.47 (m, 1H), 7.37 – 7.26 (m, 2H), 3.23 (s, 1H), 1.32 – 1.15 (m, 2H), 0.88 (h, *J* = 7.2 Hz, 1H), 0.50 (t, *J* = 7.3 Hz, 1H).

Potassium trifluoro(1-methyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthren-1-yl)borate (1t)

To a stirred dry tetrahydrofuran solution (3 mL) of 1-bromo-1-methyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (428 mg, 1.5 mmol), cooled to -78 °C, was added a solution of *n*-butyl lithium (0.66 mL, 2.5 M, 1.65 mmol, 1.1 equiv). The mixture was stirred for 40 minutes, after which triisopropylborate (692 μL, 3 mmol, 2 equiv) was added and the cooling removed. After stirring for 13 h at ambient temperature, an aqueous solution of potassium bifluoride (10.5 mL, 1M, 10.5 mmol, 7 equiv) was added and the mixture stirred for 30 minutes. The mixture was then concentrated and dried under high vacuum over night. The solids were suspended in boiling acetone and filtered, three times. The combined acetone fractions were concentrated, affording 351 mg (75%) of a white solid.

^{1}H NMR (300 MHz, Acetone-d_6) δ 8.08 – 8.02 (m, 2H), 7.42 – 7.35 (m, 2H), 7.29 – 7.23 (m, 4H), 0.97 (t, *J* = 7.2 Hz, 2H), 0.47 – 0.34 (m, 3H).

^{11}B NMR (128 MHz, Acetone-d_6) δ 6.86 – 4.23 (m).

^{13}C NMR (75 MHz, Acetone-d_6) δ 133.6, 131.3, 130.1, 127.5, 126.0, 122.5, 41.0, 30.6, 23.1.

^{19}F NMR (376 MHz, Acetone-d_6) δ -140.80 – -141.46 (m).

1-Phenyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (*exo*-1u)

A modified literature procedure was followed.[200]

In a flame-dried Schlenk flask were mixed nickel(II)chloride (13 mg, 0.1 mmol, 10 mol%) and bipyridine (23 mg, 0.15 mmol, 15 mol%). The vial was sealed and the atmosphere flushed with argon. A solution of potassium *tert*-butoxide (785

200 Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510-511.

mg, 7 mmol, 7 equiv) in *tert*-butanol/*iso*-butanol (10 mL, 7:3), followed by phenyltin trichloride (197 µL, 1.2 mmol, 1.2 equiv) and 1-bromo-1a,9b-dihydro-1*H*-cyclopropa[*l*] phenanthrene (285 mg, 1 mmol, 1 equiv). The mixture was heated to 60 °C for 24 h, after which the mixture is poured onto aqueous HCl (1N) and extracted with EtOAc. Flash chromatography (c-hexane) afforded 47 mg (18%) of white crystals.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.3 Hz, 2H), 7.37 (q, *J* = 8.1 Hz, 4H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 3.00 – 2.97 (m, 2H), 1.47 (t, *J* = 4.1 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.2, 135.0, 129.4, 129.34, 128.6, 127.9, 126.5, 125.7, 125.4, 123.3, 31.5, 30.5.

Suitable crystals for **X-ray diffraction** were obtained by slow evaporation from c-hexane.

endo-4,7-Dimethoxy-1-(4-methoxyphenyl)-1a,9b-dihydro-1H-cyclopropa[*l*]phenanthrene (1x)

A solution of 3,6-dimethoxyphenanthrene (24 mg, 0.1 mmol, 1 equiv), **5c** (20 mg, 0.1 mmol, 1 equiv), and **A** (3.9 mg, 5 µmol, 5 mol%) in a sealed micro-wave vial was heated to 100 °C for 3 h. The mixture was filtered over silica and concentrated. Flash chromatography (SiO_2, 50% CH_2Cl_2 in cy-hexane) yielded 16 mg (44% of a white solid).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.30 – 7.23 (m, 2H), 6.98 – 6.89 (m, 6H), 6.76 – 6.69 (m, 2H), 3.83 (d, *J* = 0.8 Hz, 3H), 3.76 (d, *J* = 0.8 Hz, 6H), 2.67 (s, 3H).

7-(4-methoxyphenyl)cyclohepta-1,3,5-triene (5c)

This compound was made according to a literature procedure.[201]

2'-Bromo-[1,1'-biphenyl]-2-carbaldehyde (24)

This compound was made following a literature procedure.[202]

201 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

2-Bromo-2'-(2-methylprop-1-en-1-yl)-1,1'-biphenyl (25)

Isopropyltriphenylphosphonium iodide (1.62 g, 3.75 mmol, 1 equiv) was dissolved in dry THF (15 mL) and cooled to 0 °C before adding *n*-BuLi (1.5 mL, 2.5 M, 3.75 mmol, 1 equiv). After stirring for 30 minutes, a solution of 2'-bromo-[1,1'-biphenyl]-2-carbaldehyde (975 mg, 1.5 mmol, 1 equiv) in THF (15 mL) is added drop wise and the reaction is left stirring for 12 h. Water is added en the mixture extracted with diethyl ether, washed with brine, and concentrated. Flash chromatography (c-hexane) yields 807 mg (75%) of a white powder.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.65 – 7.60 (m, 1H), 7.40 – 7.24 (m, 4H), 7.22 – 7.15 (m, 3H), 5.86 (s, 1H), 1.72 (dd, *J* = 10.0, 1.3 Hz, 6H).

2-(Cyclohepta-2,4,6-trien-1-yl)-2'-(2-methylprop-1-en-1-yl)-1,1'-biphenyl (22a)

In a dried flask, 2-bromo-2'-(2-methylprop-1-en-1-yl)-1,1'-biphenyl (807 mg, 2.8 mmol, 1 equiv) is dissolved in THF (11 mL) and cooled to -78 °C before *n*-BuLi (1.4 mL, 2.5 M, 3.1 mmol, 1.1 equiv) is added and the reaction left to stir for 40 minutes. The cap is quickly lifted and tropylium tetrafluoroborate (1.0 g, 5.6 mmol, 2 equiv) is added at once and the cooling removed. After stirring for 14 h at room temperature, water and diethyl ether are added. The mixture is washed and dried. Flash chromatography (c-hexane) yields 607 mg (72%) of a white powder.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.43 (td, *J* = 7.7, 1.5 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.24 – 7.07 (m, 4H), 6.54 – 6.41 (m, 2H), 6.17 – 5.99 (m, 2H), 5.73 (s, 1H), 5.24 (ddd, *J* = 52.9, 9.4, 5.2 Hz, 2H), 2.56 (t, *J* = 5.2 Hz, 1H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.60 (d, *J* = 1.1 Hz, 3H).

NMR (75 MHz, Chloroform-*d*) δ 160.40, 143.3, 139.8, 137.3, 135.1, 130.4, 130.2, 129.9, 129.8, 129.2, 127.9, 127.9, 127.7, 127.4, 126.6, 125.9, 125.8, 124.6, 123.9, 123.8, 42.0, 26.3, 19.4.

GC-MS (ESI)**:** R.T: 9.698 min. MS: calculated: 298.2, found 298.1.

202 Wang, H.; Zhao, W.; Zhou, Y.; Duan, Z.; Mathey, F. *Eur. J. Inorg. Chem.* **2011**, *2011*, 4585-4589.

(*E*)-2-Bromo-2'-styryl-1,1'-biphenyl (26)

Diethyl phenylphosphonate (1.16 mL, 5.56 mmol, 1.2 equiv) was dissolved in dry THF (9 mL) and cooled to 0 °C before adding *n*-BuLi (2.0 mL, 2.5 M, 5.1 mmol, 1.1 equiv). After stirring for 15 minutes, a solution of 2'-bromo-[1,1'-biphenyl]-2-carbaldehyde (1.21 mg, 4.63 mmol, 1 equiv) in THF (9 mL) is added drop wise and the reaction is left stirring for 14 h. Water is added en the mixture extracted with diethyl ether, washed with brine, and concentrated. Flash chromatography (c-hexane) yields 1.41 g (88%) of a white powder.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 – 7.79 (m, 1H), 7.75 – 7.69 (m, 1H), 7.44 (dd, *J* = 8.3, 6.9 Hz, 1H), 7.37 (ddd, *J* = 7.2, 6.1, 1.5 Hz, 2H), 7.34 – 7.25 (m, 5H), 7.23 (dd, *J* = 7.7, 1.0 Hz, 2H), 7.06 (d, *J* = 16.2 Hz, 1H), 6.81 (d, *J* = 16.3 Hz, 1H).

2-(2'-Bromo-[1,1'-biphenyl]-2-yl)-1,3-dithiolane (27)

To a solution of 2'-bromo-[1,1'-biphenyl]-2-carbaldehyde (143 mg, 0.55 mmol, 1 equiv) in dichloromethane (5.5 mL) was added 1,2-ethanedithiol (55 µL, 0.55 mmol, 1 equiv) followed by borontrifluoride etherate (40 µL, 0.33 mmol, 0.6 equiv). When the reaction was finished (follow by TLC) more dichloromethane (10 mL) was added and the mixture was extracted with water, sodium bicarbonate solution and brine, before the mixture was concentrated. Flash chromatography (c-hexane) yields 120 mg (62%) of a white solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.35 – 7.23 (m, 3H), 7.09 (dd, *J* = 7.6, 1.4 Hz, 1H), 5.39 (s, 1H), 3.59 – 3.41 (m, 2H), 3.34 – 3.15 (m, 2H).

2-(2'-(Cyclohepta-2,4,6-trien-1-yl)-[1,1'-biphenyl]-2-yl)-1,3-dithiolane (28)

A solution of 2-(2'-bromo-[1,1'-biphenyl]-2-yl)-1,3-dithiolane (120 mg, 0.34 mmol, 1 equiv) in THF (1.5 mL) is cooled to -78 °C and *n*-BuLi (143 µL, 2.5 M, 0.36 mmol, 1.05 equiv) is added. After stirring for 40 minutes, tropylium tetrafluoroborate (121 mg, 0.68 mmol, 2 equiv) is added in one portion and the cooling removed. The mixture is poured directly onto a silica column after stirring for 14 h. Flash chromatography yields 97 mg (82%) of a white solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 (t, *J* = 8.6 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.47 – 7.23 (m, 5H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.47 – 6.41 (m, 2H), 6.25 (dt, *J* = 9.2, 3.1 Hz, 2H), 5.74 (t, *J* = 8.8 Hz, 2H), 5.38 (s, 1H), 5.21 (t, *J* = 7.9 Hz, 1H), 3.58 – 3.40 (m, 2H), 3.33 – 3.16 (m, 2H).

GC-MS (ESI)**:** R.T: 14.331 min. MS: calculated: 358.2, found 358.1.

(*E*)-1,2-Bis(4-methoxyphenyl)ethene (34)

This compound was made following a literature procedure.[203]

3,6-Dimethoxyphenanthrene (35)

This compound was made from 34 following a literature procedure.[204]

Retro-cyclopropanation from cyclopropa[*l*]phenanthrenes

A typical procedure is as follows:

E-Stilbene (18 mg, 0.1 mmol, 1 equiv), 1-phenyl-1a,9b-dihydro-1*H*-cyclopropa[*l*]phenanthrene (27 mg, 0.1 mmol, 1 equiv), and [(JohnPhos)Au(MeCN)]SbF_6 (3.9 mg, 5 μmol, 5 mol%) are added to a micro-wave vial and 1,2-dichloroethane (0.4 mL) is added. The vial is sealed and heated to 120 °C for 12 h, after which triethylamine (10 μL) is added and the mixture filtered over silica gel. The conversion is determined by ^{1}H NMR spectroscopy.

Cyclization retro-cyclopropanation cascade

A typical procedure is as follows:

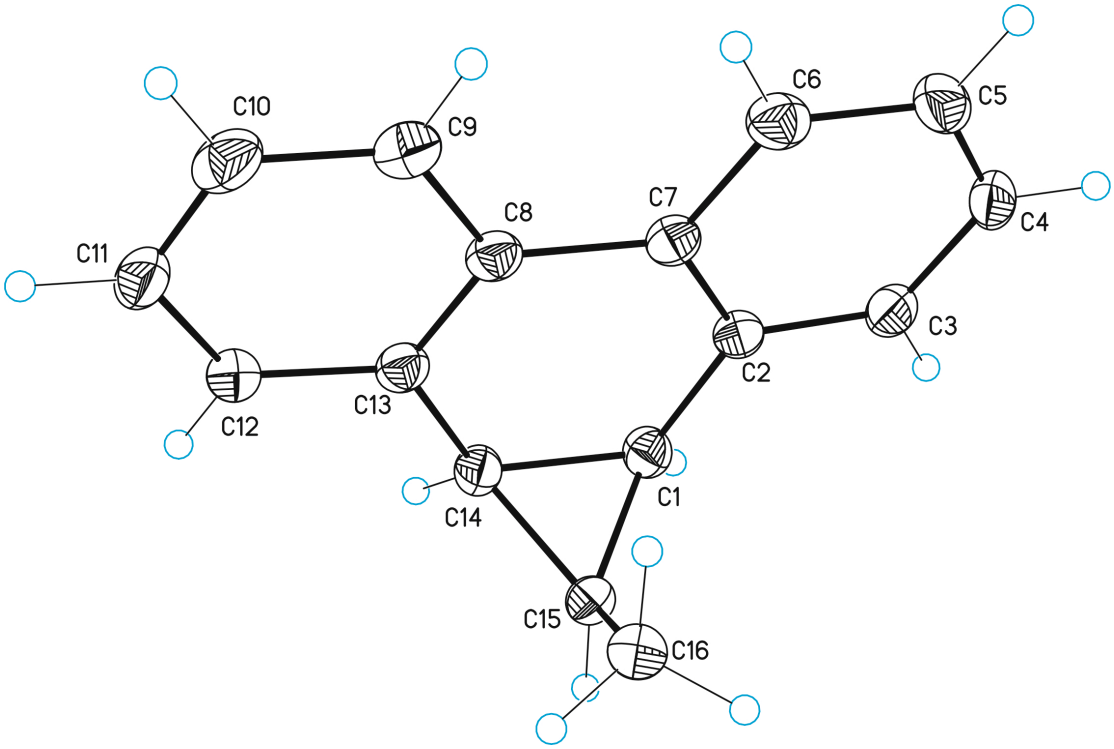
E-Stilbene (18 mg, 0.1 mmol, 1 equiv), 2-(cyclohepta-2,4,6-trien-1-yl)-2'-(2-methylprop-1-en-1-yl)-1,1'-biphenyl (30 mg, 0.1 mmol, 1 equiv), and [(JohnPhos)Au(MeCN)]SbF_6 (3.9 mg, 5 μmol, 5 mol%) are added to a micro-wave vial and 1,2-dichloroethane (0.4 mL) is added. The vial is sealed and heated to 120 °C for 12 h, after which triethylamine (10 μL) is added and the mixture filtered over silica gel. The conversion is determined by ^{1}H NMR spectroscopy.

203 Ogura, T.; Usuki, T. *Tetrahedron* **2013**, *69*, 2807-2815.
204 Harish R. Talele; Anju R. Chaudhary; Patel, P. R.; Bedekar, A. V. *Arkivoc* **2011**, *IX*, 15-37.

X-ray crystallography

Crystal structure determinations were carried out using a Bruker-Nonius diffractometer equipped with an APPEX 24K CCD area detector, a FR591 rotating anode with MoKa radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = –173 °C). Full-sphere data collection was used with w and j scans. Programs used: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solutions were achieved using direct methods as implemented in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters. ORTEP drawings are represented with 50% probability of the thermal ellipsoids.

Crystal data and structure refinement for 1q

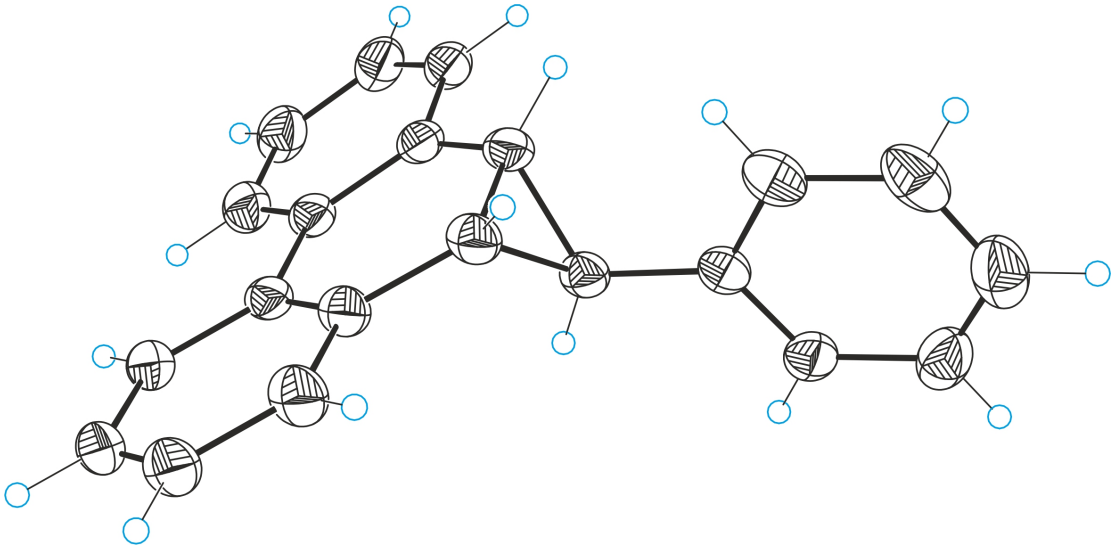


ORTEP drawings of **1q** with 50% probability of the thermal ellipsoids

Empirical formula	C16 H14	
Formula weight	206.27	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.0988(7) Å	a= 90.00 °.
	b = 5.4794(4) Å	b = 97.299(2) °.
	c = 18.3134(13) Å	g = 90.00 °.
Volume	1104.70(13) $Å^3$	
Z	4	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	440	
Crystal size	0.15 x 0.10 x 0.06 mm^3	

Theta range for data collection	2.04 to 29.98 °.
Index ranges	-15 <=h<=14 ,-7 <=k<=7 ,-25 <=l<=25
Reflections collected	36578
Independent reflections	2977 [R(int) = 0.0474]
Completeness to theta =29.98 °	92.299995%
Absorption correction	Empirical
Max. and min. transmission	0.9958 and 0.9896
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2977 / 0 / 146
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0524 , wR2 = 0.1251
R indices (all data)	R1 = 0.0774 , wR2 = 0.1362
Largest diff. peak and hole	0.304 and -0.217 e.$Å^{-3}$

Crystal data and structure refinement for 1u



ORTEP drawings of **1u** with 50% probability of the thermal ellipsoids

Empirical formula	C21 H16	
Formula weight	268.34	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 12.6579(7)Å	a= 90°.
	b = 19.8384(11)Å	b = 90°.
	c = 5.6765(3)Å	g = 90°.
Volume	1425.44(13) $Å^3$	
Z	4	
Density (calculated)	1.250 Mg/m^3	
Absorption coefficient	0.071 mm^{-1}	
F(000)	568	
Crystal size	0.40 x 0.25 x 0.15 mm^3	
Theta range for data collection	1.908 to 31.184°.	
Index ranges	-18<=h<=13,-28<=k<=28,-8<=l<=8	
Reflections collected	21744	

Independent reflections	4210[R(int) = 0.0272]
Completeness to theta =31.184°	94.5%
Absorption correction	Empirical
Max. and min. transmission	0.989 and 0.761
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4210/ 1/ 190
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0407, wR2 = 0.1078
R indices (all data)	R1 = 0.0475, wR2 = 0.1152
Flack parameter	x =2.9(10)

Largest diff. peak and hole 0.224 and -0.261 e.$Å^{-3}$

2.

Stereoselective *cis*-Vinylcyclopropanation via a Gold(I)-Catalyzed Retro-Buchner Reaction under Mild Conditions

*The work described in this chapter was performed in collaboration with **Dr. Philipp M. Holstein**, whom I would like to thank for performing part of the experiments.*

Introduction

Vinylcyclopropanes represent an important motif in natural products,[205] and have also found entry into active pharmaceutical ingredients (Figure 16).[206] More importantly, they are interesting synthons in organic chemistry,[207] as they readily undergo many synthetically useful transformations, such as rearrangements and cycloaddition reactions. The most notable reaction that vinylcyclopropanes can undergo is the *rearrangement to cyclopentenes* (Scheme 91). The aspects of this reaction are well studied and reviewed.[208]

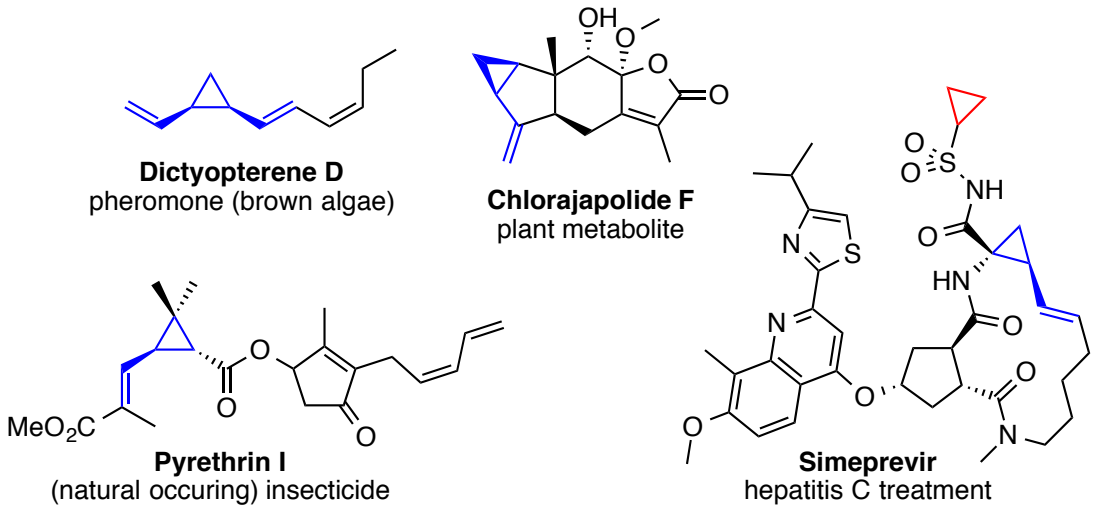


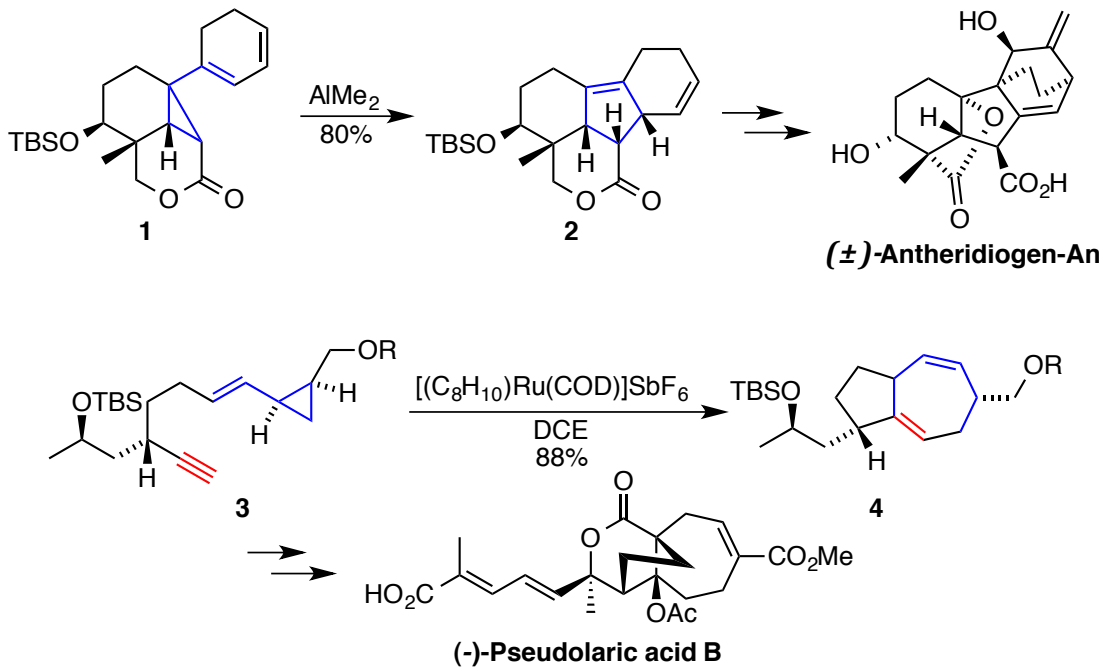
Figure 16. Examples of vinylcyclopropane containing natural or synthetic compounds.

205 a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589-8627. b) Chen, D. Y. K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631-4642. c) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625-1648. d) Faust, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2251-2253.

206 a) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712-8756. b) Bajaj, P.; Sreenilayam, G.; Tyagi, V.; Fasan, R. *Angew. Chem. Int. Ed.* **2016**, *55*, 16110-16114.

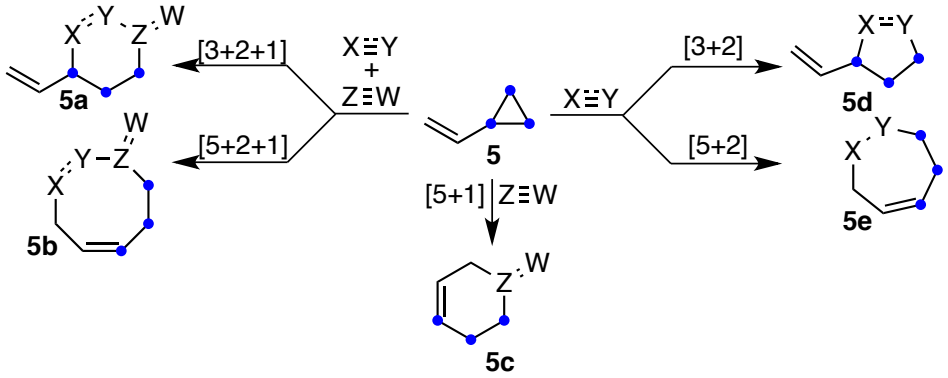
207 a) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969-2984. b) Ganesh, V.; Chandrasekaran, S. *Synthesis* **2016**, *48*, 4347-4380. c) Kulinkovich, O. G. In *Cyclopropanes in Organic Synthesis*; John Wiley & Sons, Inc: 2015, p i-x.

208 a) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197-1212. b) Hudlicky, T.; Reed, J. W. *Angew. Chem. Int. Ed.* **2010**, *49*, 4864-4876.



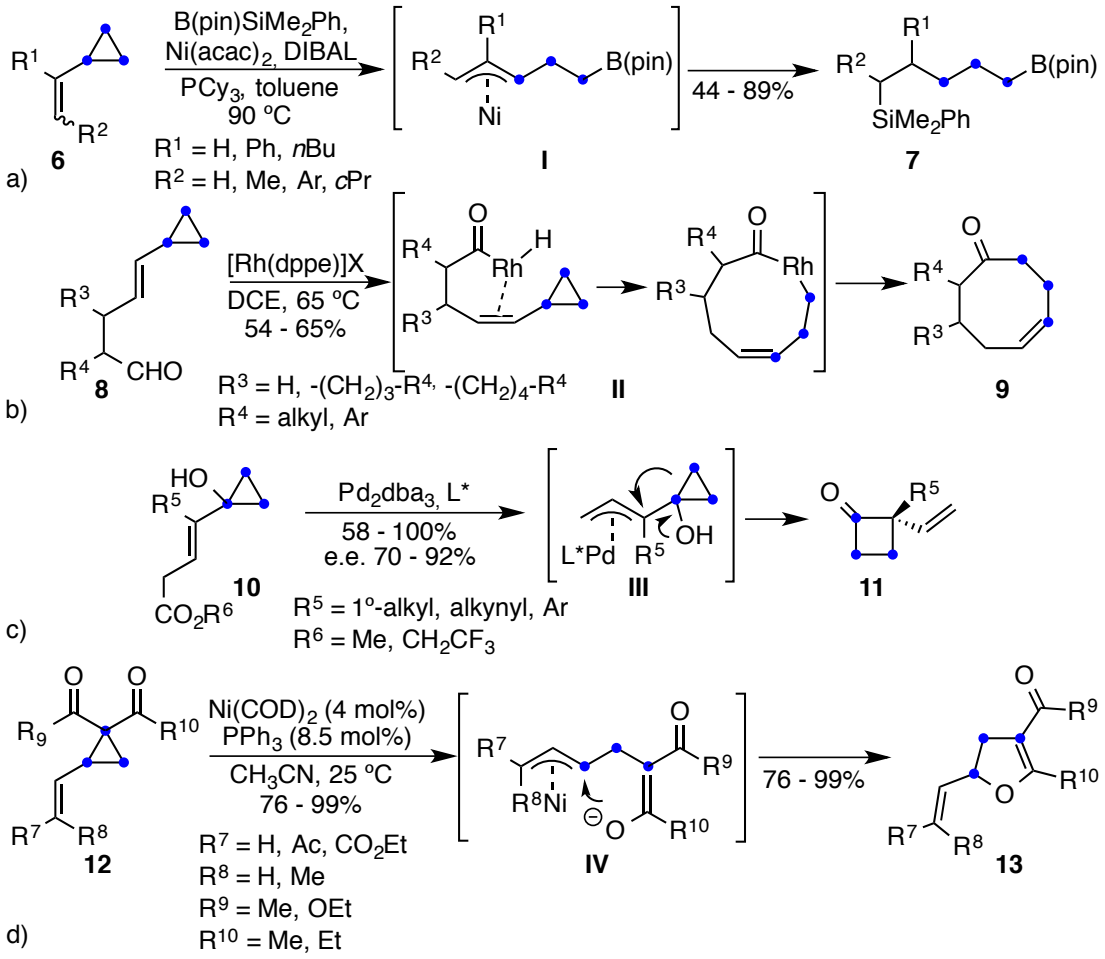
Scheme 91. *Vinylcyclopropane-cyclopentene rearrangement* in the synthesis of antheridiogen-An (top).[209] [5+2] cycloaddition in the synthesis of (-)-pseudolaric acid B (bottom).[210]

In recent years, many other reactions have been added to the palette, such as [3+n] and [5+n] cycloadditions (Scheme 92),[211] transition-metal catalyzed rearrangements[212] or other derivatizations (Scheme 93).



Scheme 92. [3+n] and [5+n] cycloadditions to vinylcyclopropanes.

209 Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574-5576.
210 Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2007**, *129*, 14556-14557.
211 a) Jiao, L.; Yu, Z.-X. *J. Org. Chem.* **2013**, *78*, 6842-6848. b) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *DOI 10.1021/acs.chemrev.6b00599*.
212 Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117-3179.



Scheme 93. Transition-metal catalyzed rearrangements or derivatizations: a) Ni-catalyzed silylboration.[213] b) Intramolecular hydroacylation.[214] c) Asymmetric Wagner-Meerwein shift[215] d) Ni-catalyzed rearrangement.[216]

The vinylcyclopropane was first introduced to the literature in 1896 by Gustavson as a byproduct in the formation of spiropentane.[217] It turned out, however, that the byproduct was actually methylcyclobutane.[218] In 1922, an authentic sample of vinylcyclopropane was finally isolated,[219] even though

213 Suginome, M.; Matsuda, T.; Yoshimoto, T.; Ito, Y. *Organometallics* **2002**, *21*, 1537-1539.
214 Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610-12611.
215 Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162-7163.
216 Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573-576.
217 Gustavson, G. J. *Prakt. Chem.* **1886**, *54*, 97.
218 Philipov, O. J. *Prakt. Chem.* **1916**, *93*, 162.
219 Demjanov, N. J.; Dojarenko, M. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 2718.

initially this discovery was met with moderate enthusiasm and was even described by some as "*incapable of existence"* until as late as 1937.[220]

Vinylcyclopropanes can be considered an activated class of cyclopropanes that compare well to 1,3-butadienes.[221] The bonds of cyclopropane have a relatively high *p* character and can therefore conjugate with the π-orbitals of the double bond (Figure 17). It has been shown by theoretical computations, photoelectron spectroscopy and electron-diffraction analysis that the σ-bond connecting the cyclopropane to the alkene is significantly shorter than expected and has a double bond character of about 13 to 15%. This attributes to the vinylcyclopropane´s enhanced reactivity.

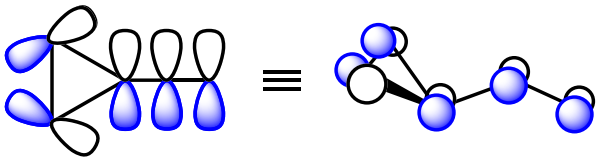


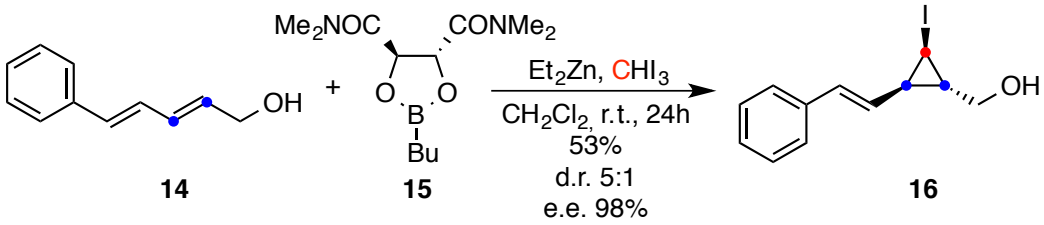
Figure 17. Conjugation of the cyclopropane orbitals with the orbitals of the π-bond according to the Walsh model.

Many methods have been developed for the synthesis of alkyl or aryl cyclopropanes, and nowadays many ways exist for their stereoselective formation.[222] Vinylcyclopropanes, on the other hand, have proven to be more challenging targets. Stereoselective syntheses mostly rely on the *Simmons-Smith reaction* or transition-metal-catalyzed decomposition of diazo compounds. In the case of the modified *Simmons-Smith reaction*, a dihydro- or halo-carbene is added to one of the alkenes of a 1,3-diene. A directing group dictates the regio- and enantioselectivity, while the stereoselectivity originates from the stereospecificity of the reaction (Scheme 94).

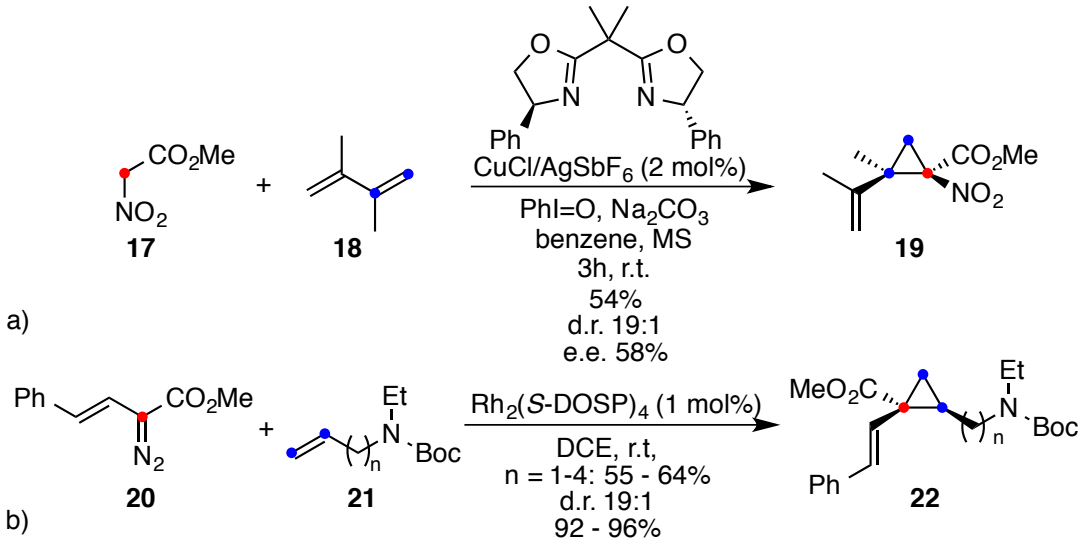
Transition-metal catalyzed reactions can take place on 1,3-dienes, or the vinylic part is already incorporated in the α,β-unsaturated diazo compound (Scheme 95). Only a handful of truly stereoselective methods exist. However, these

220 Whitmore, F. C. *Organic Chemistry*; D. van Nostrand: New York, 1937.
221 Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117-3179.
222 a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050. b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979-1029. c) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041-7095.

methods rely on the use of directing groups, pyrophoric or explosive reagents, which limit their use and scope.



Scheme 94. Stereo- and enantioselective formation of vinylcyclopropanes.[223]



Scheme 95. Stereo- and enantioselective synthesis of vinylcyclopropanes by addition of a) Carbene to 1,3-diene.[224] b) Vinylic carbene to alkene.[225]

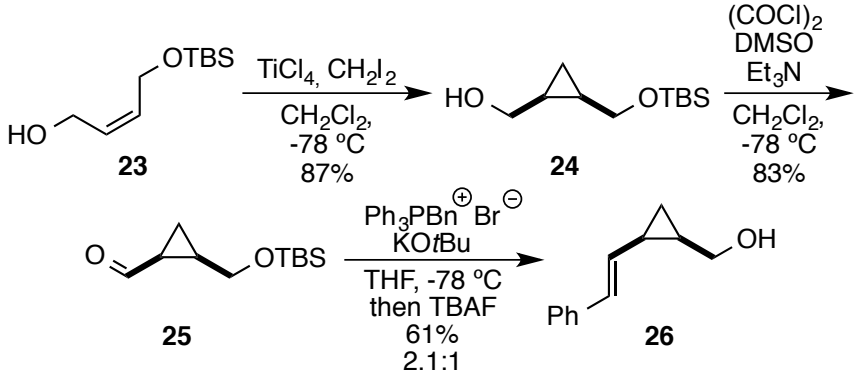
Despite of these important developments, highly stereoselective methods for the synthesis of vinylcyclopropanes that do not rely on the use of diazo reagents still remain scarce. In general, diastereopure vinylcyclopropanes are accessed either in a stepwise manner through derivatization of functionalized cyclopropane

223 Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem. - Eur. J.* **2009**, *15*, 11829-11832.

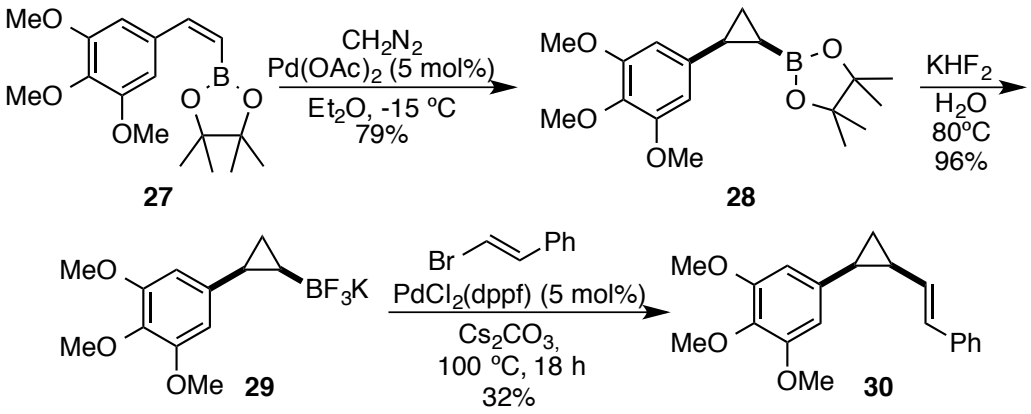
224 Moreau, B.; Alberico, D.; Lindsay, V. N. G.; Charette, A. B. *Tetrahedron* **2012**, *68*, 3487-3496.

225 Denton, J. R.; Cheng, K.; L. Davies, H. M. *Chem. Commun.* **2008**, 1238-1240.

building blocks, either by Wittig alkenylation (Scheme 96),[226] or metal-catalyzed cross coupling (Scheme 97).[227]



Scheme 96. Synthesis of diastereopure vinylcyclopropanes via Simmons-Smith reaction followed by Swern oxidation and Wittig alkenylation.[226b]



Scheme 97. Synthesis of diastereopure vinylcyclopropanes via Suzuki coupling.[227c]

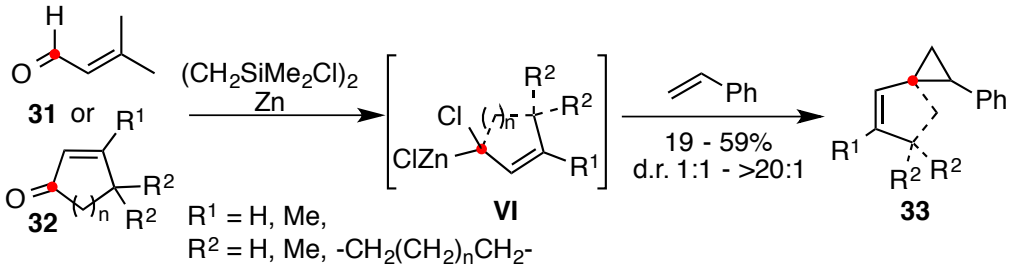
In the recent years, much effort has been made to develop safer and more efficient methods for the formation of cyclopropanes. Among others, metal carbenes or carbenoids have been generated from α,β-unsaturated carbonyls (Scheme 98), [228] tosylhydrazones (Scheme 99), [229] cyclopropenes (Scheme

226 a) Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985-6988. b) Mauleón, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 4513-4520.

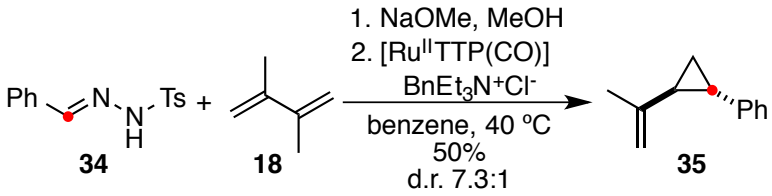
227 a) Zhou, S.-M.; Yan, Y.-L.; Deng, M.-Z. *Synlett* **1998**, *1998*, 198-200. b) Zhou, S.-m.; Deng, M.-z. *Tetrahedron Lett.* **2000**, *41*, 3951-3954. c) Ty, N.; Pontikis, R.; Chabot, G. G.; Devillers, E.; Quentin, L.; Bourg, S.; Florent, J.-C. *Bioorg. Med. Chem.* **2013**, *21*, 1357-1366.

228 a) Motherwell, W. B.; Roberts, L. R. *J. Chem. Soc., Chem. Commun.* **1992**, 1582-1583. b) Motherwell, W. B.; Roberts, L. R. *Tetrahedron Lett.* **1995**, *36*, 1121-1124.

100),[230] or propargylic ethers[231] or esters (Scheme 101)[232] and subsequent intermolecular, cyclopropanation of alkenes has been demonstrated by these methods.



Scheme 98. Formation of zinc carbenoids from α,β-unsaturated carbonyls.[228a]



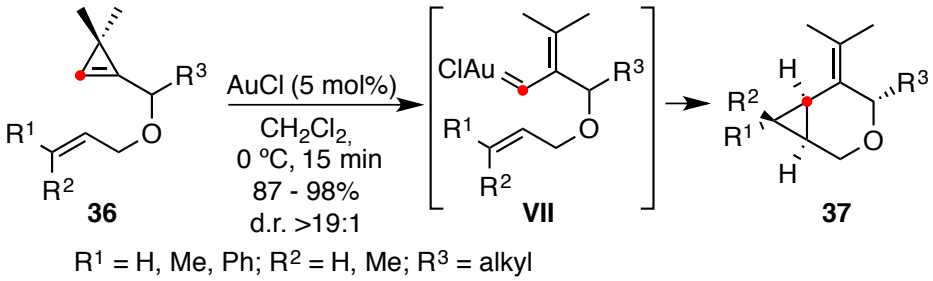
Scheme 99. Formation of vinylcyclopropanes from tosylhydrazones mediated by ruthenium-porphyrine complexes.[229c]

229 a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785-2788. b) Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433-9440. c) Zhang, J.-L.; Hong Chan, P. W.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 8733-8737.

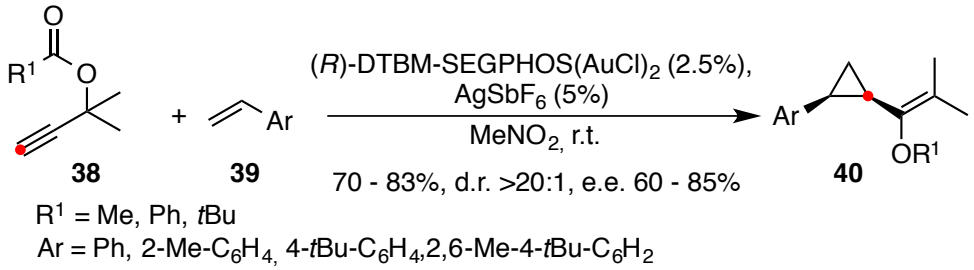
230 a) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2008**, 6405-6407. b) González, M. J.; González, J.; López, L. A.; Vicente, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 12139-12143. c) Miege, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 4144-4147. d) Miege, F.; Meyer, C.; Cossy, J. *Chem. - Eur. J.* **2012**, *18*, 7810-7822. e) Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* **2015**, *48*, 1021-1031 Qian, D.; Zhang, J. *Chem. Soc. Rev.* **2015**, *44*, 677-698.

231 Sogo, H.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 10057-10060.

232 a) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513. b) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003. c) Sperger, C. A.; Tungen, J. E.; Fiksdahl, A. *Eur. J. Org. Chem.* **2011**, *2011*, 3719-3722. d) Iqbal, N.; Sperger, C. A.; Fiksdahl, A. *Eur. J. Org. Chem.* **2013**, *2013*, 907-914.



Scheme 100. Formation of vinylcyclopropanes via the activation of cyclopropenes by gold(I).[233]



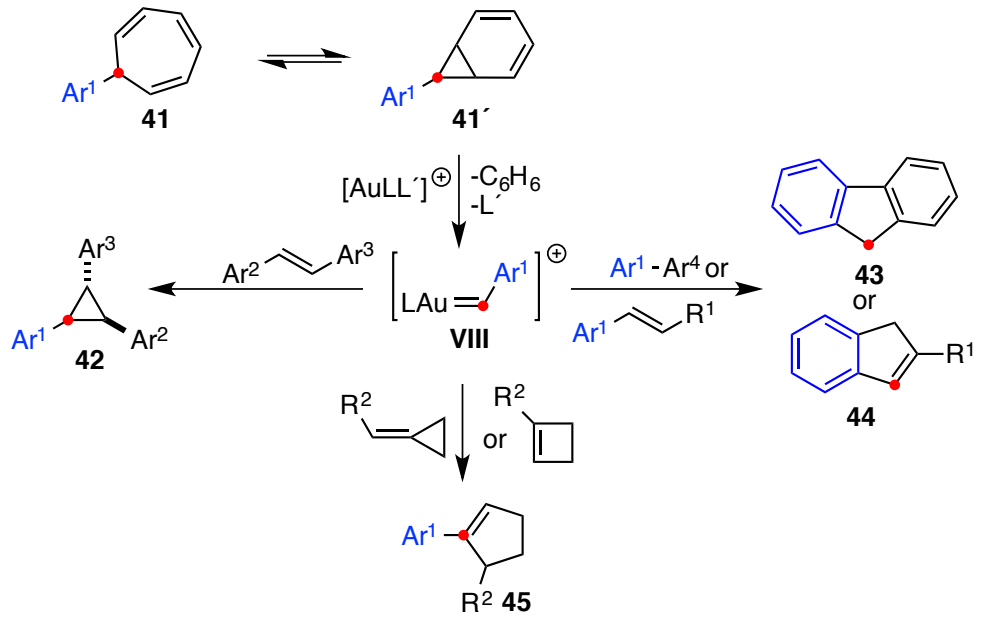
Scheme 101. Alternative methods for the formation of transition-metal carbenes for cyclopropanation reactions.[234]

We recently discovered that electrophilic gold(I) complexes are able to cleave two-carbon bonds of norcaradienes, which are in equilibrium with more stable cycloheptatrienes, to form gold(I) carbenes *in situ* (Scheme 102).[235] Starting from readily available 7-aryl substituted cycloheptatrienes, the retro-cyclopropanation reaction leads to aryl-substituted gold(I) carbenes, which undergo cyclopropanation with alkenes,[235b] intramolecular Friedel-Craft-type reactions,[235d] and [4+1] cycloadditions with methylenecyclopropanes or cyclobutenes.[235c]

233 Miege, F.; Meyer, C.; Cossy, J. *Chem. - Eur. J.* **2012**, *18*, 7810-7822.

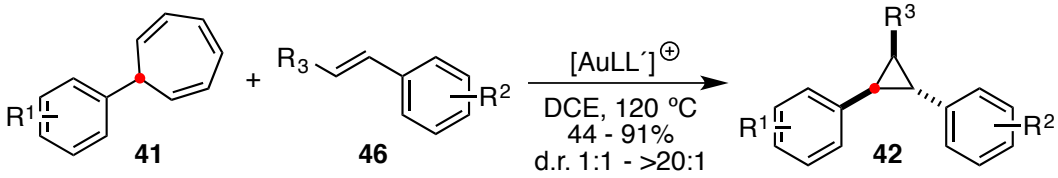
234 Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

235 a) Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881-11883. b) Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955. c) Wang, Y.; Muratore, M. E.; Rong, Z.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 14022-14026. d) Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801-809.



Scheme 102. Formation of aryl gold carbenes via the retro-Buchner reaction, and subsequent transformations.

The cyclopropanation of alkenes with aryl-cycloheptatrienes afforded bis- or tris-arylcycloropanes in moderate to good yield (Scheme 103). The stereoselectivity varied strongly depending on the aryl substituents but spanned from poor to excellent (1:1 to >20:1). The major product was determined to be the *trans*-isomer, at that time, for all compounds. However, the scope remained limited to bis- and tri-arylcyclopropanes with alkyl, methoxy, and halide substituents.

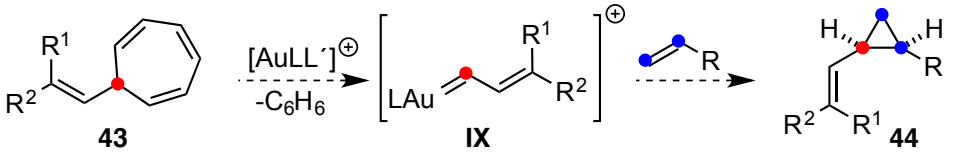


R^1 = H, 4-OMe, 4-halo, polyaromatic
R^2 = H, 2-Me, 3-NO_2, 4-Me, 4-*t*Bu, 4-CF_3, 4-Cl
R^3 = H, Me, Ph

Scheme 103. Formation of bis- or tris-arylcyclopropanes from 7-aryl cycloheptatrienes derivatives via the retro-Buchner reaction.

We reasoned that related vinyl gold carbenes could be formed in a similar manner from 7-alkenyl cycloheptatrienes to generate vinylcyclopropanes (Scheme 104). This gold carbene could benefit from increased stabilization from the vinylic π-system, and would therefore be easier to generate. Performing the

reaction at milder conditions would allow the system to be more functional-group tolerant and synthetically more interesting compounds could be prepared.



Scheme 104. The formation of vinyl gold carbenes via the retro-Buchner reaction for the preparation of 7-alkenyl cycloheptatriene derivatives.

Thus, we decided to investigate the synthesis of 7-alkenyl cycloheptatriene derivatives, which would be tested for the formation of vinyl gold(I) carbenes and the preparation of vinylcyclopropanes.

Objectives

The objective of the work summarized in this chapter was to study the formation and reactivity of 7-alkenyl cycloheptatrienes. Due to the increased stabilization by the vinylic π-system, the generation of the gold(I) carbene might be achieved under milder conditions.

The use of alkenyl gold carbenes was investigated in cyclopropanation reactions to form vinylcyclopropanes, which serve as important building blocks or synthetic intermediates.

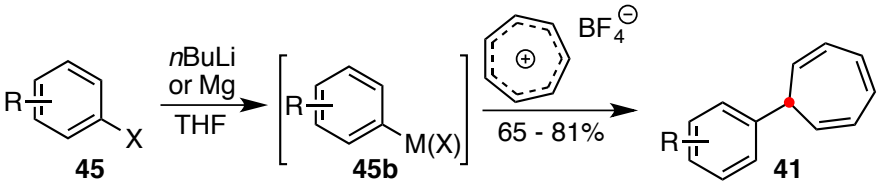
A simple, functional-group tolerant method for the generation of the desired 7-alkenyl cycloheptatrienes from readily available starting material would greatly enhance the applicability of this chemistry and was hence investigated.

And lastly, new insights into the reactivity and selectivity of gold carbenes in the cyclopropanation reaction were obtained by investigating a divers scope of substrates.

Results and Discussion

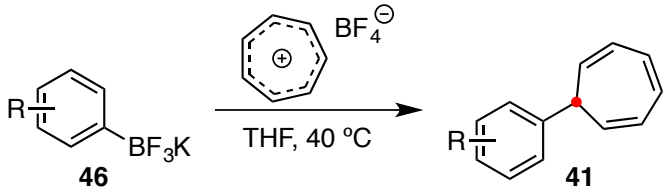
Synthesis of 7-alkenyl cycloheptatriene derivatives

The methods of choice for the preparation of aryl-cycloheptatrienes **41** are either lithium-halogen exchange, or formation of Grignard reagents from aryl halides followed by the addition of tropylium tetrafluoroborate (Scheme 105).[236]



Scheme 105. Synthesis of 7-aryl cycloheptatriene reagents from aryl halides.[236]

For a few examples, potassium trifluoroborate salts **46** could function as an appropriate nucleophile when heated in THF in the presence of tropylium tetrafluoroborate (Scheme 106).[236,237]

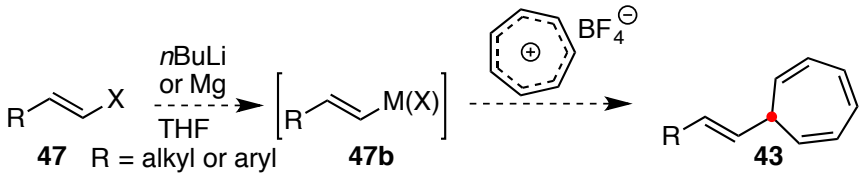


Scheme 106. Synthesis of 7-aryl cycloheptatriene reagents from potassium aryl trifluoroborates.

For the formation of alkenyl-cycloheptatrienes, on the other hand, these methods are not as convenient (Scheme 107). Compared to aryl bromides **45**, alkenyl bromides **47** are not as readily available, can have low boiling points which makes handling of the reagents more complicated, and might pose stability and storage problems. The lithium-halogen exchange or formation of Grignard reagents for alkenyl bromides has some literature precedents but methods for their preparation are more scarce.

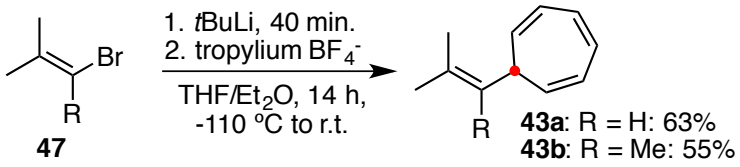
236 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

237 Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801-809.



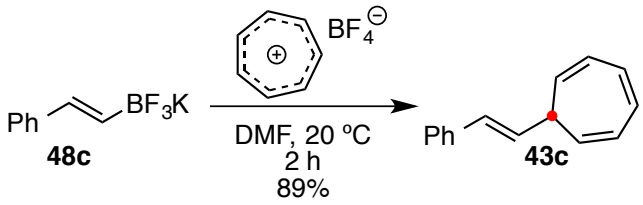
Scheme 107. Synthesis of 7-alkenyl cycloheptatriene derivatives from alkenyl halides by lithium-halogen exchange or formation of Grignard reagents.

Isocrotyl cycloheptatriene (**43a**) could be synthesized by lithium-halogen exchange of isocrotyl bromide, followed by the addition of tropylium tetrafluoroborate (Scheme 108). Varying quantities of an inseparable byproduct were always obtained. The exact cause is unknown but the impurity is probably formed through a series of [1,5]-H migrations. Careful control of the reaction conditions and caution during the work-up did not improve the isolated yields.



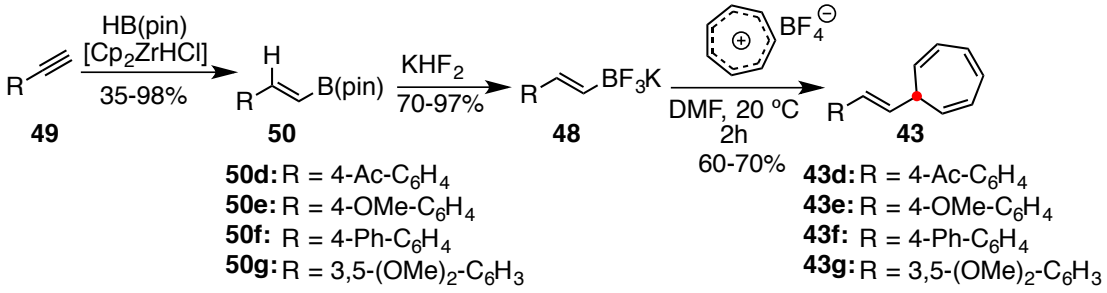
Scheme 108. Synthesis of 7-isocrotyl cycloheptatriene derivatives by lithium-halogen exchange of alkenyl bromides.

In search of a more reliable method for the formation of alkenyl-cycloheptatrienes, we contemplated a transition-metal catalyzed coupling of alkenyl bromides or alkenyl trifluoroborate salts with tropylium. In the preliminary investigations, tropylium tetrafluoroborate, tetrakis-(triphenylphosphine)palladium(0), and potassium styrenyl trifluoroborate (**48c**) or β-bromostyrene were mixed in DMF and stirred at room temperature. Remarkably, the reaction between tropylium and Molander salt **48c** finished in a mere two hours. A control experiment showed that the reaction performed equally well in the absence of palladium catalyst, and proceeds through a simple nucleophilic attack (Scheme 109).



Scheme 109. Synthesis of 7-alkenyl cycloheptatriene derivatives via potassium alkenyl trifluoroborates

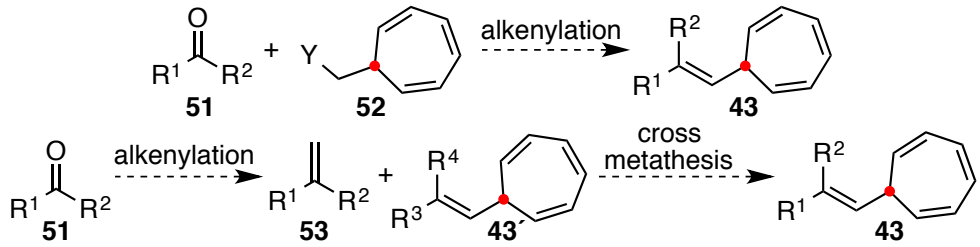
Despite having found an improved method for the formation alkenyl-cycloheptatrienes, its application is still restricted by the limited commercial availability of potassium alkenyl-trifluoroborate salts. Fortunately, these Molander salts can be easily obtained from boronic acid or ester derivatives **50**,[238] of which many derivatives are available. Other derivatives could be formed by hydrozirconation/borylation of alkynes (Scheme 110). However, the use of terminal alkynes allows variation at just a single position, while yields were poor to moderate for the hydroboration except in a few cases.



Scheme 110. Formation of potassium alkenyl trifluoroborates for the synthesis of 7-alkenyl cycloheptatrienes.

In order to find a more general and robust method for the synthesis of 7-alkenyl cycloheptatriene derivatives, an alkenylation reaction was considered as the ideal method. Aldehydes and ketones are widely-available, cheap starting materials with two substituents that can be varied. Several well-studied strategies exist for the direct alkenylation of carbonyl compounds. In addition, these strategies can also be employed to obtain terminal alkenes for cross metathesis (Scheme 111).

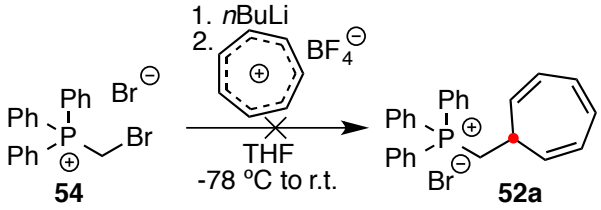
238 Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956-9960.



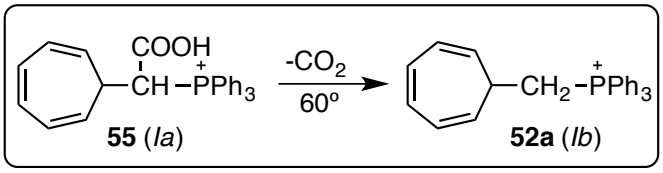
Scheme 111. The use of alkenylation or cross metathesis strategies to prepare 7-alkenyl cycloheptatriene derivatives from readily-available aldehydes and ketones.

The first attempt of the development of a suitable *Wittig* reagent stranded with synthesis of the methyl-cycloheptatriene triphenylphosphonium salt **52a** (Scheme 112), which decomposed during the reaction. A similar observation had previously been made by Ponti and co-workers.[239] This group had also studied the relation between the stability of cycloheptatrienylidens and different stabilizing carbonyl substituents. Interestingly, the isolation of the desired Wittig reagent **52a** was also reported, claiming "*gentle heating of the easily available (carboxy)(2,4,6-cycloheptatrien-I-yl)methyl triphenylphosphonium tetrafluoro-borate (Ib) in ethanol led us to the desired Ia*" (Scheme 113).[240] Following the reported procedure, the compound was stabilized by the addition of an ester moiety, which helped us obtain **57** (Scheme 114).[241] However, we were unable to perform the saponification to obtain the intermediate **55** that can undergo decarboxylation to yield the final Wittig reagent.[242] To the best of our knowledge, there are no reported procedures to perform this transformation. Alternatively, starting with the carboxylic acid functionality already in place, we were unable to add the cycloheptatriene (Scheme 114).

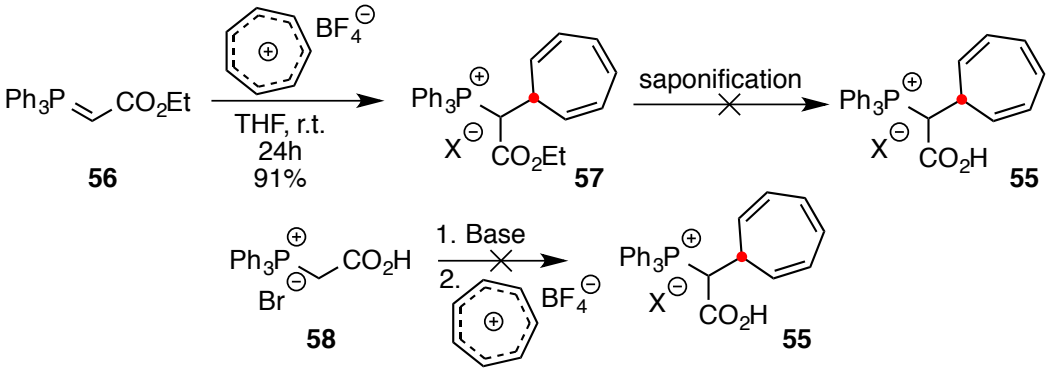
239 Cavicchio, G.; D'Antonio, M.; Gaudiano, G.; Marchetti, V.; Ponti, P. P. *Tetrahedron Lett.* **1977**, *18*, 3493-3496.
240 Cavicchio, G.; Gaudiano, G.; Ponti, P. P. *Tetrahedron Lett.* **1980**, *21*, 2333-2336.
241 Bestmann, H. J.; Schulz, H. *Chem. Ber.* **1962**, *95*, 2921-2927.
242 Cavicchio, G.; Gaudiano, G.; Ponti, P. P. *Tetrahedron Lett.* **1980**, *21*, 2333-2336.



Scheme 112. Attempted synthesis of a suitable Wittig reagent.



Scheme 113. The formation of the desired Wittig reagent by decarboxylation as reported by Ponti.[242]



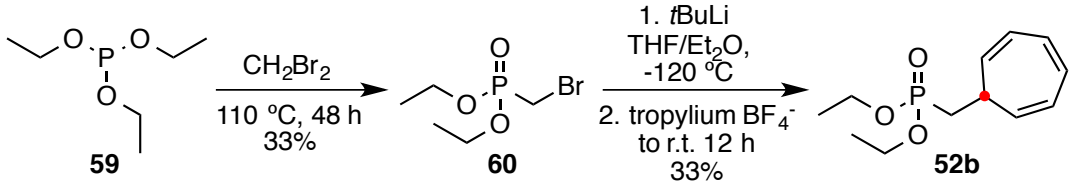
Scheme 114. Failed attempts to obtain the carboxylic acid intermediate.

Using an electron-withdrawing phosphonate rather than phosphonium salts could prevent spontaneous decomposition of the alkenylation reagent. Indeed, the corresponding *Horner-Wadsworth-Emmons* reagent **52b** was synthesized and isolated as a stable compound (Scheme 115).[243] Unfortunately, the subsequent alkenylation did not proceed in one step but had to be carried out stepwise (Scheme 116). The α-hydroxyphosphonate **61a** was formed after the nucleophilic attack by the ylid but without an additional electron-withdrawing α-substituent, the reaction stalled before giving the oxaphosphetane **61c**.[244] The α-hydroxyphosphonate **61a** was isolated and subsequently saponificated. Then,

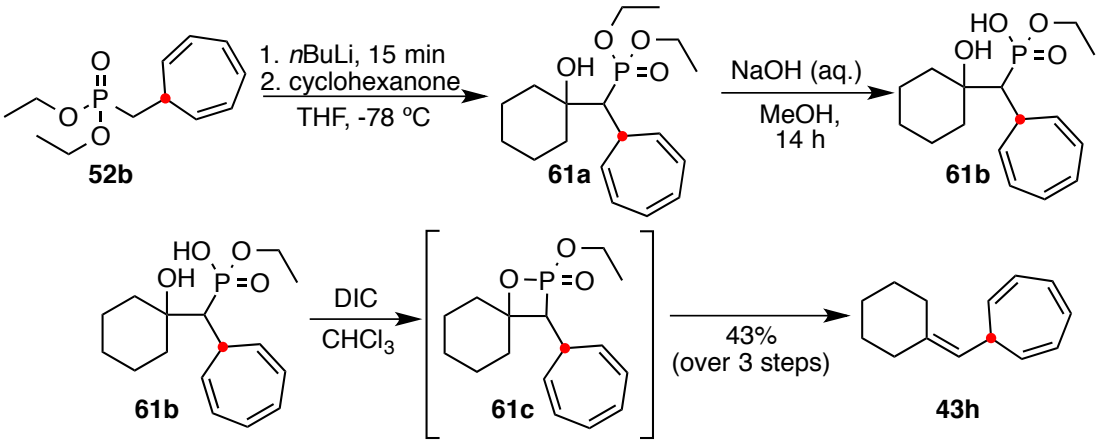
243 a) Al-Hamouz, O. C. S.; Ali, S. A. *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 3580-3591. b) Coutrot, P.; Youssefi-Tabrizi, M.; Grison, C. *J. Organomet. Chem.* **1986**, *316*, 13-18.

244 Reichwein, J. F.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 1821-1824.

the oxaphosphetane was formed by condensation of the α-hydroxyphosphonate followed by spontaneous elimination to give the desired alkene **43h**. Despite the elaborated procedure, the overall yield and *E*-selectivity was not disappointing. Using the more electron-deficient phosphonate developed by Still and Gennari, the alkenylation might take place in a single step, however, the *Still-Gennari modification* is used to form the *Z*-isomer exclusively.[245]



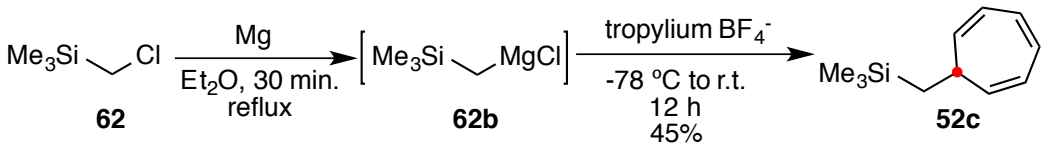
Scheme 115. Synthesis of a suitable Horner-Wadsworth-Emmons reagent **52b**.



Scheme 116. Formation of a 7-alkenyl cycloheptatriene derivative by the Horner-Wadsworth-Emmons reaction of a ketone.

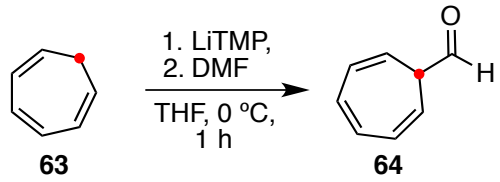
Still in search of a more user-friendly protocol for the synthesis of cycloheptatriene derivatives, the *Peterson* reagent **52c** was synthesized (Scheme 117). The reagent displayed a limited stability and could not be stored. Besides, **52a** did not react as a nucleophile in the alkenylation reaction,[246] leading solely to the recovery of starting material.

245 Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.
246 Beniazza, R.; Desvergnes, V.; Landais, Y. *Org. Lett.* **2008**, *10*, 4195-4198.



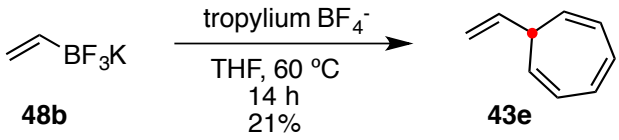
Scheme 117. Synthesis of the Peterson reagent **52c**.

The limited stability of the reagents described above can partially be accredited to the cycloheptatriene. Therefore, a method were the alkenylation partners are inverted was investigated, which required the synthesis of cycloheptatriene-7-carbaldehyde (**64**).[247] Although the synthesis of the aldehyde seemed successful, the compound proved extremely prone to decomposition and could not be used for further chemistry (Scheme 118).



Scheme 118. Synthesis of cycloheptatriene-7-carbaldehyde **64**.

The unsubstituted vinyl cycloheptatriene (**43e**), intended for the generation of derivatives via *cross metathesis*, was isolated in poor yield and rapidly decomposed (Scheme 119). Nevertheless, the compound was tested in the cyclopropanation reaction but heating **43e** under retro-Buchner conditions solely led to its decomposition. Other vinyl cycloheptatrienes with simple alkyl derivatives were more stable and could be obtained in higher yield. However, these compounds were finally not tested in cross-metathesis reactions.

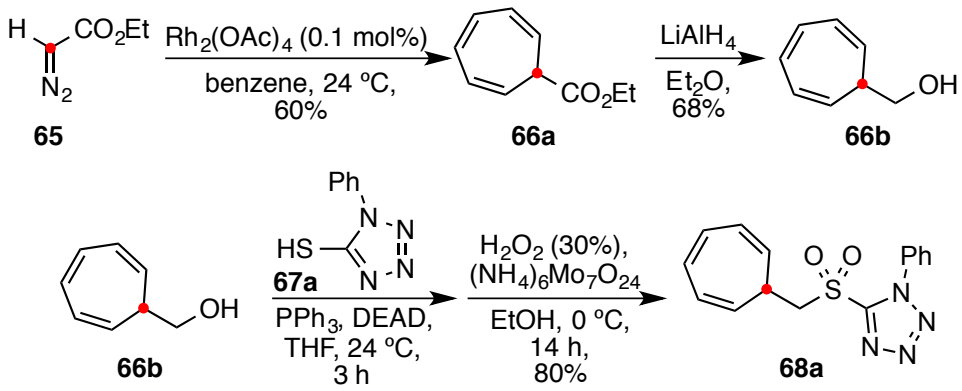


Scheme 119. Synthesis of vinyl derivative **43e**.

The *Julia-Kocienski reaction* is known to give good selectivities in alkenylation reactions.[66,67] Moreover, the required reagent can be synthesized from known or readily available intermediates. The reagent was prepared as a bench stable and

247 Weitemeyer, C.; Preuß, T.; de Meijere, A. *Chem. Ber.* **1985**, *118*, 3993-4005.

easy to manipulate solid through a one-pot Mitsunobu/oxidation sequence from 1-hydroxymethyl-2,4,6-cycloheptatriene (**66b**) and 1-phenyl-1*H*-tetrazole-5-thiol (**67a**) (Scheme 120).[248] 1-hydroxymethyl-2,4,6-cycloheptatriene (**66b**) was obtained via the rhodium-catalyzed Buchner reaction of benzene to form ester **66a**,[249] followed by reduction with lithium aluminum hydride.[250]



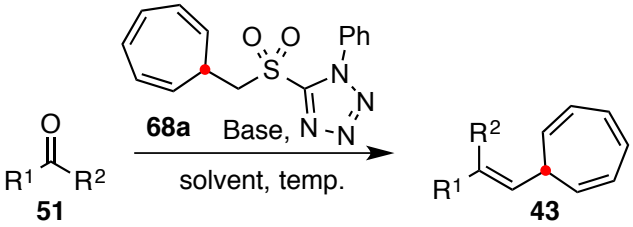
Scheme 120. Synthesis of Julia-Kocienski reagent **68a**.

The yield for the oxidation to the sulfonyl was strongly dependent on the quality of the hydrogen peroxide. Only the use of a fresh batch (~30%) led to good results. If an excess of a lower quality batch was used instead, the reaction would stop after oxidation to the sulfoxide, which could be isolated and resubmitted to the reaction conditions to yield the desired sulfonyl **68a**.

Good results were obtained for the alkenylation when the reaction was performed according to literature conditions (Table3, entry 1).[251] In order to generalize the transformation, several reaction parameters such as base, temperature, and solvent, were tailored to find optimal conditions for all our substrates. The reaction gave an excellent yield for benzaldehydes when NaHMDS was used in THF at -78 °C (Table 3, entry 1). The *E/Z* ratio was good, giving predominantly the *E*-isomer, while other solvents had a deleterious effect on the ratio (Table 3, entry 3 – 5). Surprisingly, the reaction in DME failed to yield any product despite of what was reported (Table 3, entry 2).[251]

248 Aïssa, C. *J. Org. Chem.* **2006**, *71*, 360-363.
249 Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873-876.
250 Kerber, R. C.; Ehntholt, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2927-2934.
251 Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, *1998*, 26-28.

Table 3. Optimization of the alkenylation reaction with Julia-Kocienski reagent **68a**.



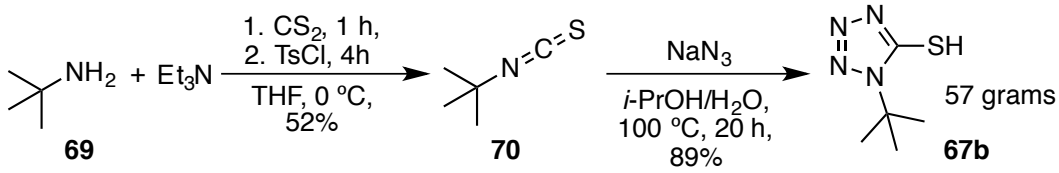
	51 (R^1, R^2)	Base	Temp	Solvent	Yield[c]	*E/Z*[c]
1	4-$MeOC_6H_4$, H	NaHMDS	-78 °C	THF	97%	20:1
2	4-$MeOC_6H_4$, H	NaHMDS	-78 °C	DME	n.r.	-
3	4-$MeOC_6H_4$, H	NaHMDS	-78 °C	DMF	53%	5:1
4	4-$MeOC_6H_4$, H	NaHMDS	-78 °C	DMF/HMPA	59%	6:1
5	4-$MeOC_6H_4$, H	NaHMDS	-78 °C	MTBE	41%	2.3:1
6	4-$MeOC_6H_4$, H	KHMDS	-78 °C	THF	71%	6:1
7	**4-$MeOC_6H_4$, H**	**LiHMDS**	**-78 °C**	**THF**	**88%**	**>25:1**
8	4-$MeOC_6H_4$, H	LDA	-78 °C	THF	30%	-
9	4-$MeOC_6H_4$, H	*n*-BuLi	-78 °C	THF	-	-
10	-$(C_2H_4)_2O$	NaHMDS	-78 °C	THF	n.r.	-
11	-$CH_2(CH_2)_3CH_2$-	NaHMDS	-78 °C	THF	n.r.	-
12[b]	-$(C_2H_4)_2O$	Cs_2CO_3	70 °C	THF	n.r.	-
13[b]	-$CH_2(CH_2)_3CH_2$-	Cs_2CO_3	70 °C	THF	n.r.	-

[a] To a solution of **68a** (0.4 mmol) and **51** (0.4 mmol) in solvent (2 mL) at -78 °C was added base (0.4 mmol). The cooling is removed after 10 minutes and the mixture is warmed to room temperature. [b] **68a** (0.4 mmol), **51** (0.4 mmol), base (0.8 mmol) were dissolved in THF and heated to 70°C for 14 h. [c] Analyzed by ^{1}H NMR of the reaction crude with diphenylmethane as IS.

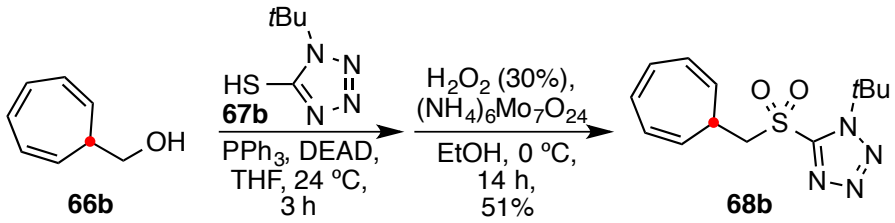
Moving to the larger potassium counter ion led to a decrease in yield and was detrimental for the selectivity (Table 3, entry 6), inspiring us to opt for the smaller lithium cation instead. Indeed, the us of LiHMDS led to excellent selectivity while maintaining a high yield (Table 3, entry 7). Stronger lithium bases led to poor results or even decomposition (Table 3, entry 8 and 9). It is interesting to remark here that the pK_a of the Julia-Kocienski reagent is estimated to lie around 24, which is perfectly matched by the HMDS bases´ strength (pK_a ~26). The reagent was conveniently deprotonated by LiHMDS at -78 °C and the desired cycloheptatriene derivatives were formed from aldehydes essentially as a single isomer. On the other hand, when similar conditions were

used for enolizable ketones, only starting material was recovered (Table 3, entry 10 and 11). Reported conditions, where several equivalents of cesium carbonate were used at elevated temperatures, gave the same outcome (Table 3, entry 12 and 13).[252]

Julia-Kocienski reagents bearing a *tert*-butyl substituent on the tetrazole are reported to be more stable under basic conditions, because the ylid cannot react with itself due to steric hindrance.[253] This has the advantage that the ylid can be pre-formed and subsequently added to a chilled solution of carbonyl compound, which allows for a better functional-group tolerance. It would also allow the reaction to be run with an excess of base, which can be used to overcome the problems observed for enolizable ketones. The required tetrazole **67b** is not commercially available and was synthesized following a literature procedure in good yield on a 57g scale (Scheme 121).[254] Then, following a similar procedure as before, the *tert*-butyl Julia-Kocienski reagent **68b** was obtained in reasonable yield on a multi-gram scale (Scheme 122). Compound **67b** is poorly soluble THF, which led to a significant amount of homo coupling for **66b**, reducing the overall yield. Better yields were obtained in a small-scale reaction when CH_2Cl_2 was used as co-solvent.



Scheme 121. Synthesis of 1-*tert*-butyl-1*H*-tetrazole-5-thiol (**67b**).

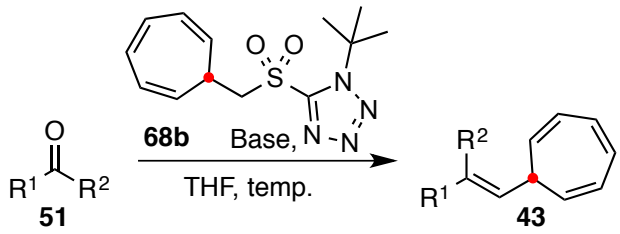


Scheme 122. Synthesis of Julia-Kocienski reagent **68b**.

252 Aïssa, C. *J. Org. Chem.* **2006**, *71*, 360-363.
253 Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, *2000*, 365-366.
254 Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. *Tetrahedron* **2010**, *66*, 5089-5100.

During the alkenylation reaction, a slightly reduced yield and selectivity were observed when reagent **68b** was used under previously optimized conditions for aldehydes (Table 4, entry 1), which is consistent with the existing literature.[253] With modified conditions, using two equivalents of the Julia-Kocienski reagent and three equivalents of base, alkenes could be obtained from enolizable ketones in good yield (Table 4, entry 2 and 6). Despite what was reported, performing the reaction at higher temperatures did not facilitate the transformation (Table 4, entry 3 and 5). Interestingly, when a sodium base was used, the yield was greatly reduced although it led to improved yields for the other Julia-Kocienski reagent **68a** (Table 4, entry 4 and 7).

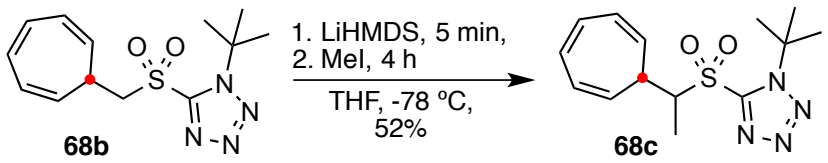
Table 4. Optimization of alkenylation conditions using Julia-Kocienski reagent **68b**.



	51 (R^1,R^2)	Base	Temp	Solvent	Yield	*E/Z*
1	4-$MeOC_6H_4$	LiHMDS	-78 °C	THF	83%	24:1
2	**-$CH_2(CH_2)_3CH_2$-**	**LiHMDS**	**-78 °C**	**THF**	**66%**	**-**
3	-$CH_2(CH_2)_3CH_2$-	LiHMDS	-40 °C	THF	65%	-
4	-$CH_2(CH_2)_3CH_2$-	NaHMDS	-78 °C	THF	29%	-
5	-$CH_2(CH_2)_3CH_2$-	NaHMDS	-40 °C	THF	13%	-
6	**-$(C_2H_4)_2O$**	**LiHMDS**	**-78 °C**	**THF**	**86%**	**-**
7	-$(C_2H_4)_2O$	NaHMDS	-78 °C	THF	26%	-

To a solution of **68b** (0.4 mmol) and **51** (0.4 mmol) in solvent (2 mL) at -78 °C was added base (0.4 mmol). The cooling is removed after 10 minutes and the mixture is warmed to room temperature. Yield determined by ^1H NMR analyzed of the crude with diphenylmethane as IS.

A third reagent was synthesized to investigate the potential of forming tetra-substituted alkenyl cycloheptatrienes (Scheme 123). Treatment of **68b** with LiHMDS at -78 °C followed by the addtion of iodomethane afforded the disubstituted reagent **68c**.

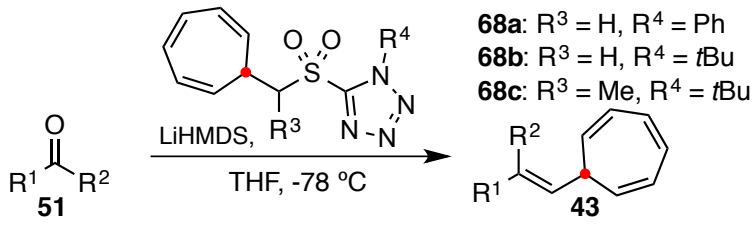


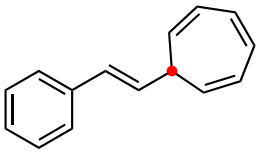
Scheme 123. Synthesis of a trisubstituted Julia-Kocienski reagent **68c**.

Having established the optimal conditions for the alkenylation of aldehydes with **68a**, or ketones with **68b**, several 7-alkenyl cycloheptatriene derivatives were synthesized (Table 5). Styrenyl cycloheptatrienes **43c, 43e**, **43g, 43i** and **43j** were efficiently formed using **68a** in good yields. Only in the case of very electron-rich substrates, a mixture of *E*- and *Z*-isomers was obtained, which could be separated by column chromatography (*E*-**43e** and *Z*-**43e**). The reduced selectivity is caused by the electron-rich substrates as the reaction intermediate in these cases evolves faster to the product, leaving less time to adopt the thermodynamically favored intermediate leading to the *E*-isomer. In the case of 3,5-dimethoxybenzaldehyde **43g,** the ratio was particularly low due to the poor solubility of the substrate in cold THF. The alkenylation reaction therefore had to take place at a higher temperature, leaving even less time for the reaction intermediate to adopt the conformation leading to the *E*-isomer. Other 7-alkenyl cycloheptatrienes were efficiently formed by **68b**, although the outcome was dependent on the protecting group in the case of piperidines **43m** and **43n**. An aliphatic aldehyde afforded the corresponding **43k** only in moderate yield as a mixture of *E*- and *Z*-isomers. When the trisubstituted Julia-Kocienski reagent **68c** was tested under otherwise similar conditions, the formation of the desired tetrasubstituted alkene **43o** was not observed. A literature study suggests that the pK_a increased significantly by the addition of another substituent: from ~24 to ~31,[255] therefore, making LiHMDS an inadequate base for this transformation. Performing the reaction with LDA instead of LiHMDS will likely lead to better results for this transformation. Unfortunately, only a small quantity of **68c** was prepared and no further experiments were performed.

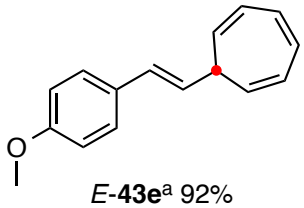
255 Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1885-1886.

Table 5. Formation of 7-alkenyl-1,3,5-cycloheptatrienes via Julia-Kocienski reaction.

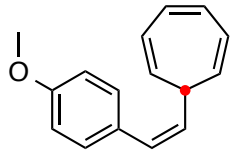




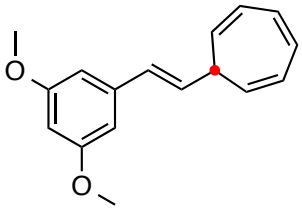
43c[a] 93%



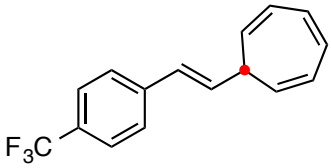
E-**43e**[a] 92%



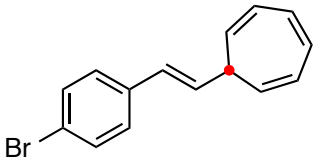
Z-**43e**[a] 5%



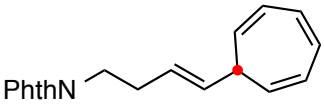
43g[a] 93% (*E*/*Z* 6:1)



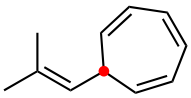
43i[a] 82%



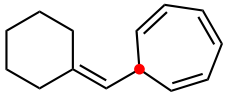
43j[a] 85%



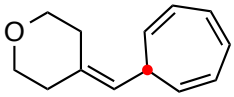
43k[a] 44% (*E*/*Z* 1.3:1)



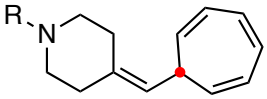
43a[b] 75%



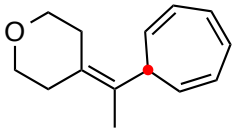
43h[b] 66%



43l[b] 86%



43m[b] R = Bn 70%
43n[b] R = Boc 25%

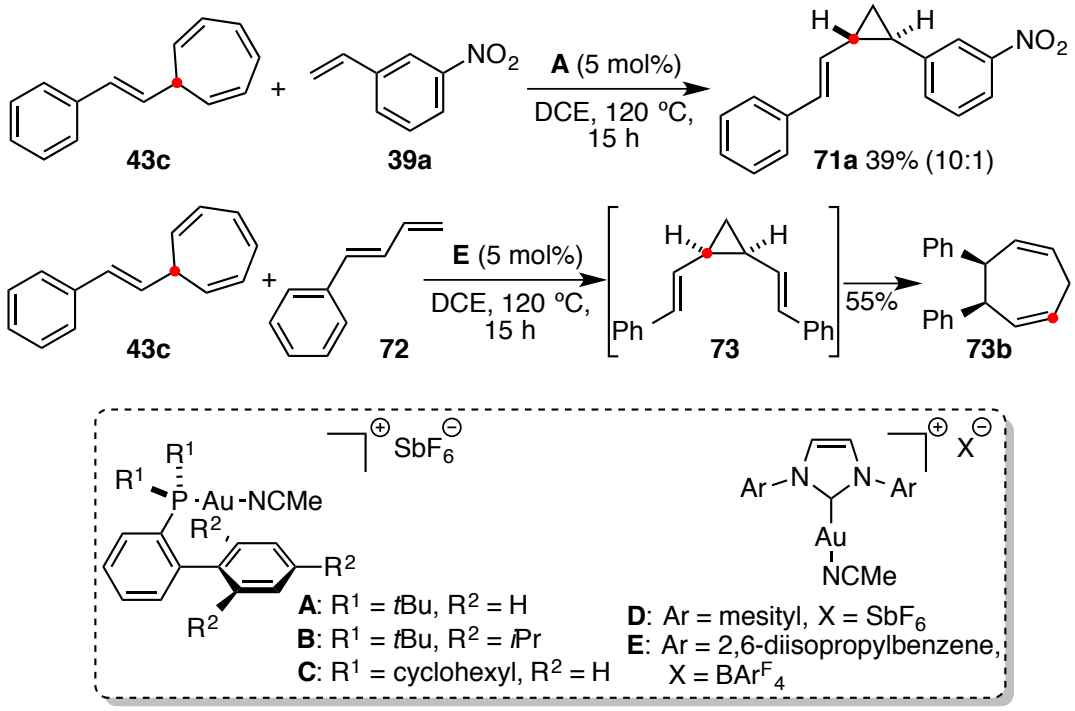


43o[c] 0%

[a] To a solution of aldehyde and **68a** (1:1) in THF at -78 °C is added base (1 equiv). [b] To a solution of carbonyl compound and **68b** (1:2) in THF at -78 °C is added base (3 equiv). [c] To a solution of carbonyl compound and **68c** (1:2) in THF at -78 °C is added base (3 equiv).

Reaction optimization and initial cyclopropanation results.

During the study on 7-aryl cycloheptatrienes, our group reported one example of a vinylcyclopropane formed from styrenyl-cycloheptatriene, with moderate yield and reasonable diastereoselectivity (**71a**; Scheme 124).[256] In another example, styrenyl-cycloheptatriene **43c** was reacted with *trans*-1-phenyl-1,3-butadiene to form a 1,2-divinylcyclopropane **73**, which spontaneously rearranges to a cycloheptadiene **73b** in moderate yield.

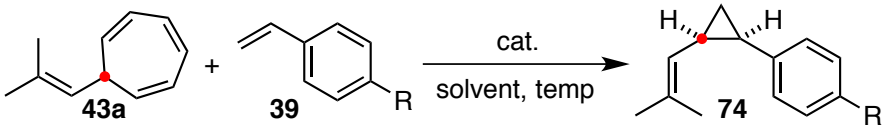


Scheme 124. Previously obtained results for the gold(I)-catalyzed alkene cyclopropanation via the retro-Buchner reaction at 120 °C.[256]

Despite these promising results, our attempts to generalize this concept were not met with success (see entries 1 in Tables 6 and 7). The optimization started with the reaction of isocrotyl-cycloheptatriene with different styrenes (Table 6). Only traces of cyclopropane were observed under the conditions previously developed (Table 6, entry 1). No reaction took place at room temperature but already small quantities of the product could be observed at 40 °C, even though the reaction was very slow at this temperature (Table 6, entry 2).

256 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

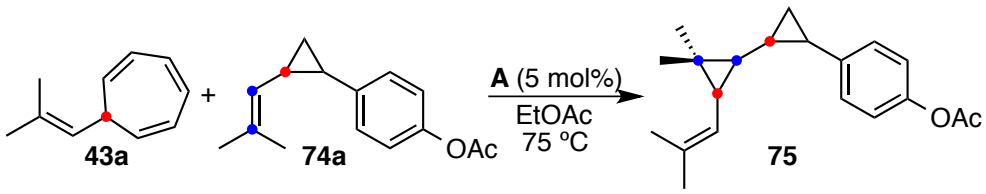
Table 6. Optimization of conditions for the cyclopropane metathesis reaction.



	R	43a:39	Solvent	Temp	Time	Cat.	Yield[a] (d.r.)
1	H	1:1	DCE	120 °C	6 h	**A** 5%	Full conv., <5%
2	H	1:1	DCE	40 °C	10 h	**A** 5%	Partial conv., n.d.
3	H	1:1	DCE	60 °C	14 h	**A** 5%	62% (7:1)
4	H	1:1	CH_2Cl_2	60 °C	14 h	**A** 5%	67% (8:1)
5	H	2:1	CH_2Cl_2	60 °C	14 h	**A** 5%	74% (5:1) [17% **75**][b]
6	H	1:1	CH_2Cl_2	60 °C	14 h	**A** 2.5%	49% (8:1)
7	H	1:1	CH_2Cl_2	60 °C	14 h	**B** 5%	43% (10:1)
8	H	1:1	CH_2Cl_2	60 °C	14 h	**C** 5%	n.r.
9	H	1:1	CH_2Cl_2	60 °C	14 h	**D** 5%	n.r.
10	H	1:1	CH_2Cl_2	60 °C	14 h	**E** 5%	43% (1.3:1)
11	OAc	1:1	CH_2Cl_2	60 °C	12 h	**A** 5%	61% (7:1)
12	OAc	1:1	DCE	60 °C	12 h	**A** 5%	57% (9:1)
13	OAc	1:1	$MeNO_2$	60 °C	12 h	**A** 5%	55% (8:1)
14	OAc	1:1	Acetone	60 °C	12 h	**A** 5%	39% (9:1)
15	OAc	1:1	THF	60 °C	12 h	**A** 5%	25% (8:1)
16	OAc	1:1	Benzene	60 °C	12 h	**A** 5%	22% (2:1)
17	OAc	1:1	$CHCl_3$	60 °C	12 h	**A** 5%	n.r.
18	OAc	1:1	Et_2O	60 °C	12 h	**A** 5%	n.r.
19	OAc	1:1	DMSO	60 °C	12 h	**A** 5%	n.r.
20	OAc	1:1	MeCN	60 °C	12 h	**A** 5%	n.r.
21	OAc	1:1	EtOAc	60 °C	12 h	**A** 5%	59% (14:1)
22	OAc	2.5:1	EtOAc	60 °C	12 h	**A** 5%	86% [15% **75**][b]
23	Me	1:1	EtOAc	60 °C	12 h	**A** 5%	36% (17:1)
24	Me	2.5:1	EtOAc	60 °C	12 h	**A** 5%	71% [15% **75**][b]
25	H	1:1	EtOAc	60 °C	12 h	**A** 5%	44% (10:1)
26	H	2.5:1	EtOAc	60 °C	12 h	**A** 5%	68% [17% **75**][b]
27	Me	1:1.5	EtOAc	60 °C	12 h	**A** 5%	63% (13:1)
28	**OAc**	**1:1.5**	**EtOAc**	**75 °C**	**12 h**	**A 5%**	**66% (12:1)**
29	Cl	1:1.5	EtOAc	75 °C	12 h	**A** 5%	51% (21:1)

To a solution of **43a** and styrene **39** in given solvent is added catalyst and the reaction is stirred in a sealed vial. Once the reaction is complete, Et_3N is added and the mixture filtered over silica. [a] The yield and d.r. (in parenthesis) are determined by ^1H NMR of the crude mixture. [b] Percentage of inseparable byproduct.

Full conversion was achieved at 60 °C and the product was obtained with a satisfying yield and reasonable stereoselectivity (Table 6, entry 3). Changing solvent to dichloromethane would increase the yield and selectivity slightly (Table 6, entry 4). Increasing the amount of cycloheptatriene could increase the formation of product (Table 6, entry 5), however, an inseparable byproduct **75** was also formed by a second cyclopropanation on the alkene of the reaction product (Scheme 29). Reduction of the catalyst loading or the use of other catalysts led to a significant drop in yield and/or selectivity (Table 6, entries 6 – 10). The product of 4-acetoxystyrene was easier to observe in ^{1}H NMR, facilitating the optimization, and an elaborate solvent screening was performed using this substrate. Polar non-protic solvents or benzene performed less well than CH_2Cl_2 (Table 6, entries 13 – 16), while coordinating solvents completely shut down the reaction (Table 6, entries 17 – 20). Surprisingly, the reaction performed well in ethyl acetate, with nearly identical yield and improved diastereoselectivity (Table 6, entry 21). Again, the yield could significantly be improved by increasing the stoichiometry of the cycloheptatriene although certain quantities of **75** would be formed (Table 6, entry 22). A similar trend was observed for other styrenes (Table 6, entries 23 – 26). Finally, it was found that increasing the amount of alkene would prevent any formation of **75**, while improving the reaction outcome (Table 6, entry 27). The reaction temperature was finally increased to 75 °C as electron-deficient styrenes did not readily react at 60 °C and the optimal conditions are as described by Table 6, entry 28.

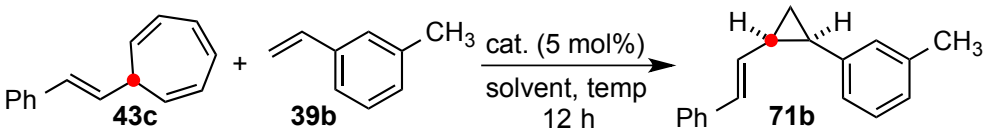


Scheme 125. A second cyclopropanation leading to an inseparable byproduct.

Surprised by the difference in optimal conditions compared to the previous work, the styrenyl-cycloheptatriene was also tested under several conditions using a different alkene (Table 7). Interestingly, similar as for the isocrotyl substrate, only a minute quantity of product was observed at 120 °C in DCE. Despite this set-back, the yield was again recovered by lowering the reaction

temperature to 75 °C (Table 9, entries 1 – 3). The outcome was improved slightly by changing to ethyl acetate as solvent (Table 9, entry 4), and catalyst **A** was shown to also be the best catalyst (Table 9, entries 5 – 8).

Table 7. Optimization of retro-Buchner/cyclopropanation conditions for **43c**.



	Temperature	Solvent	Catalyst	Outcome[a]
1	120 °C	DCE	**A** 5%	6%
2	75 °C	DCE	**A** 5%	68%
3	40 °C	DCE	**A** 5%	3%
4	**75 °C**	**EtOAc**	**A 5%**	**75%**
5	75 °C	EtOAc	**B** 5%	38%
6	75 °C	EtOAc	**C** 5%	-
7	75 °C	EtOAc	**D** 5%	-
8	75 °C	EtOAc	**E** 5%	14%

Cycloheptatriene **43c** (1.0 equiv), styrene **39b** (1.5 equiv) with catalyst (5 mol%) in given solvent at given temperature for 12 h. [a] Determined by ^{1}H NMR with diphenylmethane as internal standard.

For the styrenyl cycloheptatrienes, only one diastereomer could be identified by ^{1}H NMR, and GC-FID had to be used to confirm the diastereoselective ratio, which was as high as 83:1 in the case of **71b**. Much to our surprise, and opposed to what we had previously reported, the NMR data of the major diastereomer for **71b** seemed to match to the *cis*-, rather than the *trans*-isomer. This finding was supported by the literature.[257] The major isomers for both **71b** and **74a** were unambiguously determined to be the *cis*-isomer by 2D NMR and X-ray diffraction (Figure 18).

257 Kuo, G. H.; Helquist, P.; Kerber, R. C. *Organometallics* **1984**, *3*, 806-808.

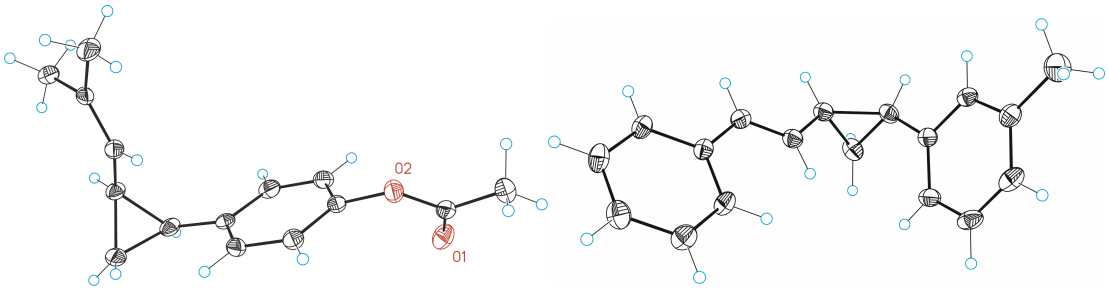


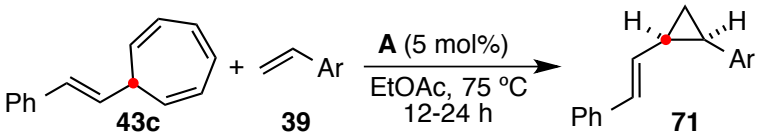
Figure 18. ORTEP representation of the major isomer for **71b** and **74a**, represented with 50% probability of the thermal ellipsoids.

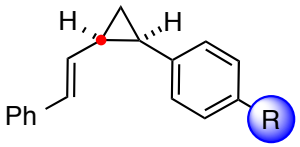
Stereoselective synthesis of vinylcyclopropanes by gold(I)-catalysis

Having established a convenient method for the synthesis of different cycloheptatriene derivatives, the scope and limitation regarding the substitutions of the cycloheptatrienes and alkenes were investigated (Table 8). The intermolecular reaction of cycloheptatriene **43c** with a variety of *ortho*-, *meta*-, and *para*-substituted styrenes gave the corresponding cyclopropanes **71a-u** in moderate to high yields with excellent *cis*-selectivities. Electron-rich styrenes were, in general, slightly better substrates for the reaction and led to higher yields of **71b**, **71d**, **71h**, and **71k**, whereas electron-poor arenes reacted more slowly leading to lower yields of **71a**, **71f**, **71j**, and **71o**. Functional groups such as aldehydes (**71m** and **71s**), esters (**71i-j**), and nitro groups (**71a**) were well tolerated, as were aryl halides (**71e** and **71g**). Disubstituted α-styrenes reacted efficiently to give cyclopropanes **71v-w**, albeit with a lower stereoselectivity in the former case. Adding one (**71x**) or two (**71y**) substituents to the β-position of the styrene resulted in a decline of the yield. When one of the β-substituents is tethered to the styrene, the loss in yield is quickly recovered, giving rise to the *endo*-tricycles **71z-ad** in good yields, essentially as single diastereomer. Stilbenes were tolerated as substrates, although leading to slightly reduced yield for **71ae-af**.

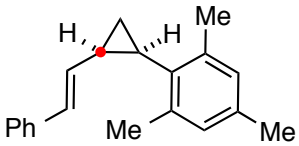
Crystals suitable for X-ray diffraction analysis were obtained for some products. With the help of these samples, a GOESY NMR experiment was designed, which allowed us to determine the configuration of the major isomer for each product where a mixture of diastereomers was observed. An example of the GOESY experiment for **71b** is shown in Figure 19, for which the configuration was corroborated by X-ray crystallography.

Table 8. Stereoselective synthesis of *cis*-aryl-vinylcyclopropanes.

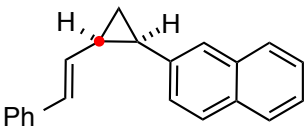




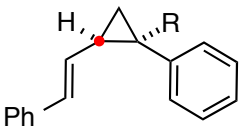
71c[a] R = H 65%, d.r. >20:1
71d[a] R = Me 69%, d.r. >20:1
71e[a] R = Cl 75%, d.r. >20:1
71f R = CF_3 59%, d.r. 19:1
71g R = F 65%, d.r. >20:1
71h R = OMe 70%, d.r. 15:1
71i R = OAc 68%, d.r. 19:1
71j R = CO_2Me 54%, d.r. >20:1
71k R = *t*Bu 70%, d.r. >20:1
71l R = Ph 83%, d.r. >20:1



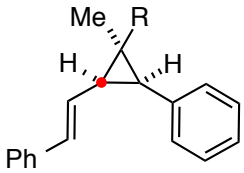
71t 47%, d.r. >20:1



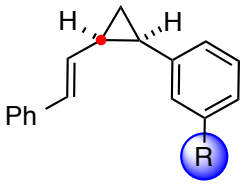
71u 73%, d.r. >20:1



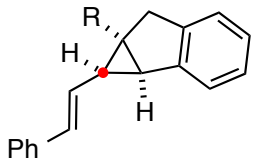
71v R = Me 73%, d.r. 5:1
71w R = Ph 73%



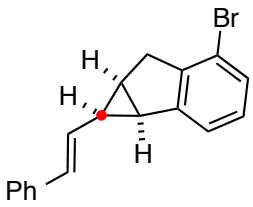
71x R = H 45%, d.r. 3:1
71y R = Me 35%, d.r. 8:1



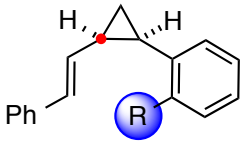
71a R = NO_2 47%, d.r. >20:1
71b[b] R = Me 75%, d.r. >20:1
71m R = CHO 72%, d.r. >20:1
71n[a] R = Br 56%, d.r. >20:1
71o R = CF_3 52%, d.r. >20:1



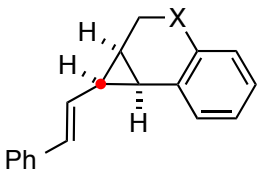
71z[a] R = H 85%, d.r. >20:1
71aa R = Me 66%, d.r. >20:1



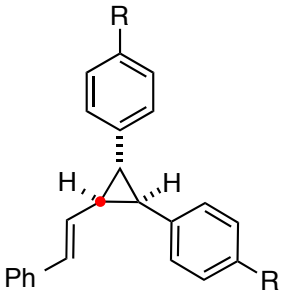
71ab 71%, d.r. >20:1



71p R = Me 65%, d.r. >20:1
71q R = F 60%, d.r. >20:1
71r[c] R = Br 71%, d.r. >20:1
71s R = CHO 47%, d.r. >20:1



71ac[a] X = CH_2 50%, d.r. >20:1
71ad[a] X = O 56%, d.r. >20:1



71ae R = H 52%
71af R = OMe 47%

Cycloheptatriene **43c** (1.0 equiv), alkene **39** (1.5 equiv) with catalyst **A** (5 mol%) in EtOAc 75 °C for 12-24 h. [a] 2 equiv of styrene used. [b] Relative configuration confirmed by X-ray crystallography. [c] 3 equiv of styrene used.

NOE correlations can be seen between H_c and H_e, H_c and H_f, and H_f and H_e, whereas H_c and H_f do not show a correlation with H_d, which are the expected interaction for an *endo*-cyclopropane. Additional interactions with and between

the substituents further confirm the structure. For other compounds, the GOESY data is shown in the experimental section.

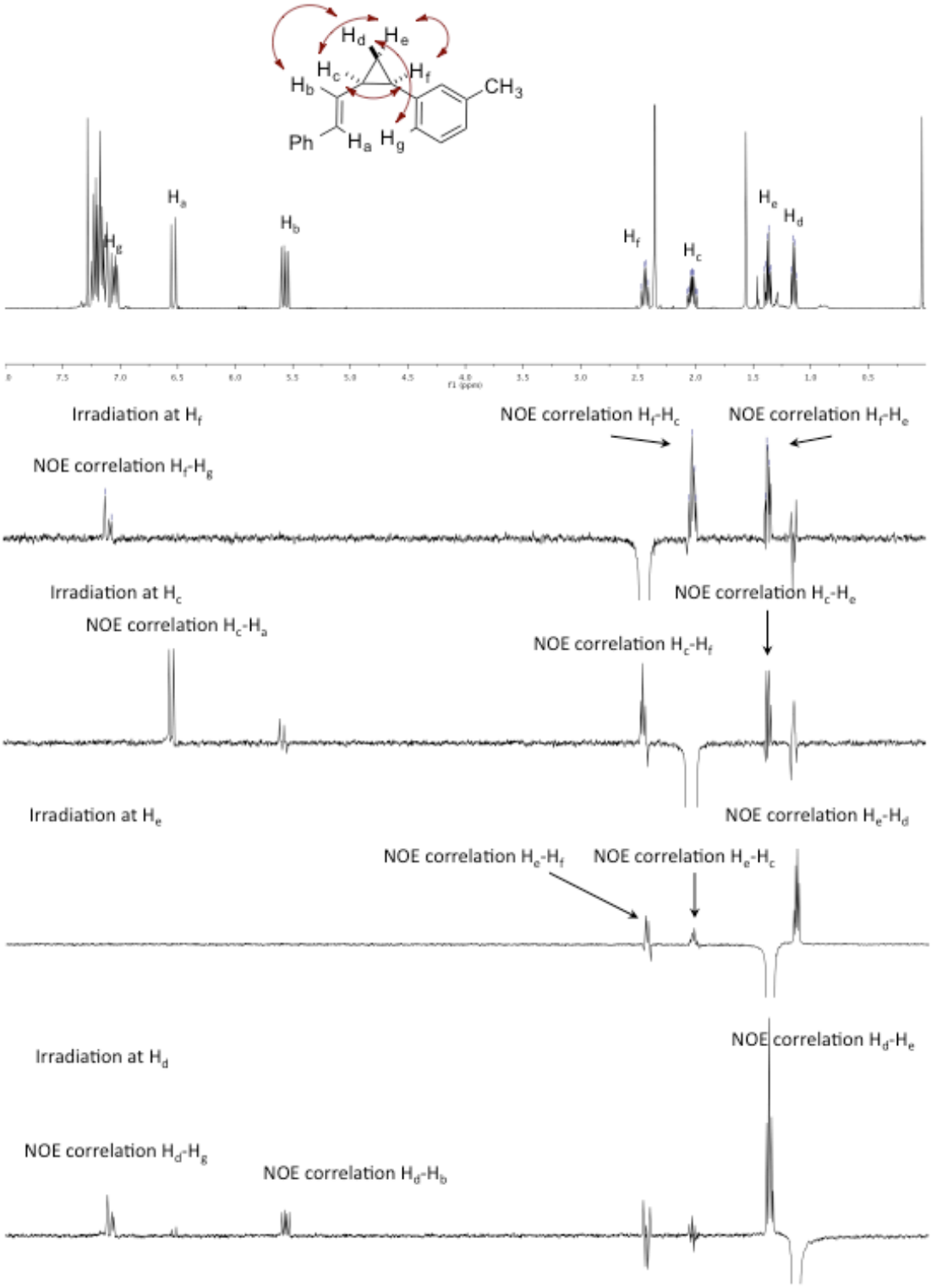
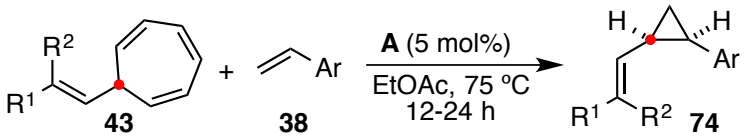
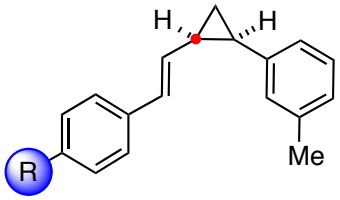


Figure 19. Determination of the major isomer for **71b** by GOESY NMR analysis.

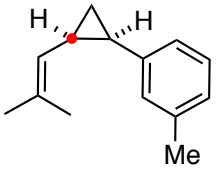
Different cycloheptatriene derivatives afforded vinylcyclopropanes with good to excellent *cis*-selectivities (Table 9). The nature of the aromatic substituent had little effect on the reaction outcome, except for the *p*-methoxy substituted compound **74a** where both a lower yield and lower stereoselectivity were obtained. Disubstituted alkenes were also well tolerated but led to lower selectivities.

Table 9. Cyclopropanation with different cycloheptatriene substrates.

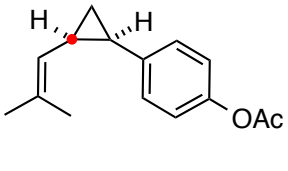




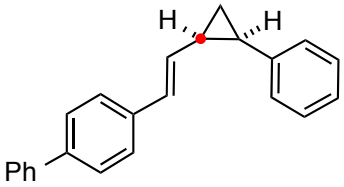
74a R = OMe 48%, d.r. 12:1
74b R = Ac 87%, d.r. >20:1
74c R = CF_3 79%, d.r. 17:1
74d R = Br 85%, d.r. >20:1



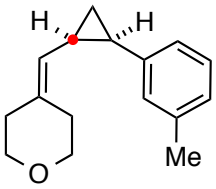
74g 69%, d.r. 9:1



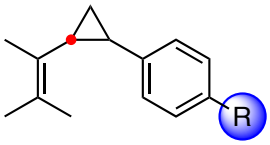
74j[b] 83%, d.r. 9:1



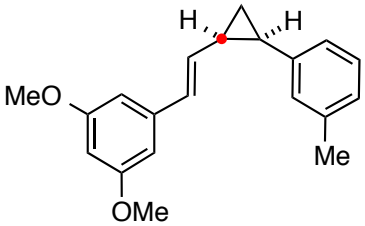
74e 64%, d.r. >20:1



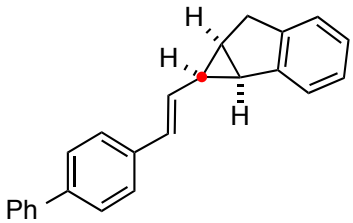
74h 70%, d.r. 6:1



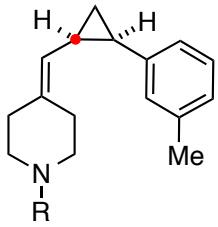
74k[b] R = H 45%, d.r. n.d
74l[b] R= OAc 86%, d.r. n.d
74m[b] R = Me 47%, d.r. n.d
74n[b] R = Cl 56%, d.r. n.d
74o[b] R = CF_3 38%, d.r. n.d



74f 69%, d.r. >20:1



74i[a] 76%, d.r. >20:1



74p R = Bn n.r.
74q R = Boc n.r.
74r R = Ts n.r.

Cycloheptatriene **43** (1.0 equiv), alkene **38** (1.5 equiv) with catalyst **A** (5 mol%) in EtOAc 75 °C for 12-24 h. [a] Relative configuration confirmed by X-ray crystallography. [b] Obtained with alkene 2 as impurity; yield determined with the aid of ^{1}H NMR.

For the tri-methyl substituted alkenyl derivatives **74k**-**o**, it was not possible to obtain the product completely free from alkene **38**, therefore the reported yields are corrected by subtraction of the impurity as determined by ^{1}H NMR from the styrene/product mixture.

A possible explanation for the poor reactivity of **43e** to form **74a** can be found in the bright red color during the reaction, whereas all other reactions have a nearly colorless or "golden" color, which could suggest the formation of a higher concentration of relatively stabilized and therefore less reactive gold(I) carbene intermediate. Fürstner and co-workers isolated a structurally similar gold carbene complex **76**.[258] Due to the powerful electron-donating substituents on the carbene, the isolated complex resembles more that of a gold-stabilized carbocation, causing the bright red color of the compound. The intermediate **XII** in the reaction of *p*-methoxy substituted **43e** undergoes similar stabilization, albeit to a lesser extend, which could cause a more carbocation-like behavior leading to a reduced carbene-like reactivity (Figure 20). The intermediates formed from other cycloheptatriene derivatives **XIII** do not benefit from such stabilization and display a more carbene-like reactivity leading to good yields. Gold complex **77** isolated by Straub has a strong carbene character and an emerald color as opposed to the bright pink color of the unstabilized dimesitylenemethane cation.[259]

258 Werlé, C.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 15452-15456.

259 Hussong, M. W.; Rominger, F.; Krämer, P.; Straub, B. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 9372-9375.

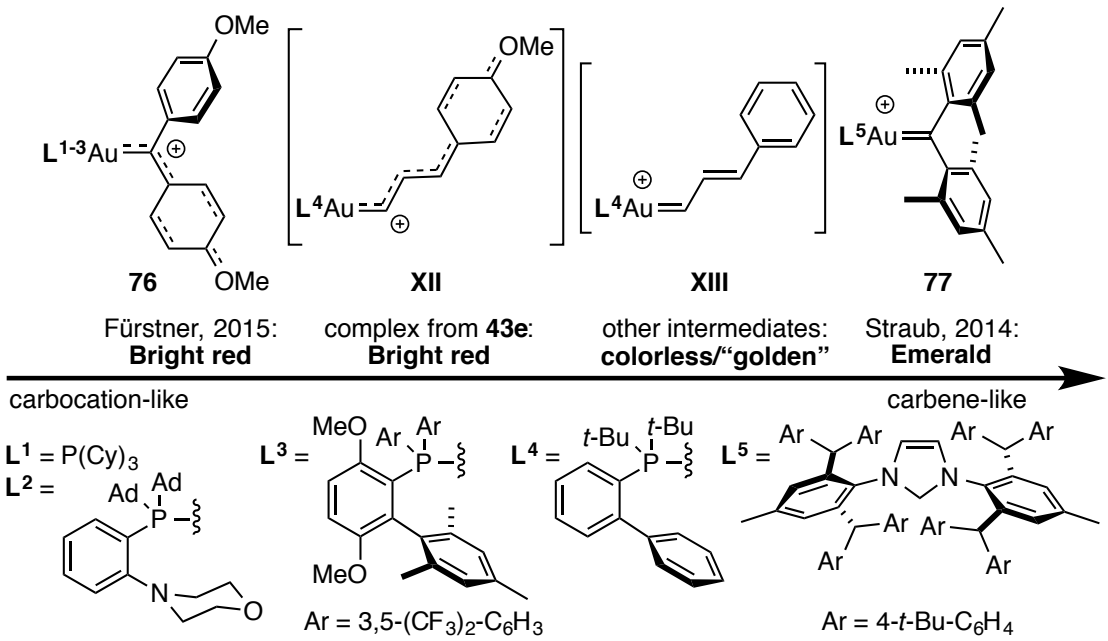


Figure 20. Continuum of gold-stabilized cations to gold carbenes and their colors.

Vinyl-aminocyclopropanes

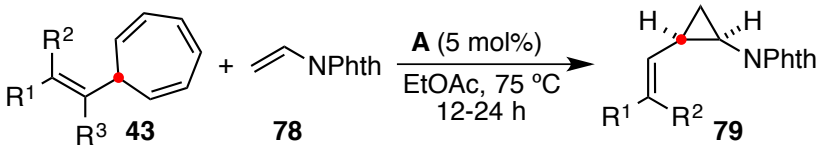
Aminocyclopropanes are a particularly attractive synthetic target due to their value as donor-acceptor cyclopropanes as synthetic intermediates[260] and their use as building blocks for medicinal chemistry.[261] We found that *N*-vinylphthalimide (**78**) reacted efficiently under our reaction conditions to form the corresponding aminocyclopropane **79**. The reaction with different cycloheptatriene derivatives **43** gave the corresponding cyclopropane products in good yields, following the same trend as observed for the reaction with styrenes (Table 10). The diastereoselectivities on the other hand, were significantly lower compared to our earlier results. In the case of **79g-i**, the *trans*-isomer was isolated as the main product. Owing to the higher polarity, the diastereomers can be separated by silica chromatography as demonstrated for **79a**, **79b** and **79c**, meaning that diastereopure aminocyclopropanes can be obtained.

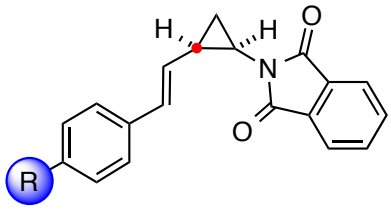
The GOESY-NMR spectra showed the unexpected inversion of the stereoselectivity for two of the substrates (Figure 21 and Figure 22). The

260 Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523.
261 Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712-8756.

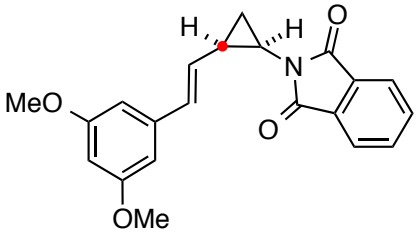
selectivity for dialklyl-cycloheptatriene derivatives used to obtain **79g** and **79h** was already lower than in the other cases (Table 9), which leads to inversion of the usual selectivity when combined with *N*-vinylphthalimide as alkene substrate.

Table 10. The formation of aminocyclopropanes from *N*-vinylphthalimides.

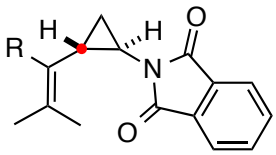




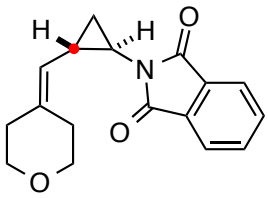
79a R = H 75% (74%)[a], d.r. 6:1
79b R = OMe 52%, d.r. 6:1
79c R = Ac 63%, d.r. -
79d R = CF_3 79%, d.r. 10:1
79e R = Ph 69%, d.r. 2.6:1[b]



79f 60%, d.r. 6:1



79g[c] R = H 59%, d.r. 4.7:1
79h R = Me 43%, d.r. n.d.



79i[c] 73%, d.r. 1.2:1

Cycloheptatriene **43** (1.0 equiv), alkene **78** (1.5 equiv) with catalyst **A** (5 mol%) in EtOAc 75 °C for 12-24 h. [a] Isolated yield for reaction on 10 mmol scale, 2.1 g isolated with d.r. 7:1. See experimental section for details. [b] Relative configuration (both cis and trans) confirmed by X-ray crystallography. [c] Major isomer depicted.

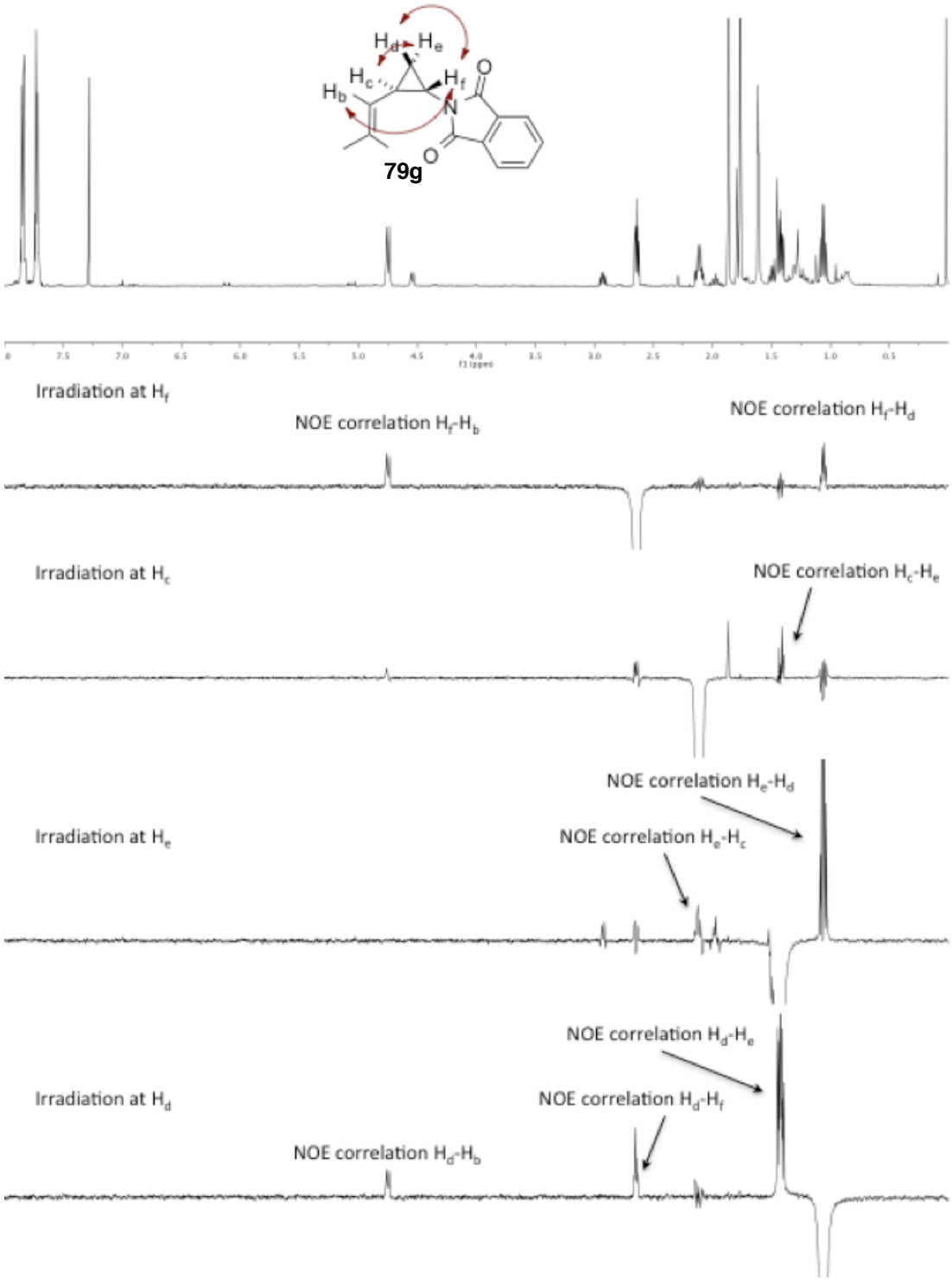


Figure 21. Determination of major isomer for **79g** by GOESY analysis .

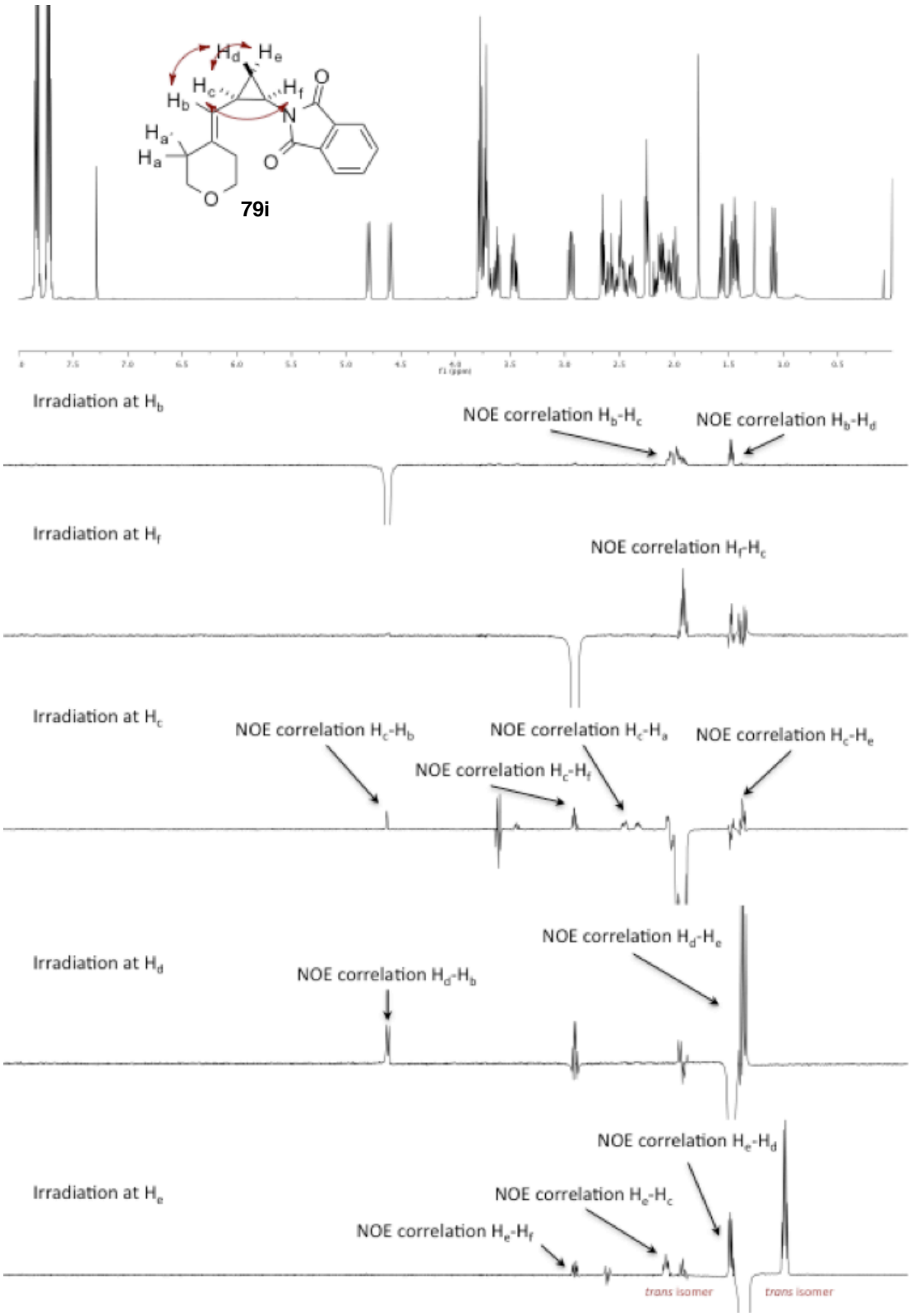
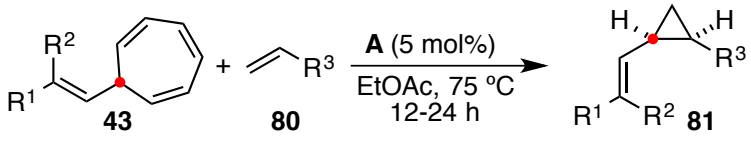


Figure 22. Determination of major isomer for **79i** by GOESY analysis

Limitations of the vinylcyclopropanation

The scope was generally limited to electron-rich alkenes that offer some form of conjugation. However, some interesting products were obtained from substrates outside this class, such as vinyl acetate and *tert*-butyl vinyl ether (Scheme 126), albeit in low yield. Compound **81a** could not be completely separated from the corresponding alkene, while **81b** was not isolated. Further exploration of the cyclopropanation of unactivated alkenes is highly worthwhile as the scope for gold(I)-catalyzed cyclopropanation reactions is still very limited.[262]



81a: R^1 = Ph, R^2 = H, R^3 = OAc (30%)
81b: R^1 = R_2 = Me, R^3 = O*t*Bu (9%)

Scheme 126. Compounds obtained that are outside the general scope.

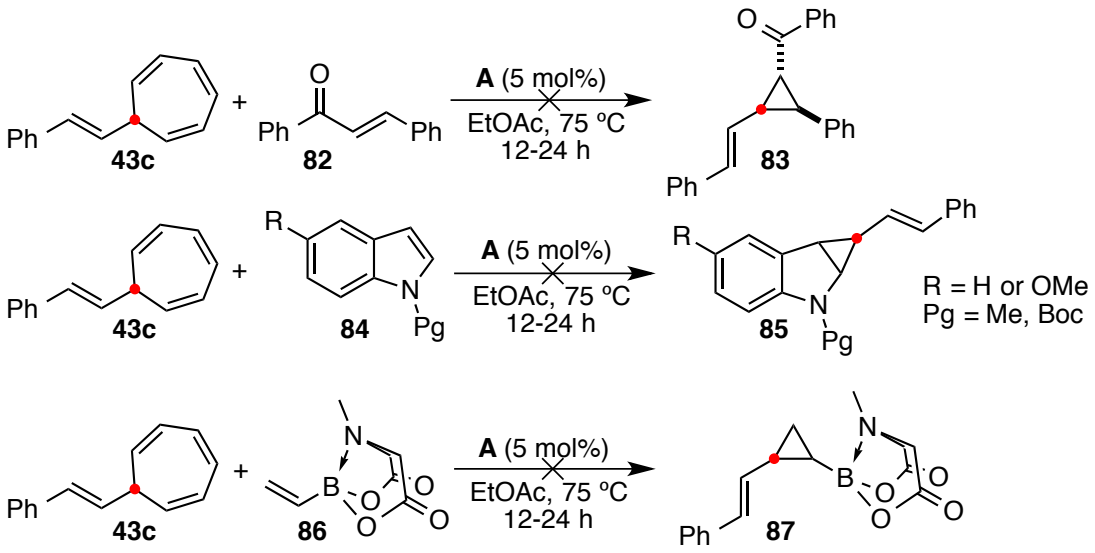
Yet, other compounds remained completely unreactive under the reaction conditions however, such as α,β-unsaturated ketones **82**, indoles **84**, or vinyl-boronates **86** (Scheme 127). Complementary methods exist to build up similar scaffolds, such as Johnson-Corey-Chaykovsky reaction or other ylid chemistry for α,β-unsaturated ketones.[263] The rhodium or palladium catalyzed decomposition of diazo compounds is reported for indoles[81,82] and vinyl boronates.[264] Surprisingly, an example was actually reported for the cyclopropanation of indole using the JohnPhos-gold complex **A** as catalyst.[265]

262 Qian, D.; Zhang, J. *Chem. Soc. Rev.* **2015**, *44*, 677-698.

263 a) Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13030-13031. b) Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W.; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006**, *128*, 9730-9740. c) Edwards, M. G.; Paxton, R. J.; Pugh, D. S.; Whitwood, A. C.; Taylor, R. J. K. *Synthesis* **2008**, *2008*, 3279-3288. d) Lin, S.; Li, M.; Dong, Z.; Liang, F.; Zhang, J. *Org. Biomol. Chem.* **2014**, *12*, 1341-1350.

264 a) E. A. Luithle, J.; Pietruszka, J.; Witt, A. *Chem. Commun.* **1998**, 2651-2652. b) Markó, I. E.; Kumamoto, T.; Giard, T. *Adv. Synth. Catal.* **2002**, *344*, 1063-1067. c) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717.

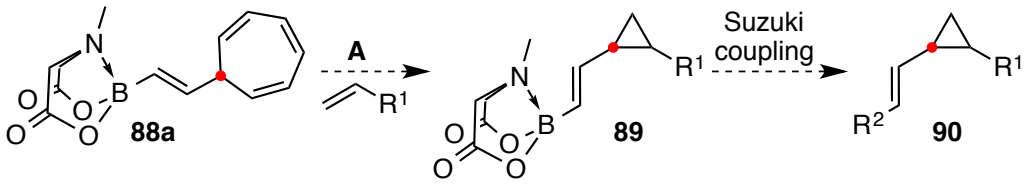
265 a) Wu, J.; Becerril, J.; Lian, Y.; Davies, H. M. L.; Porco, J. A.; Panek, J. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5938-5942. b) Fraile, J. M.; Le Jeune, K.; Mayoral, J. A.; Ravasio, N.; Zaccheria, F. *Org. Biomol. Chem.* **2013**, *11*, 4327-4332. c) Iqbal, N.; Sperger, C. A.; Fiksdahl, A. *Eur. J. Org. Chem.* **2013**, *2013*, 907-914.



Scheme 127. Unreactive substrates under the standard reaction conditions.

Notwithstanding its limitations, this method distinguishes itself as the only practical catalytic method that does not require a second stabilizing moiety on the carbene center. Moreover, our method is unique in being able to install a wide variety of vinylic moieties to only a slight excess of alkene.

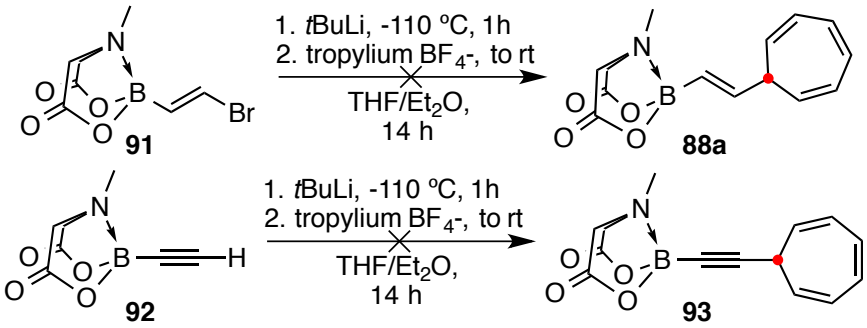
In order to find a general strategy to synthesize highly versatile vinylcyclopropanes the use of *trans*-2-2,4,6-cycloheptatriene vinyl boronic acid MIDA ester (**88a**) was considered as a substrate (Scheme 128). The slight electron-donating properties of this boronic ester would enhance the reactivity as seen in the examples of Table 8.[266] More importantly, the product would have a handle for further functionalization, which, unlike other boron compounds, is unlikely to suffer from auro-deborylation.[267]



Scheme 128. Proposed gold(I)-catalyzed cyclopropanation to form highly versatile cyclopropanes, followed by functionalization via Suzuki coupling.

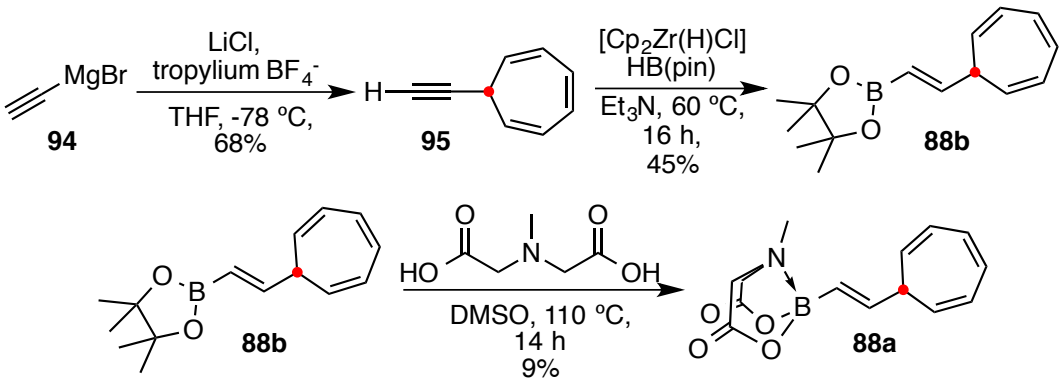
266 Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412-443.
267 Barker, G.; Webster, S.; Johnson, D. G.; Curley, R.; Andrews, M.; Young, P. C.; Macgregor, S. A.; Lee, A.-L. *J. Org. Chem.* **2015**, *80*, 9807-9816.

Ester **88a** could not be obtained by treatment with *n*-butyl lithium of either *trans*-2-bromo (**91**) or ethynyl boronic acid MIDA ester (**92**), followed by addition of tropylium tetrafluoroborate (Scheme 129).



Scheme 129. Attempted synthesis of MIDA-boronic-ester-substituted cycloheptatriene reagent.

An alternative approach proved more successful (Scheme 130). Starting from ethynylmagnesium bromide, using a method inspired by Knochel´s work,[268] ethynylcycloheptatriene (**95**) was obtained in good yield. Hydrozirconation followed by transmetallation afforded the cycloheptatriene-vinylboronic acid pinacol ester (**88b**) in moderate yield. After strong heating of the pinacol borate in DMSO in the presence of *N*-methyl aminodiacetic acid, MIDA ester **88a** was formed.



Scheme 130. Alternative route to MIDA boronic ester containing cycloheptatriene reagents.

The isolation of this compound proved very difficult, and despite obtaining a small quantity of brown crystals suitable for X-ray diffraction analysis, the characterization was complicated as well. The X-ray analysis showed a highly

268 Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.

distorted structure for the cycloheptatriene (Figure 23), and while the MIDA signals in the ^{1}H NMR are clear, the remainder of the signals suggested the presence of a mixture of compounds. It is very likely that a mixture of possible double-bond isomers for the cycloheptatriene is formed under the acidic conditions, aided by the electron-rich boron species that is conjugated through the π-system.

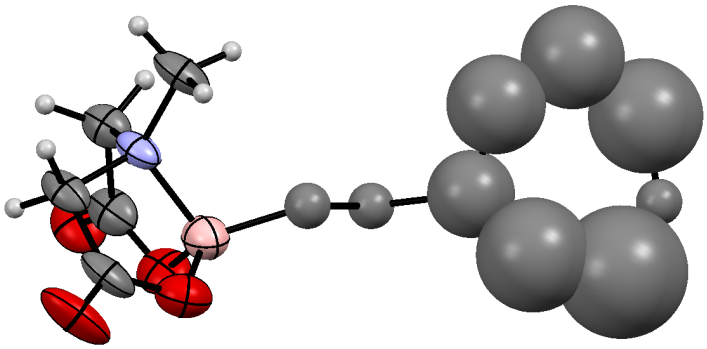
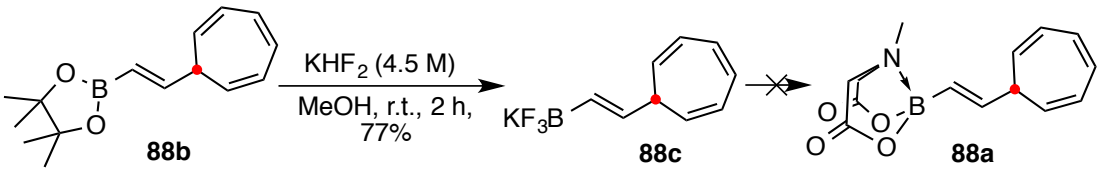


Figure 23. CYLview depiction of **88a**, represented with 50% probability of the thermal ellipsoids. While the MIDA moiety could be resolved well, the cycloheptatriene part had a high degree of distortion.

In the hope to find a milder method that would also facilitate isolation, the pinacol boronate was transformed into the potassium trifluoroborate salt **88c**, which despite treatment under various conditions did not yield MIDA boronate **88a** (Scheme 131).



Scheme 131. An alternative approach for the formation of **88a**.

Both the pinacol boronate **88b** and the impure MIDA boronate **88a** were tested in the cyclopropanation reaction. Pinacol boronate **88b** did not yield the desired cyclopropane, whereas the results for the MIDA boronate **88a** remain inconclusive considering the complexity of the spectroscopic data.

Post-cyclopropanation derivatization

Cross metathesis

In order to access functional groups that would otherwise be beyond the limitations of our method, the feasibility of using cross-metathesis on styrenyl-cyclopropanes was investigated. Apart from ring-closing metathesis[269] or cross-metathesis on terminal vinylcyclopropanes,[270] only a single example of a comparable reaction was reported.[271]

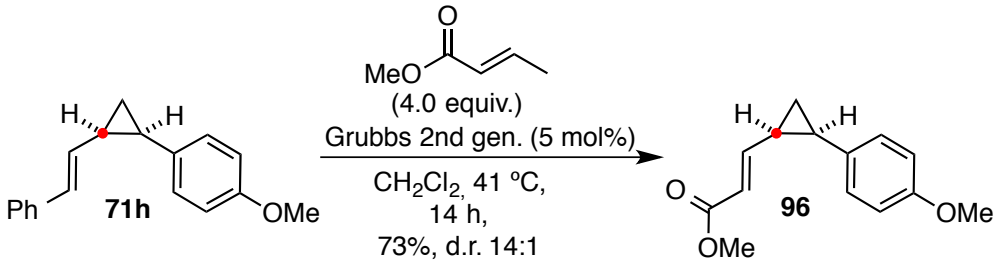
Styrenyl-cyclopropanes **71** were determined to be a *type 3* alkene according to the reactivity-index by Grubbs, as no homo dimerization was observed under the reaction conditions.[272] The use of *type 3* alkenes allows for selective cross metathesis with *type 1* or *2* alkenes without the need of a large excess of either one of the alkenes using the second generation of Grubbs catalyst. Based on the reactivity-index, methyl butenoate was chosen as the ideal alkene and indeed the reaction proceeded smoothly without erosion of the diastereomeric ratio (Scheme 132).

269 a) Itoh, T.; Mitsukura, K.; Ishida, N.; Uneyama, K. *Org. Lett.* **2000**, *2*, 1431-1434. b) Itoh, T.; Ishida, N.; Mitsukura, K.; Uneyama, K. *J. Fluorine Chem.* **2001**, *112*, 63-68. c) Tsantrizos, Y. S.; Ferland, J.-M.; McClory, A.; Poirier, M.; Farina, V.; Yee, N. K.; Wang, X.-j.; Haddad, N.; Wei, X.; Xu, J.; Zhang, L. *J. Organomet. Chem.* **2006**, *691*, 5163-5171. d) Zeng, X.; Wei, X.; Farina, V.; Napolitano, E.; Xu, Y.; Zhang, L.; Haddad, N.; Yee, N. K.; Grinberg, N.; Shen, S.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 8864-8875. e) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303-1306. f) Farina, V.; Zeng, X.; Wei, X.; Xu, Y.; Zhang, L.; Haddad, N.; Yee, N. K.; Senanayake, C. H. *Catal. Today* **2009**, *140*, 74-83. g) Hohn, E.; Paleček, J.; Pietruszka, J.; Frey, W. *Eur. J. Org. Chem.* **2009**, *2009*, 3765-3782. h) Vriesen, M. R.; Grover, H. K.; Kerr, M. A. *Synlett* **2014**, *25*, 428-432.

270 a) Lloyd-Jones, Guy C.; Murray, M.; Stentiford, Rosie A.; Worthington, Paul A. *Eur. J. Org. Chem.* **2000**, *2000*, 975-985. b) Lloyd-Jones, G. C.; Wall, P. D.; Slaughter, J. L.; Parker, A. J.; Laffan, D. P. *Tetrahedron* **2006**, *62*, 11402-11412.

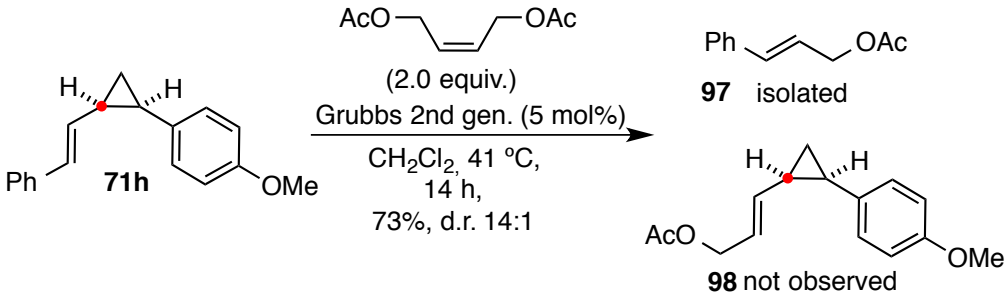
271 Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* **2000**, *41*, 8723-8727.

272 Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.



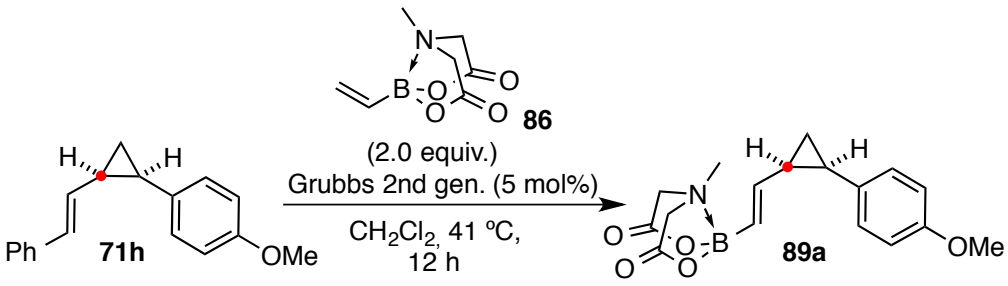
Scheme 132. Cross metathesis of vinylcyclopropanes

No product was observed for the cross metathesis between *cis*-1,4-diacetoxy-2-butene and **71h** (Scheme 133). Yet, cinnamyl acetate byproduct **97** was isolated, indicating that the cross metathesis did take place but that the desired product was lost to decomposition.



Scheme 133. Cross metathesis using *cis*-1,4-diacetoxy-2-butene did not yield the desired product.

The reaction between vinylboronic acid MIDA ester and **71h** did yield the desired compound but isolation proved very difficult and the compound could only be obtained as mixture between the vinyl boronate (**86**) and product (**89a**).



Scheme 134. Cross metathesis as a tool to form highly versatile vinylcyclopropanes.

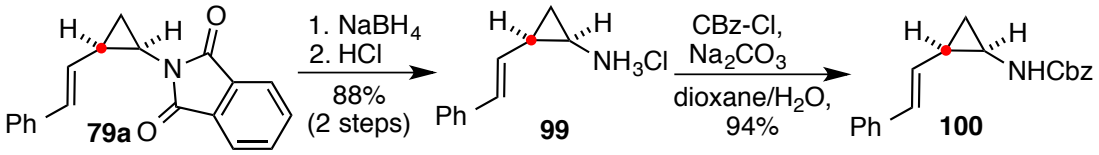
The cross metathesis can be used to either overcome synthetic barriers intrinsic to our methodology or to quickly build up a library of different

vinylcyclopropanes starting from a common intermediate which is easily and selectively obtainable through our method.

Formation of cyclopropa-β-amino esters

The importance of donor-acceptor cyclopropanes and constrained β-amino acids,[273] yet limited number of strategies to access these compounds,[274] prompted us to develop a method to access these building blocks.

Classical deprotection of the phthalimide using hydrazine failed and other methods had to be sought. Reduction of the phthalimide, followed by acidolysis with dry HCl led to the ammonium chloride salt of the unprotected amine **99**.[275] The aminocyclopropane was conveniently re-protected to form carbamate **100** (Scheme 135).



Scheme 135. Deprotection of the phthalimide and protection of the formed amine.

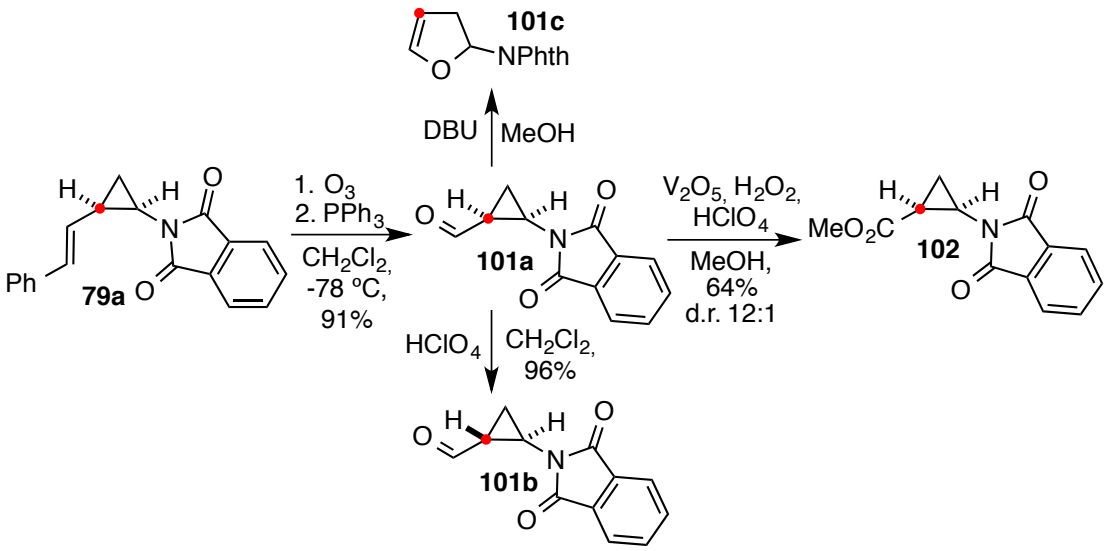
Consecutively, ozonolysis followed by reductive quenching yielded aldehyde **101a** (Scheme 136). Subsequent formation of the ester proved challenging still, as the cyclopropane was prone to opening under basic conditions, leading to the corresponding dihydrofuran **101c**. Acidic conditions, on the other hand, led to isomerization of the aldehyde; in fact, complete conversion to the *trans*-cyclopropane **101b** was achieved in two hours using a catalytic amount of perchloric acid in dichloromethane. A compromise was found using vanadium

273 a) Koglin, N.; Zorn, C.; Beumer, R.; Cabrele, C.; Bubert, C.; Sewald, N.; Reiser, O.; Beck-Sickinger, A. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 202-205. b) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277-4280. c) Lang, M.; De Pol, S.; Baldauf, C.; Hofmann, H.-J.; Reiser, O.; Beck-Sickinger, A. G. *J. Med. Chem.* **2006**, *49*, 616-624. d) Urman, S.; Gaus, K.; Yang, Y.; Strijowski, U.; Sewald, N.; De Pol, S.; Reiser, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 3976-3978.

274 a) Kraus, G. A.; Kim, H.; Thomas, P. J.; Metzler, D. E.; Metzler, C. M.; Taylor, J. E. *Synth. Commun.* **1990**, *20*, 2667-2673. b) Shimizu, M.; Onogawa, Y.; Fujisawa, T. *Synlett* **1996**, *1996*, 827-828. c) Beumer, R.; Bubert, C.; Cabrele, C.; Vielhauer, O.; Pietzsch, M.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 8960-8969.

275 Alford, J. S.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 6020-6023.

oxide in methanol under mild acidic conditions.[276] Methyl ester **102** was obtained in satisfactory yield and good diastereoselectivity.



Scheme 136. Oxidative cleavage to form aldehyde **101a** followed by oxidation to obtain **102**.

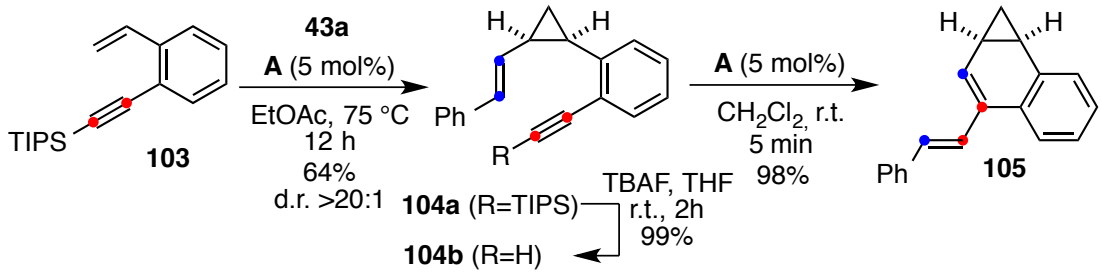
The isolation and characterization of **102** was complicated by the fact that the compound is not UV-active, not visible with electrophoretic light scattering, nor reactive towards TLC stains. As a result, the fractions obtained after purification could only be analyzed by GC-FID and NMR. The β-amino-ester could ultimately be obtained in moderate to good yield.

1,7-Enyne cyclization

Gold-catalyzed enyne cyclizations are a well-studied class of reactions able to rapidly build up chemical complexity.[277] We wondered whether it would be possible to implement such a strategy into our methodology, where the highly reactive alkyne remains untouched during the cyclopropanation. As expected, the reaction with unprotected 1-ethynyl-2-vinylbenzene led to complete decomposition of the starting materials and similarly disappointing results were obtained for the trimethylsilyl-protected styrene. However, switching to the more stable and bulky triisopropylsilyl protecting group was pivotal and enyne **103** was formed with remarkable chemo- and diastereoselectivity (Scheme 137).

276 Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 577-579.
277 a) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346. b) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028-9072.

The alkyne was deprotected by tetrabutylammonium fluoride providing 1,7-enyne **104b** in quantitative yield. The subsequent reaction was almost instantaneous when using catalyst **A** at room temperature to form cyclopropyl-diene **105** quantitatively after a single cleavage rearrangement cascade.[278]



Scheme 137. Gold(I)-catalyzed 1,7-enyne cyclization of vinylcyclopropane **104b**.

Interestingly, the dihydro-1*H*-cyclopropa[*c*]naphthalene **105** did not undergo ring opening or rearrangement during or after the enyne cyclization. The ^{1}H and ^{13}C NMR spectra demonstrate the special properties of this structure. One of two protons on the cyclopropane is shielded and observed at 0.5 ppm, while the carbon atoms at the base of the cyclopropane are shifted downfield. This indicates that cyclopropane is torsioned in such a way that its orbitals can maximally participate in the aromatic system of the naphthalene.

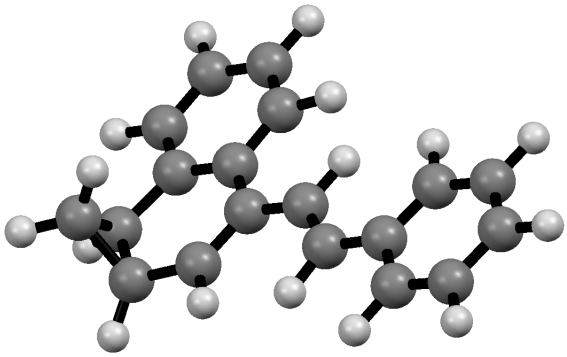
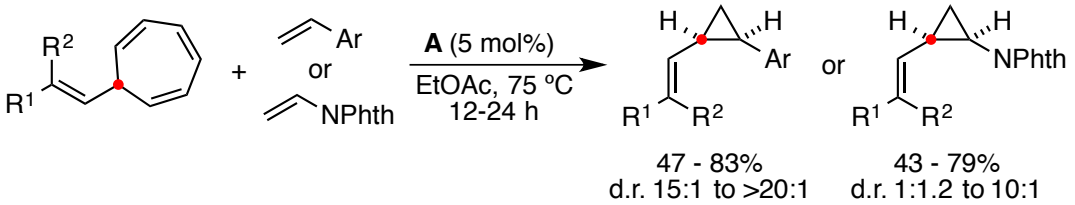


Figure 24. Representation of **105** showing the nearly perpendicular conformation of the cyclopropane.

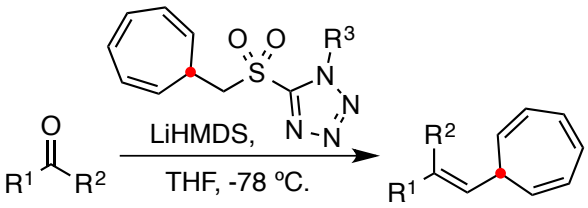
278 Cabello, N.; Rodríguez, C.; Echavarren, A. M. *Synlett* **2007**, *2007*, 1753-1758.

Conclusion

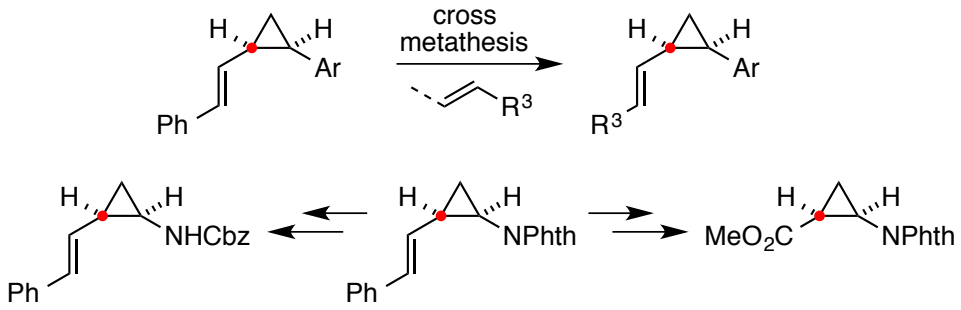
A large scope of vinylcyclopropanes has been synthesized via a gold(I)-catalyzed retro-Buchner/cyclopropanation reaction. Excellent *cis*-selectivity was achieved for the cyclopropanation of aryl alkenes, while the cyclopropanation of *N*-vinylphthalimide was less selective. The formation of vinyl gold(I) carbenes from 7-alkenyl-cycloheptatrienes takes place with significantly less heating than what is required for aryl-cycloheptatrienes.



With the development of Julia-Kocienski reagents, a broad scope of cycloheptatriene derivatives could easily be obtained from aldehydes and ketones. With ready access to 7-alkenyl cycloheptatriene derivatives, a wide variety of vinylcyclopropanes and vinyl-aminocyclopropanes that bear different vinylic substituents could be generated. The reaction was highly *cis*-selective for vinylcyclopropanes bearing a vinylic aryl moiety, while the selectivity for other cyclopropanes strongly depended on the vinylic substituents.



Despite the large scope, the method has some limitations, as unactivated alkenes did not react. Encouraging preliminary results were obtained for vinyl acetate and enol ethers but significant optimization will be necessary. In addition, vinylcyclopropanes that are otherwise beyond the limitations of our method can be obtained through cross metathesis.



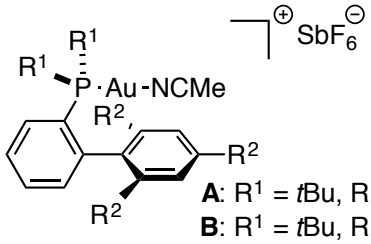
The robustness of this methodology was demonstrated by the synthesis of vinyl-aminocyclopropanes on multi-gram scale with equally good yield and selectivity, as well as their further transformation into valuable β-amino esters.

Experimental section

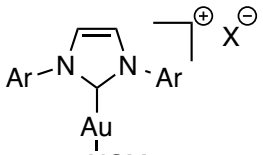
General information

All reactions were carried out under argon in anhydrous solvents obtained by passing them through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA), unless noted otherwise. All gold-catalyzed reactions were performed in HPLC-grade solvents, without a protective atmosphere. Tropylium tetrafluoroborate was purchased from Fluorochem. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck Gf234). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 °C on Bruker Avance 300, 400 and 500 Ultrashield apparatus. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (*J*) are reported in hertz (Hz). Mass spectra were recorded on a Waters LCT Premier Spectrometer (ESI and APCI) or on an Autoflex Bruker Daltonics (MALDI and LDI). Melting points were determined using a Büchi melting point apparatus.

The following gold complexes were synthesized according to literature procedures.[279]



A: R^1 = *t*Bu, R^2 = H
B: R^1 = *t*Bu, R^2 = *i*Pr
C: R^1 = cyclohexyl, R^2 = H



D: Ar = mesityl, X = SbF_6
E: Ar = 2,6-diisopropylbenzene, X = $BAr^F{}_4$

279 Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.

Preparation of vinyl cycloheptatrienes

7-(2-Methylprop-1-en-1-yl)cyclohepta-1,3,5-triene (43a)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0M, 4.5 mL, 4.5 mmol, 3.0 equiv) was added to a solution of **4b** (883 mg, 3.0 mmol, 2.0 equiv) and acetone (110 μL, 1.5 mmol, 1.0 equiv) in dry THF (15 mL, 0.1M) at -78 °C under an argon atmosphere, and stirred for 1 h before the solution was allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O, dried over Na_2SO_4, concentrated and flash chromatography (40 g, SiO_2, eluent: pentane) yielded **1g** (165 mg, 1.13 mmol, 75%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 – 6.69 (m, 2H), 6.22 – 6.17 (m, 2H), 5.57 (dt, *J* = 8.6, 1.4 Hz, 1H), 5.17 (dd, *J* = 8.9, 5.4 Hz, 2H), 2.34 (dt, *J* = 9.4, 5.6 Hz, 1H), 1.80 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.7, 130.9, 126.8, 126.3, 124.0, 38.6, 25. 7, 18.0.

HRMS-APCI: calculated for $C_{11}H_{15}$ $[M+H]^+$: 147.1168; found: 147.1166

7-(3-Methylbut-2-en-2-yl)cyclohepta-1,3,5-triene (43b)

A solution of 3-bromo-2-methyl-2-butene (2.44 mL, 20 mmol, 1 equiv) in dry THF (100 mL) and Et_2O (20 mL) is cooled to -110 °C and *tert*-butyl lithium (23.5 mL, 1.7M in hexane, 40 mmol, 2 equiv) is added. The mixture is stirred for 1.5 h at this temperature before crushed tropylium tetrafluoroborate (3.91 g, 22 mmol, 1.1 equiv) is added and the cooling removed. After stirring for an additional 16 h, the mixture is filtered over silica, concentrated and distillation affords 1.70 g (55%) of a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.69 – 6.64 (m, 2H), 6.20 (dddd, *J* = 8.9, 3.9, 2.6, 1.5 Hz, 2H), 5.24 (ddt, *J* = 8.9, 5.2, 0.9 Hz, 2H), 2.65 (tt, *J* = 5.3, 1.7 Hz, 1H), 1.88 – 1.85 (m, 2H), 1.74 (d, *J* = 1.2 Hz, 3H), 1.57 (d, *J* = 1.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.8, 128.9, 128.0, 125.6, 124.3, 42.7, 21.4, 21.0, 15.4.

(*E*)-7-Styrylcyclohepta-1,3,5-triene (43c)

To tropylium tetrafluoroborate (4.2 g, 23.8 mmol, 1.0 equiv) in DMF (100 mL) at 0 °C was added (*E*)-trifluoro(styryl)-λ^4-borane, potassium salt (5.0 g, 23.8 mmol, 1.0 equiv) in one portion. The solution was allowed to warm up slowly to 23 °C and quenched after 2 h by adding water and Et_2O. The phases were separated and the aq. phase was two times extracted with Et_2O. The combined organic phase was washed three times with a diluted solution of NaCl, followed by one washing with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by filtering over a big silica plug (100 g SiO_2, eluent: pentane), affording 4.1 g (21.1 mmol, 89%) of a colorless to faint green oil.

The characterization data matched our previously reported data.[280]

(*E*)-1-(4-(2-(Cyclohepta-2,4,6-trien-1-yl)vinyl)phenyl)ethan-1-one (43d):

Potassium (E)- 4-(acetyl)styryl trifluoroborate(48d)

To (*E*)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)ethan-1-one (2.720 g, 10.0 mmol, 1.0 equiv, prepared by hydroboration of the corresponding alkyne[281]) in MeOH (54 mL) at 0 °C was added KHF_2 (3.440 g, 44.0 mmol, 4.4 equiv) in water (12 mL). The reaction mixture was stirred for 1h at 23 °C. Then the reaction mixture was evaporated to dryness and the residue was placed in a Soxhlett cartridge and extracted with refluxing acetone for 3 h. After evaporating acetone, the residue was triturated with Et_2O and filtered affording 1.83 g (7.2 mmol, 72%) of a white powder.

NMR data are in agreement with literature.[282]

^{1}H NMR (500 MHz, DMSO-d^6) δ 7.88 – 7.81 (m, 2H), 7.47 – 7.41 (m, 2H), 6.54 (d, *J* = 18.3 Hz, 1H), 6.40 (dq, *J* = 18.2, 3.5 Hz, 1H), 2.53 (s, 3H).

280 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.
281 Murata, M.; Watanabe, S.; Masuda, Y. *J. Chem. Res.* **2002**, *2002*, 142-143.
282 Presset, M.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 12837-12843.

^{13}C NMR (101 MHz, DMSO-d^6) δ 197.2, 145.0, 134.4, 132.3 (q, *J* = 4.4 Hz), 128.5, 125.4, 26.6.

^{19}F NMR(376 MHz, DMSO-d^6) δ 138.3.

M.p.: >280 °C (decomp.).

HRMS-ESI: calculated for $C_{10}H_9BF_3O$ [M-K]$^-$: 213.0704; found: 213.0697.

(E)-1-(4-(2-(Cyclohepta-2,4,6-trien-1-yl)vinyl)phenyl)ethan-1-one (43d)

To potassium (*E*)- 4-(acetyl)styryl trifluoroborate (1.30 g, 5.16 mmol, 1.05 equiv) in DMF (20 mL) at 0 °C was added tropylium tetrafluoroborate (0.875 g, 4.92 mmol, 1.00 equiv) in one portion. The solution was allowed to warm slowly up to 23 °C and quenched after 3 h by adding water and EtOAc. The phases were separated and the aq. phase was two times extracted with EtOAc. The combined organic phase was washed three times with a diluted solution of NaCl, followed by one washing with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (220 g SiO_2, eluent: pentane to 50% Et_2O) affording **1c** (823 mg, 4.92 mmol, 71%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.49 – 7.44 (m, 2H), 6.74 – 6.68 (m, 2H), 6.65 (dd, *J* = 15.9, 7.1 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.28 – 6.23 (m, 2H), 5.34 (dd, *J* = 8.9, 5.8 Hz, 2H), 2.59 (s, 3H), 2.55 – 2.47 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 142.2, 136.0, 134.1, 131.2, 129.8, 128.9, 126.4, 125.0, 123.7, 42.2, 26.7.

M.p.: 52-53 °C.

HRMS-ESI: calculated for $C_{17}H_{17}O$ [M+H]$^+$: 237.1274; found: 237.1277.

(*E*)-7-(4-Methoxystyryl)cyclohepta-1,3,5-triene (43e)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0M, 1.5 mL, 1.5 mmol, 1.0 equiv) was added to a solution of **68a** (472 mg, 1.5 mmol, 1.0 equiv) in dry THF (15 mL, 0.1 M) at -78 °C under an argon atmosphere. After stirring for 5 minutes, *p*-anisaldehyde (365 μL, 3.0 mmol, 2.0 equiv) was added neat over the glass and stirring at -78 °C was continued for another h before the solution was

allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O, dried over Na_2SO_4 and flash chromatography (110 g, SiO_2, eluent: pentane) yielded **1b** (258 mg, 1.15 mmol, 77%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 6.91 – 6.87 (m, 2H), 6.74 – 6.71 (m, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.41 (dd, *J* = 15.9, 7.5 Hz, 1H), 5.36 (dd, *J* = 8.9, 5.7 Hz, 2H), 3.84 (s, 3H), 2.46 – 2.41 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 131.0, 130.2, 129.9, 128.9, 127.3, 124.7, 124.5, 114.0, 55.3, 42.1.

M.p.: 47-48 °C.

HRMS-APCI: calculated for $C_{16}H_{17}O$ $[M+H]^+$: 225.1274; found: 225.1271

(*E*)-4-(2-(Cyclohepta-2,4,6-trien-1-yl)vinyl)-1,1'-biphenyl (43f):

Potassium (E)-(2-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate (48f)

The product was synthesized using a modified literature procedure.[282]

To *trans*-2-(4-biphenyl)vinylboronic acid (1.07 g, 4.76 mmol, 1.0 equiv) in MeOH (95 mL) was added a solution of KHF_2 (1.635 g, 20.93 mmol, 4.4 equiv) in water (21 mL) and stirred for 3 h at 23 °C. Then the reaction mixture was evaporated to dryness and the residue was placed in a Soxhlett cartridge and extracted with refluxing acetone for 72 h. The long extraction time is necessary for obtaining good yields because of the low solubility of the product. Acetone was evaporated and the residue was triturated in Et_2O and filtered affording 1.13 g (4.76 mmol, 83%) of a white solid.

The characterization data corresponds to literature data.[282]

^{1}H NMR (500 MHz, DMSO-d^6) δ 7.68 – 7.62 (m, 2H), 7.59 – 7.54 (m, 2H), 7.47 – 7.43 (m, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 1H), 6.53 (d, *J* = 18.2 Hz, 1H), 6.26 (dq, *J* = 18.2, 3.5 Hz, 1H).

(E)-4-(2-(Cyclohepta-2,4,6-trien-1-yl)vinyl)-1,1'-biphenyl (43f)

To potassium (*E*)-(2-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate (1.23 g, 4.3 mmol, 1.05 equiv) in DMF (16.5 mL) at 0 °C was added tropylium

tetrafluoroborate (0.73 g, 4.1 mmol, 1.00 equiv) in one portion. The solution was allowed to warm slowly up to 23 °C and quenched after 2 h by adding water and EtOAc. The phases were separated and the aq. phase was two times extracted with EtOAc. The combined organic phase was washed three times with a diluted solution of NaCl, followed by one washing with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (220 g SiO_2, eluent: pentane) affording **1i** (0.95 g, 4.10 mmol, 86%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 2H), 7.58 – 7.55 (m, 2H), 7.49 – 7.42 (m, 4H), 7.37 – 7.32 (m, 1H), 6.76 – 6.66 (m, 2H), 6.62 – 6.53 (m, 2H), 6.29 – 6.21 (m, 2H), 5.36 (dd, *J* = 9.0, 5.7 Hz, 2H), 2.52 – 2.43 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 136.6, 131.3, 131.2, 130.2, 128.9, 127.4 (two signals), 127.1, 126.8, 124.8, 124.5, 42.3.

M.p.: 101-103 °C.

HRMS-ESI: calculated for $C_{21}H_{19}$ $[M+H]^+$: 271.1481; found: 271.1491.

(*E*)-7-(3,5-Dimethoxystyryl)cyclohepta-1,3,5-triene (43g):

Potassium (E)-(3,5-dimethoxystyryl)trifluoro-borane (48g)

The compound was synthesized according the literature procedure.[283]

To a solution of (*E*)-2-(3,5-dimethoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1g, 3.44 mmol, 1.0 equiv) in acetonitrile (5.4 mL, 0.64M) at 0 °C, was added a saturated aqueous solution of KHF_2 (2.3 mL, 10.3 mmol, 3.0 equiv) over 5 minutes. The reaction was left to stir over night at room whilst warming to room temperature. Then the reaction mixture was evaporated to dryness and the residue was placed in a Soxhlett cartridge and extracted with refluxing acetone for 72 h. The long extraction time is necessary for obtaining good yields because of the low solubility of the product. Acetone was evaporated and the residue was triturated in Et_2O and filtered affording 834 mg (3.09 mmol, 90%) of a white solid.

283 Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2947-2950.

NMR data are in agreement with the literature.

(E)-7-(3,5-Dimethoxystyryl)cyclohepta-1,3,5-triene (43g)

To potassium (*E*)-(3,5-dimethoxystyryl)trifluoro-λ⁴-borane (834 mg, 3.1 mmol, 1.0 equiv) in DMF (12.5 mL) at 0 °C was added tropylium tetrafluoroborate (550 mg, 3.1 mmol, 1.0 equiv) in one portion. The solution was allowed to warm slowly up to 23 °C and quenched after 2 h by adding water and EtOAc. The phases were separated and the aq. phase was two times extracted with EtOAc. The combined organic phase was washed three times with a diluted solution of NaCl, followed by one washing with brine. The organic phase was dried over $NaSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (220 g SiO_2, eluent: 1% Et_2O in pentane) affording **1f** (0.95 g, 4.10 mmol, 86%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 – 6.71 (m, 2H), 6.59 (d, *J* = 2.2 Hz, 2H), 6.57 – 6.47 (m, 2H), 6.40 (t, *J* = 2.2 Hz, 1H), 6.29 – 6.24 (m, 2H), 5.36 (dd, *J* = 8.9, 5.7 Hz, 2H), 3.84 (s, 3H), 2.47 (q, *J* = 5.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 139.4, 131.5, 131.1, 130.5, 124.6, 124.3, 104.3, 99.6, 55.4, 42.0.

HRMS-APCI: calculated for $C_{17}H_{19}O_2$ $[M+H]^+$: 255.1380; found: 255.1379.

7-(Cyclohexylidenemethyl)cyclohepta-1,3,5-triene (43h):

Diethyl (cyclohepta-2,4,6-trien-1-yl(1-hydroxycyclohexyl)methyl)phosphonate (61a)

To a solution of **52b** (226 mg, 1 mmol) in THF (4 mL) at -78 °C is added *n*-butyl lithium (0.4 mL, 2.5 M, 1 mmol) and the mixture is stirred for 15 minutes before cyclohexanone (104 µL, 1 mmol) is added and the cooling is removed. After stirring for an additional h, the reaction is quenched with NH_4Cl, extracted and dried. The material was of high enough purity to be used directly in the next step.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.60 – 6.47 (m, 2H), 6.20 – 6.10 (m, 2H), 5.20 – 4.83 (m, 2H), 4.22 – 4.06 (m, 4H), 2.33 (dd, *J* = 22.1, 4.8 Hz, 1H), 1.92 – 1.40 (m, 10H), 1.42 – 1.33 (m, 6H).

Ethyl hydrogen (cyclohepta-2,4,6-trien-1-yl(1-hydroxycyclohexyl)methyl)-phosphonate (61c)

Crude **61a** (estimated 1 mmol) is dissolved in methanol (5 mL) and an aqueous solution of NaOH (4 mL, 4 N) is added and the mixture is stirred for 72 h. The mixture is acidified until the *p*H is around 2 and extracted with CH_2Cl_2 and concentrated. The compound was of high enough purity to be used directly in the next step.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.61 – 6.48 (m, 2H), 6.14 (dt, *J* = 9.7, 5.5 Hz, 2H), 5.27 – 4.93 (m, 2H), 4.25 – 4.06 (m, 2H), 2.46 – 2.35 (m, 1H), 2.00 – 1.05 (m, 10H), 1.40 – 1.30 (m, 3H).

7-(Cyclohexylidenemethyl)cyclohepta-1,3,5-triene (43h)

Crude **61c** (estimated 1 mmol) is dissolved in $CHCl_3$ (5 mL) and diisopropyl carbodiimide (340 µL, 2.2 mmol) is added and the mixture is stirred for 4 h. Concentration and flash chromatography yields 60 mg (43% over 3 steps) of a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.69 (ddd, *J* = 3.4, 2.1, 0.8 Hz, 2H), 6.18 (dddd, *J* = 8.8, 3.9, 2.6, 1.5 Hz, 2H), 5.52 (dt, *J* = 8.4, 1.2 Hz, 1H), 5.16 (ddd, *J* = 9.6, 5.3, 0.9 Hz, 2H), 2.36 (dddd, *J* = 8.7, 6.8, 4.5, 2.7 Hz, 1H), 2.17 (t, *J* = 5.5 Hz, 2H), 2.04 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 2H), 1.64 – 1.46 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9, 131.0, 126.8, 124.0, 123.7, 37.7.

(*E*)-7-(4-(Trifluoromethyl)styryl)cyclohepta-1,3,5-triene (43i)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0M, 1.0 mL, 1.0 mmol, 1.0 equiv) was added to a solution of **68a** (314 mg, 1.0 mmol, 1.0 equiv) in dry THF (10 mL, 0.1M) at -78 °C under an argon atmosphere. After stirring for 5 minutes, 4-(trifluoromethyl)benzaldehyde (273 µL, 2.0 mmol, 2.0 equiv) was added neat over the glass and stirring at -78 °C was continued for another h before the solution was allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O, dried over Na_2SO_4 and flash chromatography (80 g, SiO_2, eluent: pentane) yielded **1d** (127 mg, 0.48 mmol, 49%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 6.74 – 6.72 (m, 2H), 6.66 – 6.56 (m, 2H), 6.32 – 6.25 (m, 2H), 5.37 (dd, *J* = 8.9, 5.8 Hz, 2H), 2.54 (q, *J* = 5.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 133.6, 131.1, 129.3, 126.3, 125.5, 125.5, 125.0, 123.7, 100.0, 42.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56.

HRMS-APCI: calculated for $C_{16}H_{14}F_3$ $[M+H]^+$: 263.1035; found: 263.1042

(*E*)-7-(4-Bromostyryl)cyclohepta-1,3,5-triene (43j)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0M, 2.0 mL, 2.0 mmol, 1.0 equiv) was added to a solution of **68a** (629 mg, 2.0 mmol, 1.0 equiv) in dry THF (8 mL, 0.25M) at -78 °C under an argon atmosphere. After stirring for 5 minutes, 4-bromobenzaldehyde (740 mg, 4.0 mmol, 2.0 equiv) was added in one portion and stirring at -78 °C was continued for another h before the solution was allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O, dried over Na_2SO_4 and flash chromatography (80 g, SiO_2, eluent: pentane) yielded **1e** (465 mg, 1.7 mmol, 85%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.30 – 7.26 (m, 2H), 6.74 – 6.72 (m, 2H), 6.57 – 6.46 (m, 2H), 6.29 – 6.24 (m, 2H), 5.35 (dd, *J* = 9.0, 5.8 Hz, 2H), 2.48 (q, *J* = 5.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.3, 131.7, 131.6, 131.1, 129.4, 127.7, 124.7, 124.0, 121.0, 42.0.

M.p.: 55-57 °C.

HRMS-APCI: calculated for $C_{15}H_{14}Br$ $[M+H]^+$: 273.0273; found: 273.0281

2-(4-(Cyclohepta-2,4,6-trien-1-yl)but-3-en-1-yl)isoindoline-1,3-dione (43k):

3-(N-phthaloyl)propionaldehyde (51i)

This compound was made according to a literature procedure.[284]

2-(4-(Cyclohepta-2,4,6-trien-1-yl)but-3-en-1-yl)isoindoline-1,3-dione (43k)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0M, 1.0 mL, 1.0 mmol, 1.0 equiv) was added to a solution of **68a** (157 mg, 0.5 mmol, 1.0 equiv) in dry THF (5 mL, 0.1M) at -78 °C under an argon atmosphere. After stirring for 5 minutes, **51i** (102 mg, 0.5 mmol, 1.0 equiv) was added neat over the glass wall and stirring at -78 °C was continued for another h before the solution was allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O, dried over Na_2SO_4 and flash chromatography (40 g, SiO_2, eluent: 10% Et_2O and 2% Et_3N in pentane) yielded a colorless oil (63 mg, 44%) as a mixture of *E* and *Z* isomers.

E isomer: **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.85 (td, *J* = 5.8, 3.1 Hz, 2H), 6.62 (dtd, *J* = 3.7, 3.1, 2.7, 0.8 Hz, 2H), 6.02 (dddd, *J* = 8.8, 3.8, 2.6, 1.4 Hz, 2H), 5.88 (ddt, *J* = 10.9, 9.5, 1.6 Hz, 1H), 5.64 – 5.57 (m, 1H), 5.01 – 4.95 (m, 2H), 3.76 (dt, *J* = 13.6, 6.9 Hz, 2H), 2.42 – 2.32 (m, 3H).

Z isomer: **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.73 (ddd, *J* = 5.7, 3.0, 1.8 Hz, 2H), 6.62 (dtd, *J* = 3.7, 3.1, 2.7, 0.8 Hz, 2H), 6.12 (dddd, *J* = 8.9, 3.8, 2.6, 1.3 Hz, 2H), 5.84 – 5.74 (m, 1H), 5.58 – 5.52 (m, 1H), 5.14 – 5.07 (m, 2H), 3.76 (dt, *J* = 13.6, 6.9 Hz, 2H), 2.53 – 2.43 (m, 2H), 2.20 (q, *J* = 6.5 Hz, 1H).

4-(Cyclohepta-2,4,6-trien-1-ylmethylene)tetrahydro-2*H*-pyran (43l)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 4.5 mL, 4.5 mmol, 3.0 equiv) was added to a solution of **4b** (883 mg, 3.0 mmol, 2.0 equiv) and tetrahydro-4*H*-pyran-4-one (139 μL, 1.5 mmol, 1.0 equiv) in dry THF (15 mL, 0.1M) at -78 °C under an argon atmosphere, and stirred for 1 h before the solution was allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O,

284 Reggelin, M.; Junker, B.; Heinrich, T.; Slavik, S.; Bühle, P. *J. Am. Chem. Soc.* **2006**, *128*, 4023-4034.

dried over Na_2SO_4 and flash chromatography (80 g, SiO_2, eluent: pentane) yielded **1h** (242 mg, 1.28 mmol, 86%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 – 6.69 (m, 2H), 6.25 – 6.18 (m, 2H), 5.65 (d, *J* = 8.5 Hz, 1H), 3.77 – 3.72 (m, 2H), 3.68 – 3.64 (m, 2H), 2.37 (dt, *J* = 8.8, 5.4 Hz, 1H), 2.33 – 2.29 (m, 2H), 2.22 – 2.18 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5, 131.0, 126.0, 125.6, 124.2, 69.6, 68.7, 37.5, 36.7, 30.1.

HRMS-APCI: calculated for $C_{13}H_{17}O$ $[M+H]^+$: 189.1274; found: 189.1274

1-Benzyl-4-(cyclohepta-2,4,6-trien-1-ylmethylene)piperidine (43m)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0M, 4.5 mL, 4.5 mmol, 3.0 equiv) was added to a solution of **68b** (883 mg, 3.0 mmol, 2.0 equiv) and 1-benzyl-4-piperidone (278 μL, 1.5 mmol, 1.0 equiv) in dry THF (15 mL, 0.1M) at -78 °C under an argon atmosphere, and stirred for 1 h before the solution was allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O, dried over Na_2SO_4 and flash chromatography (SiO_2, 1:7:16 Et_2O/CH_2Cl_2/pentane, then Et_2O) yielded **43k** (289 mg, 70%) as a colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 ? 7.31 (m, 4H), 7.30 – 7.25 (m, 1H), 6.69 (dd, *J* = 3.7, 2.6 Hz, 2H), 6.19 (dddd, *J* = 8.9, 3.9, 2.6, 1.4 Hz, 2H), 5.58 (dt, *J* = 8.6, 1.3 Hz, 1H), 5.17 (dd, *J* = 9.1, 5.3 Hz, 2H), 3.54 (s, 2H), 2.50 (dd, *J* = 6.4, 4.9 Hz, 2H), 2.42 (t, *J* = 5.7 Hz, 2H), 2.36 (dddd, *J* = 8.7, 6.9, 5.3, 2.7 Hz, 1H), 2.32 – 2.28 (m, 2H), 2.19 (td, *J* = 5.7, 5.1, 1.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 138.4, 131.0, 129.1, 128.2, 126.9, 126.3, 124.8, 124.1, 63.0, 55.2, 54.6, 37.7, 35.9, 28.7.

HRMS-APCI: calculated for $C_{20}H_{24}N$ $[M+H]^+$: 278.1903; found: 278.1912.

tert-Butyl 4-(cyclohepta-2,4,6-trien-1-ylmethylene)piperidine-1-carboxylate (43n)

A solution of lithium bis(trimethylsilyl)amide in THF (1.0M, 4.5 mL, 4.5 mmol, 3.0 equiv) was added to a solution of **68b** (883 mg, 3.0 mmol, 2.0 equiv) and 1-benzyl-4-piperidone (299 mg, 1.5 mmol, 1.0 equiv) in dry THF (15 mL, 0.1M) at -78 °C under an argon atmosphere, and stirred for 1 h before the solution was

allowed to warm to room temperature over 13 h. The reaction was quenched by the addition of water and the mixture was extracted with Et_2O, dried over Na_2SO_4 and flash chromatography (SiO_2, 1:7:16 Et_2O/CH_2Cl_2/pentane, then Et_2O) yielded **43k** (108 mg, 25%) as a colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.70 (dt, *J* = 3.6, 1.7 Hz, 2H), 6.20 (dddd, *J* = 8.8, 3.9, 2.6, 1.4 Hz, 2H), 5.67 (dt, *J* = 8.5, 1.3 Hz, 1H), 5.16 (dd, *J* = 9.1, 5.4 Hz, 2H), 3.47 (t, *J* = 5.8 Hz, 2H), 3.38 (t, *J* = 5.9 Hz, 2H), 2.37 (q, *J* = 6.4, 6.0 Hz, 1H), 2.24 (t, *J* = 5.7 Hz, 2H), 2.13 (t, *J* = 5.9 Hz, 2H), 1.49 (s, 18H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 137.3, 131.0, 126.3, 125.9, 124.3, 79.5, 62.2, 37.7, 29.7, 28.5, 28.4.

4-(Cyclohepta-2,4,6-trien-1-ylmethylene)-1-tosylpiperidine (43p)

This compound was made following a modified literature procedure.[285]

To a solution of **43m** (57 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added TFA (130 μL) and the mixture was stirred for 20 minutes. After concentration, the mixture was again dissolved in CH_2Cl_2 (1 mL) and tosyl chloride (76 mg, 0.4 mmol, 2 equiv) and triethylamine (1 mL) were added. After stirring for 12 h, the mixture was extracted and concentrated. Flash chromatography (SiO2, 0-100% Et2O in c-hexane) yields 24 mg (35%) of a colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.67 – 7.64 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.68 (dd, *J* = 3.7, 2.6 Hz, 2H), 6.17 (dddd, *J* = 8.8, 3.9, 2.6, 1.4 Hz, 2H), 5.61 (dt, *J* = 8.7, 1.2 Hz, 1H), 5.07 (dd, *J* = 9.1, 5.4 Hz, 2H), 3.09 (t, *J* = 5.8 Hz, 2H), 2.99 (t, *J* = 5.8 Hz, 2H), 2.45 (s, 3H), 2.38 – 2.34 (m, 2H), 2.30 – 2.26 (m, 1H), 2.24 (ddd, *J* = 6.4, 5.2, 1.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 135.4, 133.4, 131.0, 129.6, 127.6, 127.0, 125.4, 124.4, 47.9, 47.2, 37.6, 35.1, 28.0, 21.5.

HRMS-APCI: calculated for $C_{20}H_{24}NO_2S$ $[M+H]^+$: 342.1522; found: 342.1524.

285 Murai, K.; Komatsu, H.; Nagao, R.; Fujioka, H. *Org. Lett.* **2012**, *14*, 772-775.

Diethyl (cyclohepta-2,4,6-trien-1-ylmethyl)phosphonate (52b)

A solution of 60 (2.84 g, 12.3 mmol, 1 equiv) in THF (60 mL) and Et_2O (60 mL) is cooled to -110 °C and *tert*-butyl lithium (14.5 mL, 24.6 mmol, 2 equiv) is added. After stirring for 1 h, tropylium tetrafluoroborate (3.27 g, 18.4 mmol, 1.5 equiv) is added and the cooling is removed. When the mixture reaches ambient temperature, water is added and the mixture is extracted with EtOAc. Flash chromatography (SiO_2, 0 to 100% EtOAc in c-hexane) yields 983 mg (33%) of a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.68 (t, *J* = 3.2 Hz, 2H), 6.20 (dt, *J* = 9.2, 3.2 Hz, 2H), 5.30 (dd, *J* = 9.2, 5.3 Hz, 2H), 4.19 – 4.05 (m, 4H), 2.20 (d, *J* = 7.5 Hz, 1H), 2.11 (m, 2H), 1.40 – 1.29 (m, 6H).

(Cyclohepta-2,4,6-trien-1-ylmethyl)trimethylsilane (52c)

This compound was made following a modified literature procedure.[286]

A flask containing magnesium turnings (243 mg, 10 mmol, 2 equiv) is dried filled with argon and a crystal of iodine is added. When the magnesium is activated, a solution of chloromethyltrimethylsilane (700 µL, 5 mmol, 1 equiv) in Et_2O (4 mL) is added and the mixture is brought to reflux. Once the Grignard reagent is formed (30 min), it is added drop wise to a cooled (-78 °C) suspension of tropylium tetrafluoroborate (890 mg, 5 mmol, 1 equiv) in THF (4 mL) and the mixture was stirred before the cooling was removed. After reaching ambient temperature, the mixture is quenched with water, extracted with EtOAc and dried. Flash chromatography (SiO_2, pentane) yields 401 mg (45%) of a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.68 (dd, *J* = 3.6, 2.6 Hz, 2H), 6.14 (dddd, *J* = 8.9, 3.8, 2.5, 1.4 Hz, 2H), 5.14 (ddd, *J* = 9.3, 5.5, 0.9 Hz, 2H), 1.61 – 1.50 (m, 1H), 1.06 (d, *J* = 7.7 Hz, 2H), 0.04 (d, *J* = 0.5 Hz, 9H).

286 Beniazza, R.; Desvergnes, V. r.; Landais, Y. *Org. Lett.* **2008**, *10*, 4195-4198.

(1-(Cyclohepta-2,4,6-trien-1-yl)-2-methoxy-2-oxoethyl)triphenylphosphonium tetrafluoroborate (57)

A suspension of methyl (triphenylphosphoranylidene)acetate (1.0 g, 3.0 mmol, 1 equiv) and tropylium tetrafluoroborate (640 mg, 3.6 mmol, 1.2 equiv) in THF (9 mL) is stirred at room temperature for 24 before it is filtered and wash with THF, yielding 1.40 g (91%)of a white salt.

^{1}H NMR (300 MHz, Acetonitrile-d_3) δ 7.89 (ddq, J = 7.5, 6.6, 1.6 Hz, 3H), 7.83 – 7.67 (m, 11H), 6.72 – 6.67 (m, 2H), 6.16 (ddd, J = 41.3, 9.5, 5.0 Hz, 2H), 5.28 (dd, J = 9.4, 6.5 Hz, 1H), 5.18 (dd, J = 11.8, 6.5 Hz, 1H), 5.02 (dd, J = 9.4, 6.3 Hz, 1H), 2.36 (dq, J = 12.8, 6.4 Hz, 1H), 1.96 (p, J = 2.5 Hz, 2H).

^{31}P NMR (162 MHz, MeOD) δ 23.60.

(Carboxymethyl)triphenylphosphonium bromide (58).

This compound was made according to a literature procedure.[287]

Diethyl (bromomethyl)phosphonate (60)

This compound was made according to a literature procedure.[288]

Preparation of Julia-Kocienski reagents

5-((Cyclohepta-2,4,6-trien-1-ylmethyl)sulfonyl)-1-phenyl-1H-tetrazole (68a)

This compound was synthesized according to a modified literature procedure.[289]

To a solution of cyclohepta-2,4,6-trien-1-ylmethanol[290] (5.35 g, 43.8 mmol, 1.0 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (7.81 g, 43.8 mmol, 1.0 equiv), triphenylphosphine (11.49 g, 43.8 mmol, 1.0 equiv) in THF (175 mL, 0.25M) was added diethyl azodicarboxylate (40% toluene, 19.1 mL, 43.8 mmol, 1.0 equiv) drop wise and the reaction was left to stir for an additional 3 h. Then, ethanol

287 Galkin, V. I.; Bakhtiyarova, Y. V.; Polezhaeva, N. A.; Shaikhutdinov, R. A.; Klochkov, V. V.; Cherkasov, R. A. *Russ. J. Gen. Chem.* **1998**, *68*, 1052-1056.

288 Al-Hamouz, O. C. S.; Ali, S. A. *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 3580-3591.

289 Aïssa, C. *J. Org. Chem.* **2006**, *71*, 360-363.

290 Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873-876 Kerber, R. C.; Ehntholt, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2927-2934.

(230 mL, 0.15M) was added and the reaction was cooled to 0 °C, followed by the drop wise addition of a solution of ammonium molybdate tetrahydrate (4.31 g, 3.5 mmol, 0.15 equiv) in hydrogen peroxide (30%, 44 mL, 434 mmol, 12.5 equiv). The reaction was left to stir over night whilst warming to room temperature. Water (400 mL) was added and the mixture was extracted with CH_2Cl_2 (400 mL) 3 times. The organic layers were combined, washed with brine (400 ml), dried over Na_2SO_4 and concentrated to dryness. Flash chromatography (330 g SiO_2, eluent: 1:1:8 Et_2O:CH_2Cl_2:pentane) afforded 8.25 g (26.3 mmol, 60%) of a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 5H), 6.72 – 6.70 (m, 2H), 6.30 (dt, *J* = 9.2, 2.9 Hz, 2H), 5.40 (dd, *J* = 9.1, 6.7 Hz, 2H), 3.97 (d, *J* = 7.2 Hz, 2H), 2.97 (p, *J* = 6.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 133.0, 131.4, 129.7, 126.6, 125.2, 121.2, 57.0, 33.0.

M.p.: 98-99 °C.

HRMS-APCI: calculated for $C_{15}H_{14}N_4NaO_2S$ $[M+Na]^+$: 337.0730; found: 337.0725

1-(*tert*-Butyl)-5-((cyclohepta-2,4,6-trien-1-ylmethyl)sulfonyl)-1*H*-tetrazole (68b)

This compound was synthesized according to a modified literature procedure.[291]

To a solution of cyclohepta-2,4,6-trien-1-ylmethanol[292] (3.83 g, 31.4 mmol, 1.0 equiv), 1-*tert*-butyl-1*H*-tetrazole-5-thiol [293] (4.97 g, 31.4 mmol, 1.0 equiv), triphenylphosphine (8.24 g, 31.4 mmol, 1.0 equiv) in THF (125 mL, 0.25M) was added diethyl azodicarboxylate (40% toluene, 13.7 mL, 31.4 mmol, 1.0 equiv) drop wise and the reaction was left to stir for an additional 12 h. Then, ethanol (150 mL, 0.15M) was added and the reaction was cooled to 0 °C, followed by the drop-wise addition of a solution of ammonium molybdate tetrahydrate (3.28 g, 2.65 mmol, 0.0845 equiv) in hydrogen peroxide (30%, 33 mL, 320 mmol, 12.5 equiv). The reaction was left to stir for an additional 4 h whilst warming to room

291 Aïssa, C. *J. Org. Chem.* **2006**, *71*, 360-363.

292 a) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873-876. b) Kerber, R. C.; Ehntholt, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2927-2934.

293 Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. *Tetrahedron* **2010**, *66*, 5089-5100.

temperature. Water (200 mL) was added and the mixture was extracted with CH_2Cl_2 (200 mL) 3 times. The organic layers were combined, washed with brine (200 ml), dried over Na_2SO_4 and concentrated to dryness. Flash chromatography (330 g SiO_2, eluent: 1:1:8 Et_2O:CH_2Cl_2:pentane) afforded 4.28 g (14.5 mmol, 46%) of a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 – 6.71 (m, 2H), 6.32 (dt, *J* = 9.4, 3.3 Hz, 2H), 5.45 (dd, *J* = 9.0, 6.5 Hz, 2H), 4.12 (d, *J* = 7.1 Hz, 2H), 2.92 (p, *J* = 6.9 Hz, 1H), 1.86 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 131.4, 126.3, 121.6, 65.5, 58.0, 33.2, 29.7.

M.p.: 45-51 °C.

HRMS-APCI: calculated for $C_{13}H_{18}N_4NaO_2S$ $[M+Na]^+$: 317.1043; found: 317.1042

4-(*tert*-Butyl)-5-((1-(cyclohepta-2,4,6-trien-1-yl)ethyl)sulfonyl)-4*H*-1,2,3-triazole (68c)

To a solution of **68b** (833 mg, 3 mmol, equiv) in THF (30 mL) at -78 °C is added LiHMDS (6.6 mL, 0.5 M, 3.3 mmol, 1.1 equiv) drop wise. After stirring for 10 minutes, methyl iodide (111 μL, 6 mmol, 2 equiv) is slowly added and the cooling removed. The mixture is stirred for 4 h and concentrated. Flash chromatography (SiO_2, eluent: 1:1:8 Et_2O:CH_2Cl_2:pentane) afforded 477 mg (52%) of a light yellow solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.76 – 6.68 (m, 2H), 6.37 –6.22 (m, 2H), 5.42 (ddd, *J* = 56.4, 9.5, 6.2 Hz, 2H), 2.65 – 2.60 (m, 1H), 1.87 (s, 9H), 1.66 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 131.3, 131.2, 126.1, 125.9, 120.4, 118.4, 65.6, 61.9, 37.9, 29.7, 15.3, 11.8.

HRMS-APCI: calculated for $C_{14}H_{20}N_4NaO_2S$ $[M+Na]^+$: 331.1199; found: 311.1199.

General procedure for the gold(I)-catalyzed cyclopropanation

A solution of vinylcycloheptatriene (1.0 equiv), alkene (1.5-2.0 equiv) and gold catalyst **A** (5 mol%) in EtOAc (10 mL/mmol) was heated in a closed screw-cap tube/vial at 75 °C for 12-24 h. The reaction mixture was cooled to room

temperature, the solvent removed *in vacuo* and the crude residue was purified by column chromatography.

cis-1-Nitro-3-(2-((*E*)-styryl)cyclopropyl)benzene (71a)

This compound (yellow oil, 31.1 mg, 47%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49. mg, 250 μmol), 1-nitro-3-vinylbenzene (52 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (24 g SiO_2, eluent: gradient from pentane to 1% Et_2O in pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 1H), 8.06 (m, 1H), 7.57 (m, 1H), 7.44 (m, 1H), 7.24 – 7.18 (m, 2H), 7.17 – 7.10 (m, 3H), 6.54 (d, *J* = 15.8 Hz, 1H), 5.45 (dd, *J* = 15.7, 9.1 Hz, 1H), 2.51 (m, 1H), 2.29 – 1.97 (m, 1H), 1.48 (m, 1H), 1.24 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 141.3, 137.3, 135.5, 131.2, 129.1, 128.7, 128.6, 127.1, 125.8, 123.9, 121.4, 23.6, 23.2, 12.9.

cis-(*E*)-1-Methyl-3-(2-styrylcyclopropyl)benzene (71b)

This compound (colorless crystals, 43.7 mg, 75%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), 1-methyl-3-vinylbenzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

Suitable crystals for X-ray diffraction were obtained by slow evaporation of a solution in Chloroform.

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).[294]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 7H), 7.08 – 7.03 (m, 2H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.57 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.36 (s, 3H), 2.04 (qd, *J* = 8.9, 5.5 Hz, 1H), 1.38 (td, *J* = 8.4, 5.2 Hz, 1H), 1.15 (dt, *J* = 6.3, 5.4 Hz, 1H).

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^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 137.8, 137.6, 130.8, 130.1, 129.4, 128.4, 128.0, 126.8, 126.5, 126.0, 125.7, 23.8, 22.7, 21.5, 12.6.

M.p.: 28-30 °C.

HRMS-APCI: calculated for $C_{18}H_{19}$ $[M+H]^+$: 235.1481; found: 235.1475.

cis-((*E*)-2-(2-Phenylcyclopropyl)vinyl)benzene (71c)

This compound (colorless oil, 37 mg, 65%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), styrene (53.6 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.11 (m, 10H), 6.53 (d, *J* = 15.7 Hz, 1H), 5.55 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.48 (m, 1H), 2.05 (m, 1H), 1.39 (m, 1H), 1.16 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 , 137.9 , 130.7 , 129.7 , 129.3 , 128.5 , 128.2 , 126.7 , 126.2 , 125.8 , 24.0 , 22.8 , 12.7 .

HRMS-APCI: calculated for $C_{17}H_{17}$ $[M+H]^+$: 221.1325; found: 221.1322.

cis-1-Methyl-4-(2-((*E*)-styryl)cyclopropyl)benzene (71d)

This compound (colorless oil, 41.5 mg, 69%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1-methyl-4-vinylbenzene (60.8 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 6.96 (m, 9H), 6.59 (d, *J* = 15.7 Hz, 1H), 5.63 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.48 (m, 1H), 2.40 (s, 3H), 2.06 (m, 1H), 1.42 (m, 1H), 1.17 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 135.7, 135.6, 130.9, 129.5, 129.2, 128.9, 128.5, 126.6, 125.8, 23.7, 22.8, 21.2, 12.8.

HRMS-APCI: calculated for $C_{18}H_{19}$ $[M+H]^+$: 235.1481; found: 235.1477.

cis-1-Chloro-4-(2-((*E*)-styryl)cyclopropyl)benzene (71e)

This compound (colorless oil, 49 mg, 75%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1-chloro-4-vinylbenzene (71.3 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 - 7.32 (m, 9 H), 6.56 (d, J=15.8 Hz, 1 H), 5.52 (dd, J=15.8, 9.4 Hz, 1 H), 2.38 - 2.49 (m, 1 H), 2.01 - 2.13 (m, 1 H), 1.37 - 1.46 (m, 1 H), 1.08 - 1.19 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 , 137.4 , 131.9 , 130.7 , 130.1 , 130.0 , 128.6 , 128.3 , 126.9 , 125.8 , 23.3 , 22.8 , 12.8 .

HRMS-APCI: calculated for $C_{17}H_{16}Cl$ $[M+H]^+$: 255.0935; found: 255.0923.

cis-1-(2-((*E*)-Styryl)cyclopropyl)-4-(trifluoromethyl)benzene (71f)

This compound (colorless oil, 44 mg, 59%, d.r. 19:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1-(trifluoromethyl)-4-vinylbenzene (89.0 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J=8.2 Hz, 2H), 7.39 (d, J=8.2 Hz, 2H), 7.27 (m, 2H), 7.18 (m, 3H), 6.58 (d, J=15.8 Hz, 1H), 5.53 (dd, J=15.6, 9.2 Hz, 1H), 2.50 (m, 1H), 2.14 (m, 1H), 1.47 (m, 1H), 1.22 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2 , 137.5 , 130.6 , 129.5 , 129.4 , 128.6 , 128.4 (q, J=32.3 Hz), 127.0 , 125.8 , 125.2 (q, *J* = 3.7 Hz), 124.5 (q, J= 272.6 Hz), 23.8 , 23.3 , 13.0 .

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.2 .

HRMS-APCI: calculated for $C_{18}H_{16}F_3$ $[M+H]^+$: 289.1199; found: 289.1192.

cis-(*E*)-1-Fluoro-4-(2-styrylcyclopropyl)benzene (71g)

This compound (colorless oil, 38.8 mg, 65%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25

μmol), 1-fluoro-4-vinylbenzene (45.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 4H), 7.17 – 7.15 (m, 3H), 7.03 – 6.98 (m, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 5.49 (dd, *J* = 15.7, 9.4 Hz, 1H), 2.43 (q, *J* = 8.3 Hz, 1H), 2.03 (qd, *J* = 8.8, 5.5 Hz, 1H), 1.40 (td, *J* = 8.4, 5.2 Hz, 1H), 1.12 – 1.07 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 244.0 Hz), 137.6, 134.4 (d, *J* = 3.2 Hz), 130.7 (d, *J* = 7.9 Hz), 130.3, 129.7, 128.4, 126.7, 125.6 , 114.9 (d, *J* = 21.2 Hz), 23.0, 22.4, 12.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.17 (ddd, *J* = 13.9, 8.9, 5.4 Hz).

HRMS-APCI: calculated for $C_{17}H_{14}F$ $[M-H]^+$: 237.1074; found: 237.1068.

cis-1-Methoxy-4-(2-((*E*)-styryl)cyclopropyl)benzene (71h)

This compound (yellow oil that solidifies in the freezer, 45 mg, 70%, d.r. 15:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1-methoxy-4-vinylbenzene (51.8 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: gradient from pentane to 1% Et_2O in pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 7H), 6.89 (m, 2H), 6.56 (d, J=15.8 Hz, 1H), 5.56 (dd, J=15.8, 9.4 Hz, 1H), 3.84 (s, 3H), 2.44 (m, 1H), 2.02 (m, 1H), 1.39 (m, 1H), 1.11 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 137.9, 131.1, 130.9, 130.4, 129.4, 128.5, 126.6, 125.7, 113.9, 55.3, 23.2, 22.5, 12.8.

HRMS-APCI: calculated for $C_{18}H_{19}O$ $[M+H]^+$: 251.1430; found: 251.1425.

cis-(*E*)-4-(2-Styrylcyclopropyl)phenyl acetate (71i)

This compound (colorless solid, 47.1 mg, 68%, d.r. 19:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25

μmol), 4-vinylphenyl acetate (57.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: 99:1 pentane/Et_2O).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.25 – 7.22 (m, 2H), 7.17 – 7.12 (m, 3H), 7.05 – 7.02 (m, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 5.53 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.31 (s, 3H), 2.08 – 2.00 (m, 1H), 1.40 (td, *J* = 8.4, 5.2 Hz, 1H), 1.13 – 1.08 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 149.0, 138.0, 136.4, 130.3, 130.2, 129.8, 128.4, 126.6, 125.7, 121.1, 23.3, 22.5, 21.2, 12.9.

M.p.: 61-63 °C.

HRMS-APCI: calculated for $C_{19}H_{18}NaO_2$ $[M+Na]^+$: 301.1199; found: 301.1187.

cis-Methyl 4-(2-((*E*)-styryl)cyclopropyl)benzoate (71j)

This compound (white solid, 38.5 mg, 54%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), methyl 4-vinylbenzoate (62.6 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: gradient from pentane to 6% Et_2O in pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J=8.2 Hz, 2H), 7.31 (d, J=8.2 Hz, 2H), 7.21 (m, 2 H), 7.13 (m, 3H), 6.53 (d, J=15.8 Hz, 1H), 5.51 (dd, J=15.6, 9.2 Hz, 1H), 3.91 (s, 3 H), 2.48 (m, 1H), 2.10 (m, 1 H), 1.43 (m, 1H), 1.23 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 , 144.6 , 137.5 , 130.5 , 129.5 , 129.5 , 129.1 , 128.5 , 128.0 , 126.9 , 125.8 , 52.1 , 24.1 , 23.5 , 13.0 .

M.p.: 60-61 °C.

HRMS-ESI: calculated for $C_{19}H_{18}NaO_2$ $[M+Na]^+$: 301.1199; found: 301.1210.

cis-(*E*)-1-(*tert*-Butyl)-4-(2-styrylcyclopropyl)benzene (71k)

This compound (colorless oil, 48.4 mg, 70%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25

μmol), 1-(*tert*-butyl)-4-vinylbenzene (69.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.26 – 7.13 (m, 7H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.60 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.08 – 1.98 (m, 1H), 1.38 (td, *J* = 8.5, 5.2 Hz, 1H), 1.34 (s, 9H), 1.13 (dt, *J* = 6.4, 5.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 137.9, 135.6, 131.0, 129.3, 128.8, 128.4, 126.5, 125.7, 125.0, 34.4, 31.4, 23.5, 22.7, 12.8.

HRMS-APCI: calculated for $C_{21}H_{23}$ $[M-H]^+$: 275.1794; found: 275.1792.

cis-4-(2-((*E*)-Styryl)cyclopropyl)-1,1'-biphenyl (71l)

This compound (yellow viscous oil, 63 mg, 83%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 4-vinyl-1,1'-biphenyl (69.6 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=7.6 Hz, 2 H), 7.49 (d, J=7.9 Hz, 2 H), 7.39 (m, 2 H), 7.29 (m, 3 H), 7.12 (m, 5 H), 6.51 (d, J=15.8 Hz, 1 H), 5.57 (dd, J=15.6, 9.5 Hz, 1 H), 2.43 (m, 1 H), 2.01 (m, 1 H), 1.36 (m, 1 H), 1.13 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 139.0, 138.1, 137.8, 130.6, 129.9, 129.7, 128.9, 128.5, 127.2, 127.1, 126.9, 126.7, 125.8, 23.7, 23.1, 12.9.

HRMS-APCI: calculated for $C_{23}H_{21}$ $[M+H]^+$: 297.1641; found: 297.1638.

M.p.: 74-75 °C.

cis-(*E*)-3-(2-Styrylcyclopropyl)benzaldehyde (71m)

This compound (colorless oil, 44.7 mg, 72%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), 3-vinylbenzaldehyde (48.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: 99:1 to 80:20 pentane/ Et_2O).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.83 – 7.78 (m, 1H), 7.74 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.55 (ddt, *J* = 7.7, 2.0, 0.8 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.18 – 7.10 (m, 3H), 6.55 (d, *J* = 15.8 Hz, 1H), 5.48 (dd, *J* = 15.7, 9.3 Hz, 1H), 2.53 (td, *J* = 8.6, 6.6 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.49 – 1.44 (m, 1H), 1.25 (dt, *J* = 6.5, 5.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 140.1, 137.4, 136.4, 135.4, 130.4, 130.0, 129.4, 128.8, 128.4, 127.8, 126.8, 125.7, 23.5, 22.9, 12.6.

HRMS-APCI: calculated for $C_{18}H_{16}NaO$ $[M+Na]^+$: 271.1093; found: 271.1089.

cCis-1-Bromo-3-(2-((*E*)-styryl)cyclopropyl)benzene (71n)

This compound (colorless oil, 43 mg, 56%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1-bromo-3-vinylbenzene (94 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (br. s, 1H), 7.33 (m, 1H), 7.22 (m, 2H), 7.19 – 7.10 (m, 5H), 6.52 (d, *J* = 15.7 Hz, 1H), 5.49 (dd, *J* = 15.7, 9.4 Hz, 1H), 2.41 (m, 1H), 2.04 (m, 1H), 1.38 (m, 1H), 1.12 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 137.7, 132.4, 130.3, 129.8, 129.7, 129.3, 128.6, 127.9, 126.9, 125.8, 122.4, 23.7, 23.0, 12.7.

HRMS-APCI: calculated for $C_{17}H_{16}Br$ $[M+H]^+$: 299.0418; found: 299.0430.

cis-1-(2-((*E*)-Styryl)cyclopropyl)-3-(trifluoromethyl)benzene (71o)

This compound (colorless oil, 37.8 mg, 52%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1-(trifluoromethyl)-3-vinylbenzene (66.5 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br. s, 1H), 7.50 – 7.36 (m, 3H), 7.22 (m, 2H), 7.15 (m, 3H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.48 (dd, *J* = 15.7, 9.3 Hz, 1H), 2.48 (m, 1H), 2.10 (m, 1H), 1.44 (m, 1H), 1.18 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0 , 137.6 , 132.7 (q, *J* = 1.2 Hz), 130.6 (q, *J* = 31.9 Hz), 130.6 , 129.5 , 128.6 , 128.6 , 127.0 , 126.0 (q, *J* = 3.7 Hz), 125.8 , 123.1 (q, *J* = 3.9 Hz), 23.7 , 22.9 , 12.8 .

HRMS-APCI: calculated for $C_{18}H_{15}F_3$ $[M+H]^+$: 289.1186; found: 289.1199.

cis-(*E*)-1-Methyl-2-(2-styrylcyclopropyl)benzene (71p)

This compound (colorless oil, 38.2 mg, 65%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), 1-methyl-2-vinylbenzene (49.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.10 (m, 9H), 6.53 (d, *J* = 15.8 Hz, 1H), 5.37 (dd, *J* = 15.8, 9.8 Hz, 1H), 2.37 (m, 1H),, 2.36 (s, 3H), 2.12 (qd, *J* = 8.5, 5.1 Hz, 1H), 1.41 (td, *J* = 8.4, 5.2 Hz, 1H), 1.18 (dt, *J* = 6.7, 5.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 137.8, 137.1, 130.8, 129.6, 129.2, 128.5, 128.4, 126.5, 126.4, 125.6, 125.5, 22.9, 22.1, 19.7, 12.4.

HRMS-APCI: calculated for $C_{18}H_{19}$ $[M+H]^+$: 235.1481; found: 235.1471.

cis-(*E*)-1-Fluoro-2-(2-styrylcyclopropyl)benzene (71q)

This compound (colorless oil, 36.0 mg, 60%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), 1-fluoro-2-vinylbenzene (45.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 4H), 7.16 – 7.12 (m, 3H), 7.12 – 7.08 (m, 1H), 7.05 – 7.00 (m, 1H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.52 (dd, *J* = 15.7, 9.3 Hz, 1H), 2.48 (q, *J* = 8.3 Hz, 1H), 2.13 (qd, *J* = 8.8, 5.6 Hz, 1H), 1.42 (td, *J* = 8.4, 5.3 Hz, 1H), 1.22 – 1.15 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7 (d, *J* = 246.2 Hz), 137.7, 129.9, 129.9 (d, *J* = 4.2 Hz), 129.8, 128.4, 127.7 (d, *J* = 8.1 Hz), 126.6, 126.0 (d, *J* = 14.8 Hz), 125.7, 123.5 (d, *J* = 3.6 Hz), 115.1 (d, *J* = 21.8 Hz), 22.1, 18.1 (d, *J* = 3.6 Hz), 11.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.71 (dt, *J* = 10.3, 6.6 Hz).

HRMS-APCI: calculated for $C_{17}H_{16}F$ $[M+H]^+$: 239.1231; found: 239.1227.

cis-1-Bromo-2-(2-((*E*)-styryl)cyclopropyl)benzene (71r)

This compound (colorless oil, 51 mg, 66%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1-bromo-2-vinylbenzene (141 mg, 772 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.33 – 7.19 (m, 4H), 7.19 – 7.08 (m, 4H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.43 (dd, *J* = 15.7, 9.2 Hz, 1H), 2.52 (m, 1H), 2.21 (m, 1H), 1.46 (m, 1H), 1.22 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 137.9, 132.6, 130.2, 130.0, 129.7, 128.5, 127.9, 127.3, 127.0, 126.7, 125.8, 25.6, 22.9, 12.9.

HRMS-APCI: calculated for $C_{17}H_{16}Br$ $[M+H]^+$: 299.0422; found: 299.0430.

cis-1,3,5-Trimethyl-2-(2-((*E*)-styryl)cyclopropyl)benzene (71t)

This compound (colorless oil, 31.5 mg, 37%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1,3,5-trimethyl-2-vinylbenzene (56.6 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 2H), 7.18 – 7.08 (m, 3H), 6.83 (m, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 5.41 (dd, *J* = 15.8, 9.8 Hz, 1H), 2.39 (s, 6H), 2.29 (s, 3H), 2.19 (m, 1H), 2.09 (m, 1H), 1.63 – 1.51 (m, 1H), 0.92 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1 , 135.7 , 132.4 , 132.2 , 129.0 (two signals), 128.9 , 128.5 , 126.6 , 125.8 , 22.75 , 21.0 , 20.9 (two signals), 16.5 .

HRMS-APCI: calculated for $C_{20}H_{23}$ $[M+H]^+$: 263.1789; found: 263.1794.

cis-2-(2-((*E*)-Styryl)cyclopropyl)naphthalene (71u)

This compound (white solid, 50.5 mg, 73%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 2-vinylnaphthalene (60 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 2H), 7.80 (m, 1H), 7.77 – 7.74 (m, 1H), 7.59 – 7.37 (m, 3H), 7.25 – 7.03 (m, 5H), 6.59 (d, *J* = 15.7 Hz, 1H), 5.58 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.81 – 2.52 (m, 1H), 2.28 – 2.04 (m, 1H), 1.49 (, 1H), 1.32 (, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 136.6, 133.6, 132.3, 130.6, 129.8, 128.5, 128.3, 127.8 (two signals) , 127.7, 127.4, 126.7, 126.0, 125.8, 125.4, 24.3, 23.1, 12.9.

M.p.: 73-74 °C.

HRMS-APCI: calculated for $C_{21}H_{19}$ $[M+H]^+$: 271.1492; found: 271.1481.

cis-(1-Methyl-2-((*E*)-styryl)cyclopropyl)benzene (71v)

This compound (colorless oil, 42.9 mg, 73%, d.r. 5:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), α-methylstyrene (49.0 μL, 375 μmol) and gold catalyst A (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 5H), 7.24 – 7.21 (m, 3H), 7.15 – 7.12 (m, 2H), 6.49 (d, *J* = 15.8 Hz, 1H), 5.33 (dd, *J* = 15.8, 9.8 Hz, 1H), 1.85 (ddd, *J* = 5.9, 7.6, 9.8 Hz, 1H), 1.48 (s, 3H), 1.21 – 1.18 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 137.9, 132.7, 129.6, 128.4, 128.3, 128.1, 126.4, 126.2, 125.6, 29.7, 28.8, 22.3, 21.1.

HRMS-APCI: calculated for $C_{18}H_{19}$ $[M+H]^+$: 235.1481; found: 235.1483.

cis-(*E*)-(2-Styrylcyclopropane-1,1-diyl)dibenzene (71w)

This compound (colorless oil, 54.4 mg, 73%) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), ethene-1,1-diyldibenzene (66.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.35 (td, *J* = 7.6, 1.8 Hz, 2H), 7.31 – 7.23 (m, 7H), 7.21 – 7.16 (m, 4H), 6.60 (dd, *J* = 15.7, 2.0 Hz, 1H), 5.51 (ddd, *J* = 15.7, 9.7, 2.2 Hz, 1H), 2.45 (tdd, *J* = 8.5, 5.9, 1.8 Hz, 1H), 1.78 (ddd, *J* = 8.6, 5.0, 1.8 Hz, 1H), 1.66 – 1.62 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5, 141.4, 137.7, 131.7, 131.0, 129.2, 128.5, 128.4, 128.3, 127.2, 126.7, 126.7, 125.9, 125.8, 37.6, 31.1, 22.9.

HRMS-APCI: calculated for $C_{23}H_{20}Na$ $[M+Na]^+$: 319.1457; found: 319.1463.

cis-(E)-(2-(2-Methyl-3-phenylcyclopropyl)vinyl)benzene (71x)

This compound (colorless oil, 26.6 mg, 45%, d.r. 3:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), (*E*)-prop-1-en-1-ylbenzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (24 g SiO_2, eluent: pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.23 (m, 4H), 7.18 – 7.10 (m, 4H), 6.50 (d, *J* = 15.7 Hz, 1H), 5.62 (dd, *J* = 15.7, 9.6 Hz, 1H), 2.21 – 2.17 (dd, *J* = 6.27, 8.83 1H), 1.78 (td, *J* = 9.2, 4.9 Hz, 1H), 1.53 (dq, *J* = 11.6, 5.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 137.8, 130.3, 129.2, 128.9, 128.4, 128.1, 126.5, 125.9, 125.6, 32.6, 31.8, 20.9, 18.6.

HRMS-APCI: calculated for $C_{18}H_{19}$ $[M+H]^+$: 235.1481; found: 235.1487.

cis-(E)-(2-(2,2-Dimethyl-3-phenylcyclopropyl)vinyl)benzene (71y)

This compound (colorless oil, 21.5 mg, 35%, d.r 8:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), (2-methylprop-1-en-1-yl)benzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (24 g SiO_2, eluent: pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 10H), 6.59 (d, *J* = 15.7 Hz, 1H), 5.79 (dd, *J* = 15.7, 10.3 Hz, 1H), 2.24 (d, *J* = 8.8 Hz, 1H), 1.87 (dd, *J* = 10.2, 9.0 Hz, 1H), 1.35 (s, 3H), 1.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1, 137.6, 131.1, 129.6, 129.3, 128.5, 128.0, 126.5, 126.0, 125.7, 35.0, 32.8, 28.9, 23.6, 17.8.

HRMS-APCI: calculated for $C_{19}H_{21}$ $[M-H]^+$: 249.1638; found: 249.1643.

1-((*E*)-Styryl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene (71z)

This compound (colorless oil, 51 mg, 85%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), indene (59.8 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 1H), 7.29 – 7.20 (m, 5H), 7.20 – 7.10 (m, 3H), 6.67 (d, *J* = 15.8 Hz, 1H), 5.41 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.30 (dd, *J* = 17.4, 7.1 Hz, 1H), 3.02 (d, *J* = 17.4 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.30 – 2.23 (m, 1H), 2.09 (dd, *J* = 17.1, 8.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 142.4, 137.9, 132.0, 128.5, 126.8, 126.5, 126.1, 125.9, 125.8, 124.7, 124.2, 32.3, 32.0, 26.2, 24.3.

HRMS-APCI: calculated for $C_{18}H_{17}$ $[M+H]^+$: 233.1322; found: 232.1325.

endo-6a-Methyl-1-((_E_)-styryl)-1,1a,6,6a-tetrahydrocyclopropa[_a_]indene (71aa)

This compound (white solid, 41.5 mg, 66%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 2-methyl-1H-indene (50.3 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 1H), 7.30 – 7.10 (m, 8H), 6.67 (d, *J* = 15.8 Hz, 1H), 5.45 (dd, *J* = 15.8, 9.4 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.66 (dd, *J* = 7.9, 0.7 Hz, 1H), 2.01 (dd, *J* = 9.2, 8.2 Hz, 1H), 1.56 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 143.1, 137.8, 131.5, 128.4, 126.6, 126.4, 126.3, 125.8, 125.6, 124.3, 124.0, 38.6, 38.5, 33.7, 31.9, 22.8.

M.p.: 65-67 °C.

HRMS-APCI: calculated for $C_{19}H_{19}$ $[M+H]^+$: 247.1481; found: 247.1483.

endo-5-Bromo-6a-methyl-1-((_E_)-styryl)-1,1a,6,6a-tetrahydrocyclopropa-[_a_]indene (71ab)

This compound (yellow solid, 56.5 mg, 71%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 7-bromo-1H-indene (75 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ7.35 – 7.30 (m, 1H), 7.25 – 7.20 (m, 3H), 7.17 – 7.09 (m, 3H), 7.07 – 7.02 (m, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 5.34 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.21 (dd, *J* = 18.1, 7.0 Hz, 1H), 3.00 (d, *J* = 18.1 Hz, 1H), 2.91 (ddd, *J* = 7.9, 6.1, 1.8 Hz, 1H), 2.25 (dddd, *J* = 8.1, 7.0, 6.1, 0.9 Hz, 1H), 2.06 (dd, *J* = 17.2, 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 144.1, 137.6, 132.7, 129.2, 128.6, 128.5, 127.0, 125.8, 124.8, 123.6, 119.3, 34.1, 32.8, 26.1, 23.7.

M.p.: 75-76 °C.

HRMS-APCI: calculated for $C_{19}H_{19}$ $[M+H]^+$: 247.1483; found: 247.1481.

endo-1-((*E*)-Styryl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene (71ac)

This compound (viscous colorless semisolid, 31.5 mg, 50%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 1,2-dihydronaphthalene (67 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 1H), 7.24 – 7.08 (m, 8H), 6.55 (d, *J* = 15.8 Hz, 1H), 5.64 (dd, *J* = 15.8, 8.9 Hz, 1H), 2.81 (m, 1H), 2.57 – 2.47 (m, 1H), 2.36 (m, 1H), 2.14 – 2.04 (m, 2H), 2.02 – 1.93 (m, 1H), 1.81 (ddd, *J* = 15.0, 8.8, 3.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 136.6, 135.0, 131.5, 130.2, 128.5 (two signals), 127.6, 126.8, 126.3, 125.80, 125.77, 28.6, 27.9, 21.0, 20.0, 19.2.

HRMS-APCI: calculated for $C_{19}H_{19}$ $[M+H]^+$: 247.1489 found: 247.1481.

endo-1-((*E*)-Styryl)-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene (71ad)

This compound (white solid, 36 mg, 56%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol), 2H-chromene (68 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: gradient from 0.5% Et_2O in pentane to 1.5% Et_2O in pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 5H), 7.21 – 7.11 (m, 2H), 6.99 – 6.88 (m, 2H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.05 (dd, *J* = 15.8, 9.6 Hz, 1H), 4.45 (dd, *J* = 11.2, 0.8 Hz, 1H), 4.24 (dd, *J* = 11.2, 3.0 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.26 (dd, *J* = 17.7, 8.6 Hz, 1H), 2.00 – 1.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 137.7, 132.5, 129.8, 128.5, 127.2, 126.9, 126.4, 126.0, 122.6, 121.5, 117.1, 62.0, 28.4, 22.9, 18.6.

M.p.: 88-90 °C.

HRMS-APCI: calculated for $C_{18}H_{17}O$ $[M+H]^+$: 249.1269; found: 249.1274.

(*E*)-(3-Styrylcyclopropane-1,2-diyl)dibenzene (71ae)

This compound (47% quantified by ^{1}H NMR) was prepared according to the general procedure from (E)-7-styrylcyclohepta-1,3,5-triene (19 mg, 100 μmol), (*E*)-stilbene (32 mg, 150 μmol) and gold catalyst **A** (3.9 mg, 5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: pentane) but the alkene could not entirely be removed.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.33 (m, 6H), 7.30 – 7.16 (m, 10H), 6.59 (d, *J* = 15.8 Hz, 1H), 5.73 (dd, *J* = 15.8, 9.5 Hz, 1H), 2.88 (dd, *J* = 9.2, 6.1 Hz, 1H), 2.63 (t, *J* = 5.6 Hz, 1H), 2.37 (td, *J* = 9.3, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 138.0, 137.5, 130.2, 129.2, 129.0, 128.5, 128.4, 128.3, 126.8, 126.4, 126.2, 126.0, 125.8, 34.0, 33.6, 31.1.

(*E*)-4,4'-(3-Styrylcyclopropane-1,2-diyl)bis(methoxybenzene) (71af)

This compound (47% j quantified by ^{1}H NMR) was prepared according to the general procedure from (E)-7-styrylcyclohepta-1,3,5-triene (19 mg, 100 μmol), (*E*)-1,2-bis(4-methoxyphenyl)ethene (36 mg, 150 μmol) and gold catalyst **A** (3.9 mg, 5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: 0-20% Et_2O in pentane) but the alkene could not entirely be removed.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.32 (m, 4H), 7.28 (m, 5H), 7.13 – 7.06 (m, 4H), 6.72 (d, *J* = 15.7 Hz, 1H), 6.19 (dd, *J* = 15.7, 10.3 Hz, 1H), 3.82 (s, 6H), 2.81 (d, *J* = 8.9 Hz, 2H), 2.61 – 2.49 (m, 1H).

***cis*-(*E*)-1-(2-(4-Methoxystyryl)cyclopropyl)-3-methylbenzene (74a)**

This compound (colorless oil, 31.8 mg, 48%, d.r. 12:1) was prepared according to the general procedure from (*E*)-7-(4-methoxystyryl)cyclohepta-1,3,5-triene (56.0 mg, 25 μmol), 1-methyl-3-vinylbenzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (80 g SiO_2, eluent: pentane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 6.3, 2.3 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.92 (dd, *J* = 9.3, 1.8 Hz, 2H), 6.88 – 6.82 (m, 2H), 6.44 (d, *J* = 15.8 Hz, 1H), 5.79 (dd, *J* = 15.8, 8.6 Hz, 1H), 3.82 (s, 3H), 2.35 (s, 3H), 2.00 (ddd,

J = 8.6, 5.8, 4.2 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.34 – 1.27 (m, 1H), 1.20 (dt, *J* = 8.7, 5.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 142.2, 137.9, 130.7, 130.4, 128.3, 127.6, 126.8, 126.5, 126.4, 122.7, 114.0, 55.3, 27.3, 25.6, 21.4, 16.9.

HRMS-APCI: calculated for $C_{19}H_{21}O$ $[M+H]^+$: 265.1587; found: 265.1575.

cis-1-(4-((*E*)-2-(2-(m-Tolyl)cyclopropyl)vinyl)phenyl)ethanone (74b)

This compound (colorless oil, 61.5 mg, 87%, d.r. >20:1) was prepared according to the general procedure from (*E*)-1-(4-(2-(cyclohepta-2,4,6-trien-1-yl)vinyl)phenyl)ethan-1-one (60.7 mg, 257 μmol), 1-methyl-3-vinylbenzene (45.6 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, gradient: pentane to 50% Et_2O).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 2H), 7.23 – 7.16 (m, 3H), 7.11 – 7.08 (m, 1H), 7.07 – 7.01 (m, 2H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.69 (dd, *J* = 15.7, 9.7 Hz, 1H), 2.54 (s, 3H), 2.48 (ddd, *J* = 8.5, 6.5 Hz, 1H), 2.34 (s, 3H), 2.08 – 1.99 (m, 1H), 1.40 (ddd, *J* = 8.4, 5.2 Hz, 1H), 1.19 (ddd, *J* = 6.4, 5.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 142.6, 138.4, 137.9, 135.3, 134.6, 130.2, 128.8, 128.6, 128.2, 127.2, 126.1, 125.7, 26.6, 24.5, 23.1, 21.6, 13.1.

HRMS-ESI: calculated for $C_{20}H_{20}O$ $[M+H]^+$: 277.1587; found: 277.1587.

cis-(*E*)-1-Methyl-3-(2-(4-(trifluoromethyl)styryl)cyclopropyl)benzene (74c)

This compound (colorless oil, 59.6 mg, 79%, d.r. 17:1) was prepared according to the general procedure from (*E*)-7-(4-(trifluoromethyl)styryl)cyclohepta-1,3,5-triene (66.0 mg, 25 μmol), 1-methyl-3-vinylbenzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.25 – 7.18 (m, 3H), 7.13 – 7.03 (m, 3H), 6.55 (d, *J* = 15.8 Hz, 1H), 5.65 (dd, *J* = 15.8, 9.6 Hz, 1H), 2.49 (td, *J* = 8.5, 6.5 Hz, 1H), 2.36 (d, *J* = 0.8 Hz, 3H), 2.10 – 2.00 (m, 1H), 1.41 (td, *J* = 8.4, 5.2 Hz, 1H), 1.19 (dt, *J* = 6.5, 5.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.2 , 138.3 , 137.7 , 133.9 , 130.1 , 128.1 , 128.0 , 127.0 , 126.0 , 125.7 , 125.3 (q, *J* = 3.8 Hz), 24.2 , 22.7 , 21.4 , 12.8 .

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.50.

HRMS-APCI: calculated for $C_{19}H_{18}F_3$ $[M+H]^+$: 303.1355; found: 303.1341.

cis-(*E*)-1-(2-(4-Bromostyryl)cyclopropyl)-3-methylbenzene (74d)

This compound (white solid, 66.4 mg, 85%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-(4-bromostyryl)cyclohepta-1,3,5-triene (68.0 mg, 250 μmol), 1-methyl-3-vinylbenzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: 2 to 10% Et_2O in pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.10 (bs, 1H), 7.05 (bt, *J* = 7.9 Hz, 2H), 7.03 – 7.00 (m, 2H), 6.46 (d, *J* = 15.7 Hz, 1H), 5.55 (dd, *J* = 15.7, 9.6 Hz, 1H), 2.46 (q, *J* = 8.6 Hz, 1H), 2.02 (qd, *J* = 8.8, 5.5 Hz, 1H), 1.38 (td, *J* = 8.4, 5.2 Hz, 1H), 1.18 – 1.13 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 137.7, 136.7, 131.7, 131.4, 130.1, 128.2, 128.0, 127.2, 126.9, 126.0, 120.1, 23.9, 22.7, 21.5, 12.6.

M.p.: 56-60 °C.

HRMS-APCI: calculated for $C_{18}H_{18}Br$ $[M+H]^+$: 313.0586; found: 313.0592.

cis-4-((*E*)-2-(2-Phenylcyclopropyl)vinyl)-1,1'-biphenyl (74e)

This compound (white solid, 48.5 mg, 64%, d.r. >20:1) was prepared according to the general procedure from (*E*)-4-(2-(cyclohepta-2,4,6-trien-1-yl)vinyl)-1,1'-biphenyl (69.5 mg, 257 μmol), styrene (40.2 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.45 – 7.35 (m, 4H), 7.32 – 7.23 (m, 5H), 7.22 – 7.15 (m, 3H), 6.53 (d, *J* = 15.7 Hz, 1H), 5.56 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.45 (ddd, *J* = 8.6, 6.8 Hz, 1H), 2.02 (dddd, *J* = 8.8, 5.5 Hz, 1H), 1.36 (ddd, *J* = 8.4, 5.2 Hz, 1H), 1.14 (dd, *J* = 11.8, 5.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 139.4, 138.8, 136.9, 131.0, 129.3, 129.2, 128.8, 128.3, 127.2 (two signals), 126.9, 126.2, 126.2, 24.1, 22.9, 12.8.

HRMS-APCI: calculated for $C_{23}H_{20}$ $[M+H]^+$: 297.1635; found: 297.1638.

M.p.: 75-76 °C.

cis-(*E*)-1,3-Dimethoxy-5-(2-(2-(*m*-tolyl)cyclopropyl)vinyl)benzene (74f)

This compound (colorless oil, 50.8 mg, 69%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-(3,5-dimethoxystyryl)cyclohepta-1,3,5-triene (63.6 mg, 25 μmol), 1-methyl-3-vinylbenzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (80 g SiO_2, eluent: 1% Et_2O in pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.6 Hz, 1H), 7.10 (s, 1H), 7.04 (dd, *J* = 14.9, 7.8 Hz, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.31 (dd, *J* = 12.8, 2.2 Hz, 3H), 5.55 (dd, *J* = 15.7, 9.5 Hz, 1H), 3.75 (s, 6H), 2.44 (q, *J* = 8.5 Hz, 1H), 2.35 (s, 3H), 2.01 (qd, *J* = 8.8, 5.6 Hz, 1H), 1.37 (td, *J* = 8.4, 5.2 Hz, 1H), 1.15 (q, *J* = 5.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 139.9, 138.5, 137.6, 131.6, 130.1, 129.3, 128.0, 126.9, 126.0, 103.9, 98.7, 77.3, 55.2, 23.9, 22.6, 21.5, 12.6.

HRMS-APCI: calculated for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1693; found: 295.1698.

cis-1-Methyl-3-(2-(2-methylprop-1-en-1-yl)cyclopropyl)benzene (74g)

This compound (white crystals, 31.9 mg, 69%, d.r. >20:1) was prepared according to the general procedure from 7-(2-methylprop-1-en-1-yl)cyclohepta-1,3,5-triene (37.0 mg, 25 μmol), 1-methyl-3-vinylbenzene (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.5 Hz, 1H), 7.04 – 6.96 (m, 4H), 4.55 (dt, *J* = 8.9, 1.3 Hz, 1H), 2.36 (s, 3H), 2.26 (td, *J* = 8.6, 6.5 Hz, 1H), 1.89 (qd, *J* = 8.8, 5.8 Hz, 1H), 1.74 (d, *J* = 1.0 Hz, 4H), 1.61 – 1.60 (m, 4H), 1.25 (td, *J* = 8.5, 4.9 Hz, 1H), 0.90 – 0.85 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 137.3, 132.6, 129.9, 127.7, 126.4, 125.9, 123.1, 25.6, 22.7, 21.5, 18.3, 18.3, 12.3.

HRMS-APCI: calculated for $C_{14}H_{19}$ $[M+H]^+$: 187.1481; found: 187.1480.

cis-4-((2-(*m*-Tolyl)cyclopropyl)methylene)tetrahydro-2*H*-pyran (74h)

This compound (colorless oil, 40.2 mg, 70%, d.r. 7.5:1) was prepared according to the general procedure from 4-(cyclohepta-2,4,6-trien-1-ylmethylene)tetrahydro-2*H*-pyran (47.0 mg, 250 μmol), 1-methyl-3-vinylbenzenee (50.0 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: 2 to 10% Et_2O in pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.05 – 6.95 (m, 3H), 4.61 (d, *J* = 8.5 Hz, 1H), 3.71 (dt, *J* = 10.7, 5.3 Hz, 2H), 3.64 (ddd, *J* = 10.6, 6.2, 4.3 Hz, 1H), 3.49 (ddd, *J* = 11.0, 6.9, 4.4 Hz, 2H), 2.38 (td, *J* = 5.6, 1.1 Hz, 2H), 2.35 (s, 3H), 2.27 (td, *J* = 8.6, 6.5 Hz, 1H), 2.07 (dtt, *J* = 9.4, 7.2, 5.1 Hz, 2H), 1.89 (qd, *J* = 8.6, 5.8 Hz, 1H), 1.28 (td, *J* = 8.5, 5.0 Hz, 1H), 0.94 – 0.89 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 137.3, 135.6, 129.9, 127.7, 126.5, 125.9, 122.0, 69.6, 68.7, 36.7, 30.3, 23.0, 21.5, 17.2, 12.6.

HRMS-APCI: calculated for $C_{16}H_{20}NaO$ $[M+Na]^+$: 251.1406; found: 251.1405.

endo-1-((*E*)-2-([1,1'-Biphenyl]-4-yl)vinyl)-1,1a,6,6a-tetrahydrocyclopropa-[a]indene (74i)

This compound (white solid, 60 mg, 76%, d.r. >20:1) was prepared according to the general procedure from (*E*)-4-(2-(cyclohepta-2,4,6-trien-1-yl)vinyl)-1,1'-biphenyl (69.5 mg, 257 μmol), indene (44.8 mg, 386 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

Suitable crystals for X-ray diffraction were obtained by slow evaporation of a solution in chloroform.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 2H), 7.48 – 7.41 (m, 4H), 7.37 – 7.31 (m, 2H), 7.23 – 7.16 (m, 5H), 6.67 (d, *J* = 15.8 Hz, 1H), 5.42 (dd, *J* = 15.8, 9.4 Hz, 1H), 3.28 (dd, *J* = 17.5, 7.0 Hz, 1H), 3.01 (d, *J* = 17.5 Hz, 1H), 2.89 (ddd, *J* = 7.7, 6.2, 1.5 Hz, 1H), 2.26 (dddd, *J* = 7.8, 6.9, 0.7 Hz, 1H), 2.08 (dd, *J* = 17.2, 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 142.4, 140.9, 139.5, 136.9, 131.5, 128.8, 127.2, 127.2, 126.9, 126.6, 126.2 (two signals), 124.8, 124.3, 32.4, 32.1, 26.3, 24.4.

HRMS-APCI: calculated for $C_{24}H_{21}$ $[M+H]^+$: 309.1634; found: 309.1638.

M.p.: 146-148 °C.

4-(2-(2-Methylprop-1-en-1-yl)cyclopropyl)phenyl acetate (74j)

This compound (83% quantified by ^{1}H NMR) was prepared according to the general procedure from 7-(2-methylprop-1-en-1-yl)cyclohepta-1,3,5-triene (37 mg, 250 μmol), 4-acetoxystyrene (57 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: 0-20% Et_2O in pentane) but the alkene could not entirely be removed.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.21 – 7.17 (m, 2H), 7.03 – 6.99 (m, 2H), 4.51 (dp, *J* = 8.9, 1.4 Hz, 1H), 2.31 (s, 3H), 2.26 (td, *J* = 8.7, 6.2 Hz, 1H), 1.90 (qd, *J* = 8.8, 5.7 Hz, 1H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 1H), 1.30 – 1.25 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 148.6, 137.1, 135.9, 133.0, 129.9, 120.8.

(2-(3-Methylbut-2-en-2-yl)cyclopropyl)benzene (74k)

This compound (45% judged by ^{1}H NMR) was prepared according to the general procedure from 7-(3-methylbut-2-en-2-yl)cyclohepta-1,3,5-triene (42 μL, 250 μmol), styrene (43 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: pentane) but the alkene could not entirely be removed.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.24 – 7.09 (m, 3H), 7.05 – 6.98 (m, 2H), 2.20 (td, *J* = 8.8, 5.9 Hz, 1H), 1.94 (q, *J* = 8.4 Hz, 1H), 1.66 – 1.62 (m, 3H), 1.55 (d, *J* = 1.5 Hz, 3H), 1.38 (d, *J* = 1.2 Hz, 2H), 1.31 – 1.20 (m, 1H), 1.07 – 1.00 (m, 1H).

4-(2-(3-Methylbut-2-en-2-yl)cyclopropyl)phenyl acetate (74l)

This compound (86% judged by ^{1}H NMR) was prepared according to the general procedure from 7-(3-methylbut-2-en-2-yl)cyclohepta-1,3,5-triene (42 μL, 250 μmol), 4-chlorostyrene (45 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: pentane) but the alkene could not entirely be removed.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.02 – 6.99 (m, 2H), 6.95 – 6.90 (m, 2H), 2.18 (td, *J* = 8.8, 5.9 Hz, 1H), 1.94 (q, *J* = 8.8 Hz, 1H), 1.65 – 1.62 (m, 3H), 1.56 (d, *J* = 1.3 Hz, 3H), 1.41 – 1.36 (m, 2H), 1.31 – 1.22 (m, 2H), 1.00 (dt, *J* = 6.9, 5.6 Hz, 1H).

1-Methyl-4-(2-(3-methylbut-2-en-2-yl)cyclopropyl)benzene (74m)

This compound (47% judged by ^{1}H NMR) was prepared according to the general procedure from 7-(3-methylbut-2-en-2-yl)cyclohepta-1,3,5-triene (42 μL, 250 μmol), 4-methylstyrene (47 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: pentane) but the alkene could not entirely be removed.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.00 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 2.15 (td, *J* = 8.8, 5.9 Hz, 1H), 1.92 (q, *J* = 8.0 Hz, 1H), 1.68 – 1.64 (m, 3H), 1.57 (q, *J* = 1.5 Hz, 6H), 1.39 – 1.34 (m, 3H), 1.23 (td, *J* = 8.8, 5.2 Hz, 1H), 1.04 – 0.97 (m, 1H).

1-Chloro-4-(2-(3-methylbut-2-en-2-yl)cyclopropyl)benzene (74n)

This compound (56% judged by ^{1}H NMR) was prepared according to the general procedure from 7-(3-methylbut-2-en-2-yl)cyclohepta-1,3,5-triene (42 μL, 250 μmol), 4-chlorostyrene (45 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: pentane) but the alkene could not entirely be removed.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 – 7.13 (m, 2H), 6.96 – 6.90 (m, 2H), 2.16 (td, *J* = 8.8, 5.8 Hz, 1H), 1.95 (q, *J* = 8.6 Hz, 1H), 1.62 (t, *J* = 1.5 Hz, 3H), 1.56 (s, 3H), 1.40 – 1.37 (m, 3H), 1.32 – 1.23 (m, 1H), 1.03 – 0.96 (m, 1H).

1-(2-(3-Methylbut-2-en-2-yl)cyclopropyl)-4-(trifluoromethyl)benzene (74o)

This compound (38% judged by ^{1}H NMR) was prepared according to the general procedure from 7-(3-methylbut-2-en-2-yl)cyclohepta-1,3,5-triene (42 μL, 250 μmol), 4-acetoxystyrene (57 μL, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: pentane) but the alkene could not entirely be removed.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 2.24 (td, *J* = 8.8, 5.9 Hz, 1H), 2.08 – 1.96 (m, 1H), 1.60 (t, *J* = 1.5 Hz, 3H), 1.57 – 1.53 (m, 3H), 1.41 (dd, *J* = 2.3, 1.2 Hz, 3H), 1.35 (td, *J* = 8.7, 5.3 Hz, 1H), 1.07 – 1.03 (m, 1H).

***cis*-(*E*)-2-(2-Styrylcyclopropyl)isoindoline-1,3-dione (79a)**

This compound (white solid, 54.1 mg, 75%, d.r. 6:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 μL, 25 μmol), *N*-vinylphthalimide (87.0 mg, 500 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (120 g SiO_2, eluent: 20% Et_2O in pentane).

Multi-gram scale: This compound (white solid, 2.14 g, 74%, d.r. 7:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (1.94 g, 10 mmol), *N*-vinylphthalimide (3.46 g, 20 mmol) and gold catalyst **A** (386 mg, 0.5 mmol). The heating was stopped and reaction was quenched after 9 h by the addition of triethylamine. The crude residue was purified by flash chromatography (330 g SiO_2, eluent: 0 to 50% Et_2O in pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.26 – 7.17 (m, 4H), 7.17 – 7.12 (m, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 5.89 (dd, *J* = 15.8, 7.7 Hz, 1H), 3.03 (ddd, *J* = 7.8, 7.1, 4.9 Hz, 1H), 2.18 – 2.10 (m, 1H), 1.78 (td, *J* = 6.8, 4.9 Hz, 1H), 1.55 (ddd, *J* = 8.9, 7.9, 6.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 137.2, 134.0, 131.7, 131.2, 128.4, 127.0, 126.2, 126.0, 123.2, 28.1, 20.1, 10.7.

M.p.: 146-148 °C.

HRMS-ESI: calculated for $C_{19}H_{15}NNaO_2$ $[M+Na]^+$: 312.0995; found: 312.0997.

trans-2-(2-((*E*)-Styryl)cyclopropyl)isoindoline-1,3-dione) (*trans*-79a)

The *trans*-isomer (off-white solid, 41.0 mg, 55%) was prepared from the reaction of (*E*)-7-styrylcyclohepta-1,3,5-triene (50.0 mg, 257 μmol) with 2-vinylisoindoline-1,3-dione (89.0 mg, 515 μmol) and gold catalyst **A** (9.9 mg, 13 μmol) in the presence of diphenylmethane as internal reference (43.3 mg, 257 μmol) in *i*PrOAc at 120 °C over 27.5h. The crude was quenched with 0.5 mL Et_3N and stirred at room temperature for 1h before being charged on silica gel and purified by flash chromatography (40 g SiO_2, gradient: pentane to 30% Et_2O, the *trans*-isomer elutes first).

An ^1H NMR analysis of the crude against the internal reference shows 55% *trans*-isomer and 13% cis-isomer (ratio 4.2 : 1)

trans-isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.73 – 7.68 (m, 2H), 7.38 – 7.33 (m, 2H), 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.03 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.83 (ddd, *J* = 7.8, 4.5, 3.4 Hz, 1H), 2.25 – 2.13 (m, 1H), 1.58 (ddd, *J* = 9.4, 6.2, 4.5 Hz, 1H), 1.35 – 1.27 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 137.3, 134.2, 131.9, 130.4, 129.5, 128.6, 127.2, 126.1, 123.3, 29.5, 21.7, 13.5.

HRMS-ESI: calculated for $C_{19}H_{15}NNaO_2$ $[M+Na]^+$: 312.0995; found: 312.0997.

M.p.: 99-100 °C.

cis-(*E*)-2-(2-(4-Methoxystyryl)cyclopropyl)isoindoline-1,3-dione (79b)

This compound (yellow waxy solid, 41.8 mg, 52%, d.r. 6:1) was prepared according to the general procedure from (*E*)-7-(4-methoxystyryl)cyclohepta-1,3,5-triene (56.0 mg, 25 μmol), *N*-vinylphthalimide (87.0 mg, 500 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (120 g SiO_2, eluent: 0 to 60% Et_2O in pentane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.34 – 7.30 (m, 2H), 6.89 – 6.85 (m, 2H), 6.57 (d, *J* = 15.7 Hz, 1H), 5.92 (dd, *J* = 15.8, 7.7 Hz, 1H), 3.83 (s, 3H), 2.82 (ddd, *J* = 7.8, 4.5, 3.4 Hz, 1H), 2.22 – 2.15 (m, 1H), 1.60 – 1.55 (m, 1H), 1.34 – 1.29 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 158.9, 134.0, 131.8, 130.0, 129.8, 127.1, 127.1, 123.2, 114.0, 55.3, 29.3, 21.5, 13.3.

M.p.: 92-97 °C.

HRMS-APCI: calculated for $C_{19}H_{21}NaO$ $[M+Na]^+$: 342.1101; found: 342.1097.

cis-2-(2-((*E*)-4-Acetylstyryl)cyclopropyl)isoindoline-1,3-dione (79c)

This compound (yellow solid, 54.0 mg, 63%) was prepared according to the general procedure from (*E*)-1-(4-(2-(cyclohepta-2,4,6-trien-1-yl)vinyl)phenyl)ethan-1-one (60.7 mg, 257 μmol), 2-vinylisoindoline-1,3-dione (89.0 mg, 514 μmol) and gold catalyst **A** (9.9 mg, 13 μmol). The crude was quenched with 0.5 mL Et_3N and stirred at room temperature for 1h before being charged on silica gel and purified by flash chromatography (40 g SiO_2, gradient: pentane to 75% Et_2O).

In the reaction crude, only a trace of the *trans*-diastereoisomer was detected (4%).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.68 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.49 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 15.8, 8.1 Hz, 1H), 3.09 – 2.99 (m, 1H), 2.51 (s, 3H), 2.19 – 2.08 (m, 1H), 1.81 – 1.73 (m, 1H), 1.60 – 1.51 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 169.1, 141.9, 135.7, 134.3, 131.7, 130.2, 129.9, 128.7, 126.0, 123.4, 28.5, 26.6, 20.5, 11.3.

M.p.: 176-177 °C.

HRMS-ESI: calculated for $C_{21}H_{17}NNaO_3$ $[M+Na]^+$: 354.1101; found: 354.1108.

cis-(*E*)-2-(2-(4-(Trifluoromethyl)styryl)cyclopropyl)isoindoline-1,3-dione (79d)

This compound (white solid, 57.8 mg, 79%, d.r. 10:1) was prepared according to the general procedure from (*E*)-7-(4-(trifluoromethyl)styryl)cyclohepta-1,3,5-triene (56.0 mg, 205 μmol), *N*-vinylphthalimide (71.0 mg, 410 μmol) and gold

catalyst **A** (8.0 mg, 10.3 μmol). The crude residue was purified by flash chromatography (120 g SiO_2, eluent: 0 to 45% Et_2O in pentane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.30 – 7.25 (m, 3H), 6.51 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.06 (ddd, *J* = 7.8, 7.0, 4.9 Hz, 1H), 2.17 (ddtd, *J* = 8.9, 7.9, 7.0, 0.8 Hz, 1H), 1.79 (td, *J* = 6.8, 4.9 Hz, 1H), 1.63 – 1.55 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 140.6, 134.2, 131.6, 129.8, 129.3, 128.6, 128.1, 126.0, 125.4 (q, *J* = 3.8 Hz), 123.3, 28.3, 20.2, 11.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.60.

M.p.: 117-119 °C.

HRMS-APCI: calculated for $C_{20}H_{14}F_3NNaO_2$ $[M+Na]^+$: 380.0869; found: 380.0864.

cis-2-(2-((*E*)-2-([1,1'-Biphenyl]-4-yl)vinyl)cyclopropyl)isoindoline-1,3-dione (79e)

The *cis*-isomer (white solid, 38.5 mg, 50%) and the *trans*-isomer (white solid, 15.0 mg, 19%) were prepared according to the general procedure from (*E*)-4-(2-(cyclohepta-2,4,6-trien-1-yl)vinyl)-1,1'-biphenyl (57.2 mg, 212 μmol), 2-vinylisoindoline-1,3-dione (73.3 mg, 423 μmol) and gold catalyst **A** (8.2 mg, 11 μmol). The crude was quenched with 0.5 mL Et_3N and stirred at room temperature for 1h before being charged on silica gel and purified by flash chromatography (40 g SiO_2, gradient: pentane to 50% Et_2O, the *trans*-isomer elutes first).

Suitable crystals for X-ray diffraction of both isomers were obtained by slow evaporation of a solution in $CDCl_3$ in NMR tubes.

In addition to the structural evidence for both isomers by crystallography, their stereochemistry was independently confirmed by 1D NOESY experiments (see spectra for full details).

Cis-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 2H), 7.73 – 7.64 (m, 2H), 7.55 – 7.50 (m, 2H), 7.46 – 7.37 (m, 4H), 7.33 – 7.28 (m, 1H), 7.27 – 7.24 (m, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.93 (dd, *J* = 15.8, 7.7 Hz, 1H), 3.03 (ddd, *J* = 7.7, 7.1, 4.9 Hz, 1H), 2.21 – 2.10 (m, 1H), 1.84 – 1.75 (m, 1H), 1.55 (ddd, *J* = 8.8, 7.9, 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 140.8, 139.9, 136.4, 134.2, 131.8, 130.9, 128.8, 127.3, 127.2, 126.9, 126.5, 126.5, 123.4, 28.3, 20.4, 10.9.

M.p.: 155-156 °C.

HRMS-ESI: calculated for $C_{25}H_{19}NNaO_2$ $[M+Na]^+$: 388.1308; found: 388.1303.

Trans-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H), 7.75 – 7.69 (m, 2H), 7.63 – 7.58 (m, 2H), 7.58 – 7.52 (m, 2H), 7.47 – 7.40 (m, 4H), 7.36 – 7.30 (m, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.07 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.85 (ddd, *J* = 7.8, 4.4, 3.5 Hz, 1H), 2.26 – 2.16 (m, 1H), 1.60 (ddd, *J* = 9.5, 6.2, 4.6 Hz, 1H), 1.38 – 1.29 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 140.9, 140.0, 136.4, 134.2, 132.0, 130.0, 129.7, 128.9, 127.3 (two signals), 127.0, 126.5, 123.4, 29.6, 21.8, 13.6.

M.p.: 187-188 °C.

HRMS-ESI: calculated for $C_{25}H_{19}NNaO_2$ $[M+Na]^+$: 388.1308; found: 388.1312.

cis-(*E*)-2-(2-(3,5-Dimethoxystyryl)cyclopropyl)isoindoline-1,3-dione (79f)

This compound (yellow solid, 52.5 mg, 60%, d.r. 6:1) was prepared according to the general procedure from (*E*)-7-(3,5-dimethoxystyryl)cyclohepta-1,3,5-triene (56.0 mg, 25 μmol), *N*-vinylphthalimide (87.0 mg, 500 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (120 g SiO_2, eluent: 10 to 50% Et_2O in pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 2H), 6.28 (t, *J* = 2.3 Hz, 1H), 5.87 (dd, *J* = 15.7, 7.7 Hz, 1H), 3.72 (s, 6H), 3.05 – 2.99 (m, 1H), 2.20 – 2.07 (m, 1H), 1.78 (td, *J* = 6.8, 4.9 Hz, 1H), 1.59 – 1.49 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.01, 160.70, 139.32, 134.05, 131.64, 131.18, 126.90, 123.24, 104.13, 99.23, 55.24, 28.17, 20.05, 10.76.

M.p.: 119-121 °C.

HRMS-APCI: calculated for $C_{21}H_{19}NNaO_4$ $[M+Na]^+$: 372.1206; found: 372.1208.

trans-2-(2-(2-Methylprop-1-en-1-yl)cyclopropyl)isoindoline-1,3-dione (79g)

This compound (white solid, 35.3 mg, 59%, d.r. 4.7:1) was prepared according to the general procedure from 7-(2-methylprop-1-en-1-yl)cyclohepta-1,3,5-triene (37.0 mg, 250 μmol), *N*-vinylphthalimide (87.0 mg, 500 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (120 g SiO_2, eluent: 5 to 10% Et_2O in pentane).

The stereochemistry was confirmed by 1D NOESY experiments (see spectral data for full details).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 2H), 7.74 – 7.71 (m, 2H), 4.75 (dt, *J* = 8.8, 1.3 Hz, 1H), 2.65 (ddd, *J* = 7.5, 4.1, 3.5 Hz, 1H), 2.12 (tdd, *J* = 9.4, 6.5, 3.4 Hz, 1H), 1.87 (d, *J* = 1.1 Hz, 3H), 1.77 (d, *J* = 1.1 Hz, 3H), 1.42 (ddd, *J* = 9.7, 5.9, 4.2 Hz, 1H), 1.06 (dt, *J* = 7.3, 6.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 134.2, 134.0, 131.8, 124.1, 123.1, 28.6, 25.6, 18.3, 17.9, 13.9.

HRMS-APCI: calculated for $C_{15}H_{15}NNaO_2$ $[M+Na]^+$: 264.0995; found: 264.1004.

2-(2-(3-Methylbut-2-en-2-yl)cyclopropyl)isoindoline-1,3-dione (79h)

This compound (colorless oil, 27.4 mg, 43%, d.r. not determined) was prepared according to the general procedure from 7-(3-methylbut-2-en-2-yl)cyclohepta-1,3,5-triene (42 μL, 250 μmol), *N*-vinylphthalimide (87 mg, 500 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (SiO_2, eluent: 0-50 Et_2O in pentane).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 2.81 (dt, *J* = 7.8, 4.1 Hz, 1H), 2.29 (tt, *J* = 7.0, 3.7 Hz, 1H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.74 (t, *J* = 1.1 Hz, 3H), 1.59 (dd, *J* = 3.3, 2.0 Hz, 4H), 1.39 (ddd, *J* = 10.0, 6.0, 4.2 Hz, 1H), 1.24 (td, *J* = 7.3, 6.0 Hz, 1H).

trans-2-(2-((Tetrahydro-4*H*-pyran-4-ylidene)methyl)cyclopropyl)isoindoline-1,3-dione (79i)

This compound (colorless oil, 51.8 mg, 73%, d.r. 1.2:1) was prepared according to the general procedure from 4-(cyclohepta-2,4,6-trien-1-

ylmethylene)tetrahydro-2*H*-pyran (47.0 mg, 250 μmol), *N*-vinylphthalimide (87.0 mg, 500 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (120 g SiO_2, eluent: 10 to 60% Et_2O in pentane).

The stereochemistry was confirmed for the minor *cis*-isomer by 1D NOESY experiments (see spectral data for full details).

cis-Isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (td, *J* = 5.3, 3.0 Hz, 2H), 7.72 (td, *J* = 5.4, 3.1 Hz, 2H), 4.60 (d, *J* = 8.5 Hz, 1H), 3.75 – 3.70 (m, 1H), 3.62 (ddd, *J* = 10.5, 6.0, 4.3 Hz, 1H), 3.46 (ddd, *J* = 10.9, 7.6, 3.9 Hz, 1H), 2.55 – 2.48 (m, 1H), 2.42 – 2.34 (m, 1H), 2.15 (td, *J* = 6.2, 3.1 Hz, 1H), 2.04 (dd, *J* = 9.0, 3.9 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.56 (td, *J* = 6.5, 4.9 Hz, 1H), 1.50 – 1.44 (m, 1H).

trans-Isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (td, *J* = 5.3, 3.0 Hz, 2H), 7.72 (td, *J* = 5.4, 3.1 Hz, 2H), 4.80 (d, *J* = 8.5 Hz, 1H),3.73 – 3.67 (m, 3H), 2.65 (ddd, *J* = 7.5, 4.2, 3.4 Hz, 1H), 2.63 – 2.56 (m, 1H), 2.50 – 2.43 (m, 1H), 2.28 – 2.23 (m, 2H), 2.12 – 2.07 (m, 1H), 1.46 – 1.41 (m, 1H), 1.09 (dt, *J* = 7.3, 6.3 Hz, 1H).

cis-Isomer: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6, 138.2, 134.0, 131.8, 123.1, 119.3, 69.4, 68.6, 36.7, 30.4, 27.7, 15.1, 11.8.

trans-Isomer: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9, 136.8, 134.00, 131.8, 123.1, 122.8, 69.4, 68.8, 36.6, 30.2, 28.8, 17.0, 14.1.

HRMS-APCI: calculated for $C_{17}H_{17}NNaO_3$ $[M+Na]^+$: 306.1101; found: 306.1090.

(*E*)-2-Styrylcyclopropyl acetate (81a)

(*E*)-7-styrylcyclohepta-1,3,5-triene (19 mg, 100 μmol), was dissolved in vinyl acetate (0.4 mL) and gold catalyst **A** (3.9 mg, 5 μmol) was added. The mixture was heated to 75 °C for 12 h, concentrated to dryness and analyzed by ^{1}H NMR spectroscopy. The yield was estimated at 30% by ^{1}H NMR spectroscopy.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38 – 7.30 (m, 26H), 7.27 – 7.20 (m, 30H), 6.61 (d, *J* = 15.9 Hz, 1H), 5.97 (dd, *J* = 15.9, 8.8 Hz, 1H), 4.38 (td, *J* = 6.7, 3.8 Hz, 1H), 2.40 (d, *J* = 0.8 Hz, 6H), 1.97 – 1.85 (m, 1H), 1.34 – 1.29 (m, 1H), 0.97 (td, *J* = 6.7, 3.8 Hz, 1H).

GC-MS (ESI)**:** R.T: 7.500 min. MS: calculated: 202.1, found 202.1.

(*E*)-(2-(2-(*tert*-Butoxy)cyclopropyl)vinyl)benzene (81b)

This compound was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (19 mg, 100 μmol), *tert*-butyl vinyl ether (131 μL, 100 μmol) and gold catalyst **A** (3.9 mg, 5 μmol). This compound is estimated to be formed in 9% by ^{1}H NMR analysis of the crude reaction mixture.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 3H), 7.26 – 7.19 (m, 2H), 6.02 (dd, *J* = 15.7, 9.0 Hz, 1H), 5.38 (dd, *J* = 9.2, 5.7 Hz, 1H), 3.93 – 3.83 (m, 1H), 1.51 – 1.42 (m, 1H), 1.26 – 1.20 (m, 9H), 0.82 (dd, *J* = 8.4, 4.4 Hz, 1H), 0.54 (t, *J* = 4.9 Hz, 1H).

GC-MS (ESI)**:** R.T: 5.905 min. MS: calculated: 216.2, found 216.2.

(E)-2-(2-(Cyclohepta-2,4,6-trien-1-yl)vinyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (88a)

This compound was made following a modified literature procedure.[295]

Small scale: In an NMR tube, a mixture of **88b** (12 mg, 0.05 mmol, 1 equiv) and *N*-methylamino diacetic acid (37 mg, 0.25 mmol, 5 equiv) in *d6*-DMSO (0.5 mL) was heated to 60 °C for 64 h. The mixture was extracted with water (6 mL) and flash chromatography (SiO_2, EtOAc) afforded 7 mg (54%) of brown crystals suitable for X-ray analysis.

Synthetic scale: **88b** (94 mg, 0.4 mmol, 1 equiv), magnesium sulfate (100 mg), and *N*-methylamino diacetic acid (282 mg, 2.0 mmol, 5 equiv) in dry DMSO (4 mL) were heated to 60 °C for 14 h. The mixture was extracted with water (6 mL) and flash chromatography (SiO_2, EtOAc) afforded 9 mg (9%) of brown crystals.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.66 (t, *J* = 3.2 Hz, 2H), 6.50 (dd, *J* = 17.8, 6.4 Hz, 1H), 6.28 – 6.19 (m, 2H), 5.60 (dd, *J* = 17.8, 1.5 Hz, 1H), 5.34 – 5.25 (m, 2H), 3.94 (d, *J* = 16.3 Hz, 2H), 3.71 (d, *J* = 16.5 Hz, 2H), 2.85 (s, 3H).

^{11}B NMR (128 MHz, $CDCl_3$) δ 10.95.

295 Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 6941-6943.

(*E*)-2-(2-(Cyclohepta-2,4,6-trien-1-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (88b)

This compound was made following a modified literature procedure.[296]

A micro-wave vial was charged with zircocene hydrochloride (211 mg, 0.8 mmol, 20 mol%) in a glovebox and sealed. Then, **95** (782 mg, 4.1 mmol, 1 equiv), pinnacolborane (625 µL, 4.3 mmol, 1.05 equiv) and triethylamine (114 µL, 0.8 mmol, 20 mol%) are added and the mixture is heated to 60 °C for 24 h. The mixture is diluted with hexane and filtered over a silica plug. Concentration followed by flash chromatography (SiO_2, 0 -10% Et_2O in pentane) yield 637 mg (64%) of a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 (dd, *J* = 18.1, 6.6 Hz, 1H), 6.68 (ddt, *J* = 3.5, 2.6, 0.8 Hz, 2H), 6.23 (dddd, *J* = 8.9, 3.9, 2.6, 1.4 Hz, 2H), 5.67 (dd, *J* = 18.1, 1.6 Hz, 1H), 5.32 – 5.26 (m, 2H), 2.35 (dtd, *J* = 7.0, 5.6, 1.4 Hz, 1H), 1.31 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 131.8, 130.9, 124.7, 122.9, 83.2, 43.9, 24.8.

HRMS-APCI: calculated for $C_{15}H_{21}NaO_2{}^{11}B$ $[M+Na]^+$: 267.1527; found: 267.1527.

Potassium (*E*)-(2-(cyclohepta-2,4,6-trien-1-yl)vinyl)trifluoro-borane (88c)

A solution of **88b** (403 mg, 1.65 mmol, 1 equiv) in methanol (3.3 mL) is cooled to 0 °C and an aqueous solution of potassium bifluoride (1.1 mL, 4.5 M, 5 mmol, 3 equiv) is added slowly. The mixture is left to stir vigorously for at least another 2 h before it thoroughly dried under high vacuum. A Soxhlet extraction yielded 285 mg (77%) of a white salt.

(*E*)-2-(2-(2-(4-Methoxyphenyl)cyclopropyl)vinyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (89a)

This method is based on a literature procedure.[297]

Grubbs catalyst 2nd generation (15 mg, 0.018 mmol, 5 mol%) and **71h** (90 mg, 0.36 mmol, 1.0 equiv) were mixed in a 5 mL microwave vial. After capping, the

296 Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777-8780.

297 Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

atmosphere was evacuated and backfilled with argon three times. CH_2Cl_2 (2.3 mL, 0.155M) and vinyl boronic acid MIDA ester (132 mg, 0.72 mmol, 2.0 equiv) were added sequentially and the reaction mixture was stirred for 14h at 41 °C. The mixture was cooled to room temperature and adsorbed directly on florisil. Flash chromatography (24 g SiO_2, eluent: 0 to 50% acetone in Et_2O) yielded a mixture of **89a** and vinyl boronic acid MIDA ester.

^{1}H NMR (300 MHz, Acetone-d_6) δ 7.17 – 7.13 (m, 2H), 6.85 – 6.81 (m, 2H), 5.45 (d, *J* = 7.1 Hz, 1H), 4.02 (d, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 2.87 (s, 4H), 2.34 (td, *J* = 8.6, 6.4 Hz, 1H), 2.10 (s, 3H), 1.96 – 1.85 (m, 1H), 1.27 – 1.19 (m, 1H), 1.16 – 1.08 (m, 1H).

7-Ethynyl-cyclohepta-1.3.5-triene (95)

This compound was synthesized according to a literature procedure.[298]

Spectroscopic data matched that of the literature.

Methyl (*E*)-3-(2-(4-methoxyphenyl)cyclopropyl)acrylate (96)

This method is based on a literature procedure.[299]

Grubbs catalyst 2nd generation (21 mg, 0.025 mmol, 5 mol%) and **3g** (125 mg, 0.5 mmol, 1.0 equiv) were mixed in a 5 mL microwave vial. After capping, the atmosphere was evacuated and backfilled with argon three times. CH_2Cl_2 (3.3 mL, 0.155M) and methyl crotonate (212 μL 2.0 mmol, 4.0 equiv) were added sequentially and the reaction mixture was stirred for 14h at 41 °C. The mixture was cooled to room temperature and adsorbed directly on florisil. Flash chromatography (24 g SiO_2, eluent: 5 to 20% Et_2O in pentane) yielded 83 mg (0.36 mmol, 72%, dr: 15:1) of a grey oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.3 Hz, 2H), 6.87 – 6.83 (m, 2H), 6.27 (dd, *J* = 15.4, 10.6 Hz, 1H), 5.93 (d, *J* = 15.4 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 2.55 (q, *J* = 8.3 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.45 (td, *J* = 8.6, 5.2 Hz, 1H), 1.23 (dt, *J* = 6.7, 5.2 Hz, 1H).

298 Ferrer, S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 11178-11182.
299 Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 158.3, 150.6, 130.1, 129.4, 119.5, 113.8, 55.3, 51.2, 24.8, 22.2, 13.8.

HRMS-APCI: calculated for $C_{14}H_{16}NaO_3$ $[M+Na]^+$: 255.0992; found: 255.0980

Phthalimide deprotection and functionalization of amine.

(*E*)-2-Styrylcyclopropan-1-aminium chloride (99) was synthesized according to a modified literature procedure.[300]

(*E*)-2-(2-styrylcyclopropyl)isoindoline-1,3-dione **79a** (1.16g, 4.0 mmol, 1.0 equiv) is dissolved in dichloromethane (6 mL, 0.66M) and 2-propanol (36, 0.11M) and water (6 mL, 0.66M) is added, followed by sodium borohydride (755 mg, 20 mmol, 5.0 equiv) and the reaction is left to stir for 4 h (checked by TLC). Ethyl acetate and silica were added carefully and the mixture was poured on a silica plug and washed with Et_2O. The solvents were evaporated under reduced pressure and the crude white solid could directly be used in the next step.

The solids were dissolved in dioxane (13 mL, 0.3M) and cooled to 0 °C before dry hydrochloric acid in dioxane (13 mL, 4M) was added and the reaction was left to stir over night, warming to room temperature. The white solid was collected on a filter and the orange byproduct was washed out with Et_2O. Drying under high vacuum yielded 656 mg (3.35 mmol, 84%) of a white powder.

^{1}H NMR (500 MHz, Methanol-d4) δ 7.43 – 7.40 (m, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 6.75 (d, *J* = 15.7 Hz, 1H), 6.08 (dd, *J* = 15.7, 8.6 Hz, 1H), 2.87 (td, *J* = 7.6, 4.5 Hz, 1H), 2.07 (dt, *J* = 16.3, 8.6 Hz, 1H), 1.34 (ddd, *J* = 9.2, 7.6, 6.6 Hz, 1H), 1.02 (td, *J* = 6.7, 4.5 Hz, 1H).

^{13}C NMR (126 MHz, MeOD) δ 136.9, 134.3, 128.3, 127.3, 125.8, 123.3, 28.1, 18.4, 10.4.

M.p.: 167 °C (decomposition)

HRMS-APCI: calculated for $C_{11}H_{14}N$ $[M-Cl]^+$: 160.1121; found: 160.1128

300 Alford, J. S.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 6020-6023.

Benzyl (*E*)-(2-styrylcyclopropyl)carbamate (100)

(*E*)-2-Styrylcyclopropan-1-aminium chloride **99** (294 mg, 1.5 mmol, 1.0 equiv) was dissolved in a mixture of dioxane (12 mL) and water (12 mL) and cooled to 0 °C. Na_2CO_3 (795 mg, 7.5 mmol, 5.0 equiv) was added, quickly followed by benzyl chloroformate. (236 μL, 1.65 mmol, 1.1 equiv) and the reaction was left to stir for 1 h before being warmed to room temperature. The mixture was extracted with dichloromethane (10 mL, x3) and washed with water (20 mL) and brine (20 mL). Flash chromatography (silica, eluent: 30% Et_2O in pentane) yielded 402 mg (1.37 mmol, 91%) of a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 1H), 7.37 – 7.29 (m, 8H), 7.26 – 7.21 (m, 1H), 6.58 (d, *J* = 15.9 Hz, 2H), 5.95 (dd, *J* = 15.8, 8.5 Hz, 1H), 5.19 – 5.13 (m, 1H), 5.02 (d, *J* = 75.8 Hz, 1H), 4.73 (d, *J* = 5.9 Hz, 1H), 3.00 – 2.91 (bm, 1H), 1.91 – 1.83 (bm, 1H), 1.33 – 1.25 (bm, 1H), 0.81 (bs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 136.4, 131.7, 128.6, 128.5, 128.5, 128.1 (broad), 127.7, 127.1, 127.0, 127.0 (broad), 125.9, 66.8, 65.4, 29.7, 20.7, 14.3.

M.p.: 114-116 °C

HRMS-APCI: calculated for $C_{19}H_{19}NNaO_2$ $[M+Na]^+$: 316.1308; found: 316.1312

Oxidative cleavage to aldehyde and esterification.

***cis*-2-(1,3-Dioxoisoindolin-2-yl)cyclopropane-1-carbaldehyde (101a)**

(*E*)-2-(2-styrylcyclopropyl)isoindoline-1,3-dione **79a** (723 mg, 2.5 mmol) was dissolved in dichloromethane (100 mL, 0.025M) and cooled to -78 °C. Ozone was bubbled through the solution until a blue color appeared. Oxygen and then nitrogen gas was bubbled through the solution followed by the addition of triphenylphospine (656 mg, 2.5 mmol). The reaction was stirred at room temperature for 2 h before it was concentrated. Flash chromatography (silica, eluent: 50 to 100% Et_2O in pentane) yielded 490 mg (2.275 mmol, 91%) of a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, *J* = 2.7 Hz, 1H), 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.14 (td, *J* = 7.2, 5.8 Hz, 1H), 2.58 (dtd, *J* = 8.5, 6.9, 2.7 Hz, 1H), 2.16 (q, *J* = 6.3 Hz, 1H), 1.71 (ddd, *J* = 8.3, 7.4, 6.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6, 168.5, 134.3, 131.4, 123.4, 29.7, 26.4, 12.8.

M.p.: 107 °C

HRMS-APCI: calculated for $C_{12}H_9NNaO_3$ $[M+Na]^+$: 238.0475; found: 238.0477

Methyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1-carboxylate (102)

The oxidative esterification to 12 based on a literature procedure.[301]

2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1-carbaldehyde **101a** (43 mg, 0.2 mmol, 1.0 equiv) was dissolved in methanol (4 mL, 0.05M). Meanwhile, vanadium(V)oxide (36 mg, 0.2 mmol, 1.0 equiv) was dissolved in a H_2O_2 solution (15% 1.5 mL) at 0 °C. The solution of aldehyde **9a** is cooled to 0 °C and once the vanadium solution turns deep red, perchloric acid (1.44 μL, 70%, 0.01 mmol, 0.05 equiv) was added to it. The oxidant mixture is carefully added to the methanolic solution and left to stir for 3 h, whilst slowly warming. The reaction was quenched by adding a saturated sodium thiosulfate solution at 0 °C and stirring was continued for 1 h. The mixture was extracted with ethyl acetate (25 mL) and washed with water (20 mL, x2) and brine (20 mL). Concentration followed by flash chromatography (silica 24 g, eluent: 20 to 90% Et_2O in pentane over 1 h, fractions analyzed by GC-FID) afforded 31.1 mg (0.127 mmol, 64%) of a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.62 (s, 3H), 3.04 (td, *J* = 7.4, 5.8 Hz, 1H), 2.23 (dt, *J* = 8.6, 6.8 Hz, 1H), 1.96 (q, *J* = 6.3 Hz, 1H), 1.66 (ddd, *J* = 8.7, 7.7, 6.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 168.6, 134.1, 131.6, 123.3, 52.13, 27.5, 18.6, 13.0.

HRMS-APCI: calculated for $C_{13}H_{11}NNaO_4$ $[M+Na]^+$: 268.0580; found: 268.0574

Isomerization of aldehyde.

***trans*-2-(1,3-Dioxoisoindolin-2-yl)cyclopropane-1-carbaldehyde (101b)**

2-(1,3-Dioxoisoindolin-2-yl)cyclopropane-1-carbaldehyde **101a** (43 mg, 0.2 mmol, 1.0 equiv) was dissolved in dichloromethane (1 mL) and perchloric acid

301 Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 577-579.

(2.9 μL, 70%, 0.02 mmol, 0.1 equiv) was added. The reaction was stirred for 2 h before it was extracted with dichloromethane (5 mL) and wash with water (5 mL, 3x) and brine (5 mL), affording 41 mg (0.192 mmol, 96%) of a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 2.7 Hz, 1H), 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.13 (td, *J* = 7.2, 5.8 Hz, 1H), 2.58 (dtd, *J* = 8.4, 6.9, 2.7 Hz, 1H), 2.15 (q, *J* = 6.3 Hz, 1H), 1.70 (ddd, *J* = 8.4, 7.4, 6.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 168.5, 134.3, 131.4, 123.5, 29.7, 26.40, 12.8.

M.p.: 98 °C

Triisopropyl((2-vinylphenyl)ethynyl)silane (103)

1-Ethynyl-2-vinylbenzene

This compound was synthesized using a modified literature procedure:[302] Anhydrous potassium carbonate (622 mg, 4.5 mmol, 1.5 equiv) was added to a solution of trimethyl((2-vinylphenyl)ethynyl)silane[303] (600 mg, 3.0 mmol, 1.0 equiv) in methanol (4.5 mL, 0.667M) and the suspension was stirred for 1 h at room temperature. The mixture was extracted with pentane, washed with brine and used directly in the next step.

The crude data was consistent with the literature.[304]

Triisopropyl((2-vinylphenyl)ethynyl)silane (103)

1-Ethynyl-2-vinylbenzene (3.0 mmol, 1.0 equiv) was dissolved in dry THF (15 mL, 0.2M) and cooled to -78 °C, followed by the addition of lithium diisopropylamine (0.5M THF, 8.0 mL, 4.0 mmol, 1.2 equiv) over 10 minutes, and finally the addition of triisopropylsilyl chloride (963 μL, 4.5 mmol, 1.5 equiv). The reactions was slowly warmed to room temperature, after which it was quenched with water, extracted with Et_2O, washed with brine and dried over

302 Yeh, M.-C. P.; Liang, C.-J.; Chen, H.-F.; Weng, Y.-T. *Adv. Synth. Catal.* **2015**, *357*, 3242-3254.
303 Madhushaw, R. J.; Lin, M.-Y.; Sohel, S. M. A.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 6895-6899.
304 Barluenga, J.; Andina, F.; Aznar, F.; Valdés, C. *Org. Lett.* **2007**, *9*, 4143-4146.

Na_2SO_4. Flash chromatography (80 g, SiO_2, eluent: pentane) afforded 617 mg (2.17 mmol, 72%) of a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 1H), 7.51 – 7.48 (m, 1H), 7.34 – 7.25 (m, 2H), 7.21 (td, *J* = 7.5, 1.2 Hz, 1H), 5.83 (dd, *J* = 17.7, 1.1 Hz, 1H), 5.36 (dd, *J* = 11.0, 1.0 Hz, 1H), 1.17 (s, 18H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 135.0, 133.1, 128.4, 127.3, 124.5, 122.3, 115.5, 105.4, 95.6, 18.7, 11.3.

HRMS-APCI: calculated for $C_{19}H_{29}Si$ $[M+H]^+$: 285.2033; found: 285.2046

Cis-(*E*)-triisopropyl((2-(2-styrylcyclopropyl)phenyl)ethynyl)silane (104a)

This compound (colorless oil, 64.5 mg, 64%, d.r. >20:1) was prepared according to the general procedure from (*E*)-7-styrylcyclohepta-1,3,5-triene (49.0 mg, 25 μmol), triisopropyl((2-vinylphenyl)ethynyl)silane (107 mg, 375 μmol) and gold catalyst **A** (9.7 mg, 12.5 μmol). The crude residue was purified by flash chromatography (40 g SiO_2, eluent: pentane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.32 – 7.21 (m, 1H), 7.18 (dt, *J* = 5.0, 3.6 Hz, 4H), 7.14 – 7.08 (m, 3H), 6.46 (d, *J* = 15.7 Hz, 1H), 5.47 (dd, *J* = 15.7, 9.2 Hz, 1H), 2.70 (q, *J* = 8.4 Hz, 1H), 2.13 (qd, *J* = 8.8, 5.5 Hz, 1H), 1.47 – 1.37 (m, 1H), 1.30 – 1.21 (m, 1H), 1.16 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 137.8, 132.8, 129.98, 129.8, 128.3, 127.9, 127.6, 126.4, 125.8, 125.7, 125.4, 105.8, 94.7, 23.6, 23.1, 18.7, 12.4, 11.4.

HRMS-APCI: calculated for $C_{28}H_{37}Si$ $[M+H]^+$: 401.2659; found: 401.2665.

(*E*)-1-Ethynyl-2-(2-styrylcyclopropyl)benzene (104b)

To a solution of **12a** (46 mg, 0.115 mmol, 1.0 equiv) in THF (1.7 mL, 0.07M) was added a solution of tetrabutylammonium fluoride (1.0M THF, 575 μL, 5.0 equiv) and the reaction was stirred for 2 h. Extracting with Et_2O, drying with Na_2SO_4 and filtration of a silica plug yielded the pure compound in 27.7 mg (0.113 mmol, 99%) as a colorless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.24 – 7.17 (m, 4H), 7.15 – 7.11 (m, 3H), 6.51 (d, *J* = 15.7 Hz, 1H), 5.52 (dd, *J* =

15.7, 9.2 Hz, 1H), 3.31 (s, 1H), 2.74 – 2.66 (m, 1H), 2.18 (qd, *J* = 8.7, 5.6 Hz, 1H), 1.43 (td, *J* = 8.3, 5.4 Hz, 1H), 1.24 (dt, *J* = 6.4, 5.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 137.8, 132.8, 129.9, 129.8, 128.4, 128.3, 127.7, 126.5, 125.9, 125.7, 124.0, 82.6, 81.2, 23.2, 22.9, 17.7, 12.5, 12.3.

HRMS-APCI: calculated for $C_{19}H_{17}$ $[M+H]^+$: 245.1325; found: 245.1334

(*E*)-3-Styryl-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene (105)

Catalyst **A** (3 mg, 0.004 mmol, 5 mol%) was added to a stirred solution of (*E*)-1-ethynyl-2-(2-styrylcyclopropyl)benzene (19.3 mg, 0.079 mmol, 1.0 equiv) in CH_2Cl_2 (1.25 mL, 0.0625M). After the disappearance of the pink color, a drop of triethylamine was added and the solution was filtered over a silica plug, providing the pure compound in 19.0 mg (0.078 mmol, 98%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 3H), 7.45 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.20 (m, 4H), 6.85 (d, *J* = 15.7 Hz, 1H), 6.55 (d, *J* = 5.5 Hz, 1H), 2.54 (td, *J* = 8.3, 5.1 Hz, 1H), 2.13 (tt, *J* = 7.9, 4.0 Hz, 1H), 1.62 (td, *J* = 8.8, 3.6 Hz, 1H), -0.12 – -0.16 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 136.0, 131.1, 130.3, 130.1, 128.6, 128.4, 127.4, 127.3 (2CH), 127.0, 126.5, 125.6, 124.1, 21.2, 17.8, 10.6.

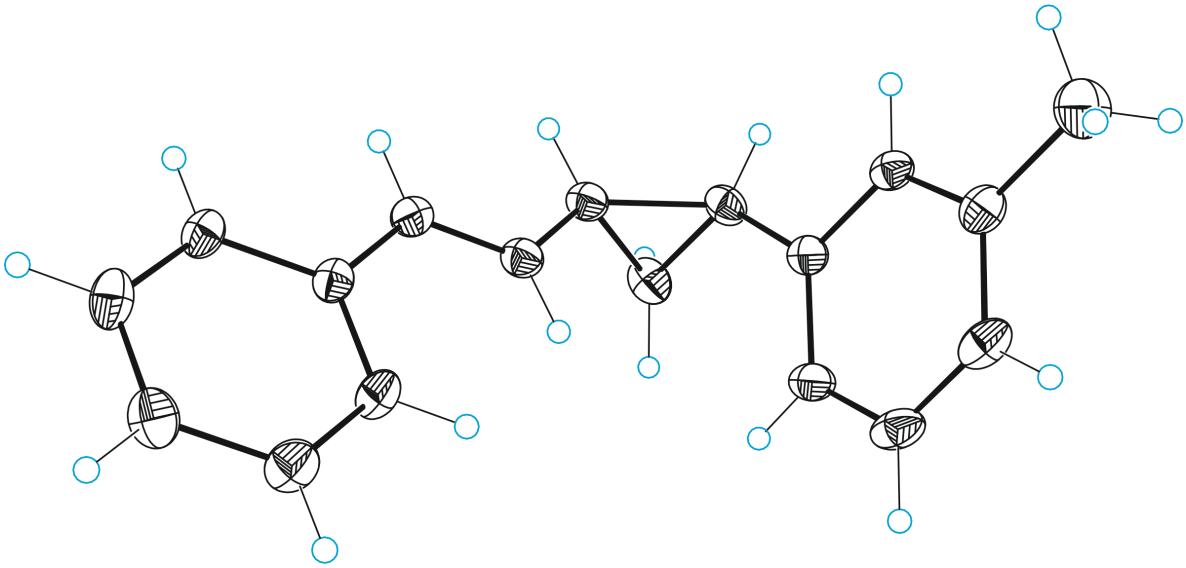
HRMS-APCI: calculated for $C_{19}H_{17}$ $[M+H]^+$: 245.1325; found: 245.1336

X-ray crystallography

Crystal structure determinations were carried out using a Bruker-Nonius diffractometer equipped with an APPEX 24K CCD area detector, a FR591 rotating anode with MoKa radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = –173 °C). Full-sphere data collection was used with w and *J* scans. Programs used: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solutions were achieved using direct methods as implemented in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined

including anisotropic displacement parameters. ORTEP drawings are represented with 50% probability of the thermal ellipsoids.

Crystal data and structure refinement for *cis*-71b

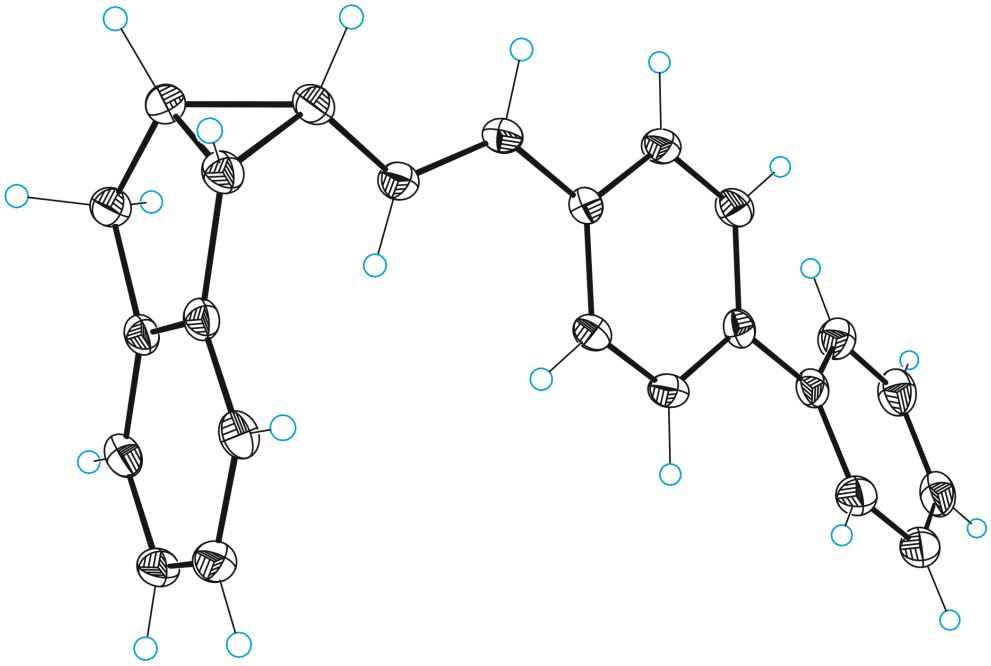


ORTEP drawings of 7**1b** with 50% probability of the thermal ellipsoids

Empirical formula	C18 H18	
Formula weight	234.32	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.035(2)Å	α= 90°.
	b = 5.7594(15)Å	β = 100.891(7)°.
	c = 13.277(3)Å	γ = 90°.
Volume	678.5(3) $Å^3$	
Z	2	
Density (calculated)	1.147 Mg/m^3	
Absorption coefficient	0.064 mm^{-1}	
F(000)	252	
Crystal size	0.20 x 0.15 x 0.06 mm^3	
Theta range for data collection	2.295 to 32.557°.	
Index ranges	-13<=h<=12,-8<=k<=5,-19<=l<=15	

Reflections collected	9047
Independent reflections	3680[R(int) = 0.0254]
Completeness to theta =32.557°	92.7%
Absorption correction	Empirical
Max. and min. transmission	0.996 and 0.874
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3680/ 1/ 164
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.0989
R indices (all data)	R1 = 0.0544, wR2 = 0.1056
Flack parameter	x =0.1(10)
Largest diff. peak and hole	0.251 and -0.211 e.$Å^{-3}$

Crystal data and structure refinement for *endo*-74i

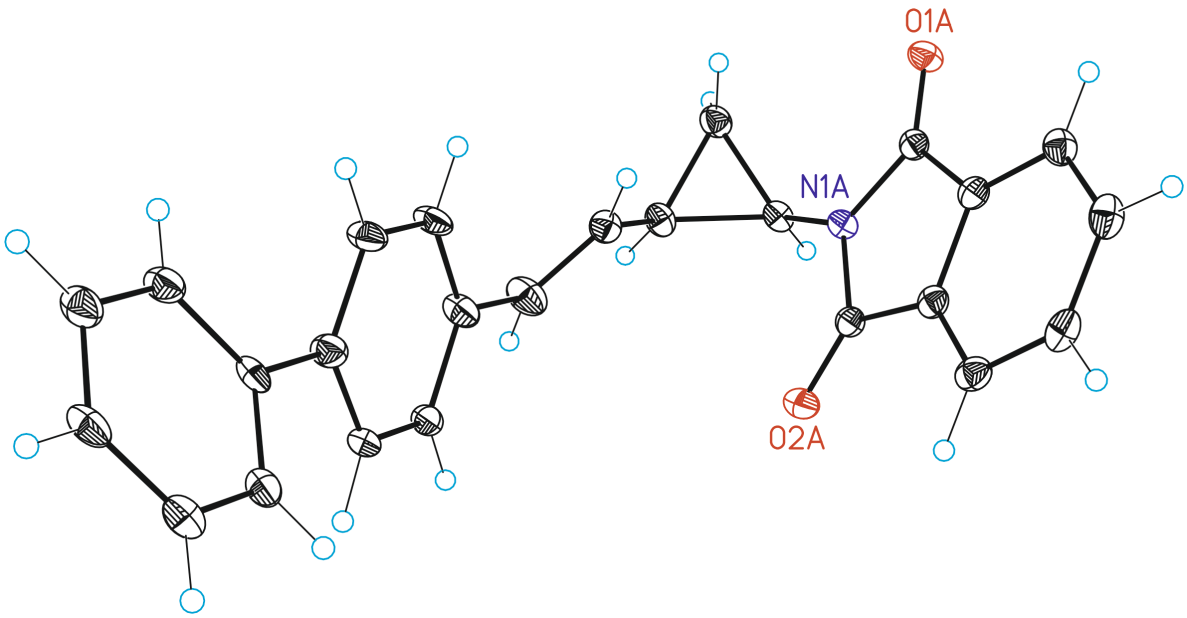


ORTEP drawings of **74i** with 50% probability of the thermal ellipsoids

Empirical formula	C24 H20	
Formula weight	308.40	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pca2(1)	
Unit cell dimensions	a = 9.9863(13)Å	α= 90°.
	b = 18.438(2)Å	β = 90°.
	c = 8.9744(13)Å	γ = 90°.
Volume	1652.4(4) $Å^3$	
Z	4	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	656	
Crystal size	0.40 x 0.40 x 0.06 mm^3	

Theta range for data collection	2.209 to 31.541°.
Index ranges	-7<=h<=14,-17<=k<=27,-12<=l<=13
Reflections collected	12057
Independent reflections	5071[R(int) = 0.0401]
Completeness to theta =31.541°	97.299995%
Absorption correction	Multi-scan
Max. and min. transmission	0.996 and 0.837
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5071/ 1/ 217
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0573, wR2 = 0.1275
R indices (all data)	R1 = 0.0810, wR2 = 0.1408
Flack parameter	x =-0.1(10)
Largest diff. peak and hole	0.289 and -0.233 e.$Å^{-3}$

Crystal data and structure refinement for *cis*-79e

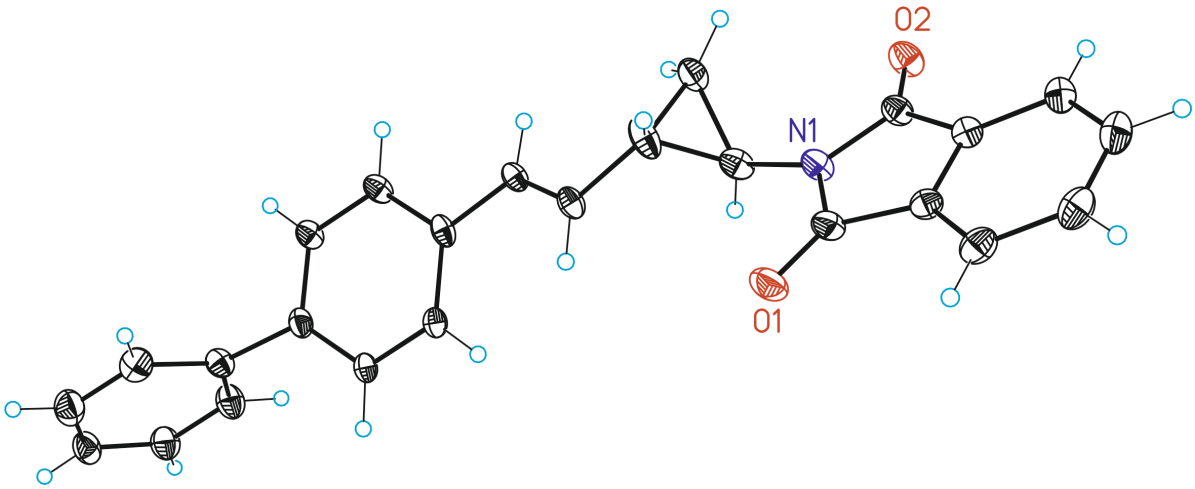


ORTEP drawings of **79e** with 50% probability of the thermal ellipsoids

Empirical formula	C25 H19 N O2	
Formula weight	365.41	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.8574(4)Å	α= 83.974(3)°.
	b = 10.5363(4)Å	β = 85.964(3)°.
	c = 19.0980(6)Å	γ = 69.875(4)°.
Volume	1850.89(13) $Å^3$	
Z	4	
Density (calculated)	1.311 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	768	
Crystal size	0.12 x 0.12 x 0.03 mm^3	
Theta range for data collection	2.202 to 28.875°.	

Index ranges	-13<=h<=12,-13<=k<=13,-23<=l<=23
Reflections collected	30805
Independent reflections	8327[R(int) = 0.0463]
Completeness to theta =28.875°	85.6%
Absorption correction	Empirical
Max. and min. transmission	0.998 and 0.768
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8327/ 230/ 669
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0491, wR2 = 0.1309
R indices (all data)	R1 = 0.0795, wR2 = 0.1458
Largest diff. peak and hole	0.377 and -0.261 e.$Å^{-3}$

Crystal data and structure refinement for *trans*-79e

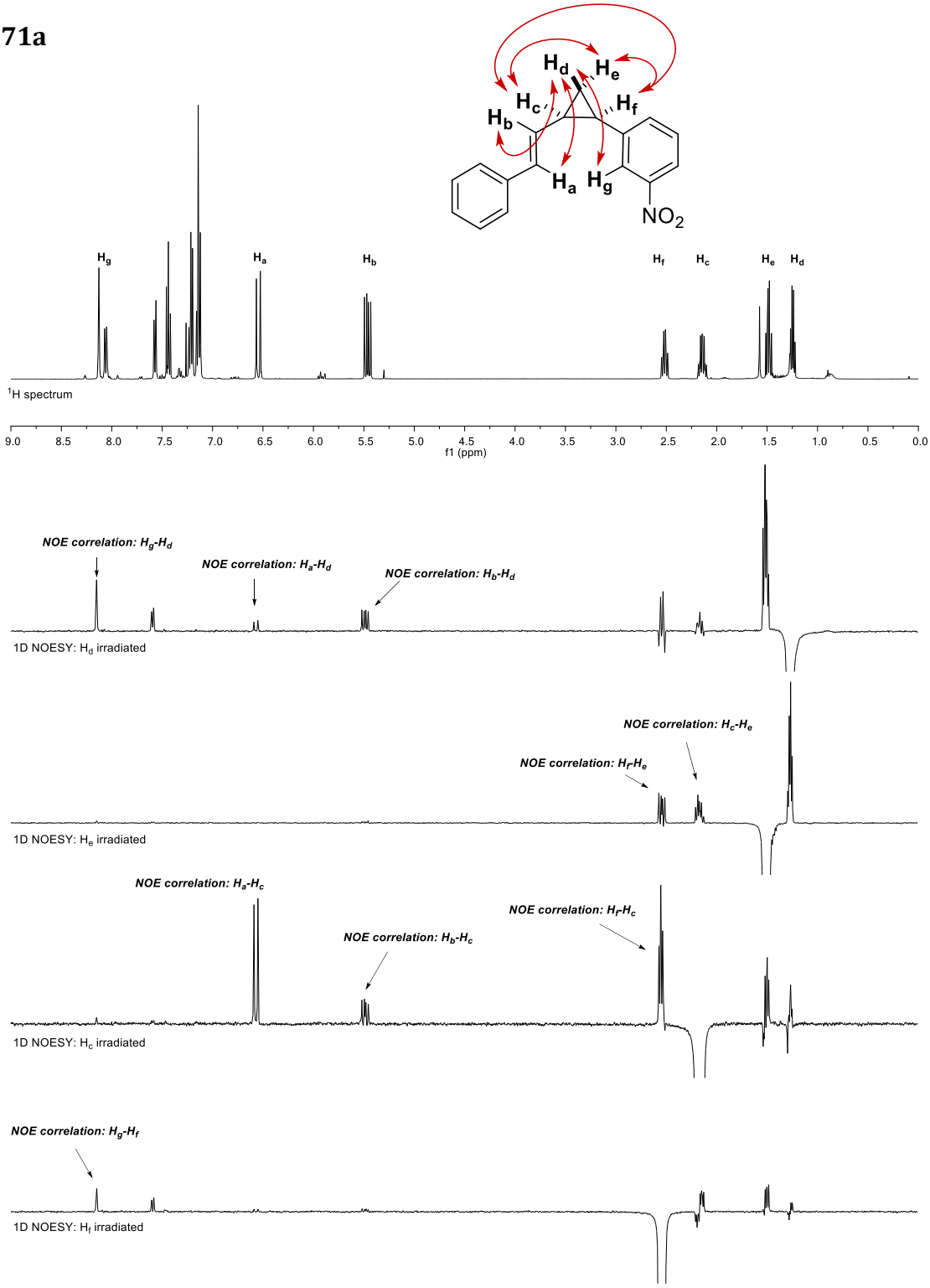


ORTEP drawings of **79e** with 50% probability of the thermal ellipsoids

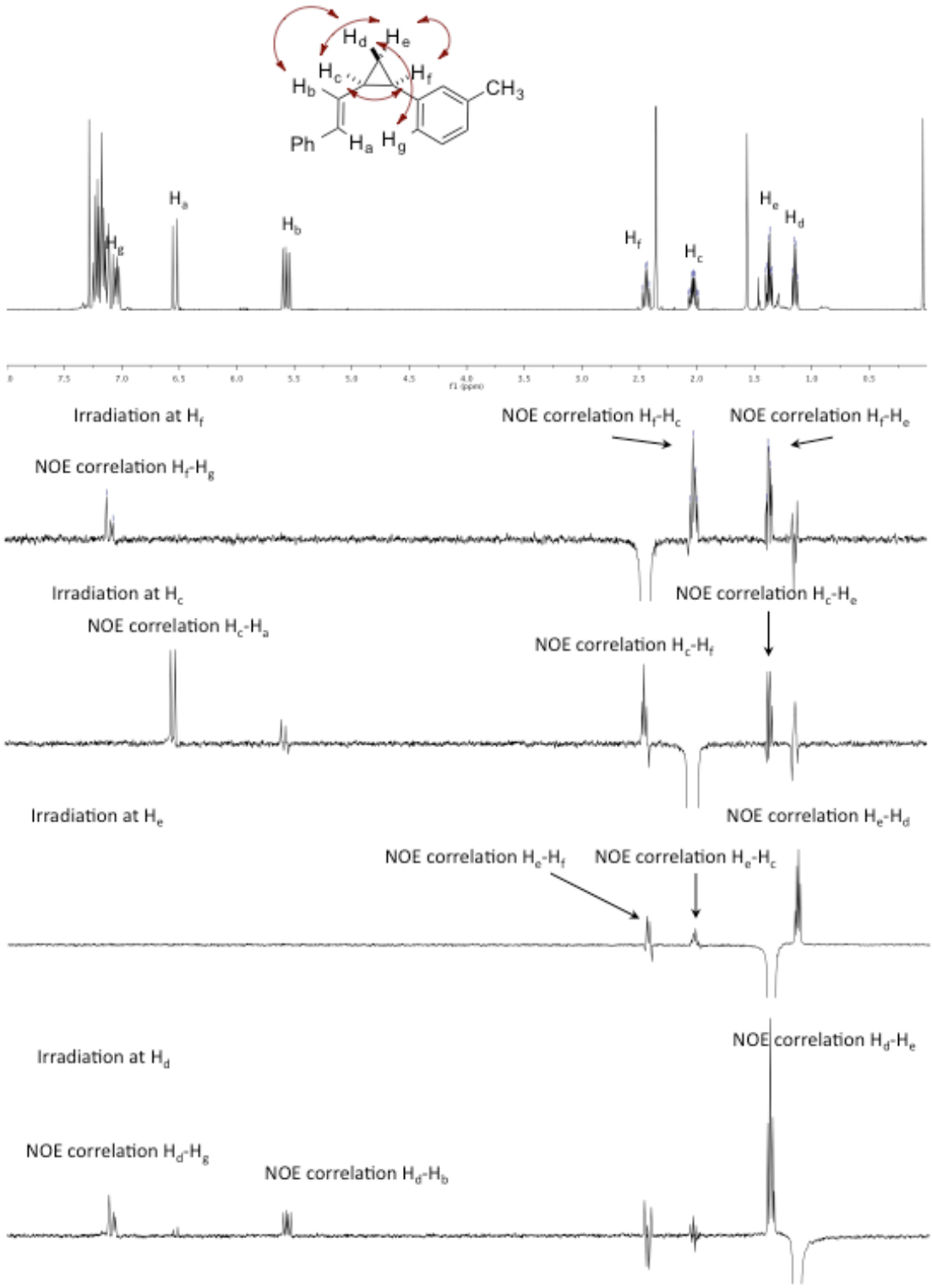
Empirical formula	C25 H19 N O2	
Formula weight	365.41	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 4.88608(8)Å	α= 90°.
	b = 39.9585(6)Å	β = 91.1105(15)°.
	c = 9.27521(15)Å	γ = 90°.
Volume	1810.55(5) $Å^3$	
Z	4	
Density (calculated)	1.341 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	768	
Crystal size	0.2 x 0.18 x 0.03 mm^3	
Theta range for data collection	2.039 to 60.660°.	
Index ranges	-11<=h<=11,-96<=k<=94,-22<=l<=20	
Reflections collected	106963	

Independent reflections	25432[R(int) = 0.0484]
Completeness to theta =60.660°	91.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.998 and 0.768
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	25432/ 710/ 532
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0910, wR2 = 0.2494
R indices (all data)	R1 = 0.1348, wR2 = 0.2737
Largest diff. peak and hole	0.865 and -0.897 e.$Å^{-3}$

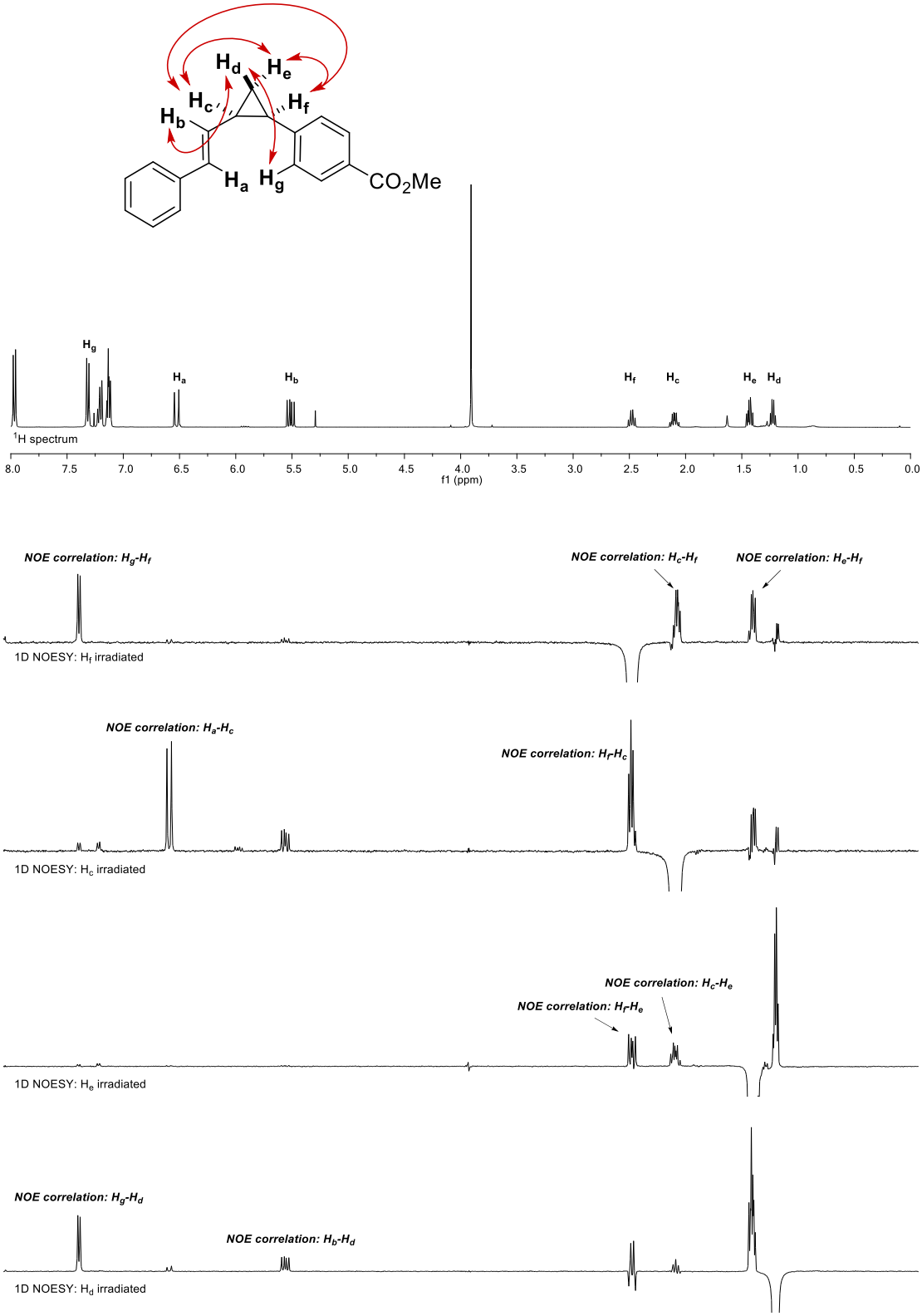
71a


Hd
He
Hc
Hf
Hb
Ha
Hg
NO2
Hg
Ha
Hb
Hf
Hc
He
Hd
1H spectrum
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
NOE correlation: Hg-Hd
NOE correlation: Ha-Hd
NOE correlation: Hb-Hd
1D NOESY: Hd irradiated
NOE correlation: Hc-He
NOE correlation: Hf-He
1D NOESY: He irradiated
NOE correlation: Ha-Hc
NOE correlation: Hf-Hc
NOE correlation: Hb-Hc
1D NOESY: Hc irradiated
NOE correlation: Hg-Hf
1D NOESY: Hf irradiated

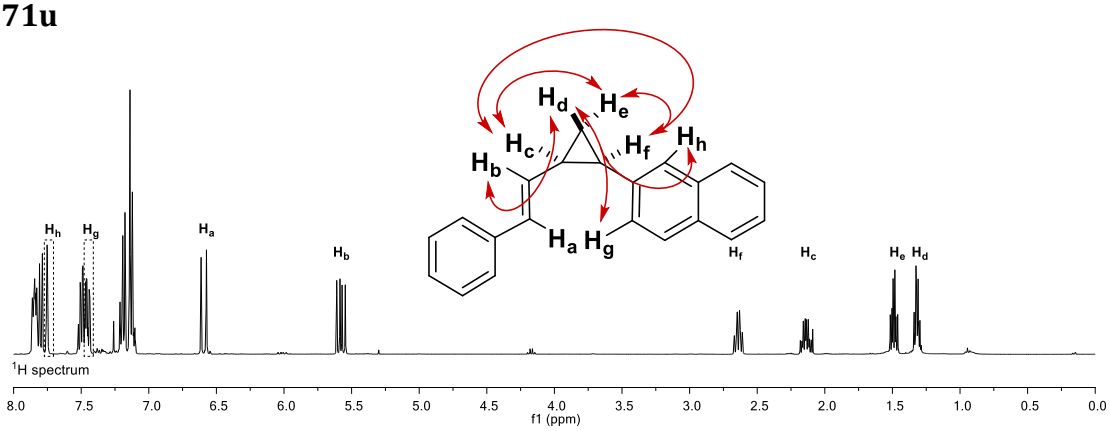
71b

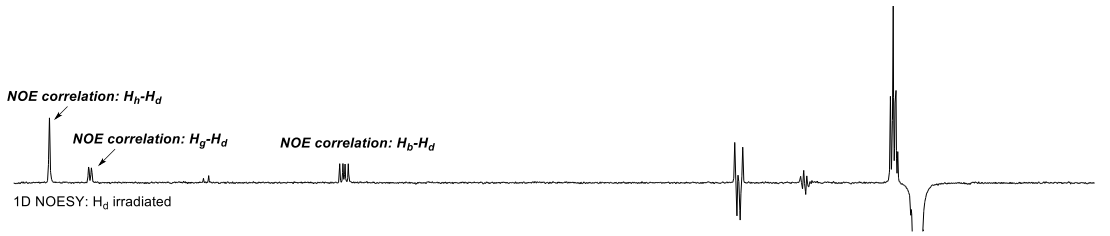

Hd He
Hc Hf
Hb
CH3
Ph Ha Hg
Ha
Hb
Hg
Hf
Hc
He
Hd
Irradiation at Hf
NOE correlation Hf-Hc
NOE correlation Hf-He
NOE correlation Hf-Hg
Irradiation at Hc
NOE correlation Hc-He
NOE correlation Hc-Ha
NOE correlation Hc-Hf
Irradiation at He
NOE correlation He-Hd
NOE correlation He-Hf
NOE correlation He-Hc
Irradiation at Hd
NOE correlation Hd-He
NOE correlation Hd-Hg
NOE correlation Hd-Hb

71j

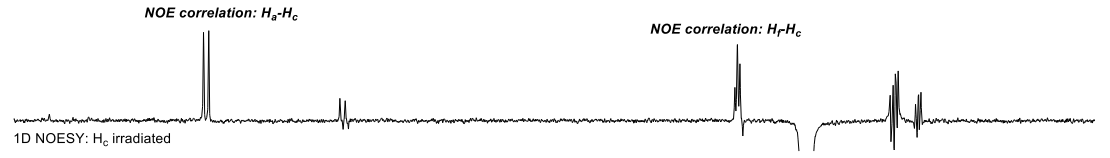

Hd
He
Hc
Hf
Hb
Ha
Hg
CO2Me
Hg
Ha
Hb
Hf
Hc
He
Hd
1H spectrum
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
NOE correlation: Hg-Hf
NOE correlation: Hc-Hf
NOE correlation: He-Hf
1D NOESY: Hf irradiated
NOE correlation: Ha-Hc
NOE correlation: Hf-Hc
1D NOESY: Hc irradiated
NOE correlation: Hc-He
NOE correlation: Hf-He
1D NOESY: He irradiated
NOE correlation: Hg-Hd
NOE correlation: Hb-Hd
1D NOESY: Hd irradiated

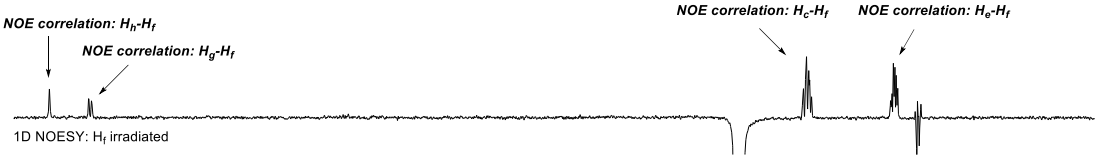
71u


Hd
He
Hc
Hf
Hh
Hb
Ha
Hg
Hh
Hg
Ha
Hb
Hf
Hc
He
Hd
1H spectrum
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

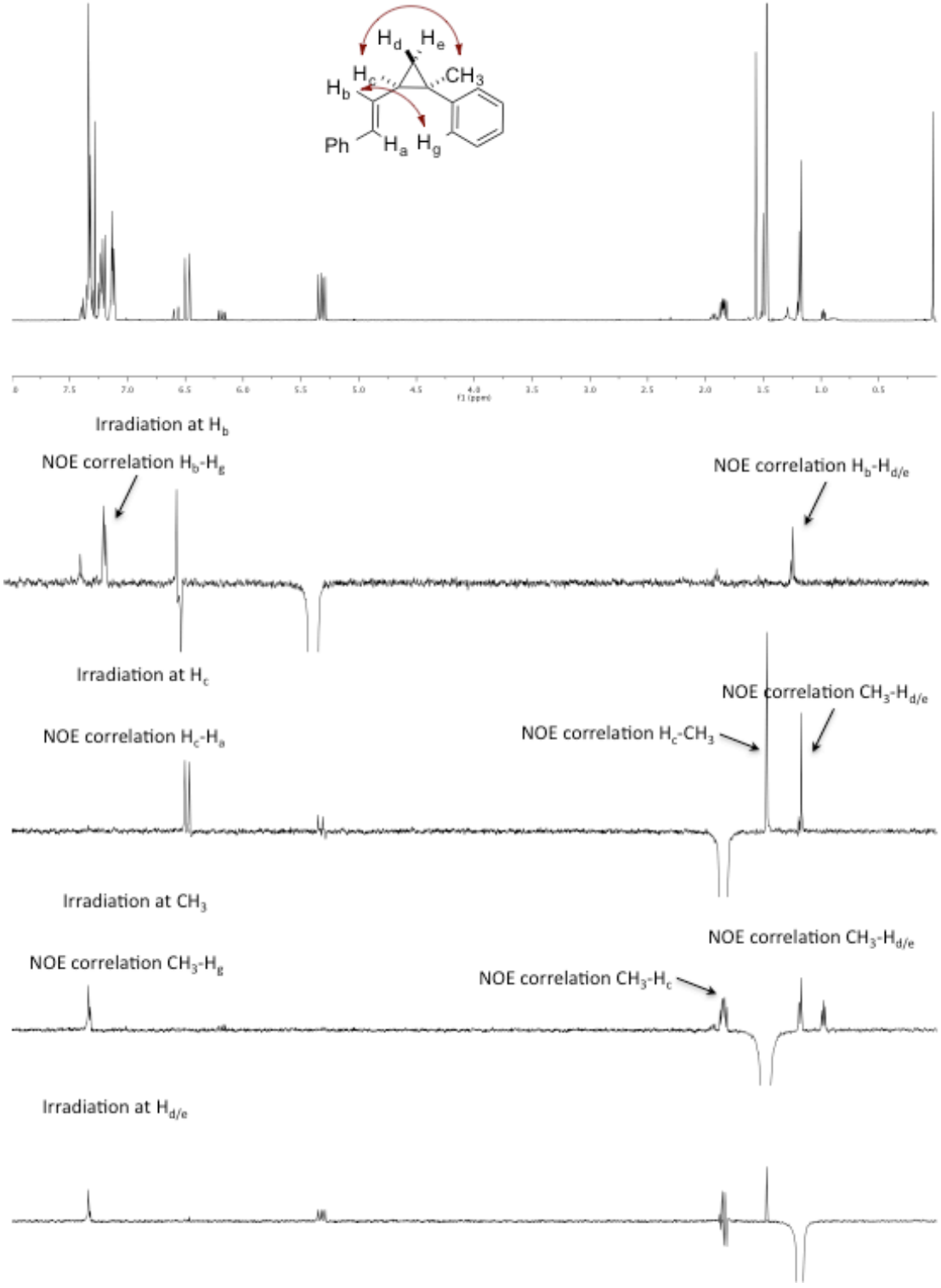

NOE correlation: Hh-Hd
NOE correlation: Hg-Hd
NOE correlation: Hb-Hd
1D NOESY: Hd irradiated


NOE correlation: Hc-He
1D NOESY: He irradiated

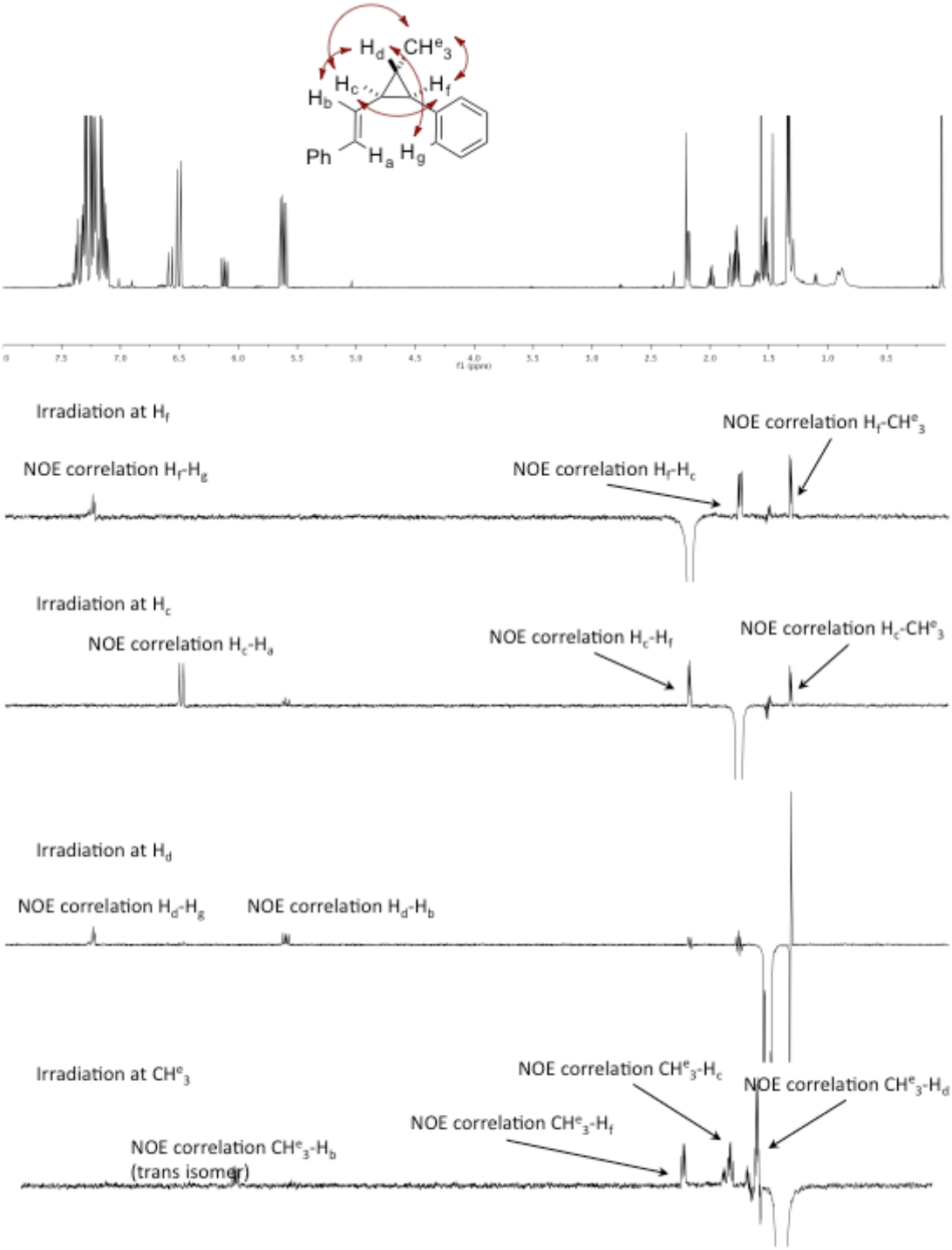

NOE correlation: Ha-Hc
NOE correlation: Hf-Hc
1D NOESY: Hc irradiated


NOE correlation: Hh-Hf
NOE correlation: Hg-Hf
NOE correlation: Hc-Hf
NOE correlation: He-Hf
1D NOESY: Hf irradiated

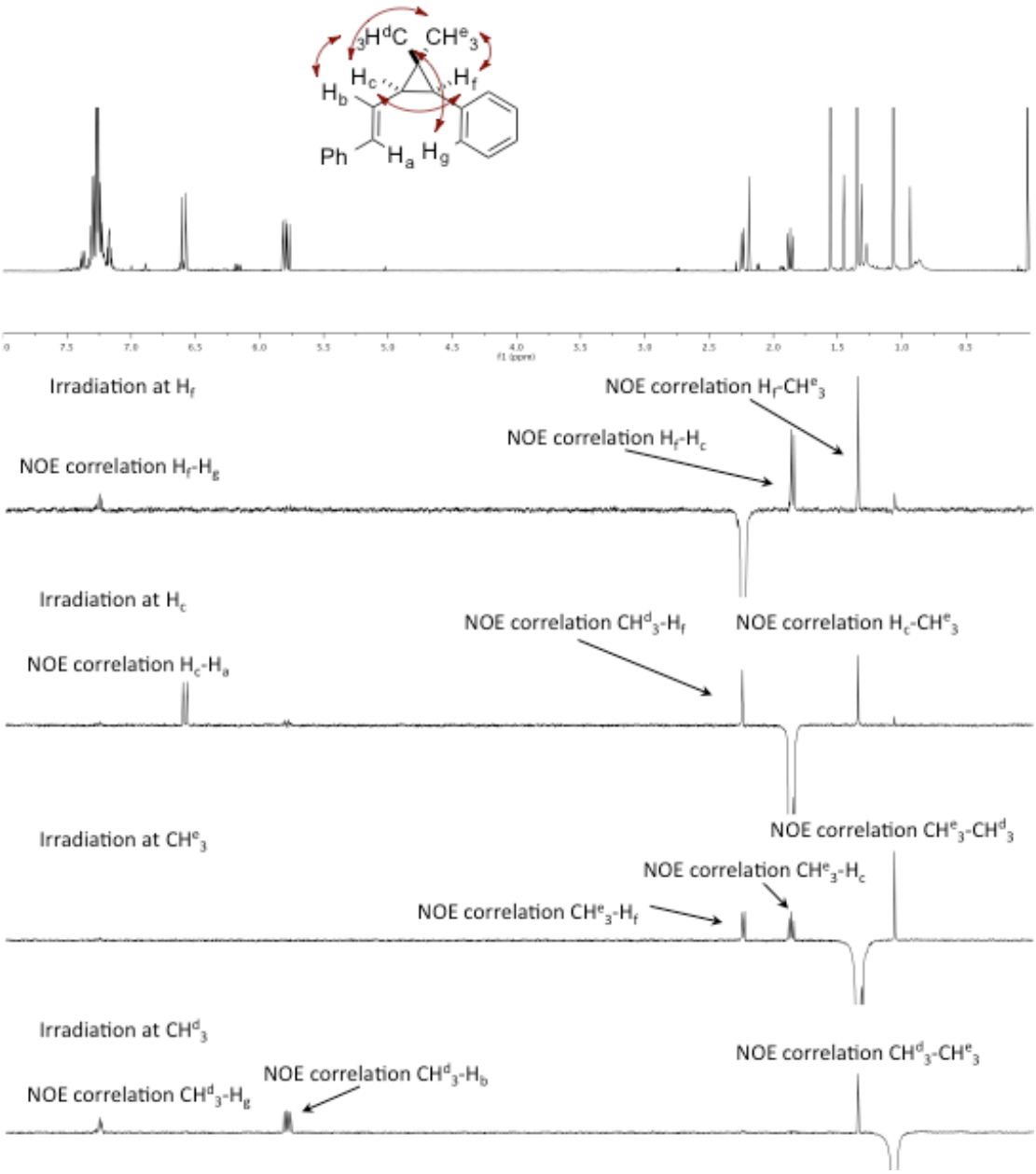
71v


Hd He
Hc
CH3
Hb
Ph
Ha Hg
Irradiation at Hb
NOE correlation Hb-Hg
NOE correlation Hb-Hd/e
Irradiation at Hc
NOE correlation CH3-Hd/e
NOE correlation Hc-Ha
NOE correlation Hc-CH3
Irradiation at CH3
NOE correlation CH3-Hd/e
NOE correlation CH3-Hg
NOE correlation CH3-Hc
Irradiation at Hd/e

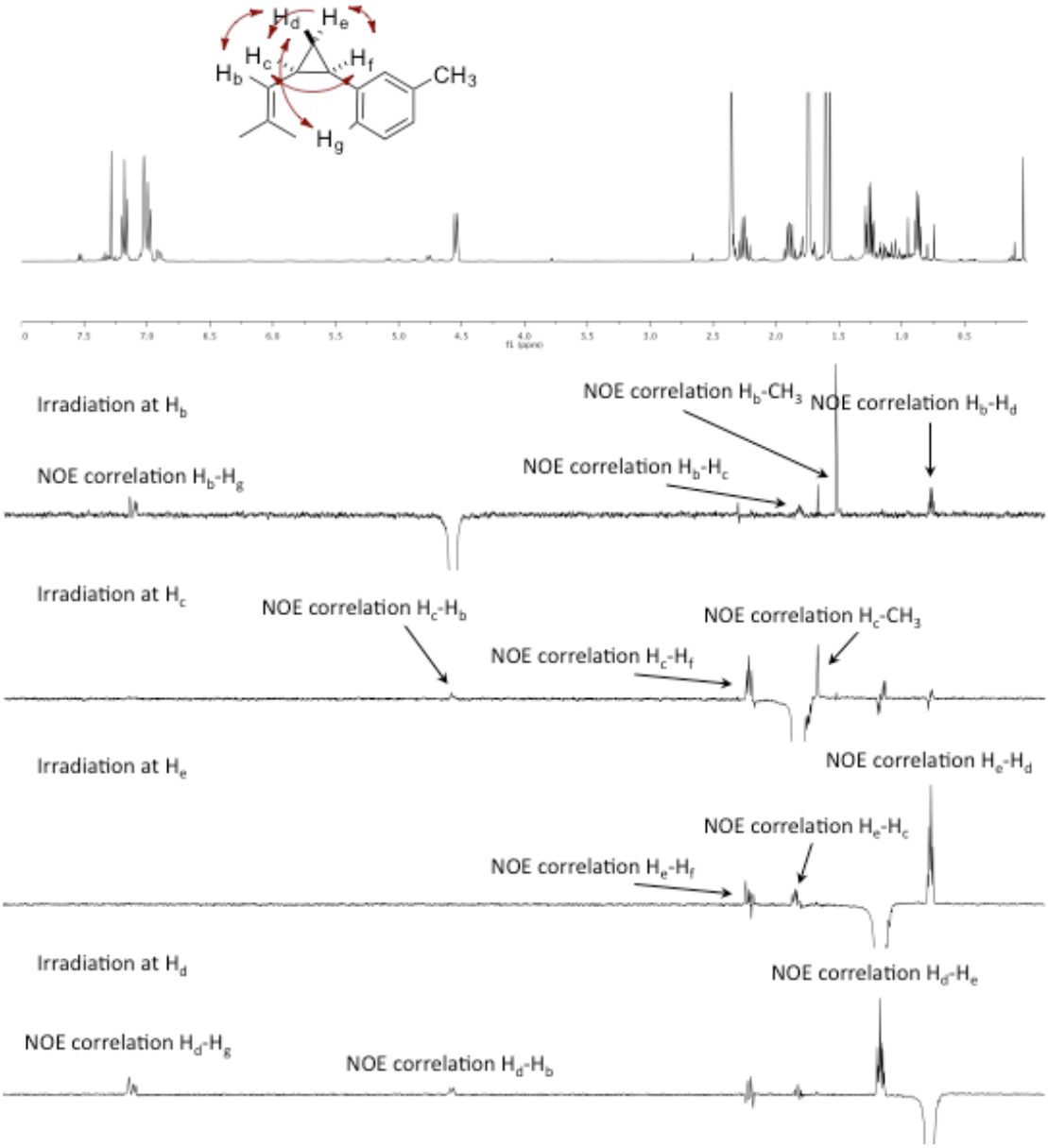
71x


Hd
CHe3
Hc
Hf
Hb
Ph
Ha
Hg
Irradiation at Hf
NOE correlation Hf-Hg
NOE correlation Hf-Hc
NOE correlation Hf-CHe3
Irradiation at Hc
NOE correlation Hc-Ha
NOE correlation Hc-Hf
NOE correlation Hc-CHe3
Irradiation at Hd
NOE correlation Hd-Hg
NOE correlation Hd-Hb
Irradiation at CHe3
NOE correlation CHe3-Hb
(trans isomer)
NOE correlation CHe3-Hf
NOE correlation CHe3-Hc
NOE correlation CHe3-Hd

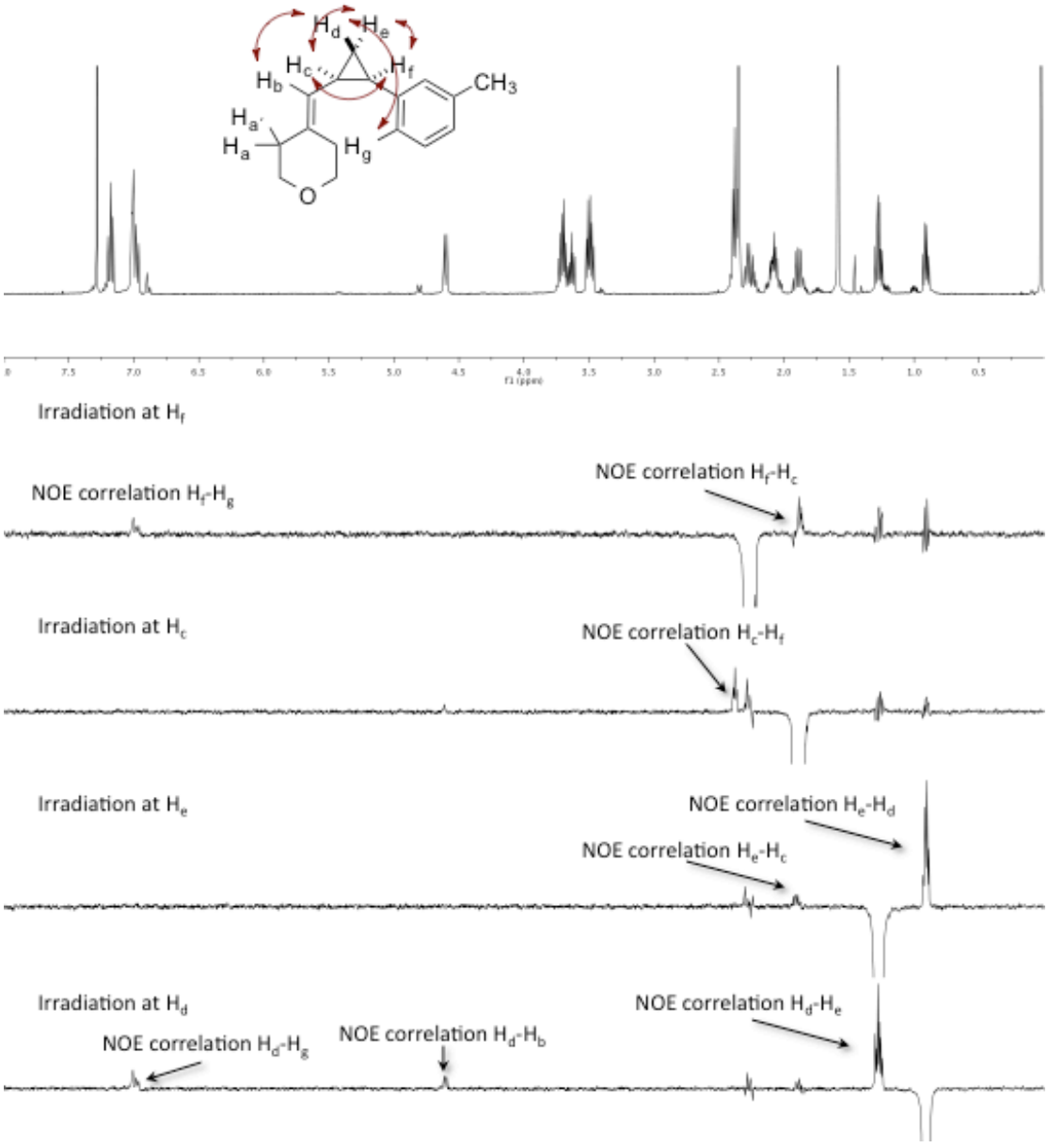
71y


Irradiation at H_f
NOE correlation H_f-CH^e_3
NOE correlation H_f-H_c
NOE correlation H_f-H_g
Irradiation at H_c
NOE correlation CH^d_3-H_f
NOE correlation H_c-CH^e_3
NOE correlation H_c-H_a
Irradiation at CH^e_3
NOE correlation CH^e_3-CH^d_3
NOE correlation CH^e_3-H_c
NOE correlation CH^e_3-H_f
Irradiation at CH^d_3
NOE correlation CH^d_3-CH^e_3
NOE correlation CH^d_3-H_b
NOE correlation CH^d_3-H_g

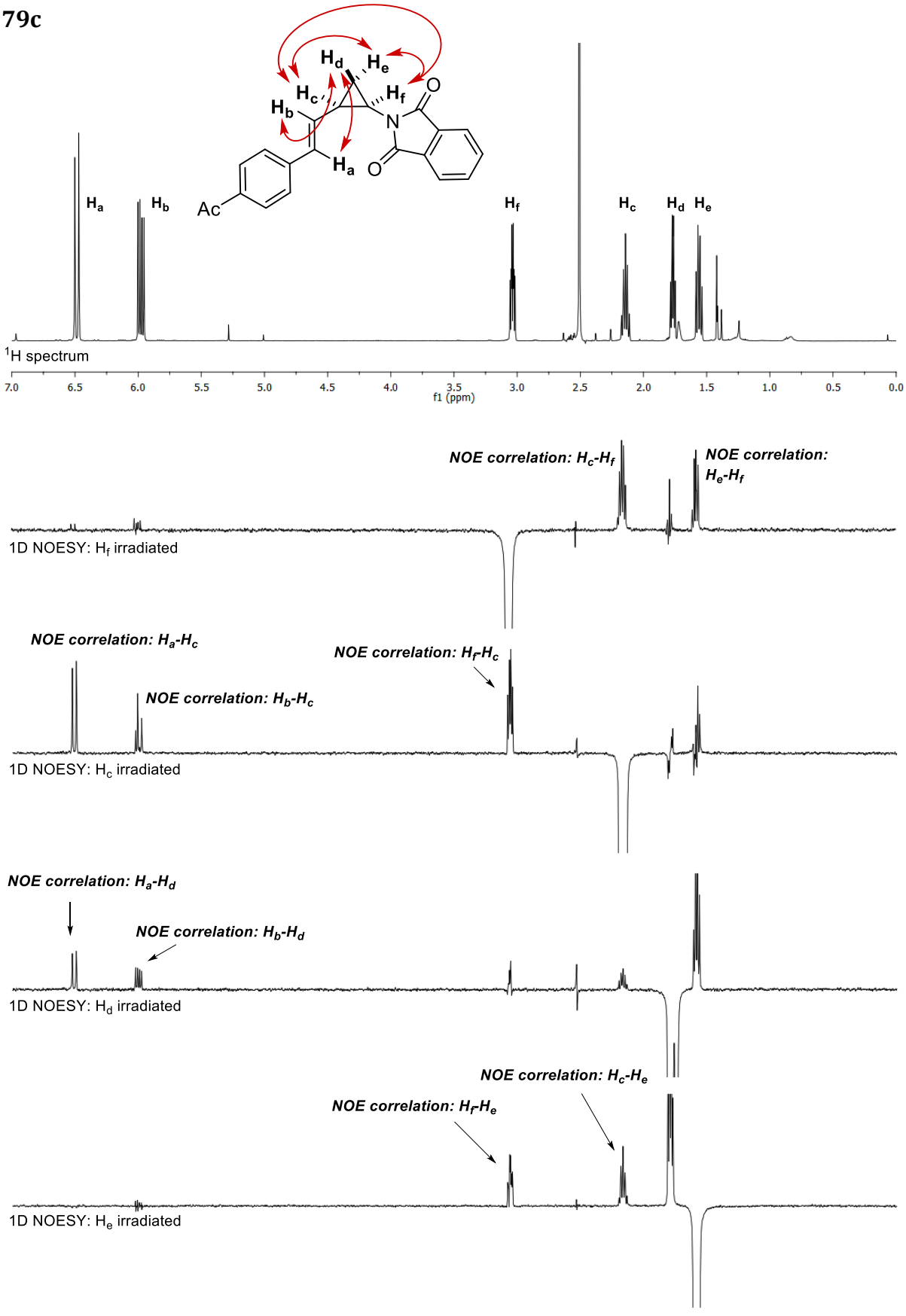
74g


Hd
He
Hc
Hf
Hb
CH3
Hg
Irradiation at Hb
NOE correlation Hb-CH3
NOE correlation Hb-Hd
NOE correlation Hb-Hg
NOE correlation Hb-Hc
Irradiation at Hc
NOE correlation Hc-Hb
NOE correlation Hc-CH3
NOE correlation Hc-Hf
Irradiation at He
NOE correlation He-Hd
NOE correlation He-Hc
NOE correlation He-Hf
Irradiation at Hd
NOE correlation Hd-He
NOE correlation Hd-Hg
NOE correlation Hd-Hb

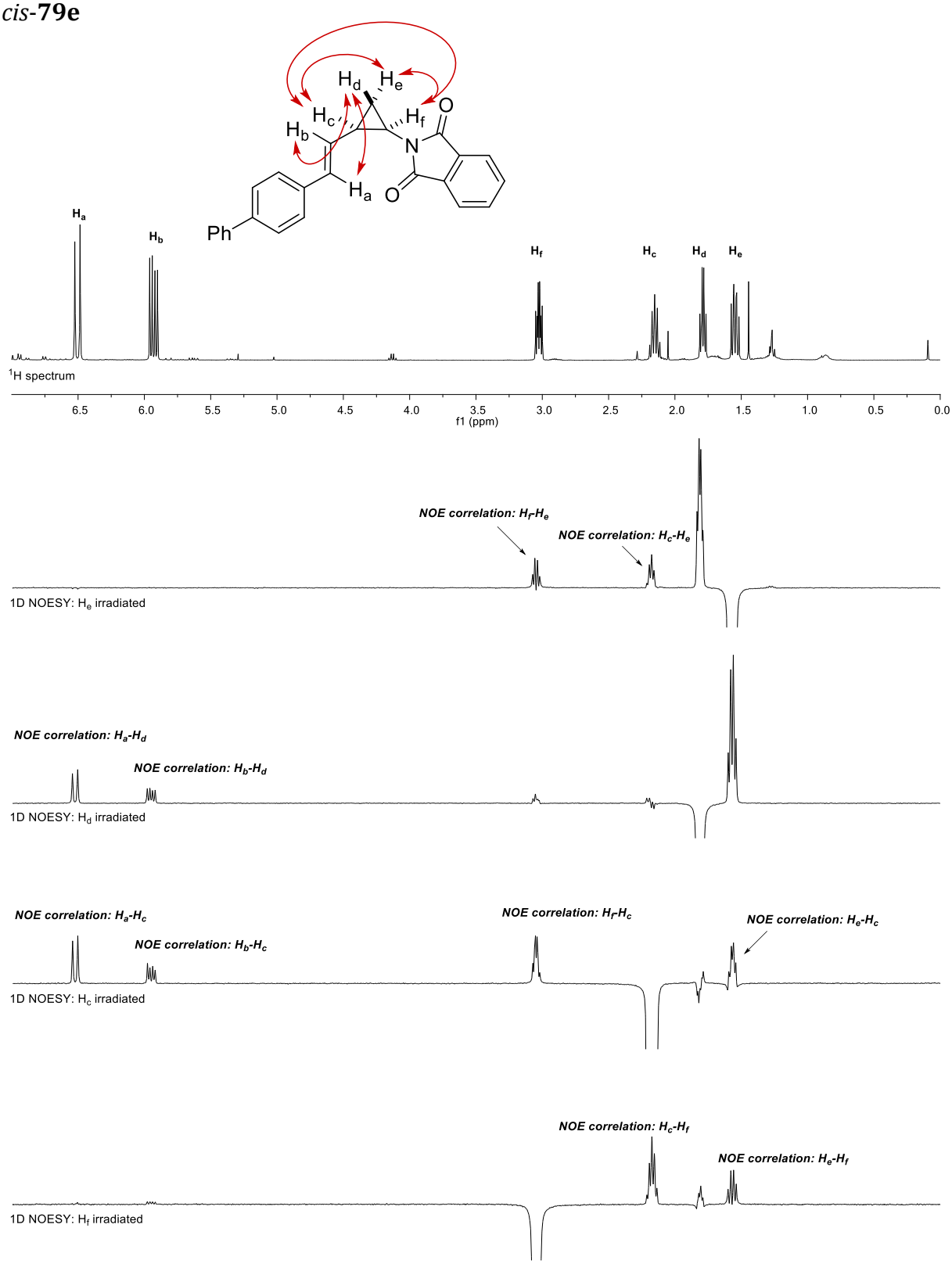
74h


Hd
He
Hc
Hf
Hb
CH3
Ha'
Ha
Hg
O
Irradiation at Hf
NOE correlation Hf-Hg
NOE correlation Hf-Hc
Irradiation at Hc
NOE correlation Hc-Hf
Irradiation at He
NOE correlation He-Hd
NOE correlation He-Hc
Irradiation at Hd
NOE correlation Hd-Hg
NOE correlation Hd-Hb
NOE correlation Hd-He

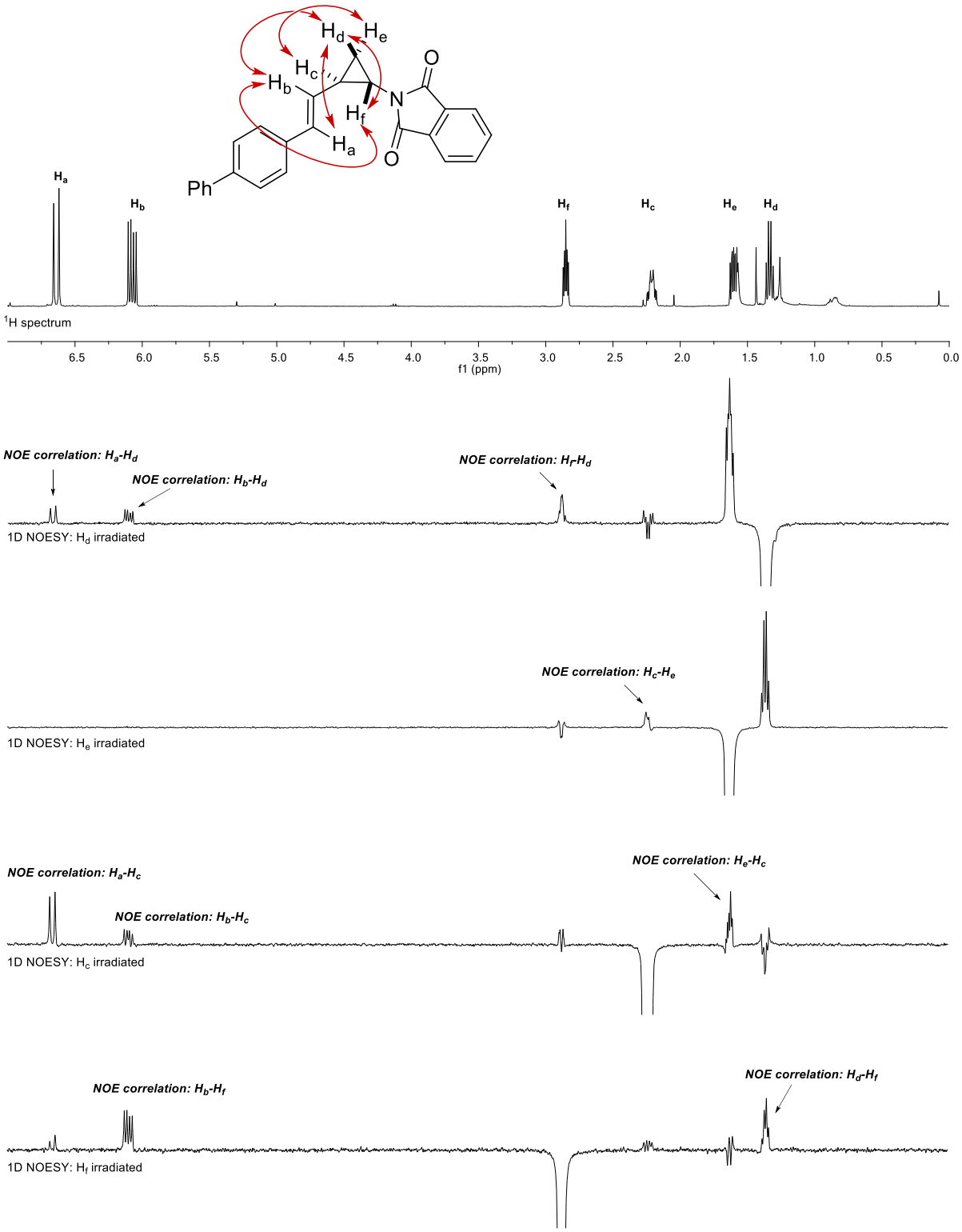
79c


Hd
He
Hc
Hf
Hb
Ha
O
N
O
Ac
Ha
Hb
Hf
Hc
Hd
He
1H spectrum
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
NOE correlation: Hc-Hf
NOE correlation: He-Hf
1D NOESY: Hf irradiated
NOE correlation: Ha-Hc
NOE correlation: Hf-Hc
NOE correlation: Hb-Hc
1D NOESY: Hc irradiated
NOE correlation: Ha-Hd
NOE correlation: Hb-Hd
1D NOESY: Hd irradiated
NOE correlation: Hc-He
NOE correlation: Hf-He
1D NOESY: He irradiated

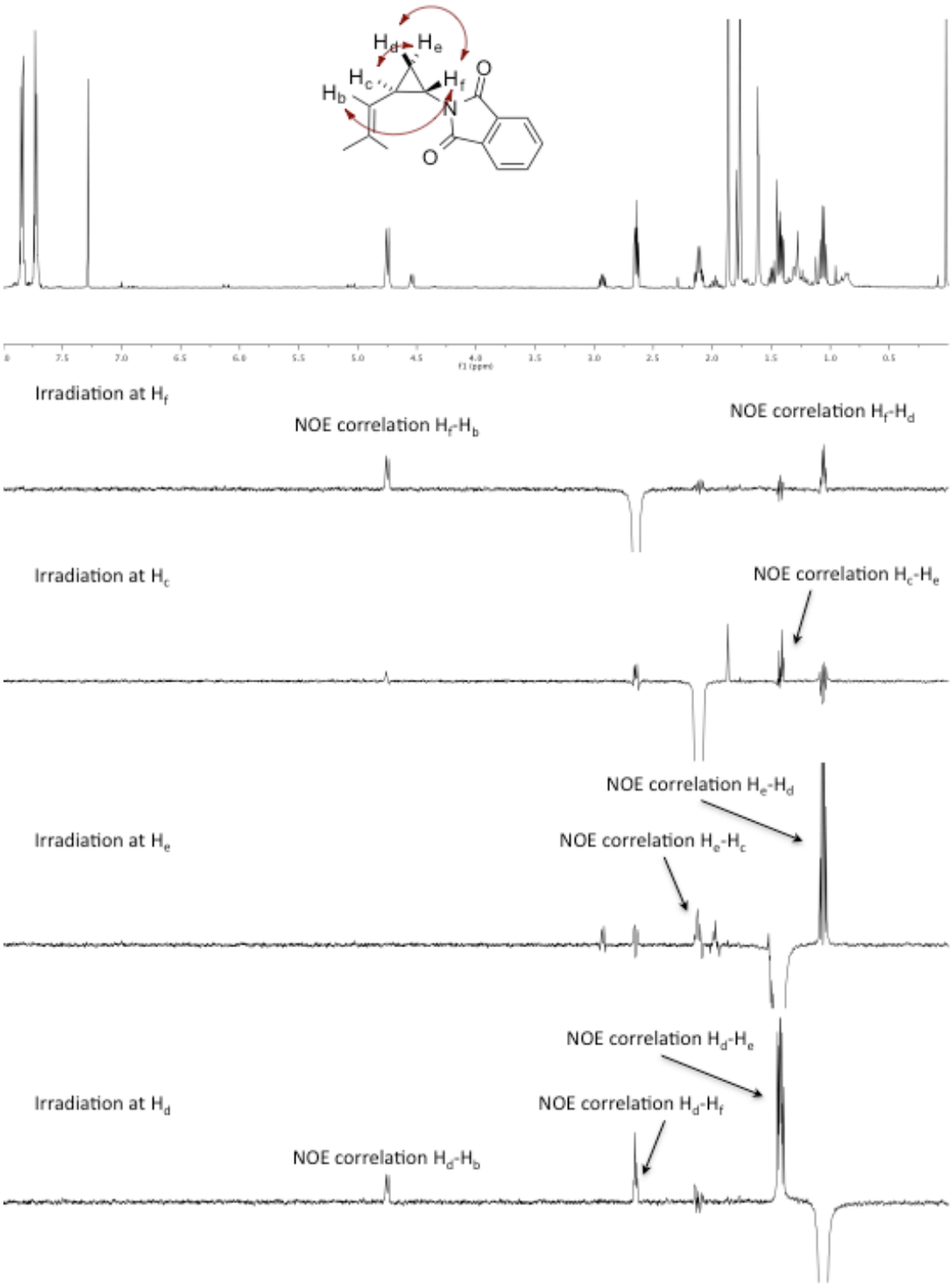
cis-**79e**


Hd
He
Hc
Hf
O
Hb
N
Ha
O
Ph
Ha
Hb
Hf
Hc
Hd
He
1H spectrum
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
NOE correlation: Hf-He
NOE correlation: Hc-He
1D NOESY: He irradiated
NOE correlation: Ha-Hd
NOE correlation: Hb-Hd
1D NOESY: Hd irradiated
NOE correlation: Ha-Hc
NOE correlation: Hb-Hc
NOE correlation: Hf-Hc
NOE correlation: He-Hc
1D NOESY: Hc irradiated
NOE correlation: Hc-Hf
NOE correlation: He-Hf
1D NOESY: Hf irradiated

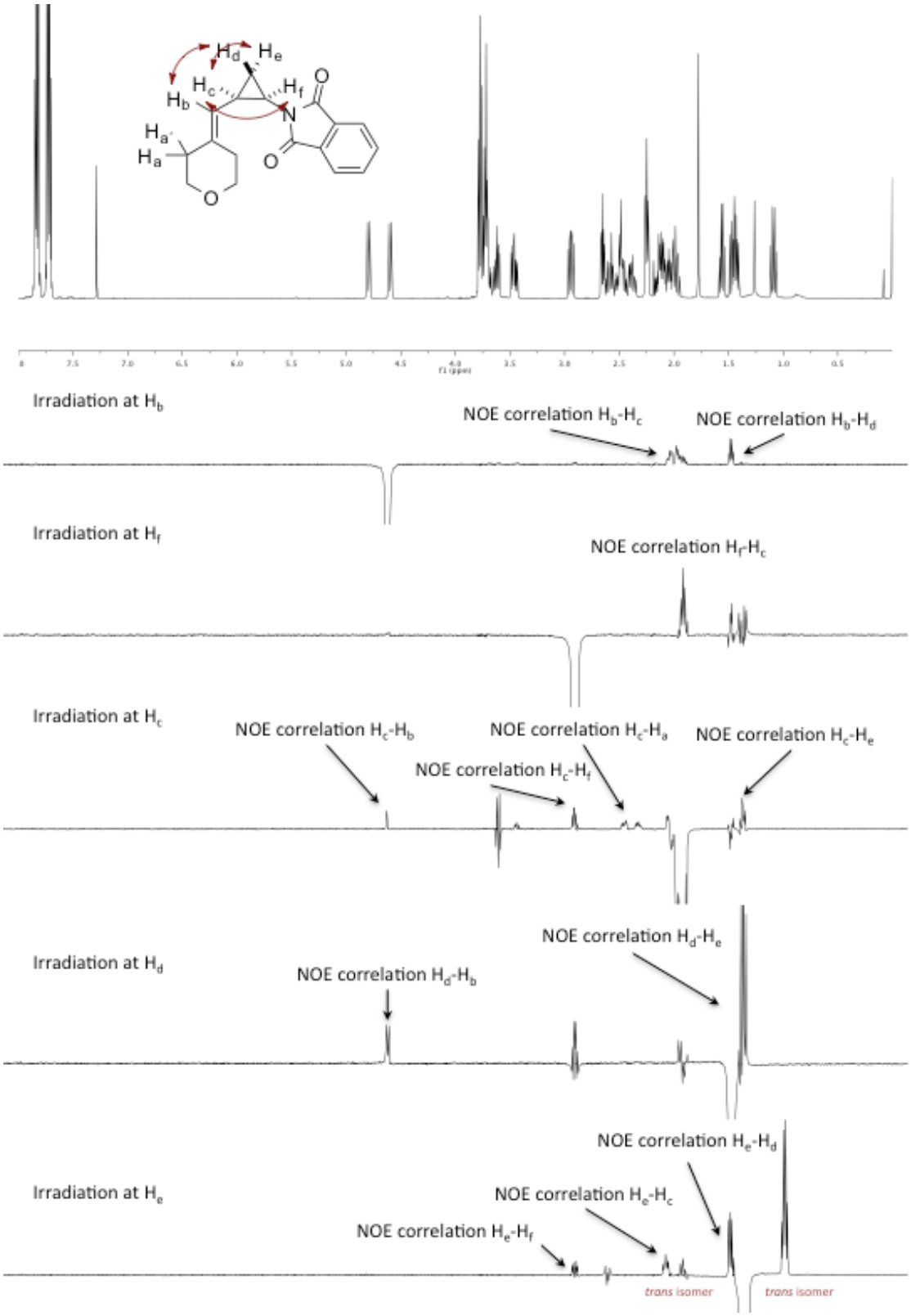
trans-**79e**


Hd
He
Hc
Hb
Hf
Ha
N
O
O
Ph
Ha
Hb
Hf
Hc
He
Hd
1H spectrum
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
NOE correlation: Ha-Hd
NOE correlation: Hb-Hd
NOE correlation: Hf-Hd
1D NOESY: Hd irradiated
NOE correlation: Hc-He
1D NOESY: He irradiated
NOE correlation: Ha-Hc
NOE correlation: Hb-Hc
NOE correlation: He-Hc
1D NOESY: Hc irradiated
NOE correlation: Hb-Hf
NOE correlation: Hd-Hf
1D NOESY: Hf irradiated

78g


Hd
He
Hc
Hf
Hb
O
N
O
Irradiation at Hf
NOE correlation Hf-Hb
NOE correlation Hf-Hd
Irradiation at Hc
NOE correlation Hc-He
NOE correlation He-Hd
Irradiation at He
NOE correlation He-Hc
NOE correlation Hd-He
Irradiation at Hd
NOE correlation Hd-Hf
NOE correlation Hd-Hb

78i


Irradiation at H_b
NOE correlation H_b-H_c
NOE correlation H_b-H_d
Irradiation at H_f
NOE correlation H_f-H_c
Irradiation at H_c
NOE correlation H_c-H_b
NOE correlation H_c-H_a
NOE correlation H_c-H_e
NOE correlation H_c-H_f
Irradiation at H_d
NOE correlation H_d-H_e
NOE correlation H_d-H_b
Irradiation at H_e
NOE correlation H_e-H_d
NOE correlation H_e-H_c
NOE correlation H_e-H_f
trans isomer
trans isomer

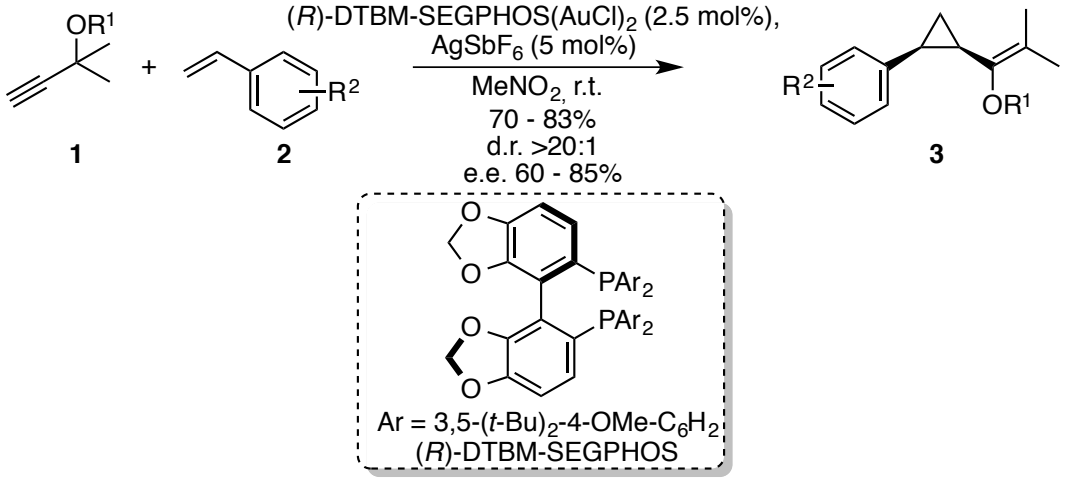
3.

Mechanistic Studies and the Origin of Diastereoselectivity

*The work described in this chapter was performed in collaboration with **Dr. Philipp M. Holstein**, whom I would like to thank for performing the DFT calculations and part of the kinetic experiments.*

Introduction

Stereoselective, let alone enantioselective, gold(I)-catalyzed alkene cyclopropanation reactions extremely rare. In the benchmark publication by Toste and co-workers from 2005 on *cis*-selective gold(I)-catalyzed alkene cyclopropanations, propargyl esters are used to generate vinyl gold carbenes, which undergo cyclopropanation with a variety of alkenes.[305] While most of the examples only display a modest selectivity and were generated with the simple cationic triphenylphospinegold(I) complex, excellent diastereo- and enantioselectivity can be achieved by switching to the bulky and chiral (*R*)-DTBM-SEGPHOS ligand (Scheme 138).



Scheme 138. Diastereo- and enantioselective alkene cyclopropanation.[305]

To explain the selectivity, a model was proposed by the group of Toste in which a concerted carbene transfer to the alkene takes place perpendicular to the gold-C1 bond (Figure 25). The incoming alkene can orient itself such that its substituents can either point away from the ligand (path A), or point towards the ligand where it experiences unfavorable steric interactions (path B). The model explains the preference of the *cis*- over the *trans*-isomer and is consistent with the fact that increasing the steric bulk of the ligand leads to improved diastereoselectivity. However, no explanation was given for the origin of the enantioselectivity and the absolute configuration of the products was not determined.

305 Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

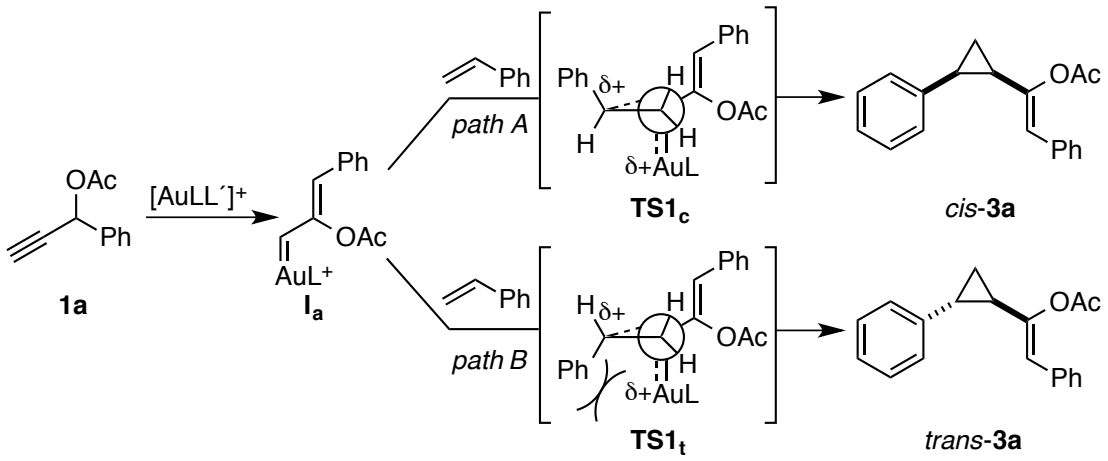


Figure 25. Proposed stereochemical model: *path A* is preferred as no unfavorable steric interactions are experienced, which is the case for *path B*, leading to good diastereoselectivities.[305]

A more elaborated model to explain the diastereoselectivity for this cyclopropanation reaction was developed by Soriano and Marco-Contelles based on DFT calculations.[306] Using a simple cationic phosphine-gold(I) complex as catalyst model, four possible transition structures were identified (Figure 26): Two structures leading to the *cis*-product, **TS1$_{I}$** and **TS1$_{II}$**, and two to the *trans*-product, **TS1$_{III}$** and **TS1$_{IV}$**. The C=C bond of the incoming alkene can either be antiperiplanar to the gold-C1 bond as in **TS1$_{II}$** and **TS1$_{III}$**, or at a gauche disposition for **TS1$_{I}$** and **TS1$_{IV}$**, which are found at higher energy and can thus be discarded. Transition state **TS1$_{II}$** leading to the *cis*-isomer is favored by about 1.3 kal·mol^{-1} compared to **TS1$_{III}$**, which leads to the *trans*-isomer. This stabilization is ascribed to favorable π-π interactions in **TS1$_{II}$**, whereas those interactions are absent for **TS1$_{III}$**.

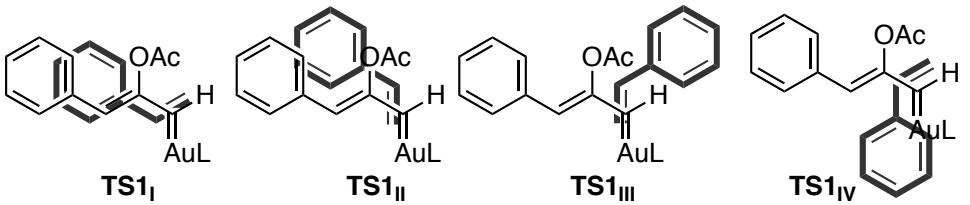
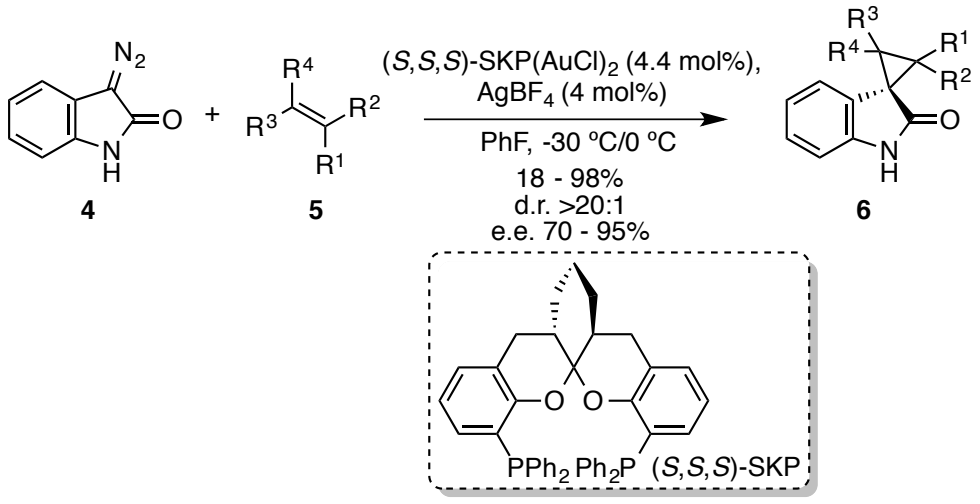


Figure 26. Transition-state models as found by Marco-Contelles *et al.* 2008.[306]

Another highly selective gold(I)-catalyzed alkene cyclopropanation was reported by Ding and co-workers in 2013, where gold(I) carbenes are formed from diazooxindoles and react with a variety of alkene in poor to excellent yield and

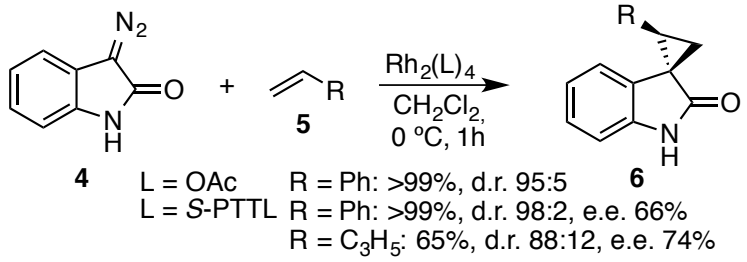
306 Soriano, E.; Marco-Contelles, J. *Chem. - Eur. J.* **2008**, *14*, 6771-6779.

good to excellent diastereo- and enantioselectivity using a spiroketal bisphosphine ligand (Scheme 139).[307] Even in the case of 1-hexene, an enantiomeric excess of 70% is reported but unfortunately no explanation for the high selectivity is given.



Scheme 139. Stereo- and enantioselective alkene cyclopropanation with diazooxindoles.[307]

Shortly before, a similar reaction was investigated using the achiral $[Rh_2(OAc)_4]$ and chiral $[Rh_2(S\text{-PTTL})_4]$ complexes (Scheme 140).[308] High diastereoselectivities were reported for both complexes, >19:1, and an e.e. of 48-74% was achieved with the chiral complex. For the excellent diastereoselectivity the authors propose that the incoming alkene is guided by the nitrogen atom of the oxindole, while avoiding steric interactions with the bulky catalyst (Figure 27). After rotation of the alkene, the spiro cyclopropyloxindole is formed. The origin of the enantioselectivity was not explained.



Scheme 140. Rhodium(II)-catalyzed alkene cyclopropanation with diazooxindoles.[308]

307 Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197-8200.

308 Awata, A.; Arai, T. *Synlett* **2013**, *24*, 29-32.

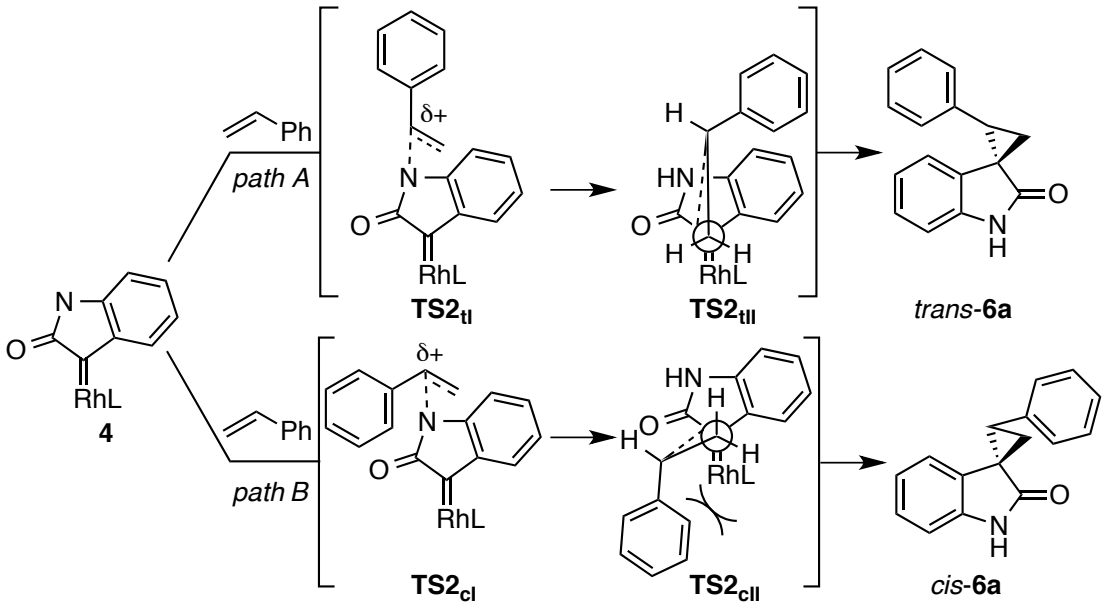


Figure 27. Proposed stereochemical model: the incoming alkene is guided by the nitrogen, while avoiding steric interaction with the catalyst in *path A* leading to excellent selectivities.[308]

Several computational studies have been performed to understand the diastereoselectivity for alkene cyclopropanations with diazo acetate derivatives using a similar family of rhodium(II) catalysts. [309] In each case the diastereoselectivity is ascribed to the steric interaction between the ester and the incoming alkene, counterbalanced by the interaction of the other α-substituent with the alkene. Thus, the stereoselective outcome is dependent on the nature of R^1 and R^2 (Figure 28).

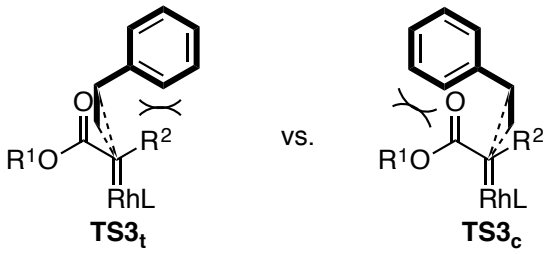


Figure 28. Proposed stereochemical model for rhodium(II) catalyzed alkene cyclopropanation with diazoacetate derivatives.

309 a) Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902-15911. b) Hansen, J. r.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555-6563. c) Bonge, H. T.; Hansen, T. *Tetrahedron Lett.* **2010**, *51*, 5298-5301. d) Bonge, H. T.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 2309-2320.

Recently, the group of Chen studied the mechanism of the reaction between diazooxindoles and styrene derivatives as reported by Arai (Scheme 140) using elaborate catalyst models of the $Rh_2(OAc)_4$ and Rh_2(S-PTTL)$_4$ complexes.[310] Instead of highlighting steric interactions between the substrates and catalyst, favorable interactions between the substrates were found to be the origin of the high diastereoselectivity (Figure 29). For the achiral catalyst, the end-on approach of the alkene (**TS2$_I$** and **TS2$_{II}$**) was favored over the side-on approach (**TS2$_{III}$** and **TS2$_{IV}$**). Within the end-on transition states, a difference of 1.8 kcal·mol^{-1} was found between the *cis*- and *trans*-pathway (**TS2$_I$** vs. **TS2$_{II}$**). The difference is partially ascribed by π-π interactions and the authors demonstrate that removing the π-π interaction, by replacing the aromatic alkene substituent for an alkyl chain, reduces the energy difference between the two transition structures. The origin of selectivity is similar to what was reported by Soriano and Marco-Contelles for the gold(I)-catalyzed cyclopropanation. The energy difference between the *cis*- and *trans*-transition-state structures for the chiral catalyst was found to be greater, 2.2 kcal·mol^{-1}, which was in agreement with experimental observations. The bulky ligands rigidify the transition-state structures, limiting the freedom of the incoming alkene to avoid steric interaction, which leads to increased contribution of the π-π interaction on the stabilization. Enantioselectivity is induced by π-π interactions and CH-π between the substrates and catalyst system.

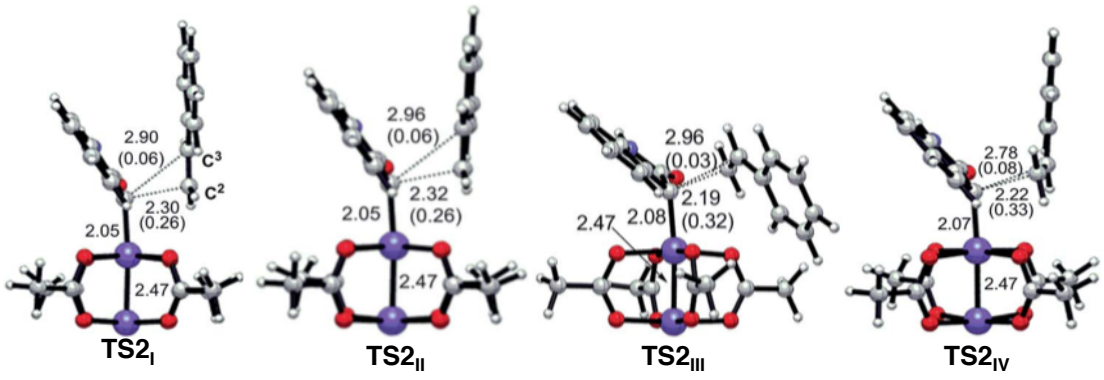


Figure 29. Transition states for the Rh-catalyzed cyclopropanation.[310]

310 Xue, Y.-S.; Cai, Y.-P.; Chen, Z.-X. *RSC Advances* **2015**, *5*, 57781-57791.

The mechanism of the retro-Buchner reaction for 7-aryl cycloheptatrienes has been investigated by DFT calculations in a previous study by our group (Figure 30).[311] The calculations clearly identify the gold-mediated cleavage of two C-C bonds of norcaradiene in a two-step process to form the gold carbene as the rate-determining event. The values for the energy barriers were in good qualitative agreement with the observed experimental values, although the calculations were performed on a simplified catalyst model where the ligand was substituted for trimethylphosphine. The mechanism for cyclopropanation was not investigated and thus no explanation for the stereoselective outcome could be proposed.

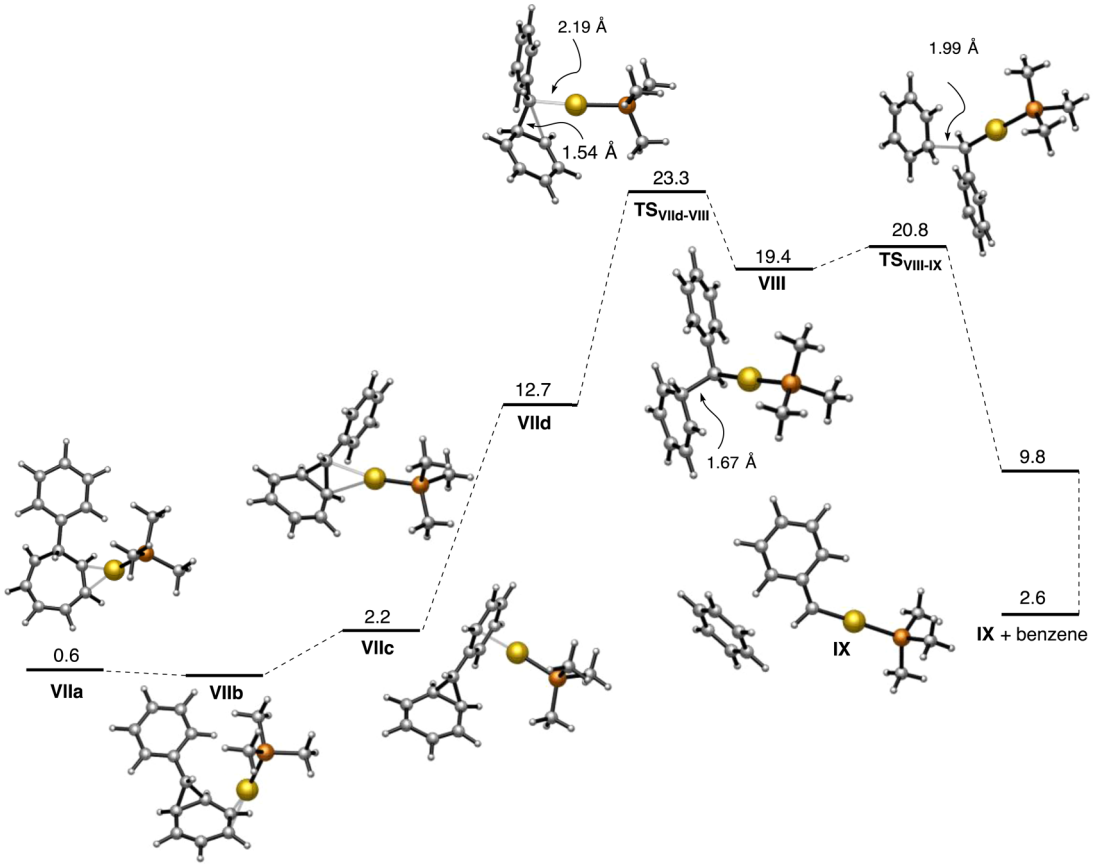


Figure 30. Calculated mechanism for the retro-Buchner reaction of 7-aryl cycloheptatrienes.[311]

311 Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801-809.

The mechanism of the retro-Buchner reaction for gold, as well as for copper and silver was described in greater detail, in 2016 by Song and co-workers (Figure 31).[312] Calculations were performed using the unsimplified version of the JohnPhos-gold complex **A** as catalyst. The findings are in close qualitative agreement with the work reported by our group, while the values are giving a better quantitative representation of the experimental values (23.3 vs. 27.1 kcal·mol^{-1}). Interestingly, the energy barriers for the retro-Buchner reaction using a silver-acetonitrile complex or copper-acetonitrile complex were found to lie at 26.9 kcal·mol^{-1}. The calculations suggest that the formation of silver or copper complexes through the retro-Buchner reaction could take place at temperatures comparable to the ones for gold.

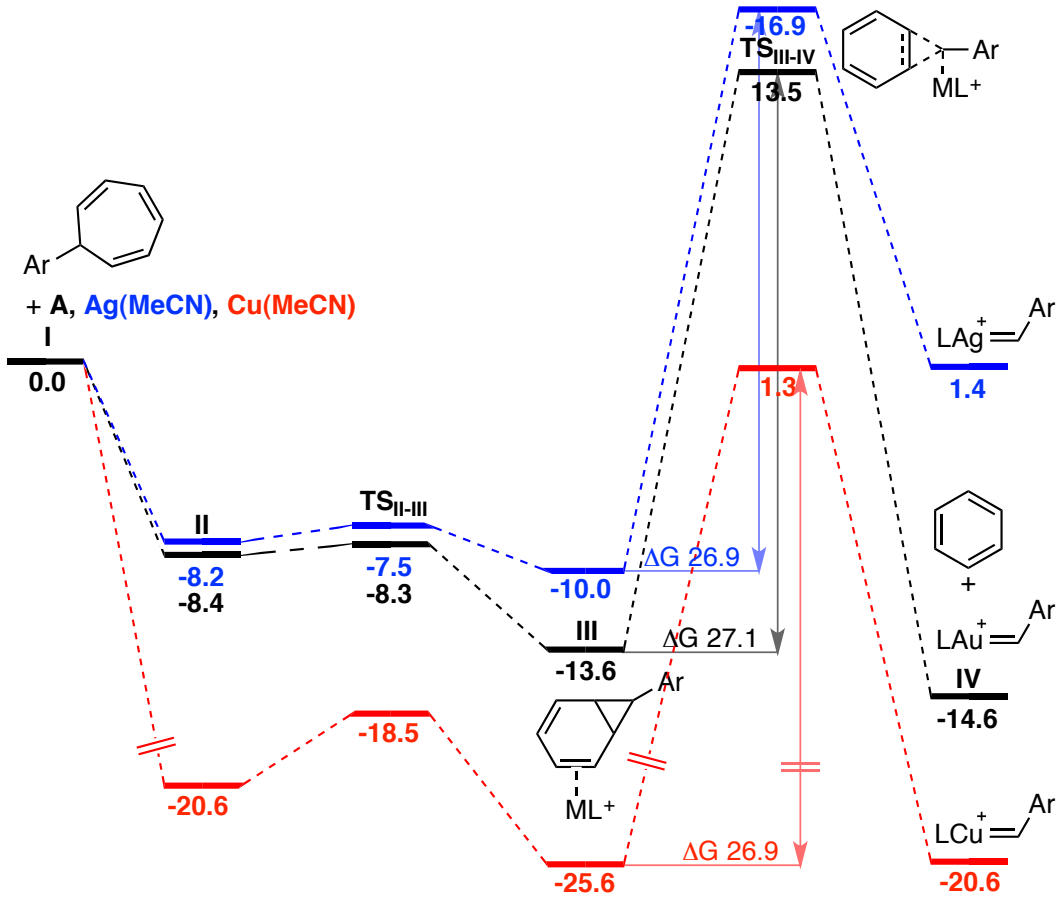
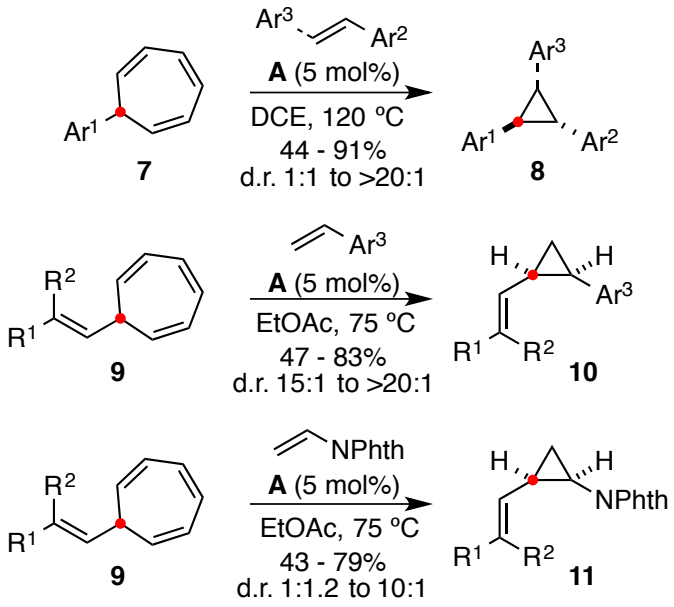


Figure 31. Calculated mechanism for the retro-Buchner reaction of 7-aryl cycloheptatrienes using gold(I), silver(I), and copper(I) catalysts.[313]

312 Song, Z.; Liu, C.; Chen, X.; Yan, W.; Cao, Y.; Xie, H.; Lei, Q.; Fang, W. *Comput. Theor. Chem.* **2016**, *1084*, 25-35.

313 Xue, Y.-S.; Cai, Y.-P.; Chen, Z.-X. *RSC Advances* **2015**, *5*, 57781-57791.

The excellent *cis*-selectivity obtained in the cyclopropanation of vinyl gold(I) carbenes with styrenes described in *chapter 2* stands in stark contrast with the seemingly erroneous *trans*-selectivity obtained for aryl gold(I) carbenes from our previous work (Scheme 141).[314] In addition, the cyclopropanation of *N*-vinylphthalimides with vinyl gold(I) carbenes was significantly less selective nonetheless generally favoring the *cis*-isomer.



Scheme 141. Results obtained for the cyclopropanation reaction using 7-aryl or 7-alkenyl cycloheptatriene derivatives.

The mechanistic investigations performed thus far fail to offer an explanation for the observed differences in selectivity. The original model by Toste and co-workers does not take the electronic differences between the substrates into account. The more advanced models do take these effects into account through strengthening or weakening of the π-π interactions, however even these models do not explain the complete loss or inversion of the diastereoselectivity observed in some cases.

This chapter summarizes the study of the mechanism and the factors influencing the stereoselective outcome.

314 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

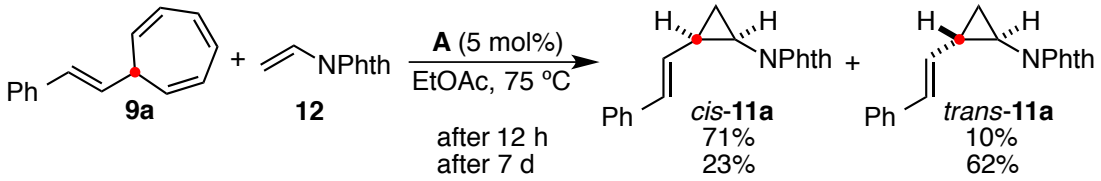
Objectives

The objective of the work reported in this chapter was to find an explanation for the excellent diastereoselectivity for aryl vinylcyclopropanes but at the same time, the diminished selectivity for aminocyclopropanes, or the seemingly erratic selectivity for bis-arylcyclopropanes from our group´s previous work.

Elucidating the factors controlling the diastereoselectivity will allow us to design new systems with better catalytic profiles.

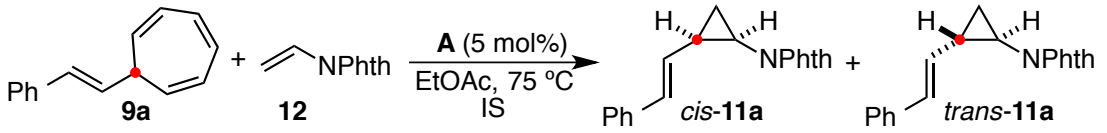
Results and discussion

During the course of the investigations on the formation of vinyl gold(I) carbenes and cyclopropanation reaction described in *chapter 2*, excellent *cis*-selectivities were obtained for the [(JohnPhos)Au(MeCN)]SbF_6 (**A**) catalyzed reaction of styrenyl-cycloheptatriene derivatives with styrenes. At the same time, lower selectivities were observed for the cyclopropanation of *N*-vinylphthalimides as alkene, or when other alkenyl-cycloheptatrienes were used, while the inverse selectivity was observed for the combination of *N*-vinylphthalimides with some alkenyl-cycloheptatrienes. In addition to the lower selectivities obtained for certain substrates, we observed that prolonged reaction times caused a lower diastereoselective outcome, for some examples (Scheme 138).



Scheme 142. Reduction of the diastereomeric ration over time for the vinyl-aminocyclopropanes.

In order to get a better understanding of the underlying process causing this unexpected behavior, the gold(I)-catalyzed reaction of **9a** with 1**2** was followed over time (Figure 32).



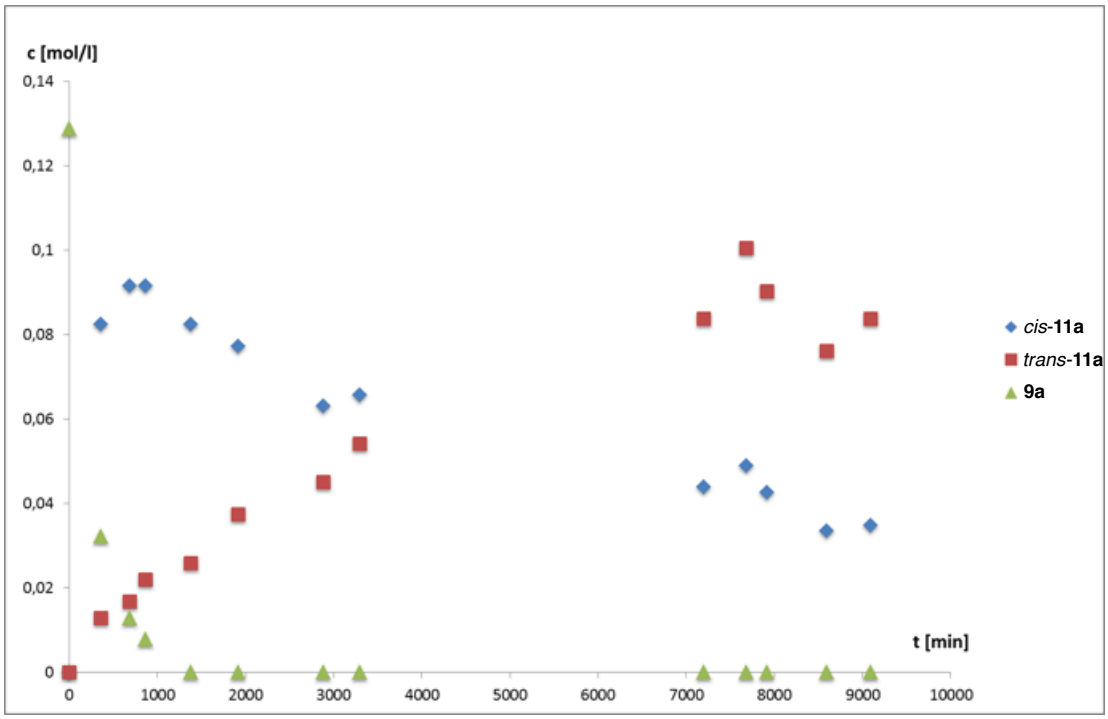


Figure 32. Plot of the kinetic experiment for the cyclopropanation of *N*-vinyl phthalimide (**12**) using **9a.** Diphenylmethane was used as internal standard.

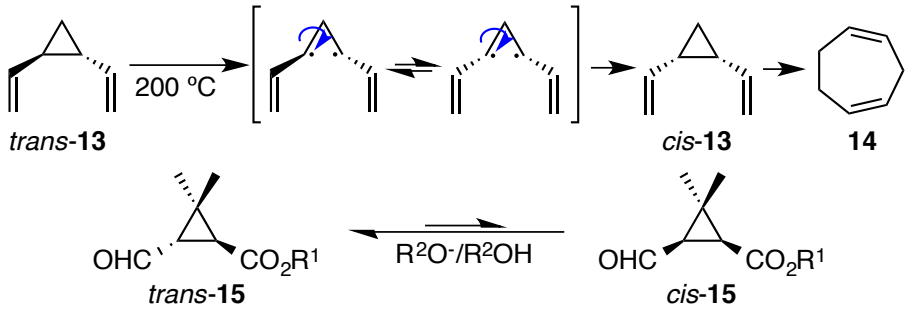
A fast consumption of cycloheptatriene **9a** along with the formation of *cis*-**11a** was observed by ^{1}H NMR analysis. Interestingly, the amount of *trans*-**11a** continues to slowly rise after the cyclopropanation reaction is complete, depleting the amount of *cis*-**11a** until an equilibrium is reached. The data clearly indicate that apart from the initial selectivity obtained during the cyclopropanation reaction, a slow background reaction is isomerizing the initial product.

Both radical, [315] and substituent mediated cis-trans isomerizations for cyclopropanes have been reported (Scheme 143).[316] In order to rule out a

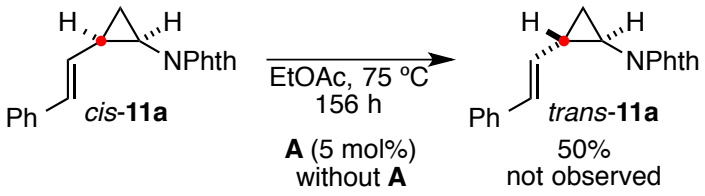
315 a) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. In *Organic Reactions*; John Wiley & Sons, Inc.: 2004. b) Krüger, S.; Gaich, T. *Beilstein J. Org. Chem.* **2014**, *10*, 163-193.

316 a) Ortiz de Montellano, P. R.; Dinizo, S. E. *J. Org. Chem.* **1978**, *43*, 4323-4328. b) Sasaki, T.; Eguchi, S.; Ohno, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1469-1470. c) Feit, B. A.; Elser, R.; Melamed, U.; Goldberg, I. *Tetrahedron* **1984**, *40*, 5177-5180. d) Yamaguchi, K.; Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J.*

temperature or substrate induced isomerization, pure *cis*-**11a** was submitted to the reaction conditions in the absence of catalyst **A** (Scheme 144). Indeed, no isomerization was observed in the absence of **A**, whereas the *trans*-isomer was obtained upon addition of the catalyst, indicating that a gold-mediated isomerization is taken place rather than an unrelated background reaction. Such a cyclopropane isomerization had not been experimentally observed previously, although a related process had been calculated by our group.[317]



Scheme 143. Cyclopropane isomerization through a diradical intermediate (top),[318] or substituent mediated mechanism(bottom).[319]



Scheme 144. Mechanistic experiments performed to elucidate the origin of diastereoselectivity.

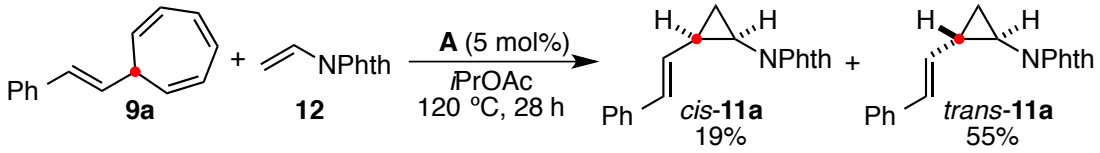
The rate of isomerization was temperature dependent, and *trans*-**11a** could be isolated in a synthetically relevant yield of 55% by performing the cyclopropanation at 120 °C on a reasonable time scale (Scheme 145).

Org. Chem. **2003**, *68*, 9255-9262. e) Marcoux, D.; Goudreau, S. R.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 8939-8955. f) Xu, X.; Zhu, S.; Cui, X.; Wojtas, L.; Zhang, X. P. *Angew. Chem. Int. Ed.* **2013**, *52*, 11857-11861.

317 Pérez-Gálan, P.; Herrero-Gómez, E.; Hog, D. T.; Martin, N. J. A.; Maseras, F.; Echavarren, A. M. *Chem. Sci.* **2011**, *2*, 141-149.

318 Krüger, S.; Gaich, T. *Beilstein J. Org. Chem.* **2014**, *10*, 163-193.

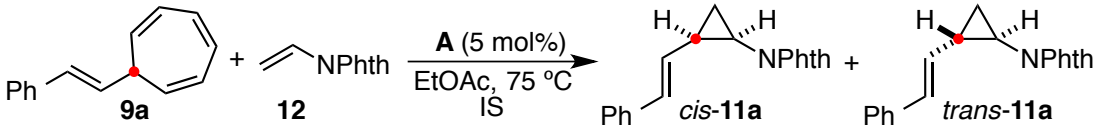
319 Ortiz de Montellano, P. R.; Dinizo, S. E. *J. Org. Chem.* **1978**, *43*, 4323-4328.



Scheme 145. Formation of *trans*-**11a** on a synthetically relevant scale by performing the cyclopropanation at a higher temperature.

Estimation of activation energies

The initial rate for the cyclopropanation reaction of **9a** with **12** could be obtained from the reaction profile data by plotting the concentration of **9a** versus the reaction time (Figure 33).



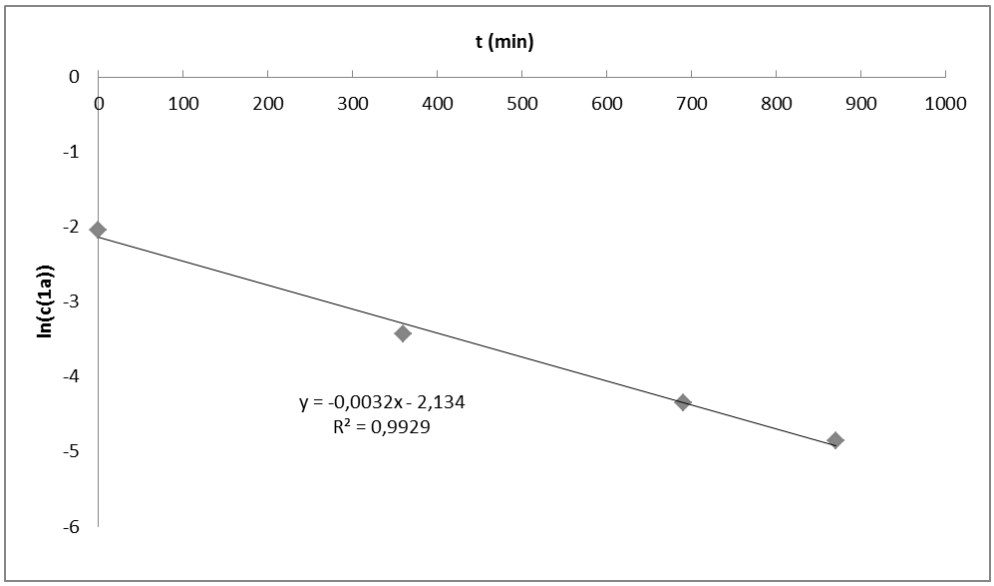


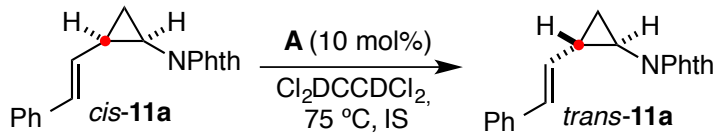
Figure 33. Initial rate plot for consumption of **9a**.

A pseudo-first order reaction kinetic can be assumed because of the excess of substrate relative to gold catalyst **A**. A reaction rate constant of k= -5.33 10^{-5} mol·s^{-1} for the consumption of cycloheptatriene **9a** was determined. Using the Eyring equation, the value for the energy of activation was estimated to be 27.0 kcal·mol^{-1}.

$$\Delta G^{\ddagger} = \frac{-RT\ln(-k_r h)}{k_B T}$$

Equation 1. Eyring equation rewritten to give $\boldsymbol{\Delta G^{\ddagger}}$, where R = 8.31 J·K^{-1}·mol^{-1}, T = 348 K, k_r = -5.33·10^{-5} mol·s^{-1}, h = 6.63·10^{-34} J·s, k_B = 1.38·10-23 J·K^{-1}.

In the same way, the initial-rate study of the isomerization reaction was performed (Figure 34). The conversion of pure *cis*-**11a** into *trans*-**11a** under the reaction conditions was followed over time.



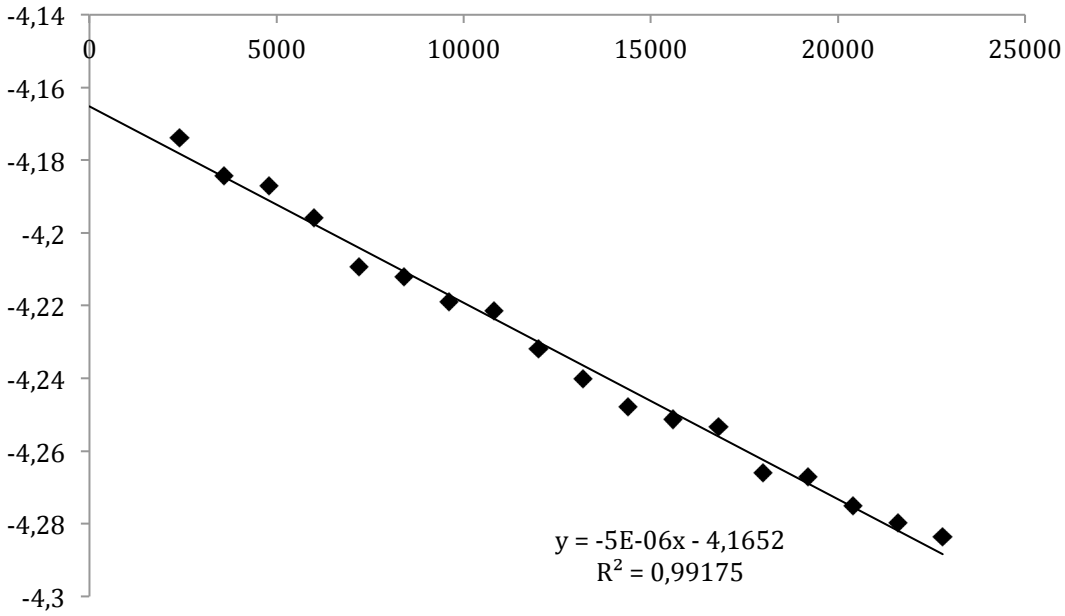


Figure 34. Initial rate plot for the isomerization of *cis*-**11a**.

A reaction rate constant of k = -5.00·10^{-6} mol·s^{-1} for the disappearance of the *cis*-isomer was derived from this plot. Using the Eyring equation, we were able to determine the value for the energy of activation to be 28.9 kcal·mol^{-1}.

$$\Delta G^{\ddagger} = \frac{-RT\ln(-k_r h)}{k_B T}$$

Equation 2. Eyring equation rewritten to give $\boldsymbol{\Delta G^{\ddagger}}$, where R = 8.31 J·K^{-1}·mol^{-1}, T = 348 K, k_r = -5.00·10^{-5} mol·s^{-1}, h = 6.63·10^{-34} J·s, k_B = 1.38·10-23 J·K^{-1}.

Computational investigations of the cyclopropanation mechanism

In order to get a better understanding of which factors play a role in the determination of the diastereoselectivity during the cyclopropanation reaction, the complete reaction pathways for the formation of **10a**, **11a**, and **11b** were studied by DFT calculations at the M06/6-31G(d) / M06/6-311+G(2d,p) (C, H, N, O, P) and SDD (Au) levels, taking into account the solvent effect (SMD = dichloromethane) and employing JohnPhos as the phosphine ligand.[320]

The formation of **10a** starts with the retro-Buchner reaction of **9a**, which involves a stepwise cleavage of two C-C bonds, through a Wheland-type intermediate, of complex **II** to form the vinyl gold carbene **V** (Figure 35). The cleavage of the second C-C goes through the highest lying intermediate and thus determines the activation barrier for the formation of gold(I)-carbene **V**. The activation barrier was calculated to be 25.1 kcal·mol^{-1}, which corresponds to the experimentally estimated value of 27.0 kcal·mol^{-1}.

The subsequent cyclopropanation of styrene with **V** to form **10a** proceeds through an asynchronous concerted mechanism, with an energy difference of 3.1 kcal·mol^{-1} between the *cis*- and *trans*-pathways, leading exclusively to the kinetic product *cis*-**10a**, as observed experimentally (d.r. >25:1).

The pathway of cyclopropanation of *N*-vinylphthalimide (**12**) with **V** to form **11a** passes through closely related transition states (Figure 36). Interestingly,

320 a) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378-6396. b) Frisch, M. J. T., G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg,J.J.;Dapprich,S.;Daniels, A.D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09 (Revision D.01)* **2013**, *Gaussian, Inc.: Wallingford, CT*.

despite the observed diastereoselectivity (6:1) being inferior to that of styrene, the energy difference between the pathways, with a value of 4.8 kcal·mol^{-1}, is actually greater.

The pathway of the retro-Buchner reaction of **11b** to form gold(I)-carbene **XIV**, and subsequent cyclopropanation of **12** was also calculated (Figure 37). The formation of the gold carbene involves a similar stepwise double C-C bond cleavage. The energy barrier is determined by the first bond cleavage and is slightly elevated compared to the other substrates, 28.5 kcal·mol^{-1}. A similar reaction pathway was calculated for the cyclopropanation too, albeit with a smaller difference between the *cis*- and *trans*-pathways, 2.1 kcal·mol^{-1}, yet still large enough for a completely selective reaction.

The origin of diastereoselectivity

Steric interactions alone fail to explain the energy difference between the transition states (Figure 38), as the overall interaction is comparable in both *cis*- and *trans*-transition-state complexes. However, the bulky ligand does play an important role in the selectivity as it creates a rigid catalyst-ligand system, where only two approaches of the incoming alkene are possible. On the other hand, electronic interactions do provide an explanation,[321] as the interplanar distances and stabilization energy are within the typical range for π-π interactions (3.6 Å, 5 kcal·mol^{-1}) in the *cis*-transition state.[322]

Further evidence that π-π interactions are responsible for a significant stabilization of the *cis*-transition state was found by comparing the energies calculated for the reaction pathway (Table 11, row 1) with additional calculations where dispersion correction was disabled (Table 11, row 2) or enabled (Table 11, row 3). Without dispersion interactions, the *cis*-transition state is only marginally more stable, which would result in a poor intrinsic diastereoselectivity, whereas by including the dispersion interactions the obtained energy difference would match the observed diastereoselectivity.

321 a) Soriano, E.; Marco-Contelles, J. *Chem. - Eur. J.* **2008**, *14*, 6771-6779. b) Song, Z.; Liu, C.; Chen, X.; Yan, W.; Cao, Y.; Xie, H.; Lei, Q.; Fang, W. *Comput. Theor. Chem.* **2016**, *1084*, 25-35.

322 Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4808-4842.

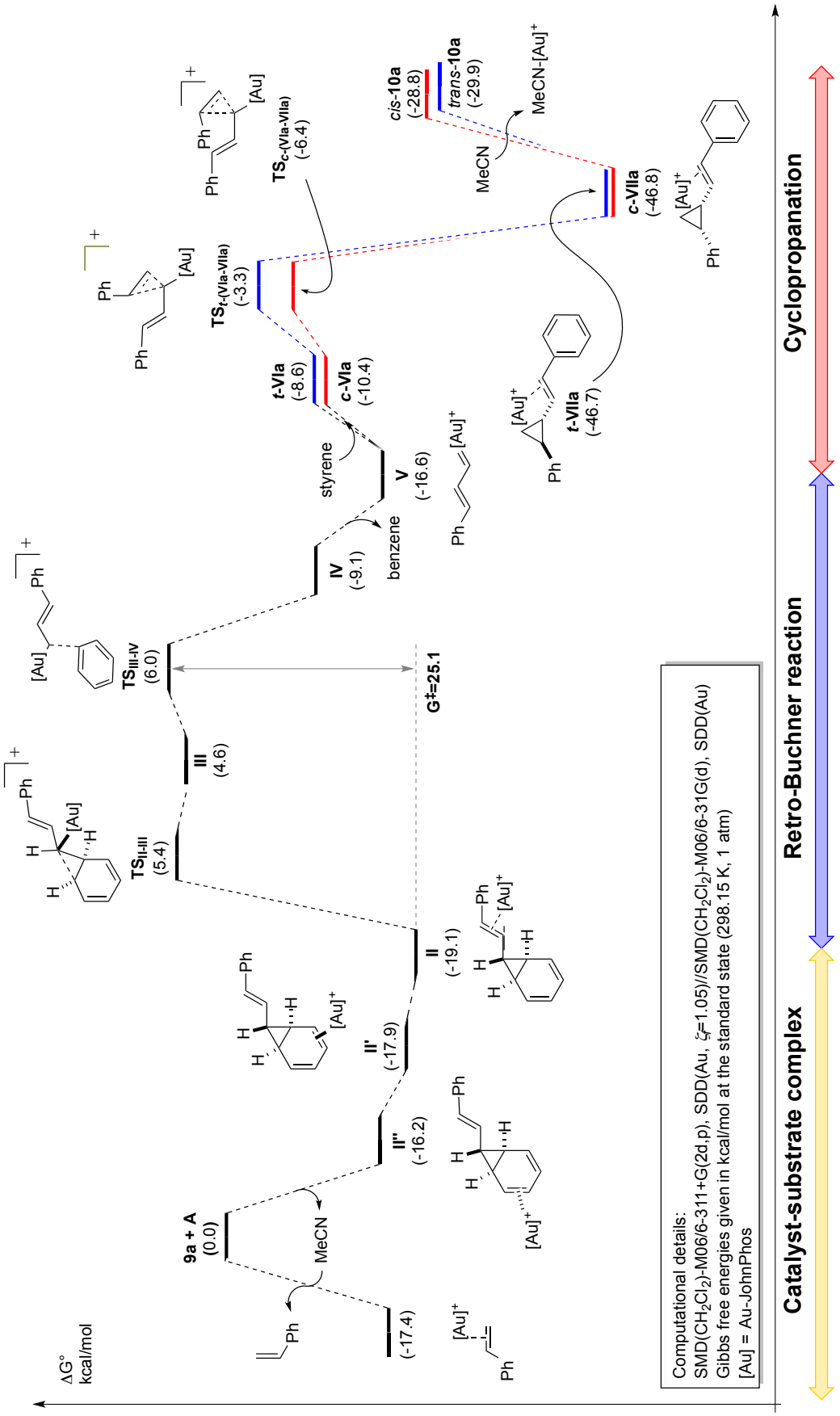


Figure 35. Reaction profile for the retro-Buchner reaction and cyclopropanation of styrene with **9a** to give **10a**.

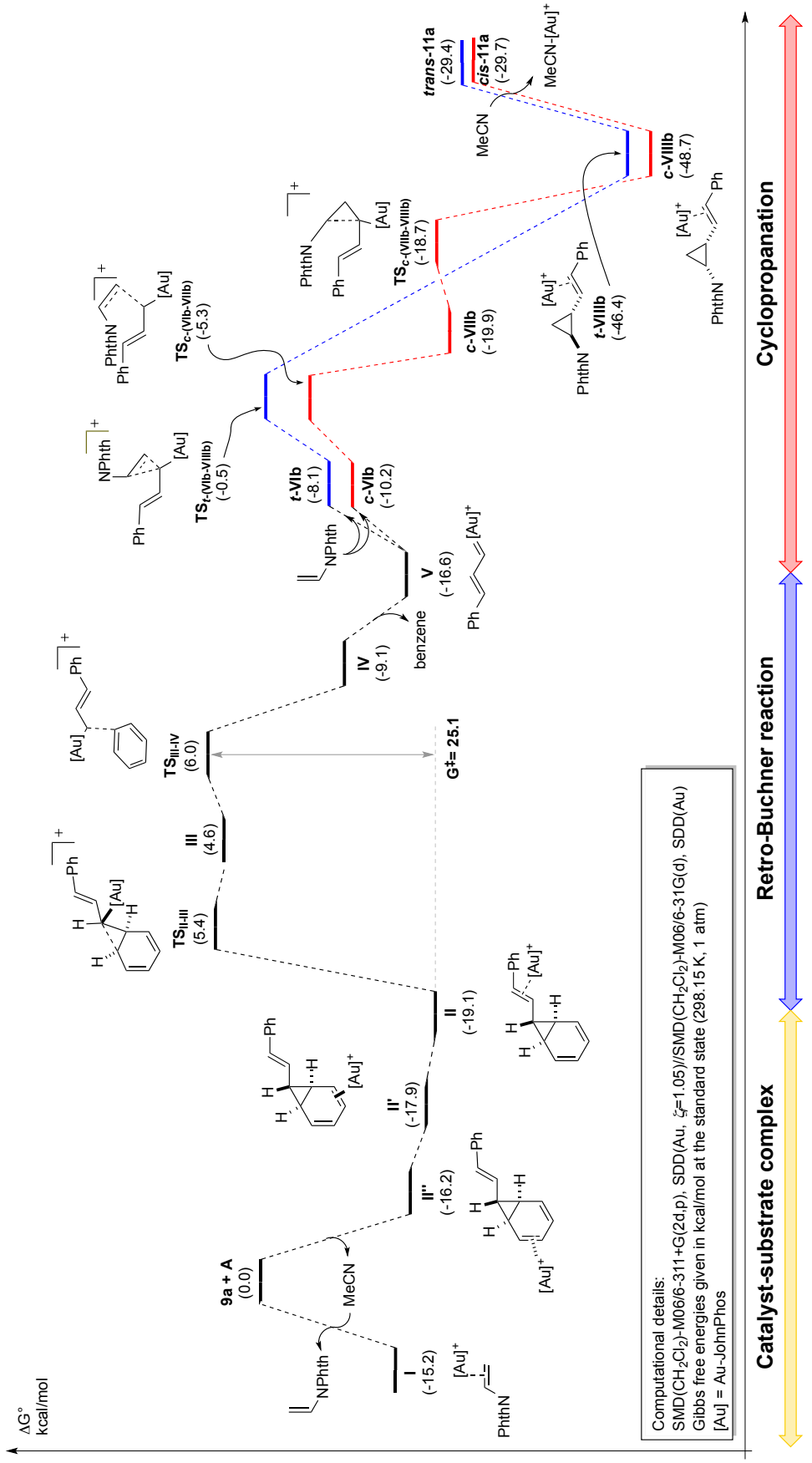


Figure 36. Reaction profile for the retro-Buchner reaction and cyclopropanation of **12** with **9a** to give **11a**.

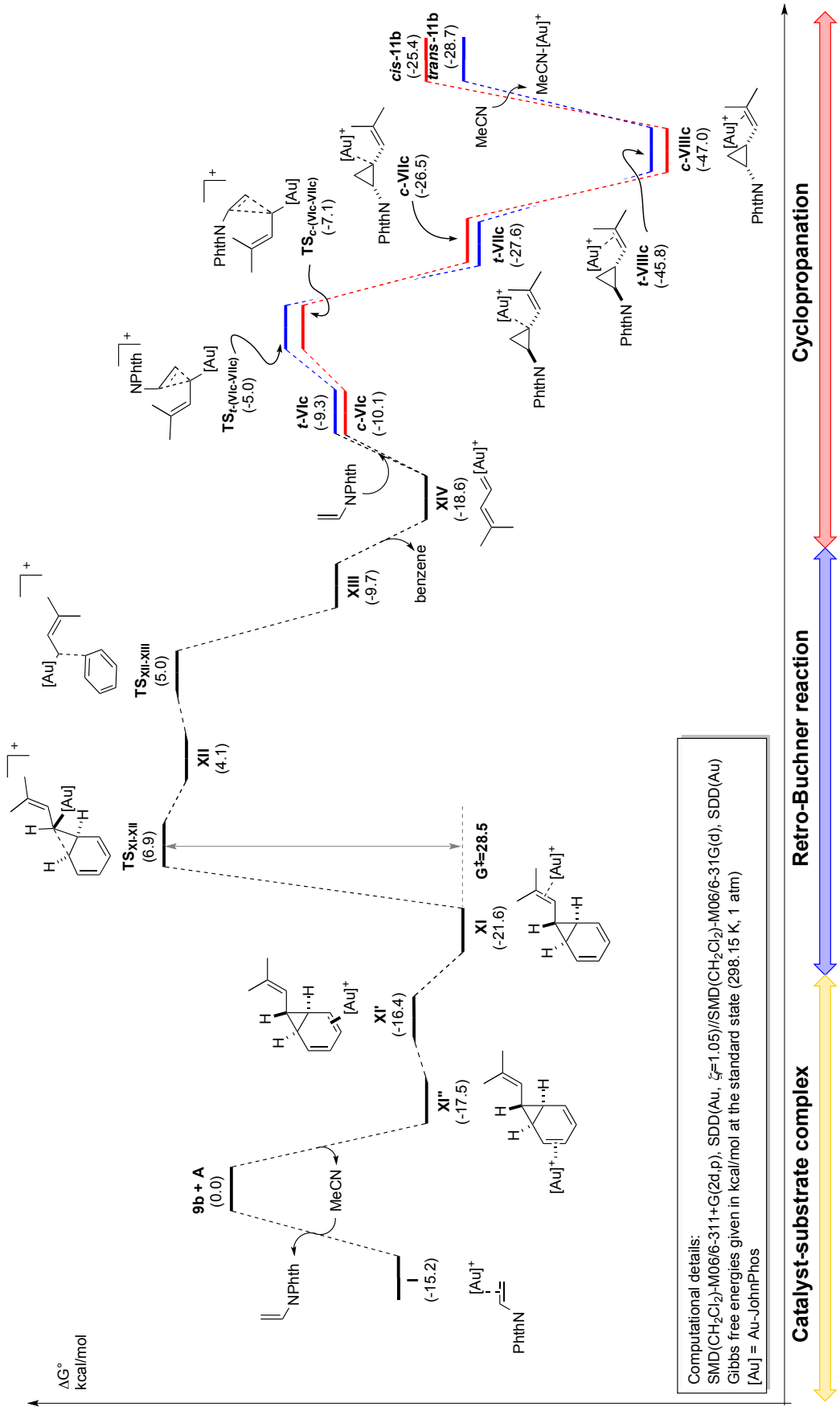


Figure 37. Reaction profile for the retro-Buchner reaction and cyclopropanation of **12** with **9b** to give **11b**.

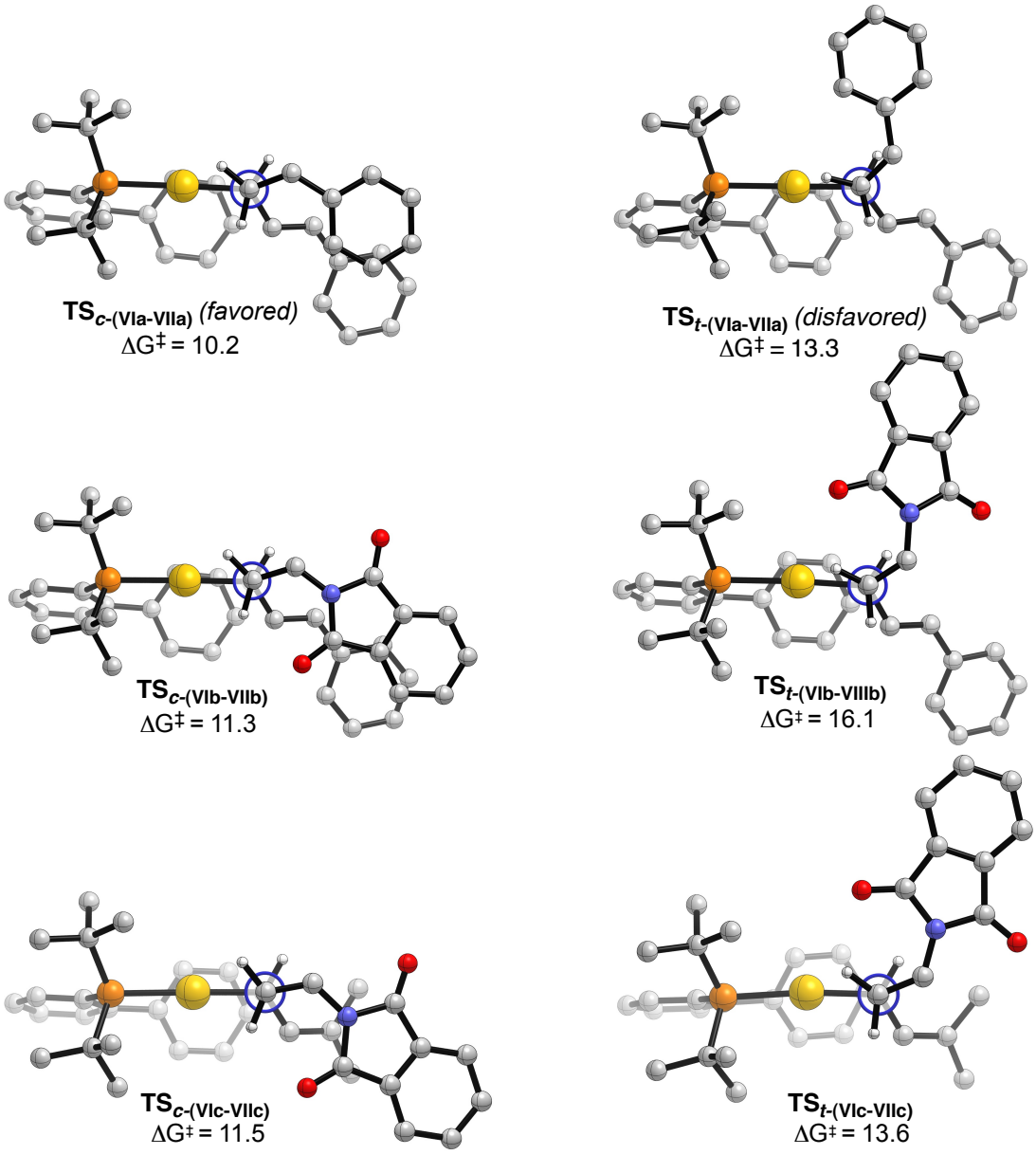


Figure 38. Transition-state geometries for the three calculated pathways of the gold(I)-catalyzed cyclopropanation.

Table 11. Calculation of difference in activation energies (ΔΔE) between *cis*- and *trans*-cyclopropanation using different calculation methods.

Functional	$TS_{VIa\text{-}VIIa}$-$TS_{VIb\text{-}VIIIb}$[a]	$TS_{XVa\text{-}XVIa}$-$TS_{XVb\text{-}XVIb}$[a]	TS_{Xa}-TS_{Xb}[a]
M06	4.8	3.1	3.1
PBE	1.7	0.7	1.3
PBE-D3(BJ)	6.0	3.7	3.2

[a] Values given in kcal·mol^{-1}.

The color-filled *reduced density gradient* (RDG) isosurface can be used to identify the weak van der Waals (vdW) interactions, in green, between the π-systems in the transition states (Figure 39-40).[323] Van der Waals interactions are clearly present in the *cis*-transition state, whereas those interactions are absent for the *trans*-transition state. Thus, the high diastereoselectivity can be explained by the favorable noncovalent interactions for the *cis*-TS, whereas no such favorable interactions exist for the *trans*-TS. Remarkably, even in the case of **TS$_{VIc\text{-}VIIc}$** (Figure 41) lacking the phenyl substituents at the carbene, π-π interactions between the alkene and the phthalimide result in stabilization of the *cis*-TS.

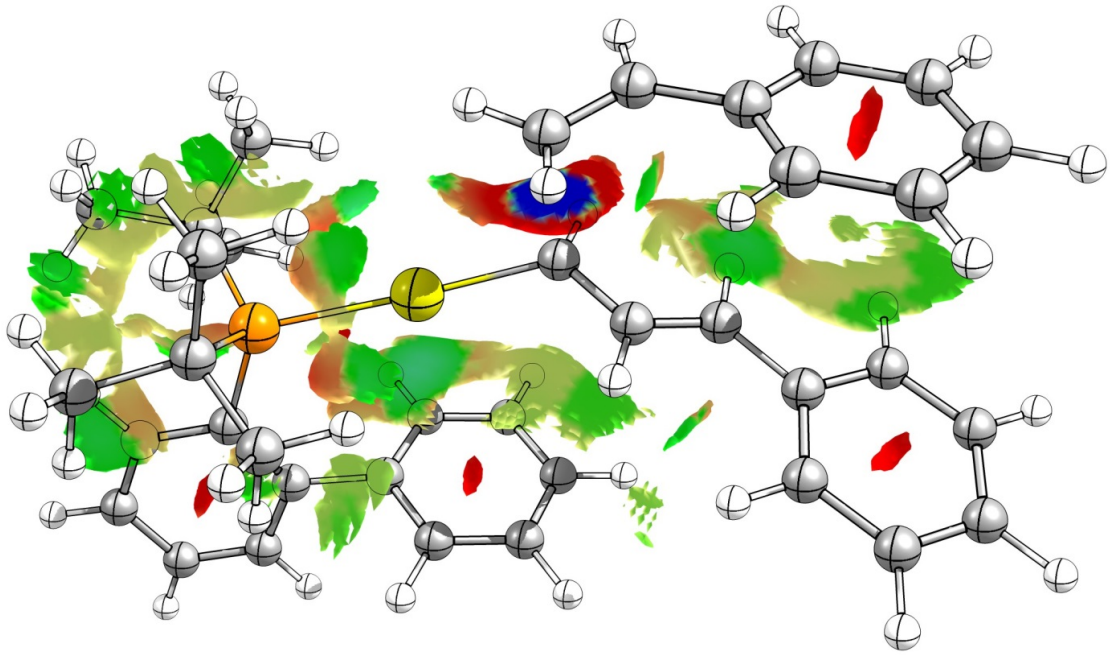
The calculated mechanisms reveal a unified stereochemical model for all three reactions, explaining the diastereoselectivity in the cyclopropanation step. Our calculations build upon the principle of the steric bulk of the phosphine ligand postulated by Toste,[324] which forces the substrate to adopt a particularly rigid geometry. Moreover, our work is in agreement with what was previously postulated by Marco-Contelles and Chen, considering the non-covalent interactions to explain the difference between the transition states.[325] In addition, the work described herein manages to quantify and visualize the exact contribution of this stabilization.

323 Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498-6506.

324 Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

325 Soriano, E.; Marco-Contelles, J. *Chem. - Eur. J.* **2008**, *14*, 6771-6779 Xue, Y.-S.; Cai, Y.-P.; Chen, Z.-X. *RSC Advances* **2015**, *5*, 57781-57791.

TS*c*-(VIa-VIIa)



TS*t*-(VIa-VIIa)

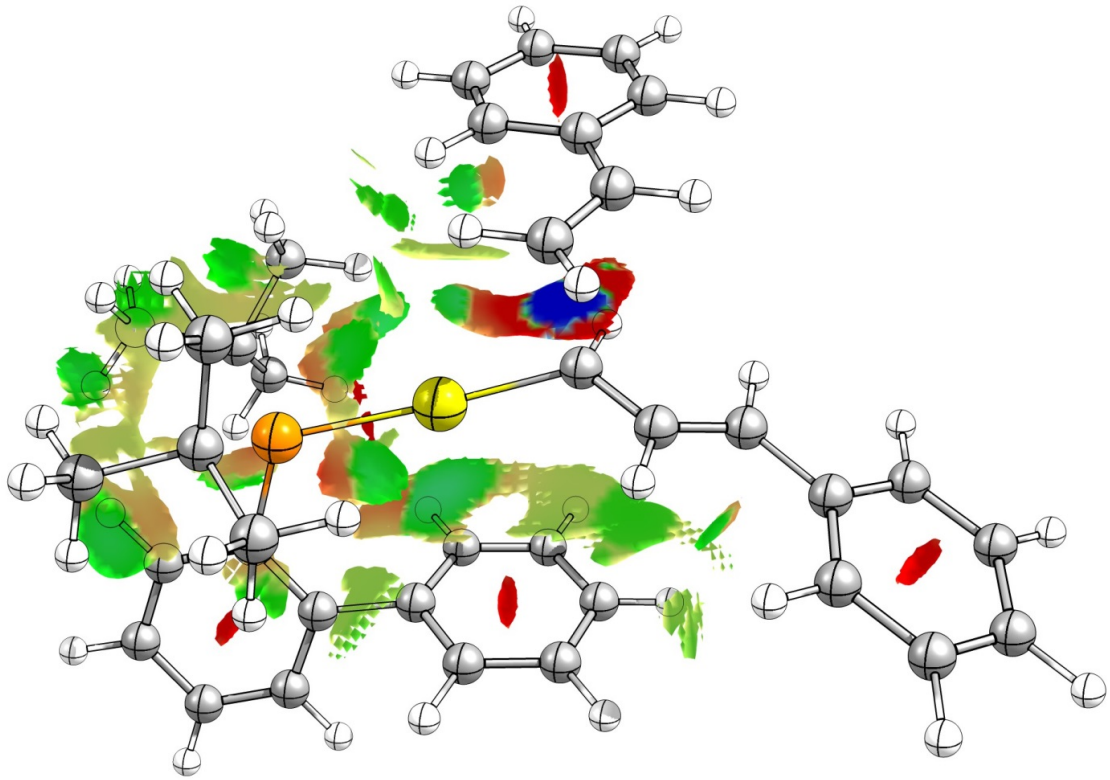
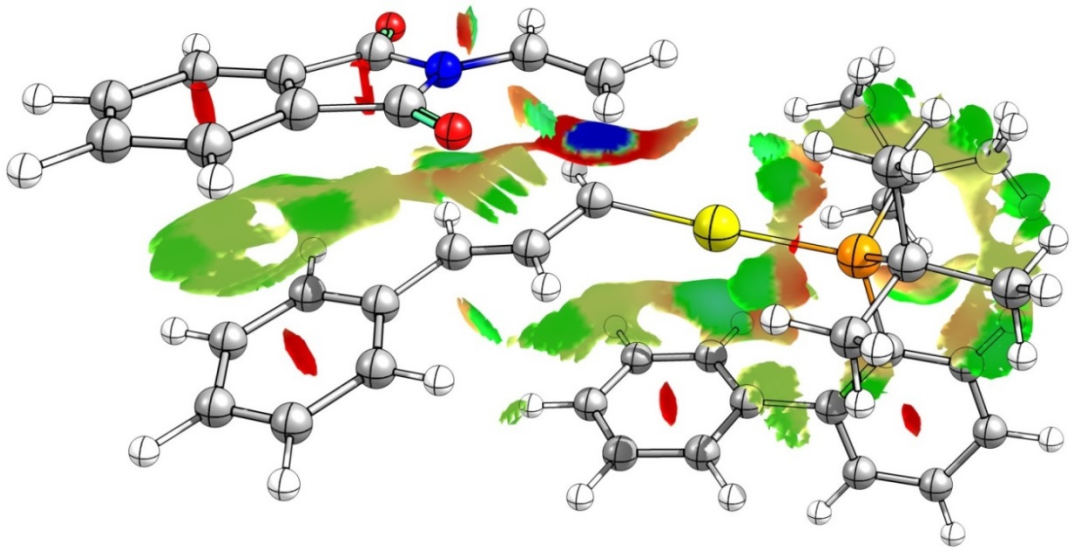


Figure 39. Color-filled RDG isosurface representation.

$TS_{c\text{-(VIb-VIIb)}}$



$TS_{t\text{-(VIb-VIIIb)}}$

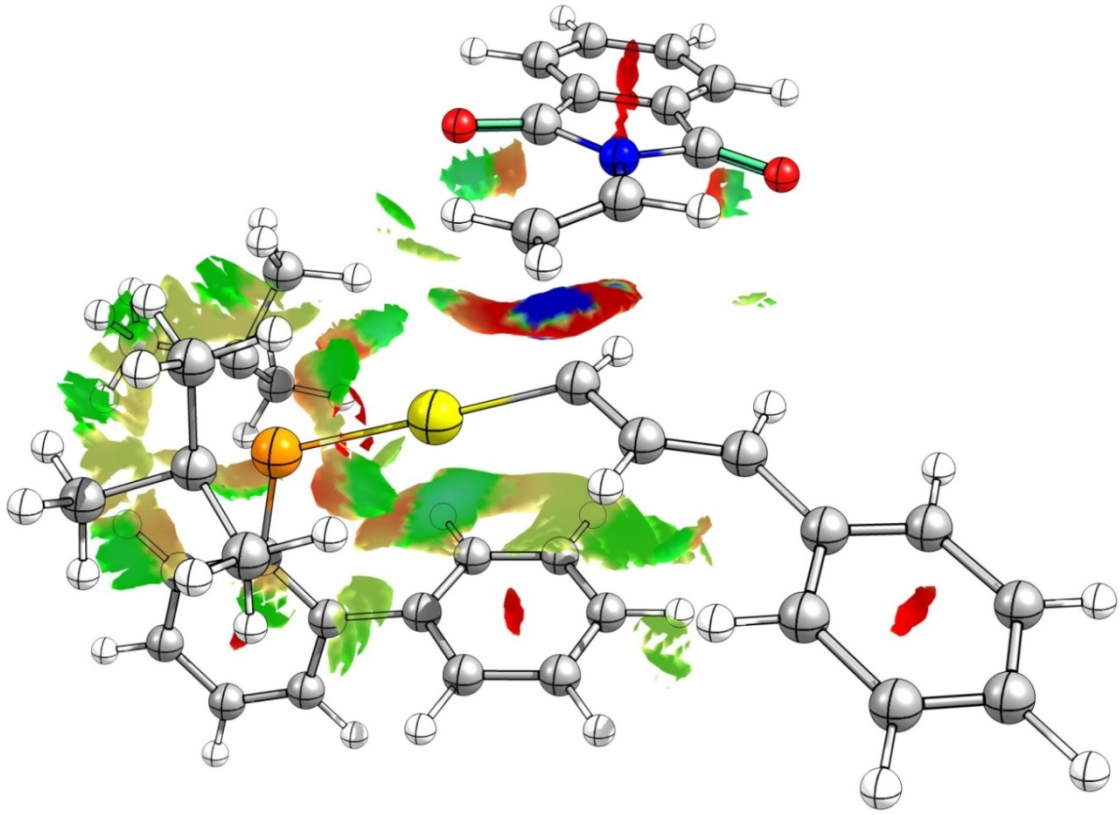
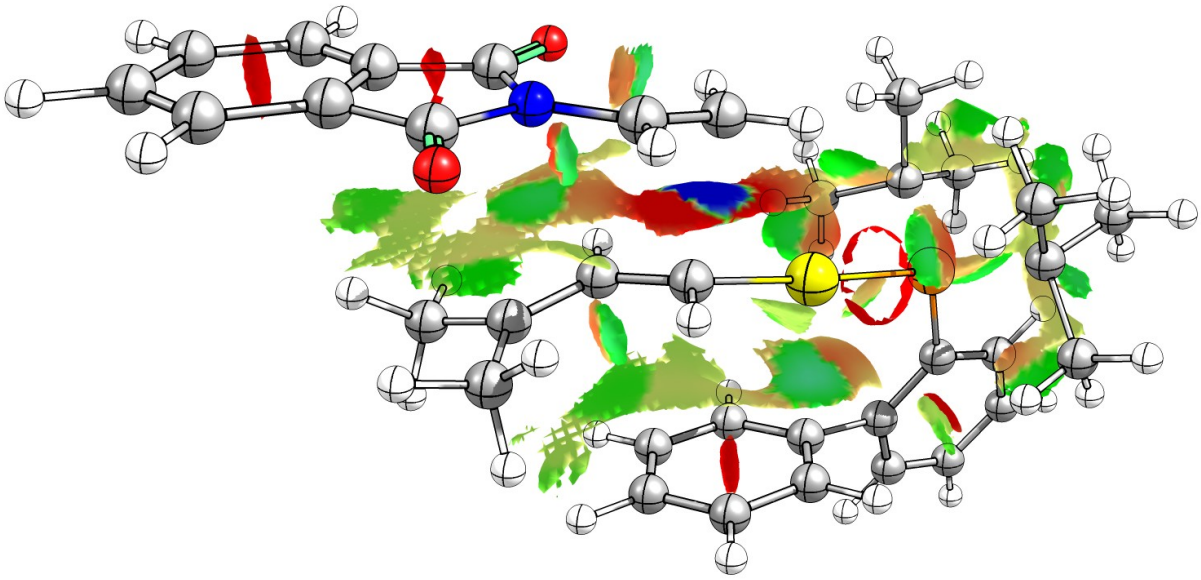


Figure 40. Color-filled RDG isosurface representation.

TS*c*-(VIc-VIIc)



TS*t*-(VIc-VIIc)

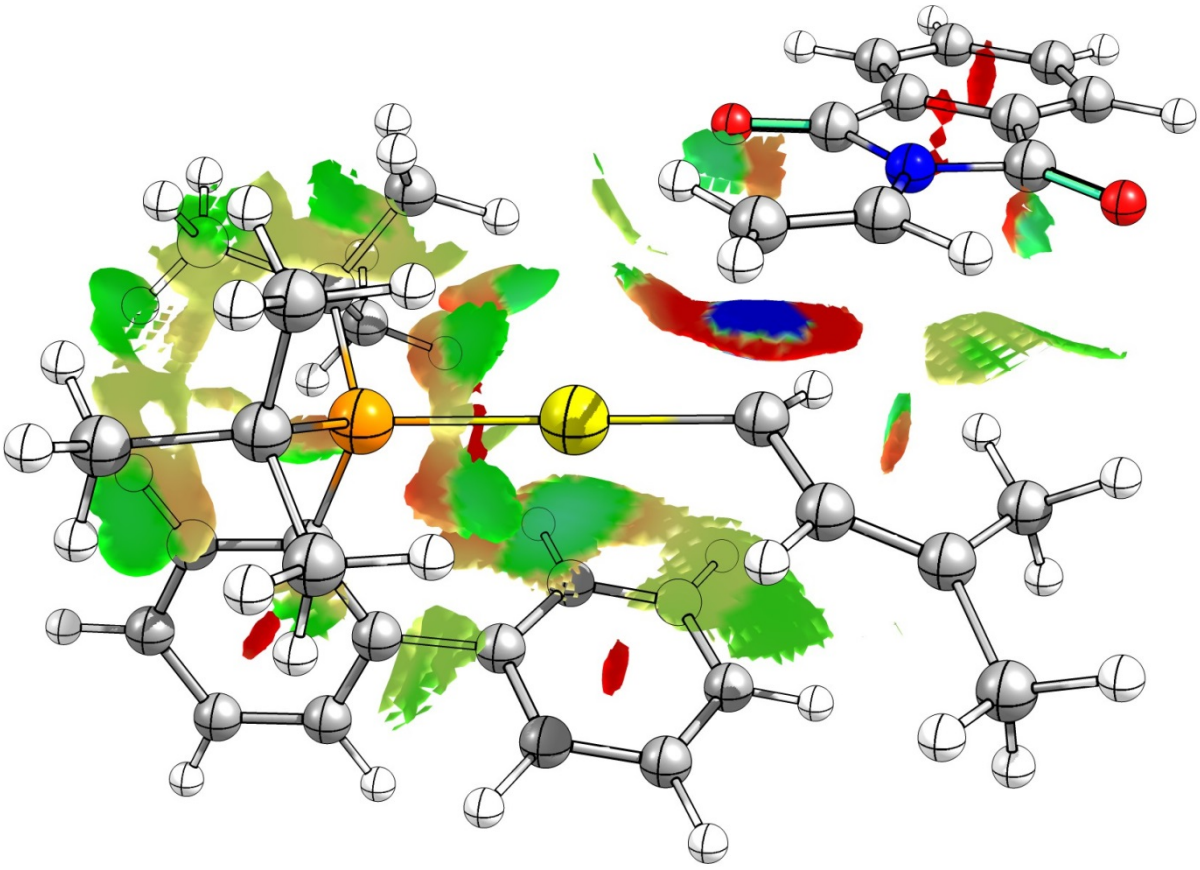


Figure 41. Color-filled RDG isosurface representation.

Isomerization of vinylcyclopropanes

The intrinsic selectivity for the cyclopropanation is very high; even for the poorest performing substrate, the energy difference between the *cis*- and *trans*-transition state is greater than 2 kcal·mol^{-1}. The low selective outcome therefore has to come from an isomerization reaction of the product. Several possible reaction pathways were considered for the isomerization of *cis*-**11a** to *trans*-**11a**. An isomerization of the *cis*-cyclopropanes to the corresponding *trans*-isomers via a mechanism involving the intermediacy of gold-carbene **V** could immediately be excluded due to a prohibitively high activation barrier (43.4 kcal·mol^{-1}).[326] Instead, we identified two transition states of linear, carbocationic structure; $\mathbf{TS_{c\text{-}VIIIb\text{-}tVIIIb}}$, where the positive charge is stabilized through participation of the nitrogen lone pair, and $\mathbf{TS_{c\text{-}Xb\text{-}t\text{-}Xb}}$, where the positive charge is stabilized as an allylic cation (Figure 42). The stability of the transition states depends on how well the carbocation can be stabilized.

In $\mathbf{TS_{c\text{-}VIIIb\text{-}tVIIIb}}$ the positive charge vicinal to the phthalimide moiety has to be stabilized through participation of the nitrogen lone pair leading to an iminium-like structure. This finding is supported by natural population analysis (NPA). The stabilization by the electronegative heteroatoms of the phthalimide remains limited and the positive charge is localized (NPA charge = +0.39; Figure 45). The high charge separation within the structure leads to an elevated transition-state energy with a high activation barrier of 38.4 kcal·mol^{-1}.

In the case of $\mathbf{TS_{c\text{-}Xb\text{-}t\text{-}Xb}}$, natural bond orbital (NBO, Figure 44) analysis showed that the positive charge is stabilized as an allylic cation, where the charge is completely delocalized (NPA charge = +0.08). The additional stabilization leads to an activation barrier of 29.4 kcal·mol^{-1}, which perfectly matches the experimental value of 28.9 kcal·mol^{-1}. It can therefore be concluded that the isomerization is proceeding via $\mathbf{TS_{c\text{-}Xb\text{-}t\text{-}Xb}}$ with an activation barrier of 29.4 kcal·mol^{-1}, making it the turnover-limiting step of the overall catalytic process.

326 a) Batiste, L.; Fedorov, A.; Chen, P. *Chem. Commun.* **2010**, *46*, 3899-3901. b) Fedorov, A.; Batiste, L.; Bach, A.; Birney, D. M.; Chen, P. *J. Am. Chem. Soc.* **2011**, *133*, 12162-12171. c) Batiste, L.; Chen, P. *J. Am. Chem. Soc.* **2014**, *136*, 9296-9307.

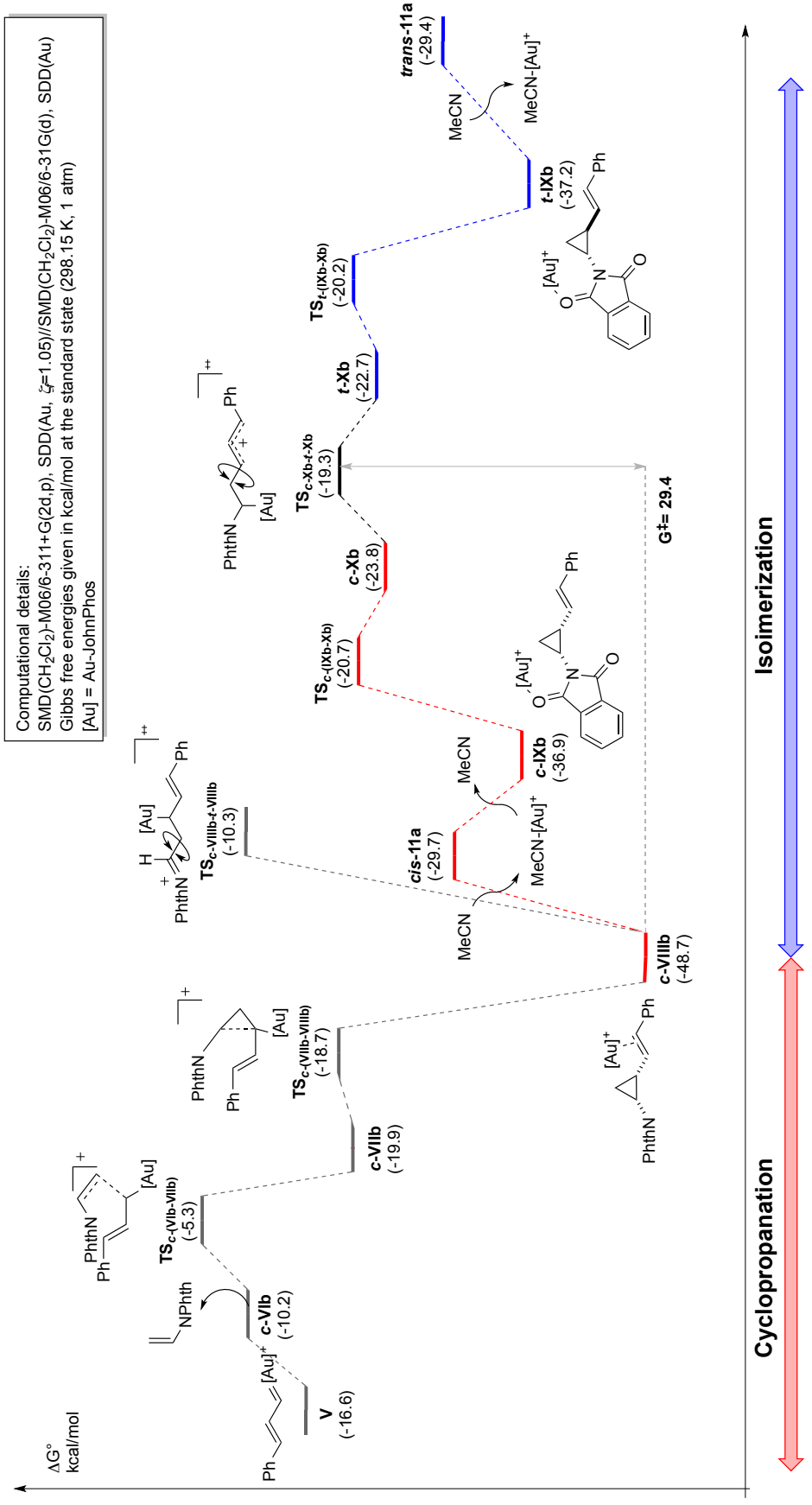


Figure 42. Reaction profile of the gold(I)-catalyzed isomerization reaction of *cis*-**11a** to *trans*-**11a**.

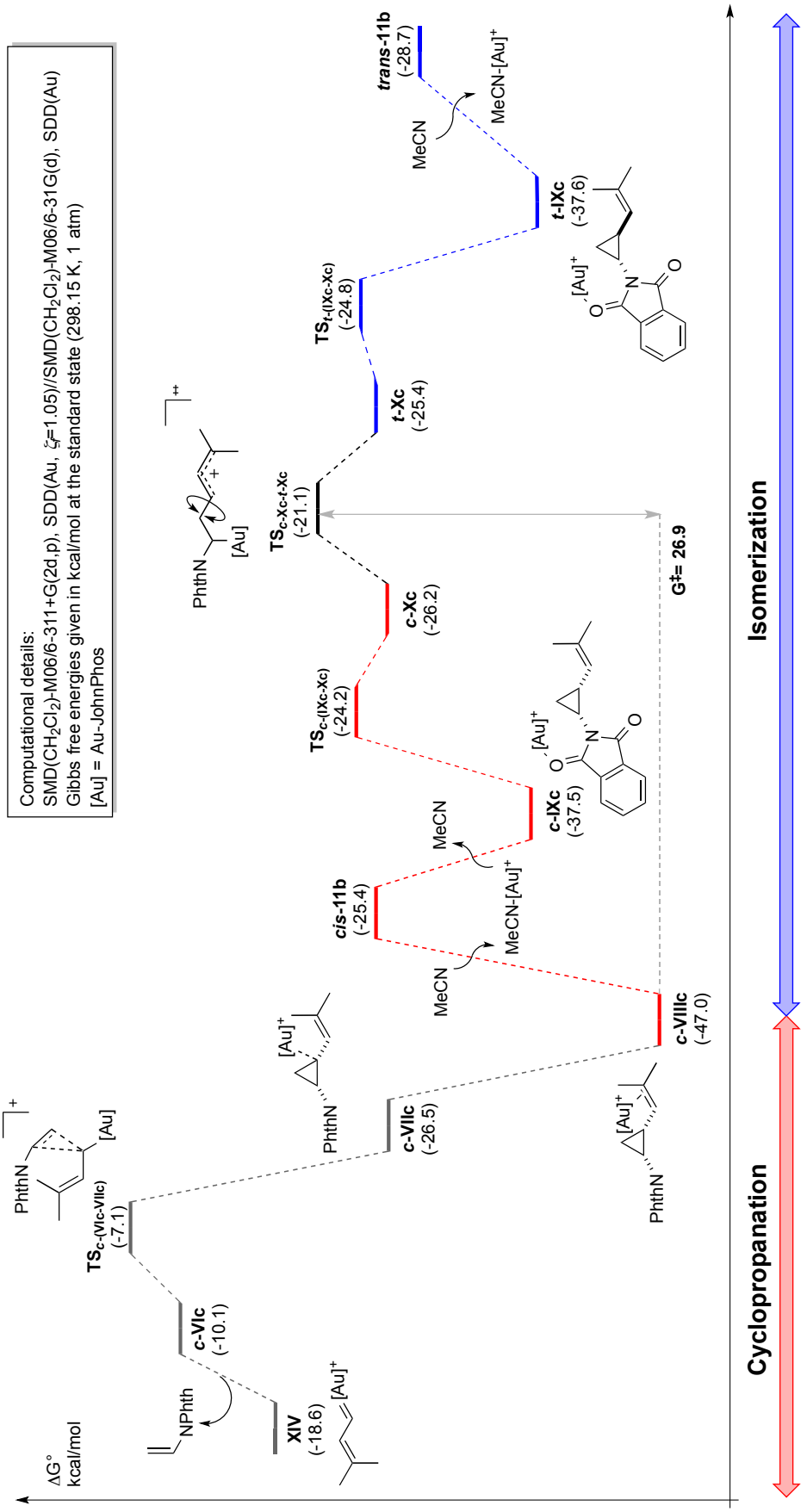


Figure 43. Reaction profile of the gold(I)-catalyzed isomerization reaction of *cis*-**11b** to *trans*-**11b**.

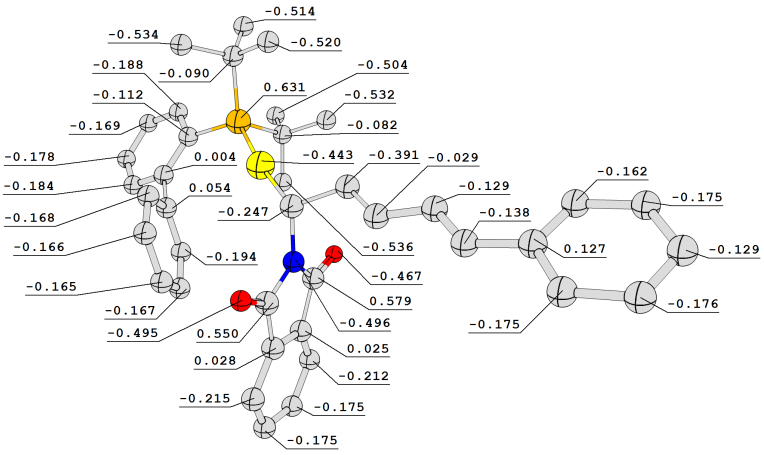


Figure 44. NBO analysis of **TS**$_{c\text{-Xb-}t\text{-Xb}}$: charges were calculated from previously optimized geometries using NBO version 6.0.[327]

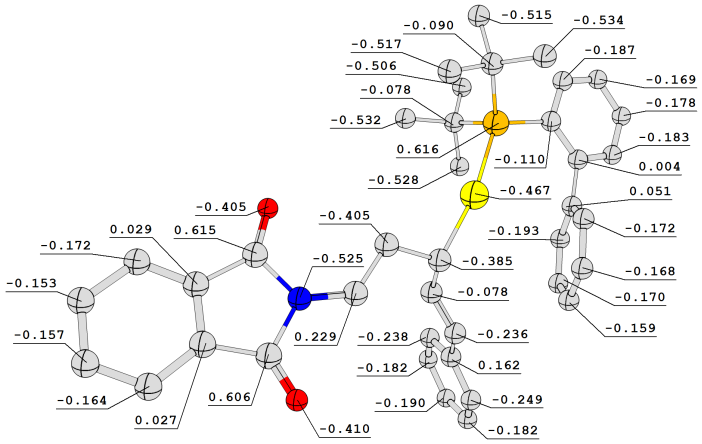


Figure 45. NBO analysis of **TS**$_{c\text{-VIIIb-}t\text{-VIIIb}}$: charges were calculated from previously optimized geometries using NBO version 6.0.[327]

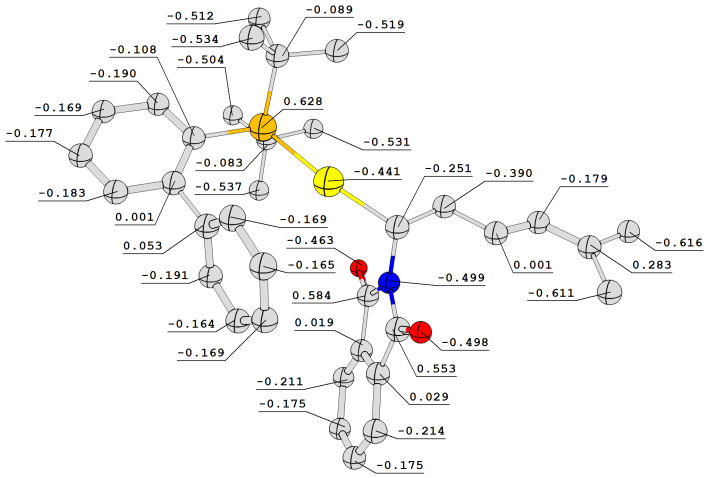
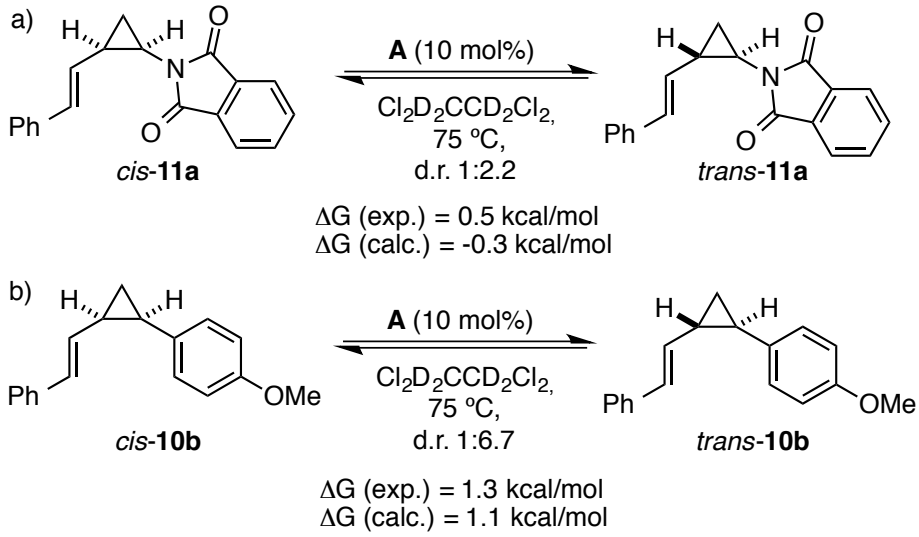


Figure 46. NBO analysis of **TS**$_{c\text{-Xc-}t\text{-Xc}}$: charges were calculated from previously optimized geometries using NBO version 6.0.[327]

327 Glendening, E. D.; Landis, C. R.; Weinhold, F. *J. Comput. Chem.* **2013**, *34*, 1429-1437.

For the isomerization of *cis*-**11b** to *trans*-**11b**, a similar pathway was calculated (Figure 43). Interestingly, while the energy barriers for the alternative pathways remain relatively unchanged (39.9 kcal·mol^{-1}), the activation energy for $\mathbf{TS_{c\text{-}Xc\text{-}t\text{-}Xc}}$ is lowered by 2.5 kcal·mol^{-1}. The *gem*-dimethyl substituents provide excellent stabilization for the allylic cation (Figure 46), and can thereby lower the energy barrier to 26.9 kcal·mol^{-1}. For this class of substrates, the rate-limiting step is no longer the isomerization but the formation of gold carbene **XIV** instead (28.5 kcal·mol^{-1}). The overall selectivity is no longer under kinetic control and the major product obtained is the thermodynamically favored *trans*-isomer.

The diastereomeric ratio after isomerization depends on the relative thermodynamic stability of the products. Therefore, the energy difference between the *cis*- and *trans*-isomers for two classes of cyclopropanes could be calculated by allowing the mixture to reach equilibrium (Scheme 146).



Scheme 146. Equilibration experiment for **11a** and **10b**.

The diastereomeric ratio can be transformed to obtain an equilibrium constant k_{eq}, which can be used to solve the following equation to obtain the difference in Gibbs free energy for the two isomers. Signifying that *trans*-**10b** is more stable by 1.3 kcal·mol^{-1} and *trans*-**11a** is more stable by 0.5 kcal·mol^{-1}, which is in good agreement with the calculated values.

$$\Delta G^{\theta} = -RT \ln k_{eq}$$

Equation 3. Eyring equation rewritten to give ΔG^{θ}, where R = 8.31 J·K^{-1}·mol^{-1}, T = 348 K, k_{eq} = 0.148 (**10b**), 0.465 (**11a**) mol·s^{-1}.

Implications and outlook

During the cyclopropanation reaction, the difference in transition-state energies for the *cis*- and *trans*-pathway is large enough to place the reaction entirely under kinetic control, thus leading exclusively to the *cis*-isomer in all observed examples. The energy barriers for cyclopropanation and isomerization lie very close to each other. Depending on the substrate, it is possible to separate one pathway from another, as can be seen for the aryl alkenes where the difference between the energy barriers is large enough to prevent the isomerization reaction, in the case of **10a**. In other examples, where the energy barriers lie much closer, slow isomerization takes place leading to a lower stereoselective outcome, as seen for **11a**. In the last example, the carbene formation is the rate-limiting step rather than the isomerization and the reaction is under thermodynamic control, which is the case for **11b**.

We suspected that a related isomerization reaction is taking place for the bis-aryl cyclopropanes that were previously reported,[328] which would explain the seemingly random stereoselective outcome for this transformation. To verify our suspicion, the reaction between 7-(2,4-dimethoxyphenyl)cyclohepta-1,3,5-triene (**7a**) and 4-acetoxystyrene was followed at 120 °C by ^{1}H NMR over time (Figure 47).

328 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

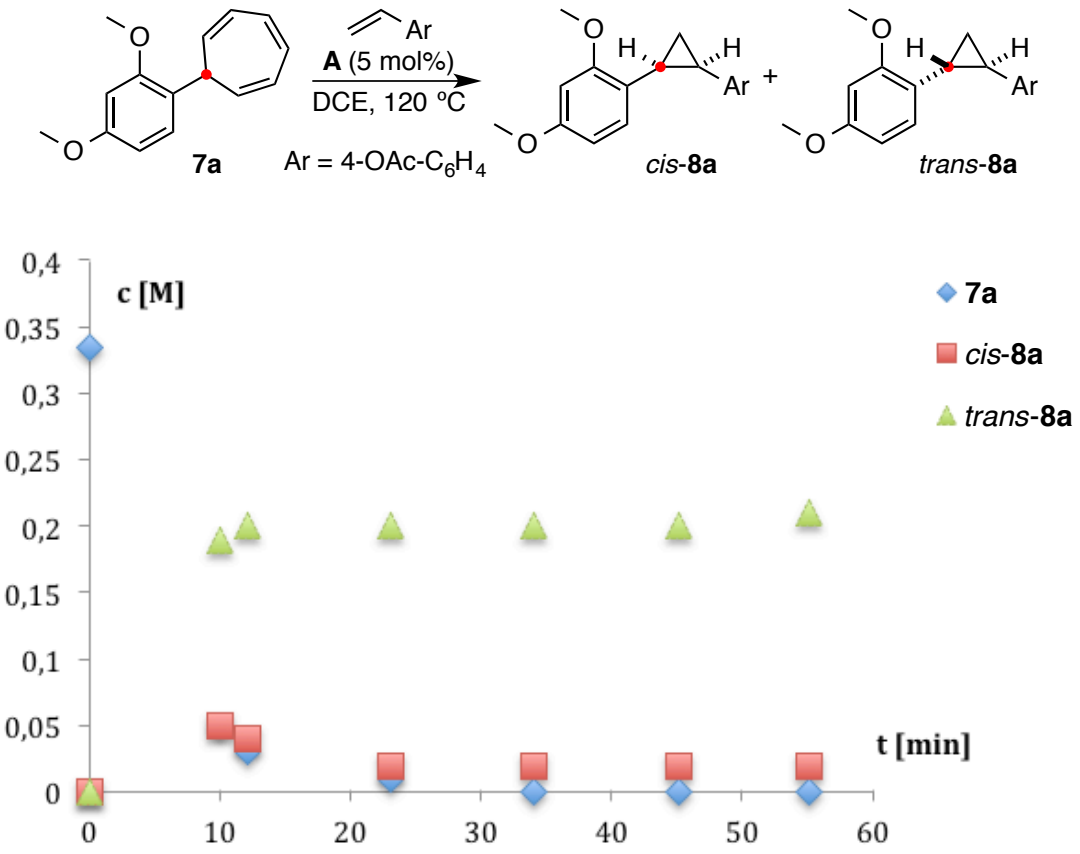


Figure 47. Plot of the kinetic experiment for the cyclopropanation of 4-acetoxystyrene with **7a**.

The temperature at which the reaction was followed caused the reaction to proceed very fast, which complicates the full picture. Still, the data suggests that initially the *cis*-product is formed, which is then isomerized to the *trans*-product. With the increased understanding of the factors that control the selectivity during the cyclopropanation, and with the isomerization reaction in mind, some of the diastereomeric ratios obtained for the bis-aryl cyclopropanes could be explained. Although the cyclopropanation reaction itself was *cis*-selective, performing the reaction at a higher temperature led to rapid isomerization of the products bearing electron-rich substituents and therefore the *trans*-isomer was obtained as major product. In other cases, however, the putative *trans*-isomer was the opposite of what we would predict based on our current mechanistic understanding. Re-evaluation of the spectroscopic data led us to conclude that

for some of these examples, the major product was the *cis*-isomer rather than *trans*-isomer as was reported.[329]

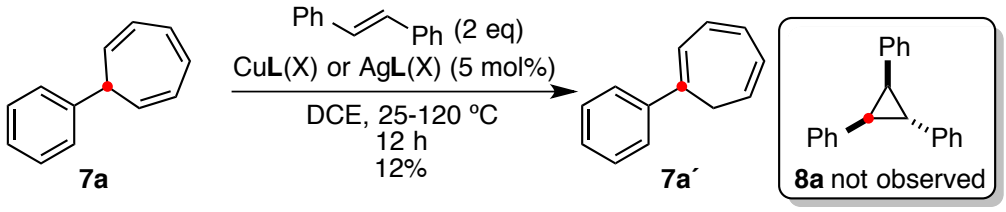
The retro-Buchner reaction with copper(I) and silver(I) complexes

The energy profile for the gold(I)-catalyzed retro-Buchner reaction of 7-aryl cycloheptatrienes, that was calculated previously by our group, and the energy profile for 7-alkenyl cycloheptatrienes are in close qualitative agreement.[311] The group of Chen has computationally investigated the possibility of performing a retro-cyclopropanation with gold(I), silver(I) and copper(I) in the gas phase.[326] It was found that although the energy barriers for formation of copper(I) carbenes is higher than for gold(I), it is a viable pathway. Alternatively, the formation of silver(I) carbenes is unfavorable due to weaker σ- and π- C-metal bond. Recently, the computational investigations for the retro-Buchner reaction of 7-aryl cycloheptatriene derivatives have been repeated by the group of Song and an identical pathway to ours was observed for the cationic [(JohnPhos)Au(MeCN] complex.[312] In addition, the pathways for copper(I)- and silver(I)-acetonitrile complexes were investigated, which in contrast to the work of Chen, predicts the possibility of forming both copper(I) and silver(I) carbenes through a retro-cyclopropantion reaction. The indication that copper(I) might be able to catalyze a retro-cyclopropanation following a similar pathway as gold(I) prompted us to perform a series of experiments in order to investigate the possibility of performing the retro-Buchner reaction with other metals. The formation of copper(I) or silver(I) carbenes from 7-phenyl-1,3,5-cycloheptatriene (**7a**), and subsequent trapping with *E*-stilbene was investigated (Scheme 147). Scorpionate ligands, which have successfully been employed in silver and copper catalyzed cyclopropanation or C-H insertion reactions,[330] as well as IPr-copper complexes, along with JohnPhos-complexes where used in this screening (Figure 48). No reaction occurred at 100°C or below, whereas at 120°C only degradation of the cycloheptatriene was observed through a background reaction via a [1,5]-H migration. In parallel, the intramolecular trapping of the carbene was

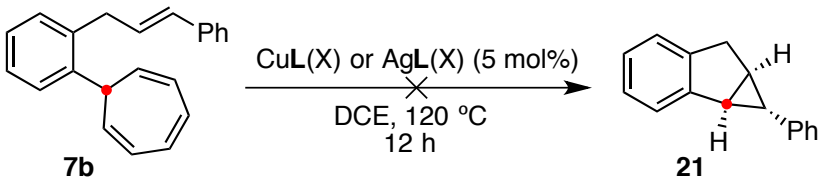
329 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2017**, *139*, 2529-2529.

330 a) Caballero, A.; Pérez, P. J. *J. Organomet. Chem.* **2015**, *793*, 108-113. b) Díaz-Requejo, M. M.; Pérez, P. J. *J. Organomet. Chem.* **2005**, *690*, 5441-5450.

attempted using substrate **7b** , which was found to react with gold(I) to give **21** in almost quantitative yield (Scheme 148).[331] However, even at 120 °C, no reaction was observed for copper(I) or silver(I).



Scheme 147. Attempted carbene formation via the retro-Buchner reaction using copper(I) and silver(I) complexes.



Scheme 148. Attempted intramolecular trapping of copper(I) or silver(I) carbenes generated via the retro-Buchner reaction.

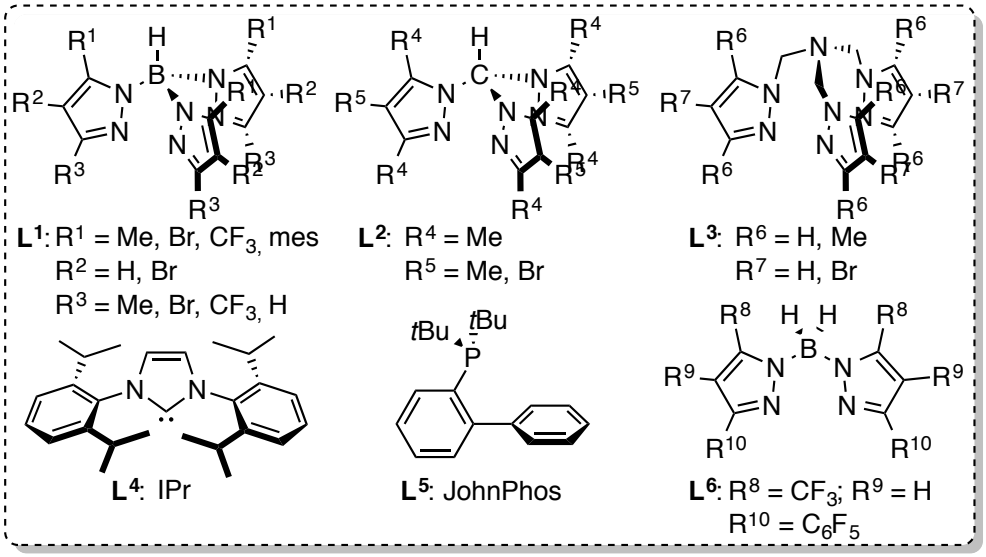
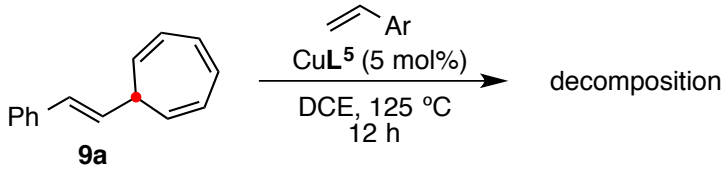


Figure 48. Ligands used to obtain copper(I) and silver(I) complexes to examine the retro-Buchner reaction.

The gold(I)-catalyzed retro-Buchner reaction of 7-alkenyl cycloheptatriene derivatives takes place at considerably lower temperatures because of the

331 Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.

additional stabilization through the allylic system. It stands to reason that the same is true for copper(I) or silver(I) and the activation barrier for the retro-Buchner reaction is lowered for these metals, as well. However, no reaction was observed for the mixture of 7-styrenyl cycloheptatriene (**9a**), 3-methylstyrene and [(JohnPhos)Cu(MeCN)]SbF_6 at 75 °C, while the reaction went to full conversion at 125 °C without the formation of cyclopropane, cyclopentene, or C-H insertion product.



Scheme 149. Attempted copper(I)-catalyzed retro-Buchner reaction of 7-styrenyl cycloheptatriene.

Despite what was predicted by DFT calculations by the group of Song,[312] the formation of carbene complexes via retro-Buchner reaction with copper(I) or silver(I) did not take place for 7-aryl cycloheptatriene derivative **7a**. Therefore, the calculations must have underestimated the activation barrier for this transformation. When the retro-Buchner reaction with copper(I) was attempted for compound **9a**, for which the activation barrier was expected to be even lower, no evidence of carbene formation was obtained.

Conclusion

The mechanism of the cyclopropanation reaction was studied experimentally and by DFT calculations. The rate-limiting step of the reaction is the formation of the gold(I) carbene with an energy barrier of 25 to 29 kcal·mol^{-1}, depending on the alkenyl substituents of the cycloheptatriene reagent. The vinyl gold(I) carbene then easily undergoes a highly *cis*-selective cyclopropanation with the olefinic substrate.

From the calculations, a stereochemical model could be derived that is useful for other gold(I)-catalyzed cyclopropanation reactions, as well. The high selectivity originates from stabilization for the *cis*-pathway via favorable π-π interactions, which are absent for the *trans*-pathway. The bulky ligand plays an important role in creating a rigid system, which limits the approach of the incoming alkene.

An unprecedented gold(I)-mediated isomerization reaction of *cis*-cyclopropanes was elucidated, which proceeds through a linear cationic structure where the positive charge is stabilized by the allylic fragment. The nature of the cyclopropane and vinylic substituents have an impact on the height of the activation barrier as increased stabilization of the allylic cation by the vinylic substituents and electron-rich aryl groups lower the activation energy for the isomerization.

A similar isomerization reaction takes place for the bis-arylcyclopropanes, which explains the varying diastereoselectivity observed in our previous work.

Theoretically, it is possible to avoid the isomerization altogether if the activation energy for the carbene formation can be lowered sufficiently, as the cyclopropanation and isomerization are two separate reaction paths. On the other hand, the isomerization reaction can also be exploited to obtain the *trans*-cyclopropane instead.

Experimental section

General information

All reactions were carried out under argon in anhydrous solvents obtained by passing them through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA), unless noted otherwise. All gold-catalyzed reactions were performed in HPLC-grade solvents, without a protective atmosphere. The diastereoselectivity of the cyclopropanation reactions depends in some cases on the reaction time and temperature. The exact reaction times and temperatures are given for each example and have to be respected when reproducing this work. Tropylium tetrafluoroborate was purchased from Fluorochem. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck Gf234). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 °C on Bruker Avance 300, 400 and 500 Ultrashield apparatus. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (*J*) are reported in hertz (Hz). Mass spectra were recorded on a Waters LCT Premier Spectrometer (ESI and APCI) or on an Autoflex Bruker Daltonics (MALDI and LDI). Melting points were determined using a Büchi melting point apparatus.

Gold complex **A**,[332] copper(I) and silver(I) Tp,[333] Tpm,[334] and Tpa complexes,[335] and [(JohnPhos)Cu(MeCN)]PF_6 were was synthesized according to literature procedures.[336]

332 Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.
333 Martín, C.; Muñoz-Molina, J. M.; Locati, A.; Alvarez, E.; Maseras, F.; Belderrain, T. R.; Pérez, P. J. *Organometallics* **2010**, *29*, 3481-3489.
334 Haldón, E.; Álvarez, E.; Nicasio, M. C.; Pérez, P. J. *Inorg. Chem.* **2012**, *51*, 8298-8306.
335 Haldón, E.; Delgado-Rebollo, M.; Prieto, A.; Álvarez, E.; Maya, C.; Nicasio, M. C.; Pérez, P. J. *Inorg. Chem.* **2014**, *53*, 4192-4201.
336 Grirrane, A.; Álvarez, E.; García, H.; Corma, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 7253-7258.

7-(2,4-Dimethoxyphenyl)cyclohepta-1,3,5-triene (7a)

To a solution of 1-bromo-2,6-dimethoxy-benzene (6.033 g, 27.8 mmol, 1.05 equiv) in dry Et_2O (132 mL) at −78 °C was added drop wise *n*-BuLi (15.571 mL, 1.87 M in hexanes, 29.1 mmol, 1.10 equiv) under argon. The mixture was stirred for 30 min at −78 °C, and then tropylium tetrafluoroborate (4.710 g, 26.5 mmol, 1.00 equiv) was added in one portion. The cooling bath was removed and the reaction was allowed to warm up to 23 °C and stirred for 2.5 h. The reaction was quenched by addition of brine. The aqueous phase was extracted with Et_2O, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The crude residue was purified by flash chromatography (120 g SiO_2, eluent: gradient from c-hexane to 10% EtOAc) affording 4.550 g (4.92 mmol, 71%) of a yellow oil. Dimethoxybenzene was removed from the product via Kugelrohr distillation (80 °C at 2.4×10^{-1} mbar) affording 4.040 g (17.7 mmol, 67%) of **7a** as a yellow oil. The product contains 6% of an impurity, presumably a regioisomer of the cycloheptatriene.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J*= 8.0 Hz, 1H), 6.83 – 6.75 (m, 2H), 6.63 – 6.55 (m, 2H), 6.34 – 6.27 (m, 2H), 5.50 (dd, *J*= 8.9, 5.6 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.18 – 3.11 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 158.4, 130.9, 129.3, 127.6, 124.4, 124.1, 104.4, 99.0, 55.4 (2 signals), 40.2.

HRMS-ESI: calculated for $C_{15}H_{17}O_2$ $[M+H]^+$: 229.1223; found: 229.1228.

***trans*-4-((2-(2,4-Dimethoxyphenyl)cyclopropyl)phenyl acetate (8)**

A solution of the cycloheptatriene **7a** (45.9 mg, 201 μmol, 2.0 equiv), 4-vinylphenyl acetate (16.3 mg, 101 μmol, 1.0 equiv), diphenylmethane (17 μl, 101 μmol, 1.0 equiv) as internal standard(1.0 equiv) and gold catalyst **A** (3.9 mg, 5 μmol, 0.05 equiv) in d^2-1,1,2,2-tetrachloroethane (0.6 mL) was added to Young-NMR tube. The atmosphere was exchanged by three vacuum/Argon cycles and the tube was sealed. The NMR-tube was placed in a NMR machine, preheated to 120 °C. The reaction was monitored by ^{1}H NMR every 10 min for 5 h.

The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography (4 g SiO_2, eluent: gradient from c-hexane to 20% EtOAc) affording **8** (28.9 mg, 92.59 μmol, 92%, d.r. 12:1) as a pale yellow oil.

The stereochemistry was confirmed by 1D NOESY experiments

^{1}H NMR (400 MHz, CDCl3) δ 7.24 – 7.17 (m, 2H), 7.03 – 6.97 (m, 2H), 6.89 (d, *J*= 8.1 Hz, 1H), 6.49 – 6.41 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.34 – 2.28 (m, 4H), 2.08 – 2.00 (m, 1H), 1.37 – 1.32 (m, 1H), 1.31 – 1.26 (m, 1H).

^{13}C NMR (101 MHz, CDCl3) δ 169.8, 159.3, 159.2, 148.7, 140.9, 127.3, 126.1, 123.2, 121.4, 104.0, 98.6, 55.6, 55.5, 25.7, 21.6, 21.3, 16.4.

HRMS-ESI: calculated for $C_{19}H_{21}O_4$ $[M+H]^+$: 313.1434; found: 313.1446.

(*E*)-7-Styrylcyclohepta-1,3,5-triene (9a)

This compound was prepared as described in *chapter 2*.

Reaction progress monitored by ^{1}H NMR for the gold(I)-catalyzed retro-Buchner reaction of 7a

The reaction was monitored by ^{1}H NMR, integrations were normalized against diphenylmethane (CH_2 at 4.07 ppm). For **7a** the CH at 3.22 ppm, for *cis*-**8** the CH_3-C(O) at 2.25 ppm and ***trans*-8** the CH at 2.39 ppm were integrated. The given concentration in Table E1 can be considered as correct within the experimental error. The cyclopropanation reaction proceeds very fast at 120 °C. Already after 10 min it is complete, full conversion of styrene and 85% conversion of **7a** is reached. *In situ* formed *cis*-**8** is converted, most likely, into ***trans*-8**. The d.r. is changing during the course of the reaction from 3.7:1 (10 min) to 10.8:1 (45 min).

Table E1. Measured concentration during the cyclopropanation of 4-vinylphenyl acetate using **7a**.

Time [min]	c(7a) [mol/l]	c(*cis*-8) [mol/l]	c(*trans*-8) [mol/l]
10	0,05	0,05	0,19
12	0,03	0,04	0,20
23	0,01	0,02	0,20
34	0,00	0,02	0,20
45	0,00	0,02	0,20
55	0,00	0,02	0,21
66	0,00	0,02	0,20
77	0,00	0,02	0,20
87	0,00	0,02	0,20
98	0,00	0,02	0,20
109	0,00	0,02	0,22
119	0,00	0,02	0,19
130	0,00	0,02	0,20
141	0,00	0,02	0,20
152	0,00	0,02	0,19
162	0,00	0,02	0,19
173	0,00	0,02	0,19

Initial rate studies for the gold(I)-catalyzed retro-Buchner reaction of 9a.

Cycloheptatriene **9a** (100.0 mg, 515 µmol, 1 equiv), *N*-vinyl phthalimide (**12**) (178.0 mg, 1.03 mmol, 2 equiv), gold catalyst **A** (19.9 mg, 26 µmol, 5 mol%) and diphenylmethane (86 µL, 515 µmol, 1 equiv) were added to a small round-bottom flask and the atmosphere was exchanged for argon with three vacuum/Argon cycles before adding EtOAc (4 mL). The round-bottom flask was placed in a preheated oil bath and stirred at 75 °C.

Aliquots of the reaction mixture were taken, filtered in a pipette over silica gel with EtOAc and were then concentrated to dryness. ^{1}H NMR spectra were recorded (8 scans, $CDCl_3$, 400 MHz) and the concentration of the products quantified by integration against the internal standard diphenylmethane.

Table E2. Measured concentration (^{1}H NMR) during the cyclopropanation of *N*-vinyl phthalimide using **9a**.

t (min)	c(*cis*-11a)	ln (c(*cis*-11a))	c(*trans*-11a)	ln (c(*trans*-11a))	c(9a)	ln (c(9a))
0	0	-	0	-	0,13	-2,05
360	0,08	-2,49	0,01	-4,35	0,03	-3,43
690	0,09	-2,39	0,02	-4,09	0,01	-4,35
870	0,09	-2,39	0,02	-3,82	0,01	-4,86
1380	0,08	-2,49	0,03	-3,66	0,00	-
1920	0,08	-2,56	0,04	-3,29	0,00	-
2880	0,06	-2,76	0,05	-3,10	0,00	-
3300	0,07	-2,72	0,05	-2,92	0,00	-
7200	0,04	-3,13	0,08	-2,48	0,00	-
7680	0,05	-3,02	0,10	-2,30	0,00	-
7920	0,04	-3,16	0,09	-2,40	0,00	-
8595	0,03	-3,40	0,08	-2,58	0,00	-
9090	0,03	-3,36	0,08	-2,48	0,00	-

A reaction rate constant of k= -5.33 10^{-5} s^{-1} = for the consumption of cycloheptatrienes **1a** was determined. Using the rewritten Eyring equation below, we were able to estimate the value for the energy of activation to be 27.0 kcal·mol^{-1}.

$$\Delta G^{\ddagger} = -RT\, ln\frac{-k_r h}{k_B T}$$

Where:

$\Delta G^{\ddagger}$	=	Gibbs energy of activation	120998.3	J·mol^{-1}
R	=	*Gas constant*	*8.3144598*	J·K^{-1}·mol^{-1}
T	=	Absolute temperature	348	K
k_r	=	Reaction rate constant	-5.33·10^{-5}	mol·s^{-1}
h	=	*Planck constant*	*6.626070040·10^{-34}*	J·s
k_B	=	*Boltzmann´s constant*	*1.38064852·10^{-23}*	J·K^{-1}

Initial rate studies for the gold(I)-mediated isomerization of 11a.

cis-(*E*)-2-(2-styrylcyclopropyl)isoindoline-1,3-dione **11a** (4.5 mg, 0.0155 mmol), gold catalyst **A** (1.2 mg, 0.00155 mmol, 10 mol%) and diphenylmethane (2.6 μL, 0,0155 mmol) were added to a Young NMR tube and the atmosphere was flushed

with argon three times before adding 1,1,2,2,-tetrachloroethane-*d2* (0.4 mL). The mixture was heated in a Bruker NMR machine to 75 °C for 7 h, while performing ^{1}H measurements every 20 minutes (Table S3).

Table E3. Measured concentration (^{1}H NMR) of *cis*-**11a** during its isomerization to *trans*-**11a**

Concentration of *cis*-11a[a] (M)	ln(concentration of *cis*-11a)[b]	Time (s)
~~0,01574~~ [c]	~~-4,133~~[c]	~~0~~[c]
~~0,01632~~ [c]	~~-4,146~~ [c]	~~1200~~[c]
~~0,02118~~ [c]	~~-4,161~~[c]	~~2400~~[c]
0,02605	-4,174	3600
0,02638	-4,184	4800
0,02729	-4,187	6000
0,02693	-4,196	7200
0,03389	-4,209	8400
0,03467	-4,212	9600
0,03572	-4,219	10800
0,03779	-4,221	12000
0,04145	-4,232	13200
0,04171	-4,240	14400
0,04197	-4,248	15600
0,05034	-4,251	16800
0,05060	-4,253	18000
0,04467	-4,266	19200
0,05675	-4,267	20400
0,05216	-4,275	21600
0,05120	-4,280	22800
0,05758	-4,284	24000

[a] The disappearance of the *cis*-isomer was used for our data set as the accuracy was better compared to the appearance of the *trans*-isomer. [b] We are assuming 1st-order kinetics; hence the concentration is presented as the natural logarithm. [c] The first three data points were omitted to reduce the experimental error.

A reaction rate constant of $-5\cdot10^{-6}$ for the disappearance of the *cis*-isomer was derived from these data. Using the rewritten Eyring equation below, we were able to estimate the value for the energy of activation to be 28.9 kcal·mol^{-1}.

$$\Delta G^{\ddagger} = -RT\, ln\frac{-k_r h}{k_B T}$$

Where:

$\Delta G^{\ddagger}$	=	Gibbs energy of activation	120998.3	J·mol^{-1}
R	=	*Gas constant*	*8.3144598*	J·K^{-1}·mol^{-1}
T	=	Absolute temperature	348	K
k_r	=	Reaction rate constant	-5·10^{-6}	mol·s^{-1}
h	=	*Planck constant*	*6.626070040·10^{-34}*	J·s
k_B	=	*Boltzmann´s constant*	*1.38064852·10^{-23}*	J·K^{-1}

Estimation of the energy difference between the *cis*- and *trans*-isomers for 10b and 11a.

10b: *cis*-(E)-1-methoxy-4-(2-styrylcyclopropyl)benzene **10b** (3.8 mg, 0.03 mmol), gold catalyst **A** (2.3 mg, 0.003 mmol, 10 mol%) and diphenylmethane (4.8 μL, 0,03 mmol) were added to a Young NMR tube and the atmosphere was flushed with argon three times before adding chloroform-*d1* (0.4 mL). The mixture was heated to 75 °C for 7 days, until equilibrium was reached, with a cis/trans ratio of 0.148:1.

11a: *cis*-(*E*)-2-(2-styrylcyclopropyl)isoindoline-1,3-dione **11a** (4.5 mg, 0.0155 mmol), gold catalyst **A** (1.2 mg, 0.00155 mmol, 10 mol%) and diphenylmethane (2.6 μL, 0,0155 mmol) were added to a Young NMR tube and the atmosphere was flushed with argon three times before adding 1,1,2,2,-tetrachloroethane-*d2* (0.4 mL). The mixture was heated to 75 °C for 2 weeks, until equilibrium was reached, with a cis/trans ratio of 0.465:1.

Using the ratio of the as the equilibrium constant, k_{eq}, in the following equation, we estimated the difference in Gibbs free energy for the two isomers:

$$\Delta G^{\theta} = -RT \ln k_{eq}$$

Where:

ΔG^{θ}	=	Gibbs energy of activation	5446.5 (**10a**), 2246.7 (**11a**)	J·mol^{-1}
R	=	*Gas constant*	*8.3144598*	J·K^{-1}·mol^{-1}
T	=	Absolute temperature	348	K
k_{eq}	=	Reaction rate constant	0.148 (**10a**), 0.465 (**11a**)	mol·s^{-1}

Signifying that ***trans*-10b** is more stable by **1.3** kcal·mol^{-1} and ***trans*-11a** is more stable by **0.5** kcal·mol^{-1}.

General conditions for the polarity-inverted push-pull cyclopropane opening.

A solution of **11a** (7.2 mg, 25 μmol), **A** (1 mg, 1.25 μmol, 5 mol%) and nucleophile (25 μmol) in *n*-butyl acetate (0.25 mL) was heated to 90 °C for 24 h. The mixture was filtered over silica, concentrated and analyzed by ^{1}H NMR and GC-MS.

General conditions for the copper(I) and silver(I) catalyzed retro-Buchner reaction.

Intermolecular: In a glovebox, a Schlenk flask is charged with 7-phenyl-1,3,5-cycloheptatriene (0.1 mmol), *E*-stilbene (0.2 mmol), copper(I) or silver(I) catalyst (5 μmol, 5 mol%), and DCE (0.4 mL) before being sealed and heated to 120 °C for 12 h. The mixture was filtered over silica, concentrated and analyzed by ^{1}H NMR and GC-MS.

Intramolecular: In a glovebox, a Schlenk flask is charged with 7-(2-cinnamylphenyl)cyclohepta-1,3,5-triene (0.1 mmol), copper(I) or silver(I) catalyst (5 μmol, 5 mol%), and DCE (0.4 mL) before being sealed and heated to 120 °C for 12 h. The mixture was filtered over silica, concentrated and analyzed by ^{1}H NMR and GC-MS.

Computational details of the DFT calculations

Calculations were performed using SMD(CH_2Cl_2)-M06/6-311+G(2d,p), SDD(Au, ζ_f=1.05)//SMD(CH_2Cl_2)-M06/6-31G(d), SDD(Au) at the standard state (298.15 K, 1 atm). Full geometry optimizations were performed in solution, with the SMD method,[337] and using Gaussian 09[338] defaults for dichloromethane. In the article,

337 Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378-6396.

338 Frisch, M. J. T., G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.;

all energies are given in kcal/mol. In the experimental section, energies are given in Hartree. The nature of the stationary points was characterized by a vibrational analysis performed within the harmonic approximation at 298 K and 1 atm. Transition states were identified by the presence of one imaginary frequency and minima by a full set of real frequencies.

Single point energies were calculated for all six cyclopropanation transition states using SMD(CH_2Cl_2)-PBE-D3(BJ)/6-311+G(2d,p), SDD(Au, ζ_f=1.05).

Optimized geometries were visualized using CYLview.[339]

Reduced density gradient surface

The Reduced density gradient surface was generated for the cyclopropanation transition states using Multiwfn.[340] The isosurface was visualized using ChemCraft, with the surface contour set at 0.5 and the color range fixed from -0.035 to 0.02.

Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg,J.J.;Dapprich,S.;Daniels, A.D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09 (Revision D.01)* **2013**, *Gaussian, Inc.: Wallingford, CT*.

339 Legault, C. Y.; *CYLview*, Ed. Universite de Sherbrooke: Sherbrooke, Candada, 2009 http://www.cylview.org.

340 Lu, T.; Chen, F. *J. Comput. Chem.* **2012**, *33*, 580-592.

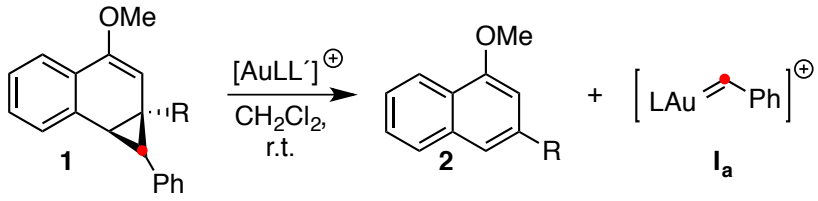
4.

New Cycloheptatriene Derivatives for the Room-Temperature Retro-Buchner Reaction

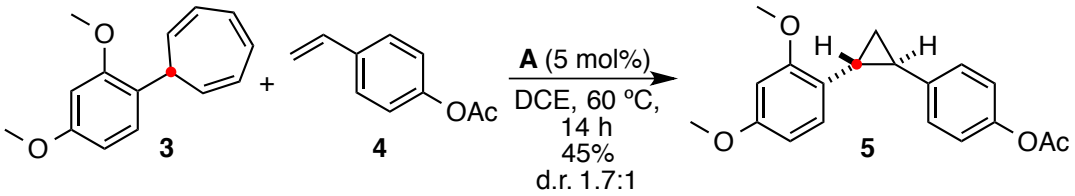
*The work described in this chapter was performed in collaboration with **Evaristo Villaseco Arribas**, whom I co-supervised as a La Caixa - ICIQ summer fellow.*

Introduction

The gold(I)-catalyzed retro-Buchner reaction was initially observed by our group when 3-methoxy-dihydro-1*H*-cyclopropa[a]naphthalene derivatives **1** spontaneously underwent a retro-cyclopropanation reaction at room temperature (Scheme 150).[341] This observation led to the development of cycloheptatriene derivatives for the convenient formation of gold(I) carbenes at 120 °C. During the course of the investigation, it was observed that electron-donating substituents on the aryl or alkenyl moiety of the cycloheptatriene derivatives would lower the temperature at which the transformation had to be performed, using the [(JohnPhos)Au(MeCN)]SbF_6 complex (**A**) (Scheme 151). This phenomenon can be rationalized by the increased stabilization of the cationic transition-states and Wheland-type intermediate (**III**) during the retro-Buchner reaction (Scheme 152).

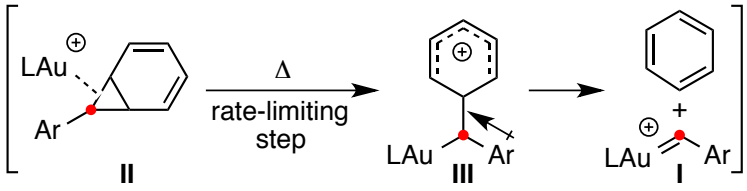


Scheme 150. Gold(I)-catalyzed retro-cyclopropanation reaction.[341]



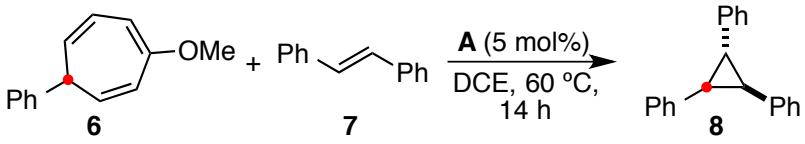
Scheme 151. Retro-Buchner reaction of electron-rich cycloheptatriene derivatives at 60 °C.

341 Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881-11883.



Scheme 152. The double C-C bond cleavage catalyzed by gold(I) of norcaradiene. The rate-limiting step is the first C-C bond cleavage leading to the Wheland-type intermediate. A carbene is formed after the second C-C bond cleavage.

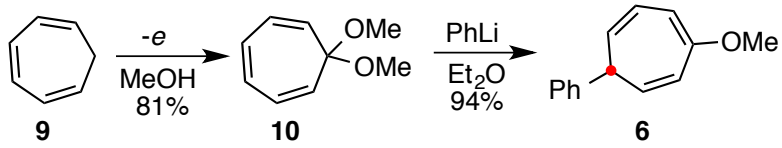
Electron-rich cycloheptatriene derivatives can be obtained by using arene derivatives bearing electron-donating moieties. However, the arene substituents would be transferred to the gold(I) carbene and therefore to the cyclopropane product of the reaction. Rather than limiting the scope of the reaction to electron-rich aryl carbenes, it would be much more desirable to implement the electron-rich moieties in the cycloheptatriene part of the carbene precursor. This would allow the retro-Buchner reaction to take place at low temperature while maintaining a large scope of aryl substituents. In order to confirm this hypothesis, a kinetic experiment was performed in our group using 4-methoxy-7-phenyl-1,3,5-cycloheptatriene (**6**), which demonstrated an impressive rate enhancement (Scheme 153).[342] Unfortunately, the promising results were outweighed by the limited synthetic options to obtain a library of aryl derivatives and the overall poor yield for the preparation of **6** in our hands, despite the good yield reported in the original work (Scheme 154).[343]



Scheme 153. Retro-Buchner reaction of 4-OMe-7-phenyl-1,3,5-cycloheptatriene (**6**) at 60°C.[342]

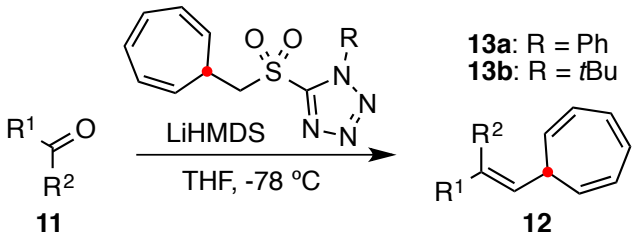
342 Wang, Y. PhD. Dissertation, ICIQ/Universitat Rovira i Virgili, 2014.

343 a) Shono, T.; Nozoe, T.; Maekawa, H.; Kashimura, S. *Tetrahedron Lett.* **1988**, *29*, 555-558. b) Tatsuya, S.; Hirofuni, N.; Tetsuo, N.; Shigenori, K. *Tetrahedron Lett.* **1990**, *31*, 895-898.



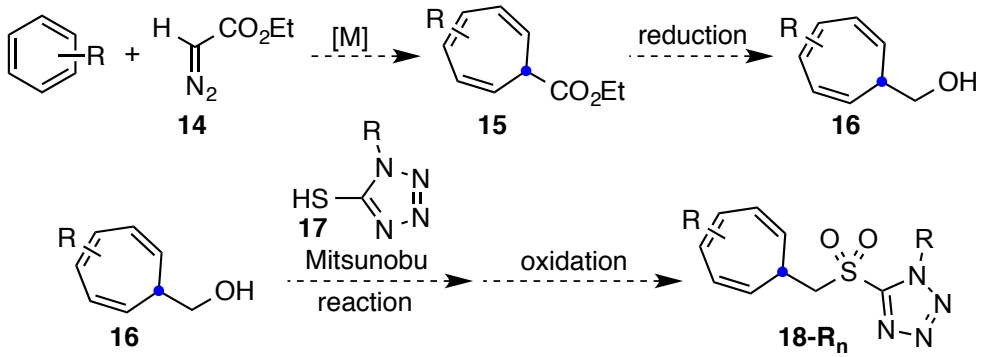
Scheme 154. Formation of **6** as originally reported.[343]

The methodology developed in *chapter 2* for the formation of 7-alkenyl cycloheptatrienes using Julia-Kocienski reagents **13a-b** provides access to a variety of cycloheptatriene reagents from aldehydes and ketones in a single step (Scheme 155).



Scheme 155. Formation of 7-alkenyl cycloheptatriene derivatives using Julia-Kocienski reagents **13a** or **13b**.

The alkenylation strategy allows rapid variation of the alkenyl substituents. Alternatively, a modification of this strategy can be exploited to obtain new cycloheptatriene derivatives by starting from other aromatic compound rather than benzene (Scheme 156).



Scheme 156. Synthetic plan for the formation of new cycloheptatriene derivatives.

With new cycloheptatriene reagents in reach, the influence of different substituents can be investigated, ultimately leading to low-temperature carbene formation and its use in stereo- and enantioselective cyclopropanation reactions.

Objectives

Our objective was to synthesize modified Julia-Kocienski reagents, starting from electron-rich arenes rather than benzene, which bear an electron-donating moiety on the cycloheptatriene. The Julia-Kocienski reagents would be used in an alkenylation reaction to obtain new classes of electron-rich 7-alkenyl cycloheptatriene reagents.

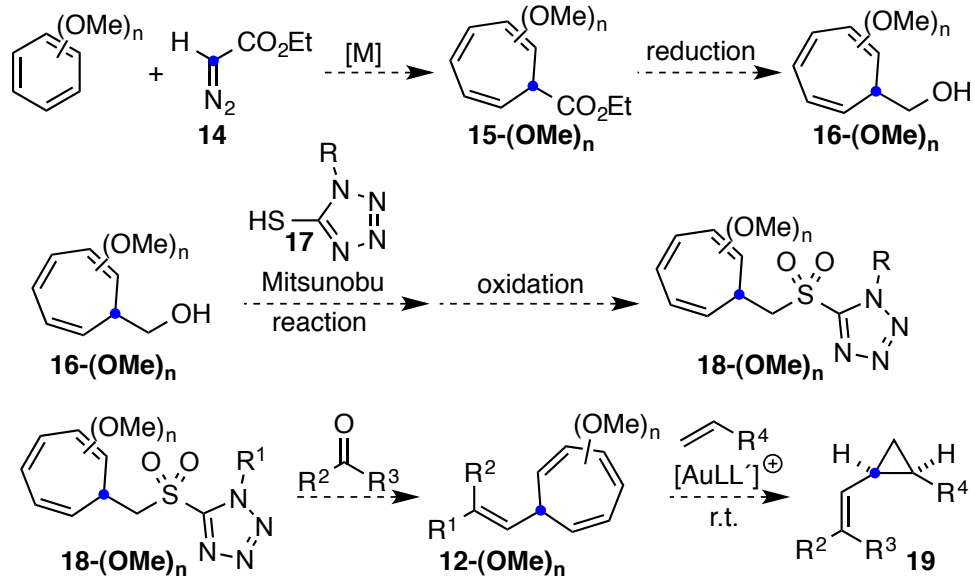
The reagents would be tested for their propensity to undergo the gold(I)-catalyzed retro-Buchner reaction at lower temperatures.

Successful development of a new cycloheptatriene reagent that provides carbenes at room temperature, will allow further investigation of catalysts, scope, diastereo- and enantioselectivity in different metal-carbene mediated transformations.

Results and discussion

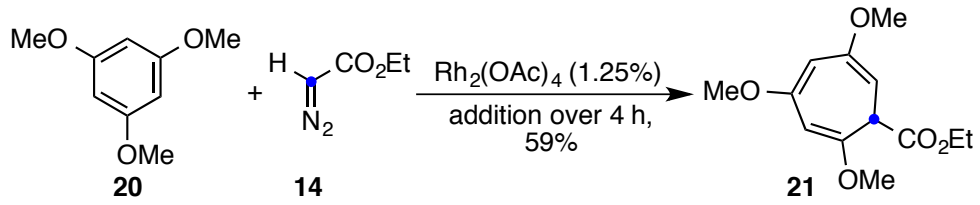
7-Substituted polymethoxy-1,3,5-cycloheptatriene derivatives

The synthetic approach for the Julia-Kocienski reagents developed in *chapter 2* can be exploited for the formation of new cycloheptatriene derivatives. Electron-rich substituents have demonstrated an impressive rate enhancement. Therefore, the synthesis and investigation of cycloheptatrienes bearing additional electron-donating groups was targeted (Scheme 157).

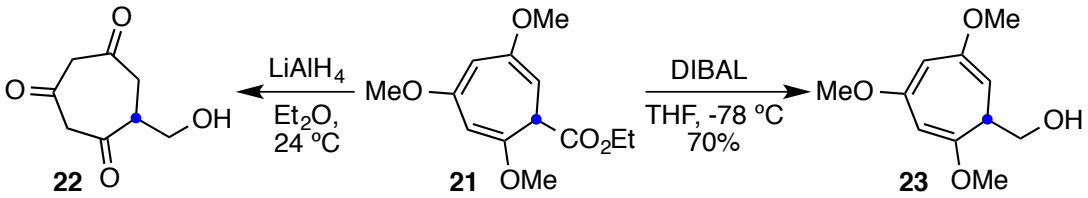


Scheme 157. Synthetic approach for the formation of new cycloheptatriene reagents for the room temperature retro-Buchner reaction.

The Buchner ring expansion of 1,3,5-trimethoxybenzene (**20**) exclusively leads to a single regioisomer while the three methoxy substituents bolster the electron-richness, making it an ideal starting point for this investigation. The Buchner reaction of 1,3,5-trimethoxybenzene afforded the desired 1,3,5-trimethoxy-7-carboxylate-1,3,5-cycloheptatriene (**21**) in good yield, under similar conditions as for benzene (Scheme 158). The reduction of ester **21** with $LiAlH_4$ led to the alcohol but the three methoxy ethers were hydrolyzed at the same time, affording triketone **22** (Scheme 159). Instead, the desired alcohol **23** could be isolated by performing the reduction with DIBAL (Scheme 159).

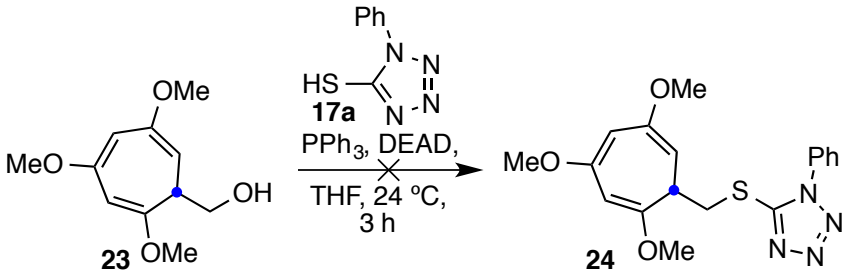


Scheme 158. Buchner ring expansion of 1,3,5-trimethylbenzene.

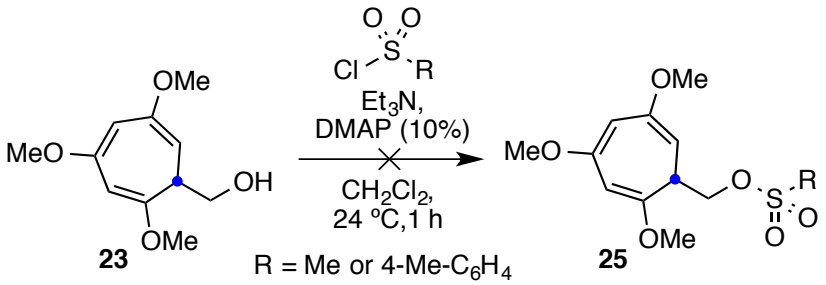


Scheme 159. Reduction of ester **21** with $LiAlH_4$ and DIBAL.

The Mitsunobu reaction under the conditions in *chapter 2* led to the decomposition of **23** (Scheme 160). An attempt of circumvent the Mitsunobu reaction by transforming the alcohol into a leaving group separately, which could then be replaced by nucleophilic attack of thiol **17**, led to no avail as the material decomposed, as well. (Scheme 161). The rapid decomposition is likely caused by the elimination of the alcohol moiety once it has been functionalized.



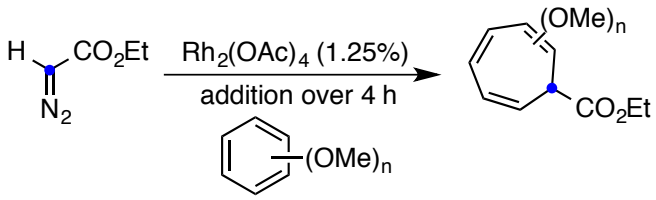
Scheme 160. Attempted Mitsunobu reaction for the formation of thioether **24**.

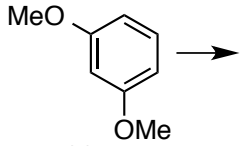
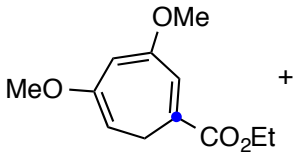
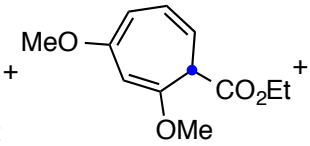
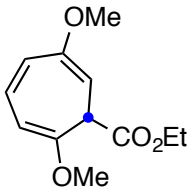
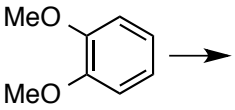
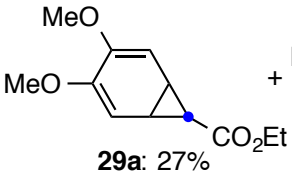
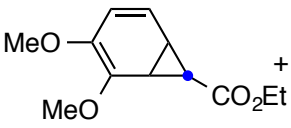
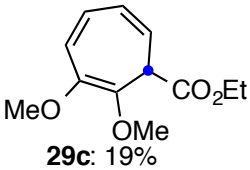
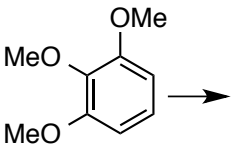
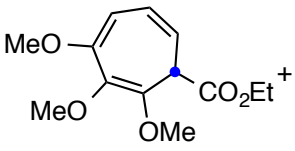
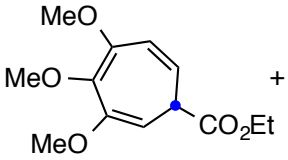
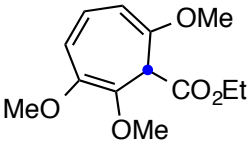


Scheme 161. Attempted formation of leaving groups for the nucleophilic substitution of the alcohol.

The Buchner reaction of other methoxy-substituted arenes was performed in the hope to find a system that would be less prone to decomposition during the thioether formation (Table 12).

Table 12. Scope of the Buchner reaction for methoxy arenes.



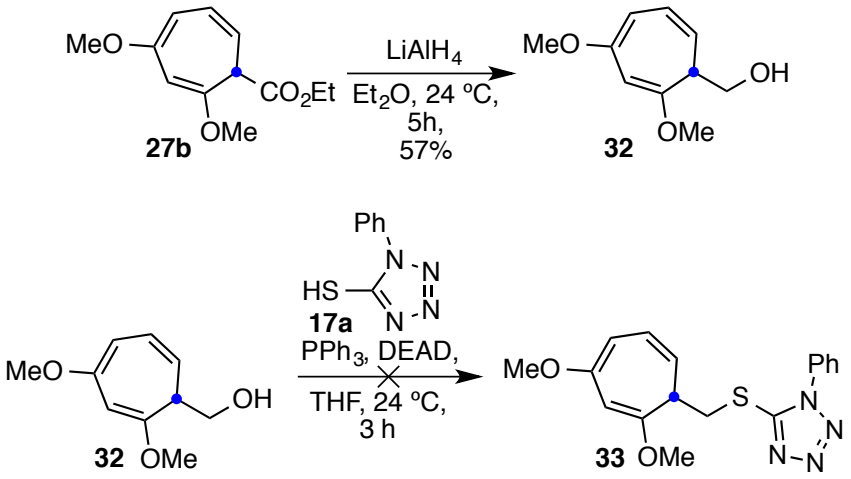
Arene	Product		
 **26**	 **27a**: 30%	 **27b**: 13%	 **27c**: not observed
 **28**	 **29a**: 27%	 **29b**: 20%	 **29c**: 19%
 **30**	 **31a**: n.d.	 **31b**: n.d.	 **31c**: n.d.

Methoxy arene (24 mmol), $[Rh_2(OAc)_4]$ (0.04 mmol) in CH_2Cl_2 (40 mL), addition of ethyl diazoacetate (28.8 mmol, 1M) over 4 h. Isolated yields.

The major compound isolated from the Buchner reaction of 1,3-dimethoxybenzene was the isomerized 1-carboxylate-3,5-dimethoxy-1,3,5-cycloheptatriene (**27a**) (Table 12, row 1), along with by 1,3-dimethoxy-1,3,5-cycloheptatriene derivative **27b** in poor yield, while the 1,5-dimethoxy derivative **27c** was not observed. The products of 1,2-dimethoxybenzene (veratrole) were isolated as a mixture of **29a**, **29b** and **29c** in a 3:2:2 ratio by distillation but **33c** was removed after flash chromatography (Table 12, row 2). Interestingly, by ^{1}H NMR spectroscopy it was observed that **29a** and **29b** exist exclusively in the norcaradiene conformation while **29c** appears exclusively as

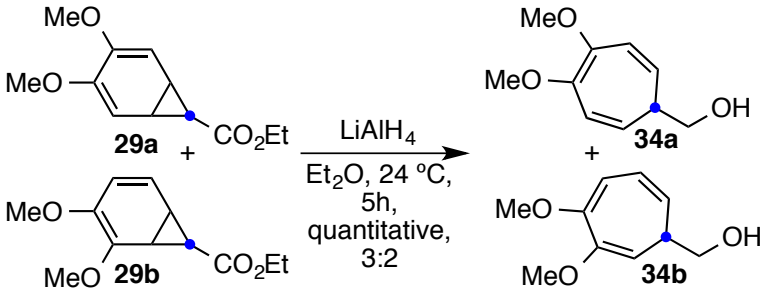
the cycloheptatriene, although **29b** was previously reported to exist in the cycloheptatriene conformation.[344] The products of 1,2,3-trimethoxybenzene **41a-c** were obtained as mixtures of the isomers and starting material after purification by flash chromatography (Table 12, row 3).

The synthesis of electron-rich cycloheptatriene derivatives was continued with the Buchner products of Table 12. Reduction of **27b** afforded the desired alcohol **32** in moderate yield but the subsequent Mitsunobu reaction led to decomposition (Scheme 162).



Scheme 162. Reduction of ester **27b** with $LiAlH_4$ and attempted Mitsunobu reaction of **32**.

The reduction of a mixture of veratrole derivatives **29a** and **29b** obtained through distillation resulted in a mixture of alcohols **34a** and **34b** with the same ratio in quantitative yield (Scheme 163), while the reduction of **29c** led to decomposition.

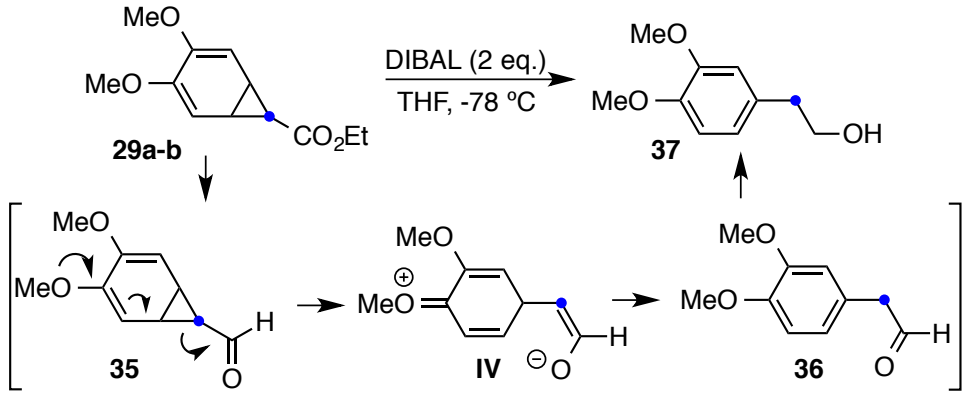


Scheme 163. Reduction of veratrole derivatives **29a** and **29b** to the corresponding alcohols.

344 Matsumoto, M.; Shiono, T.; Mutoh, H.; Amano, M.; Arimitsu, S. *J. Chem. Soc., Chem. Commun.* **1995**, 101-102.

When the reduction was carried out on the batches of **29a-b** that were purified by flash chromatography rather than distillation, complete decomposition was observed. It is possible that a relatively stable cycloheptatriene-rhodium species is not removed by column chromatography, which later forms a rhodium-hydride that is responsible for the decomposition. Cycloheptatrienes have been reported to act as ligands for rhodium, to form very stable complexes.[345] In addition, the rhodium-catalyzed transformation of cycloheptatriene to norbornadiene has been proposed,[346] which could offer an alternative explanation for the decomposition.

Reduction of the **29a-b** mixture with DIBAL led to the unexpected isolation of arylethanol **37** (Scheme 164). The aldehyde formed during the DIBAL reduction can undergo opening of the cyclopropane leading to the corresponding enolate. This process is assisted by the electron-donating substituents on the aromatic ring. Rearomatization and tautomerization of the aldehyde, followed by a second reduction leads to the alcohol (Scheme 164).



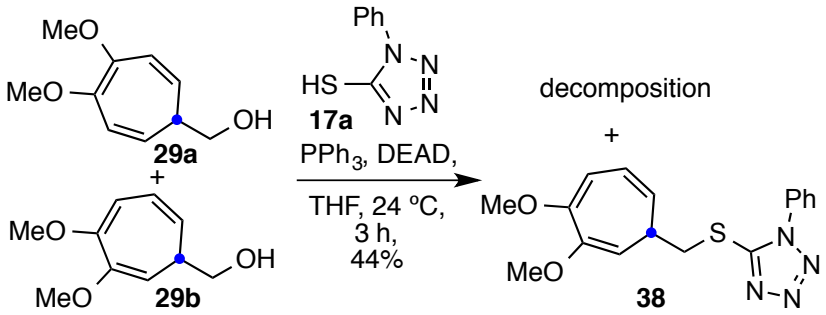
Scheme 164. Formation of arylethanol **37** during the DIBAL reduction of **29a-b**.

The Mitsunobu reaction was performed on the mixture of alcohols **29a** and **29b** with thiol **17a**. Interestingly, **29a** decomposed under the reaction conditions, while the product of **29b** was isolated in moderate yield (Scheme 165). Oxidation of **38** afforded Julia-Kocienski reagent **39** in low yield (Scheme 166).

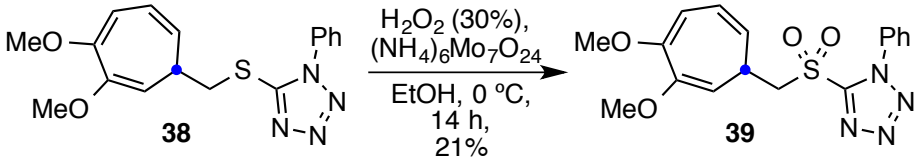
345 a) Brown, J. M.; Coles, D. G. *J. Organomet. Chem.* **1973**, *60*, C31-C34. b) Maurer, E.; Rieker, S.; Schollbach, M.; Schwenk, A.; Egolf, T.; von Philipsborn, W. *Helv. Chim. Acta* **1982**, *65*, 26-45. c) Wadepohl, H.; Galm, W.; Wolf, A. *J. Organomet. Chem.* **1993**, *452*, 193-195.

346 Bonati, F.; Wilkinson, G. *J. Chem. Soc.* **1964**, 3156-3160.

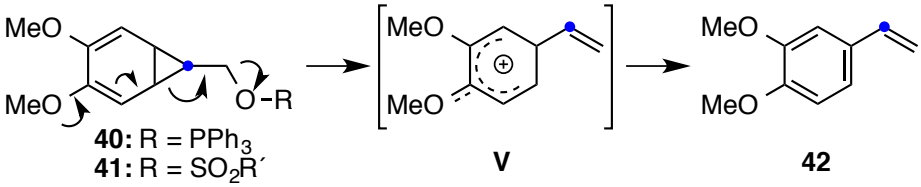
The reduced yield in these two transformations is due to the decomposition of alcohol **29b** and thioether **38** under the reaction conditions, which became apparent from the isolation of 3,4-dimethoxystyrene (**42**; Scheme 167).



Scheme 165. Treatment of alcohols **29a** and **29b** under Mitsunobu conditions exclusively led to the formation of **38**.

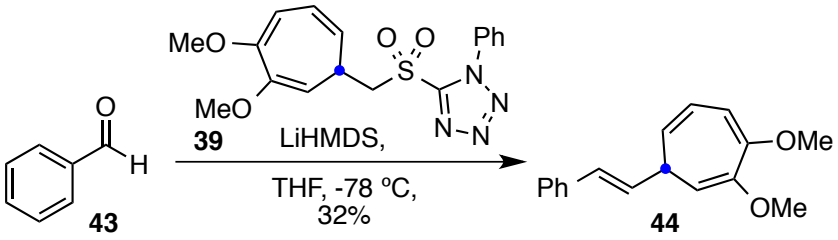


Scheme 166. Oxidation of thioether **38** to form the Julia-Kocienski reagent **39**.



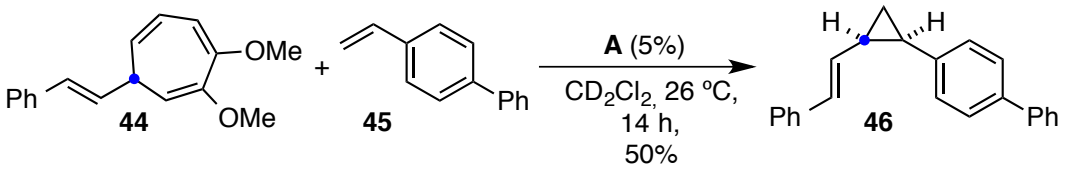
Scheme 167. Proposed decomposition pathway of polymethoxy cycloheptatriene derivatives to form **42**.

Julia-Kocienski reagent **39** was used to synthesize new cycloheptatriene derivative **44**. Using the conditions optimized in *chapter 2*, the desired 2,3-dimethoxy-7-styrenyl-1,3,5-cycloheptatriene (**44**) was obtained in moderate yield (Scheme 168).



Scheme 168. Synthesis of new alkenyl cycloheptatriene reagent **44** using Julia-Kocienski reagent **41**.

The new cycloheptatriene derivative **44** was submitted to gold(I) catalyst **A** in the presence of 4-vinylbiphenyl using deuterated dichloromethane as a solvent, so the reaction could be followed by ^{1}H NMR spectroscopy at different temperatures (Scheme 169). Product formation was observed at room temperature (26 °C) and no further changes were observed after 14 h. The yield of the *cis*-isomer of **46** was estimated to be 50% with a conversion of also 50% by ^{1}H NMR spectroscopy of the crude reaction mixture. The *trans*-isomer was not observed in the crude reaction mixture or in the purified product.



Scheme 169. First example of the gold(I)-catalyzed retro-Buchner reaction performed at room temperature.

The yield obtained with the new cycloheptatriene derivative was lower than what was reported in *chapter 2* for the same product (83%, d.r. >20:1). The diastereoselectivity is equal or better as no traces of the *trans*-isomer could be identified. The lower conversion is likely due to performing the reaction with one equivalent of **45** in a different solvent, rather than the optimized conditions described in *chapter 2*.

The new Julia-Kocienski reagent and the new cycloheptatriene derivative served as a good proof of principle. With these results, the feasibility of performing the gold(I)-catalyzed retro-Buchner reaction at room temperature has been demonstrated. However, the synthesis of the new Julia-Kocienski reagents suffers from a low overall efficiency, due to the poor selectivity of Buchner

reaction leading to mixtures of regioisomers, and the inefficient Mitsunobu reaction. Thus, a more efficient approach is still desired.

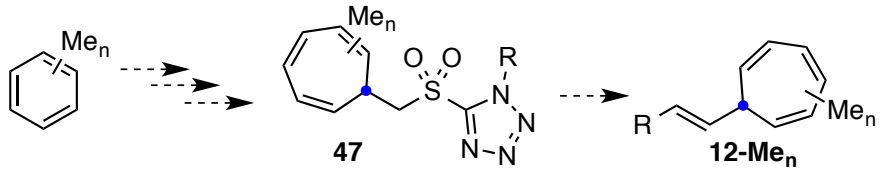
In aromatic rings, the influence of methoxy substituents in the *ortho*, *meta*, or *para* positions on the reactivity is well established.[347] In cycloheptatrienes, the effect of the substituents and their position is not so well defined. However, an interesting consequence of the number of methoxy substituents and their position on the cycloheptatriene moiety was observed. The more electron-rich the cycloheptatriene is, the higher the stabilization of the transition states leading to the gold(I) carbene will be, the lower the temperature needs to be for the retro-Buchner reaction to take place. However, the major decomposition pathway during the alcohol derivatization is the formation of (poly)methoxy styrene by elimination of a leaving group (Scheme 167). The decomposition pathway also benefits from the increased electron density. Therefore, having too few electron-donating substituents will negatively influence the retro-Buchner reaction, while having too many will tip the scales in the other direction and the substrate becomes unstable. Having methoxy groups in the 2 and 3 position struck the balance right; leaving enough stabilization for the retro-Buchner reaction to take place at room temperature, while being stable enough to undergo substitution reactions, even though still a significant amount of material decomposed during the formation of Julia-Kocienski reagent **39**.

347 Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165-195.

7-Substituted polymethyl-1,3,5-cycloheptatriene derivatives.

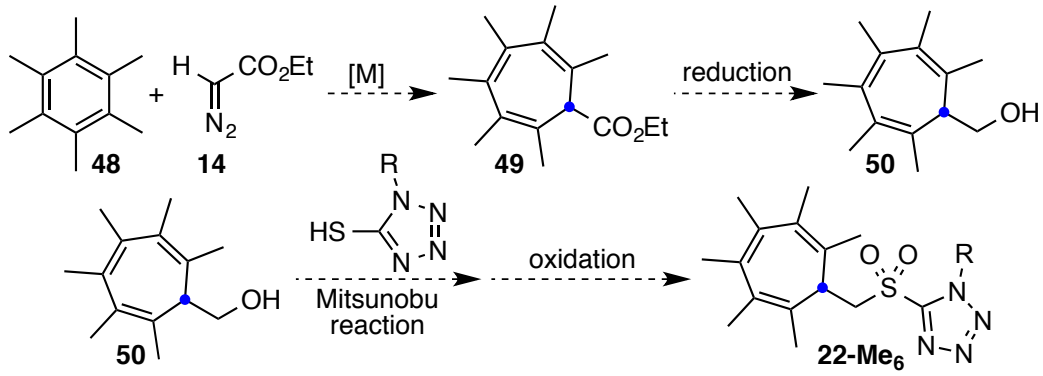
The methyl group can be considered a mildly electron-donating group, despite only contributing by induction through the σ-system and hyperconjugation, it can adequately stabilize carbocations.[347] Methoxy groups, on the other hand, are inductively withdrawing but are strongly donating through the π-system. In addition, the methyl group is chemically much more inert than a methoxy substituent, especially as the methoxy groups in the cycloheptatriene derivatives can be considered methyl enol ethers.

In order to overcome the low efficiency during the synthesis of 7-substituted polymethoxy-1,3,5-cycloheptatrienes originating from poor selectivity or decomposition of intermediates, the use of 7-substituted polymethyl-1,3,5-cycloheptatrienes **12** was investigated (Scheme 170).



Scheme 170. Synthetic plan for the formation of polymethyl cycloheptatriene derivatives.

The investigation began with hexamethylbenzene, as the six methyl groups combined can compensate as electron-donating moiety, while avoiding regioselectivity issues (Scheme 171).

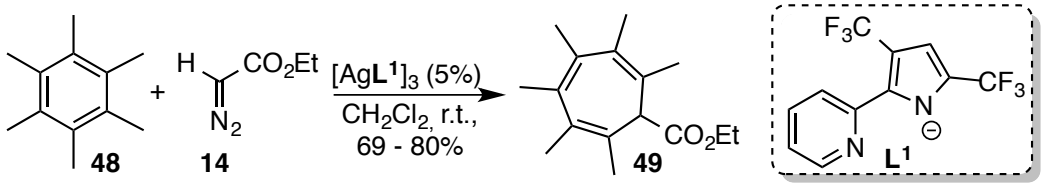


Scheme 171. Proposed synthetic plan for the synthesis of Julia-Kocienski reagent **22** from hexamethylbenzene.

A survey of the literature revealed that no synthetically useful methods exist for the formation of 1,2,3,4,5,6-hexamethyl,-1,3,5-cycloheptatriene derivatives. The

Buchner reaction of hexamethyl benzene (**48**) has been performed without catalyst by heating hexamethylbenzene in the presence of large quantities of the appropriate diazo compound in a sealed vessel.[348] Both hexamethylbenzene and hexamethylcycloheptatriene have been reported to form stable complexes with transition metals,[349] which would explain the lack of catalytic methods.

The single example of transition-metal catalyzed ring expansion uses a silver(I)-pyridylpyrrolide catalyst (Scheme 172).[350] However, the reaction was performed on a small scale and was analyzed by GC-MS only.



Scheme 172. Silver(I)-catalyzed Buchner ring expansion of hexamethylbenzene. Mindiola, 2013.[350]

With the lack of literature precedents, a preliminary catalyst screening was performed using silver(I)-pyridylpyrrolide complex [Ag**L**^{1}]$_3$, which was synthesized as reported, rhodium(II)acetate dimer, which had led to good results for methoxyaryls, and the more active rhodium(II)trifluoroacetate dimer, for which good results have been reported in the Buchner reaction of polysubstituted aryls (Table 13).[351]

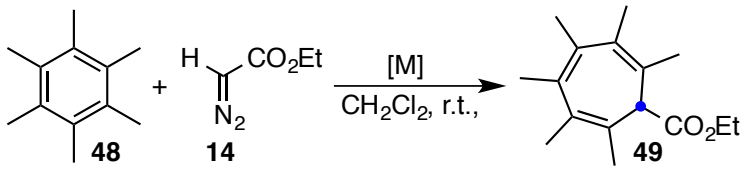
348 a) Takeuchi, K. i.; Kurosaki, T.; Yokomichi, Y.; Kimura, Y.; Kubota, Y.; Fujimoto, H.; Okamoto, K. *J. Chem. Soc., Perkin Trans. 2* **1981**, 670-674. b) Knoche, H. *Chem. Ber.* **1966**, *99*, 1097-1105. c) Tamm, M.; Dreβel, B.; Fröhlich, R. *J. Org. Chem.* **2000**, *65*, 6795-6797. d) Takeuchi, K. i.; Yokomichi, Y.; Kurosaki, T.; Kimura, Y.; Okamoto, K. *Tetrahedron* **1979**, *35*, 949-956.

349 a) Pampaloni, G. *Coord. Chem. Rev.* **2010**, *254*, 402-419. b) Tamm, M.; Dreβel, B.; Fröhlich, R. *J. Org. Chem.* **2000**, *65*, 6795-6797.

350 Komine, N.; Flores, J. A.; Pal, K.; Caulton, K. G.; Mindiola, D. J. *Organometallics* **2013**, *32*, 3185-3191.

351 Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873-876.

Table 13. Optimization for the Buchner reaction of hexamethylbenzene.



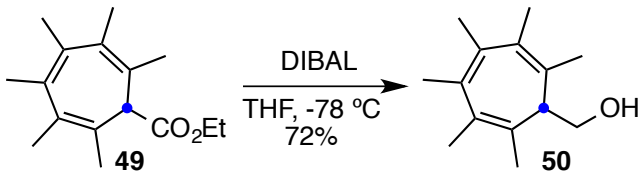
48 14 49

	[M] (%)	EDA (equiv)	Time: addition (total)	Yield
1	[Ag**L¹**]$_3$ (5%)	2	0 (8h)	10%
2	$Rh_2(OAc)_4$ (5%)	2	4h (8h)	-
3	$Rh_2(TFA)_4$ (5%)	2	4h (8h)	14%
4	$Rh_2(TFA)_4$ (5%)	4	3h (7h)	21%
5	$Rh_2(TFA)_4$ (1%)	2	4h (8h)	17%
6	$Rh_2(TFA)_4$ (1%)	0.5	4h (8h)	27%

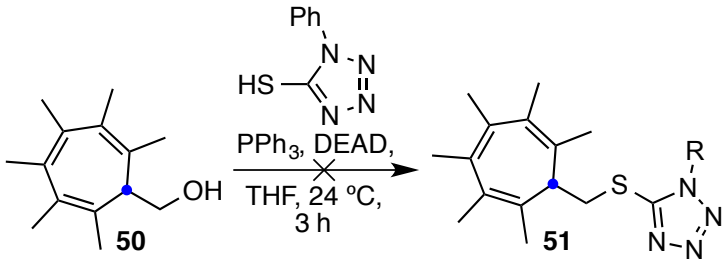
Hexamethylbenzene (1 mmol) and catalyst in CH_2Cl_2 (25 mL). Ethyl diazoacetate (**14**) is added over given time to the mixture, which is left for the total time. Isolated yields.

Following the reported procedure, only a small amount of **49** was obtained using [Ag**L¹**]$_3$ (Table 13, entry 1), while the rhodium(II)acetate dimer proved inactive for this transformation (Table 13, entry 2). Initially, poor results were also obtained for the rhodium(II)trifluoroacetate dimer (Table 13, entry 3), but could be improved by increasing the amount of diazo compound **14** (Table 13, entry 4). The transformation was equally effective with a lower catalyst loading (Table 13, entry 5). The yield could further be improved by using **14** as limiting reagent rather than hexamethylbenzene (Table 13, entry 6). Despite the moderate yield, this is the first use of rhodium(II)trifluoroacetate dimer in the Buchner reaction of hexamethylbenzene. More importantly, this is the first example of a transition-metal catalyzed Buchner reaction for hexamethyl benzene at a synthetically relevant scale.

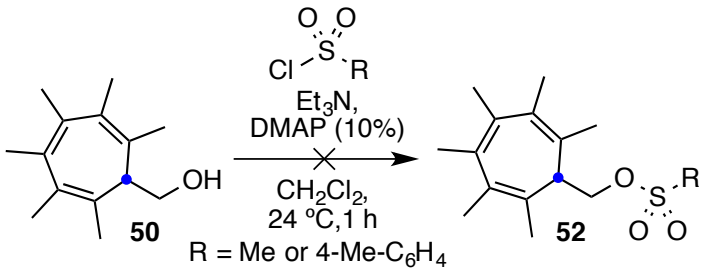
Having established a method to obtain modest amounts of ester **49**, the synthesis of the envisioned Julia-Kocienski reagent was investigated. Ester **49** was reduced to the alcohol with DIBAL at -78 °C in good yield (Scheme 173). Nevertheless, the formation of thioether **51** using the Mitsunobu reaction failed as alcohol **50** decomposed instead (Scheme 174). As for the previous approach, it was attempted to convert the alcohol into a good leaving group for the direct nucleophilic substitution of **52** but this also led to decomposition (Scheme 175).



Scheme 173. Reduction of **49** with DIBAL.



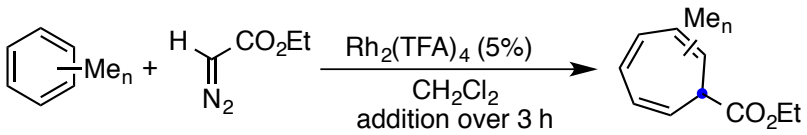
Scheme 174. Attempted formation of thioether under Mitsunobu conditions.

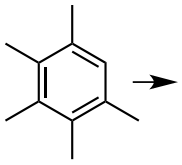
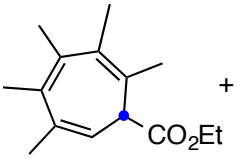
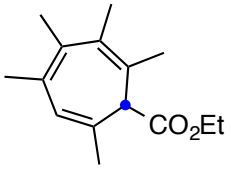
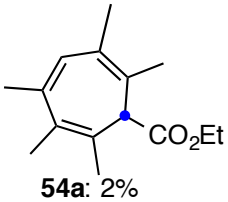
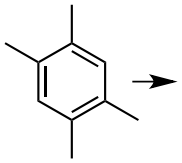
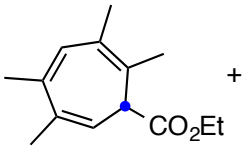
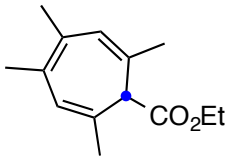
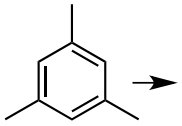
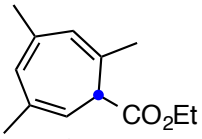


Scheme 175. Attempt to turn the alcohol into a good leaving group.

The decomposition observed for the hexamethyl derivative is reminiscent of the degradation observed for the poly-methoxy cycloheptatriene derivatives. Therefore, a similar strategy was followed in the hope to find a system that would be less prone to decomposition during the thioether formation. Hence, the Buchner reaction of other methyl-substituted arenes was performed (Table 14). The Buchner reaction of pentamethylbenzene (**53**) afforded a mixture of regioisomers in poor yield (Table 14, row 1). Better yields, albeit still low, were obtained for the two possible regioisomers for 1,2,4,5-tetramethylbenzene (**55**) Table 14, row 2). Gratifyingly, the single product for 1,3,5-trimethylbenzene (mesitylene) **58** was obtained in good yield (Table 14, row 3). Interestingly, no double-bond isomerization products were observed.

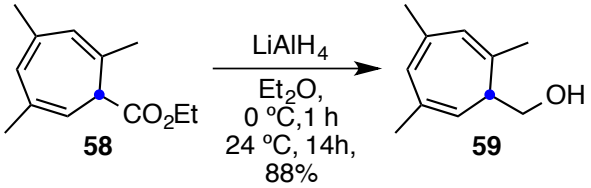
Table 14. Scope of the Buchner reaction for methyl-substituted arenes.



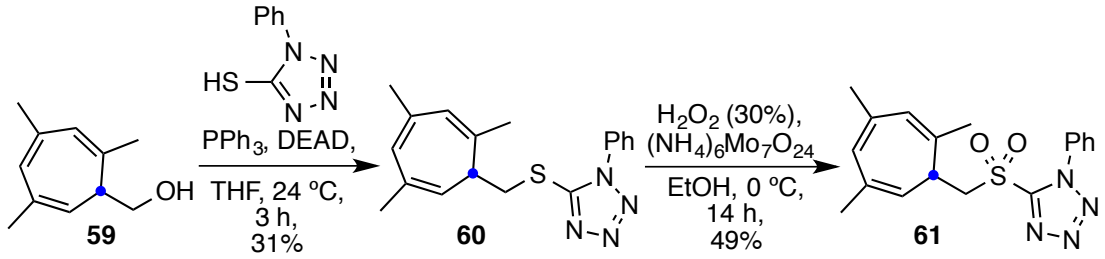
Arene	Product
 **53**	 **54a**: 5% +  **54a**: 2% +  **54a**: 2%
 **55**	 **56a**: 21% +  **56a**: 11%
 **57**	 **58**: 59%

Poly-methylbenzene (1 mmol) and catalyst in CH_2Cl_2 (25 mL). Ethyl diazoacetate is added over 3 h and the mixture is left for an additional 6 h. The yields reported are of the isolated compounds.

The Buchner product of mesitylene was obtained in good yield for this transformation. More importantly, only a single isomer can be formed. The investigations were continued with the reduction of ethyl 1,3,5-trimethyl-7-carboxylate-1,3,5-cycloheptatriene (**58**) using $LiAlH_4$ to form alcohol **59** in good yield (Scheme 176). The subsequent Mitsunobu reaction afforded thioether **60** in moderate yield and was followed by the oxidation to the sulfonyl **61** (Scheme 177). Although the Mitsunobu reaction and oxidation can be performed as a one-pot transformation, it was chosen to isolate thioether **60** to confirm the conversion for both steps separately.



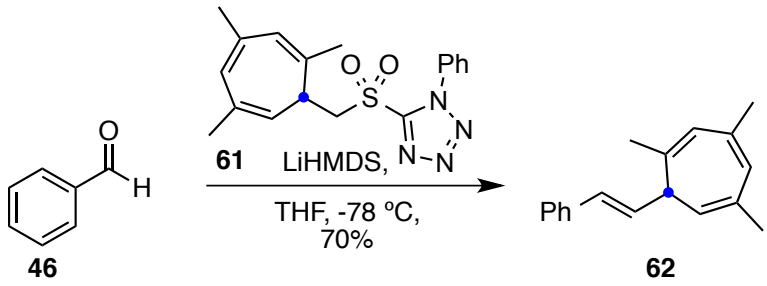
Scheme 176. Reduction of ester **58** with $LiAlH_4$.



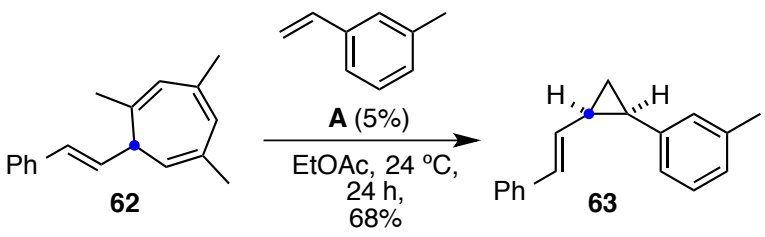
Scheme 177. Formation of Julia-Kocienski reagent **61** by the Mitsunobu reaction and oxidation.

The new Julia-Kocienski reagent **61** was used in the alkenylation of benzaldehyde to give 1,3,5-trimethyl-7-styrenyl-1,3,5-cycloheptatriene **62** in good yield using the conditions established in *chapter 2* (Scheme 178).

With the new mesityl derived cycloheptatriene derivative **62**, the gold(I)-catalyzed retro-Buchner reaction and cyclopropanation of 3-methylstyrene was performed in ethyl acetate at 24 °C (Scheme 179). Cyclopropane **63** was obtained in good yield (68%), albeit slightly lower than what was reported in *chapter 2* (75%, d.r. >20:1). The diastereoselectivity was equal or better compared to what was reported in *chapter 2* as no trace of the *trans*-isomer could be observed.



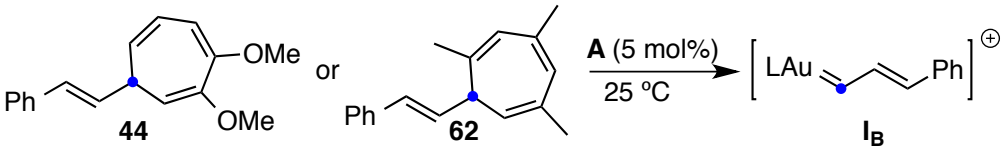
Scheme 178. Formation of new cycloheptatriene derivative **62** using Julia-Kocienski reagent **61**.



Scheme 179. The gold(I)-catalyzed retro-Buchner reaction and cyclopropanation at room temperature using new cycloheptatriene derivative **62**.

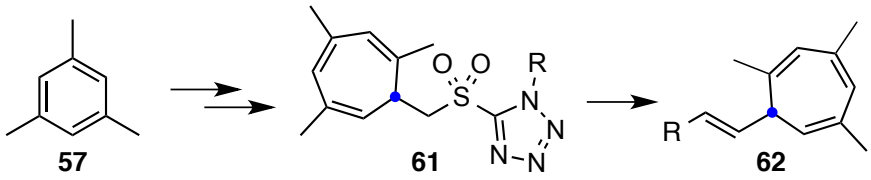
Outlook

The feasibility of performing the gold(I)-catalyzed retro-Buchner reaction at room temperature has been demonstrated with two new cycloheptatriene derivatives, **44** and **62** (Scheme 180).



Scheme 180. Formation of gold(I) carbenes via the retro-Buchner reaction of cycloheptatriene reagents **44** and **62**

The sequence using trimethylcyloheptatriene derivatives **62** is the preferred method for further development, as there are no issues with regioselectivity during the synthesis, and the overall performance of the synthetic approach is higher, as the methyl groups are more inert (Scheme 181).

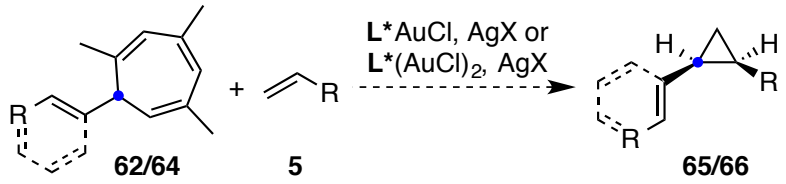


Scheme 181. Key intermediates for the synthesis of 7-substituted-1,3,5-trimethylcycloheptatriene reagents.

Although the chemistry described in this chapter serves as a good proof of principle, reaction optimization of the individual steps for the formation of the Julia-Kocienski reagent **61** are required. While the yield for the Buchner ring expansion is not disappointing, it uses a high catalyst loading and other reaction parameters have not been optimized, yet.

With a lower activation barrier for the retro-Buchner reaction, the carbene formation might no longer be limited to the use of JohnPhos-gold complex **A**. Therefore, a more efficient and possibly more selective catalyst can be found through careful screening of different gold(I) catalysts. Elaborate screening of

chiral ligands might eventually even lead to an efficient diastereo- and enantioselective transformation.[352]



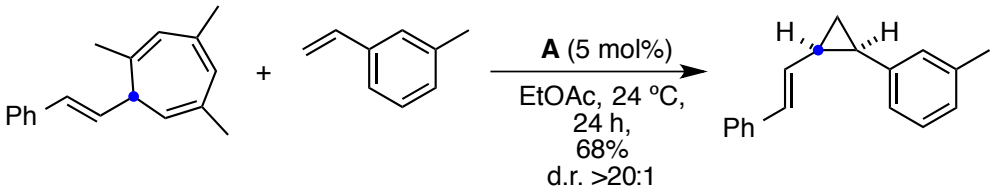
Scheme 182. Asymmetric alkene cyclopropanation by gold(I) carbenes through the retro-Buchner reaction.

In conclusion, the generalization of the retro-Buchner reaction at room temperature for the formation of gold(I) carbenes will place it at par with "conventional" diazo compound chemistry. Expansion of this chemistry to other transition metals would fully unlock the potential of this methodology.

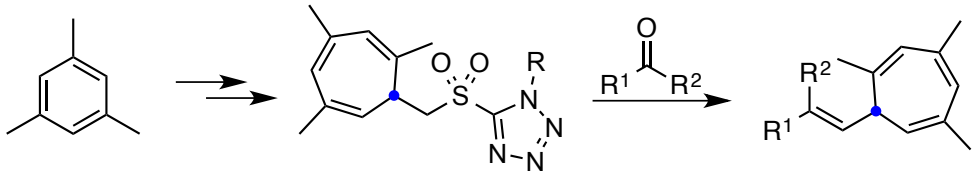
352 Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

Conclusion

The feasibility of performing the gold(I)-catalyzed retro-Buchner reaction at room temperature has been demonstrated for two new cycloheptatriene derivatives. The yield obtained in the gold(I)-catalyzed cyclopropanation reaction was comparable to what was previously reported in *chapter 2*, while the diastereoselectivity was equal or better.



The use 2,3-dimethoxy-7-styrenyl-1,3,5-cycloheptatriene derivatives enables the formation of gold(I) carbenes via the retro-Buchner reaction at room temperature. However, the synthesis of the starting material has several drawbacks, while the gold(I) catalyzed cyclopropanation did not reach full conversion. Alternatively, 7-substituted 1,3,5-trimethyl-1,3,5-cycloheptatriene derivatives seem to be more promising substrates as the methyl groups are chemically more inert, which leads to a more robust synthesis of the Julia-Kocienski reagents.



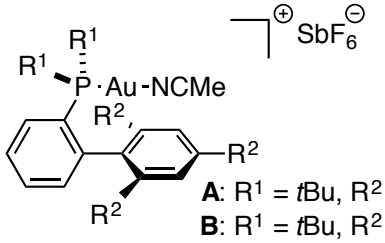
During the course of the investigation, the first transition-metal catalyzed Buchner ring expansion of hexamethylbenzene on a synthetically useful scale was developed.

Experimental section

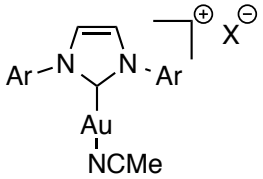
General information

All reactions were carried out under argon in anhydrous solvents obtained by passing them through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA), unless noted otherwise. All gold-catalyzed reactions were performed in HPLC-grade solvents, without a protective atmosphere. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck Gf234). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 °C on Bruker Avance 300, 400 and 500 Ultrashield apparatus. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (*J*) are reported in hertz (Hz).

The following gold complexes were synthesized according to literature procedures.[353]



A: R^1 = *t*Bu, R^2 = H
B: R^1 = *t*Bu, R^2 = *i*Pr
C: R^1 = cyclohexyl, R^2 = H



D: Ar = mesityl, X = SbF_6
E: Ar = 2,6-diisopropylbenzene, X = $BAr^F{}_4$

353 Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.

Ethyl 2,4,6-trimethoxycyclohepta-2,4,6-triene-1-carboxylate (21)

A solution of 1,3,5-trimethoxybenzene (4.0 g, 24.0 mmol, 1 equiv) and $Rh_2(OAc)_4$ (13 mg, 0.03 mmol, 0.25 mol%) in CH_2Cl_2 at room temperature is degassed by bubbling argon through for 30 minutes and ethyl diazoacetate (3.8 mL, 87% in CH_2Cl_2, 28.8 mmol, 1.2 equiv) is added over 4 h. The reaction is left to stir for an additional 10 h before it is evaporated to dryness. Flash chromatography (SiO_2, 10-50% Et2O in pentane) yielded 3.6 g (59%) of a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.53 (d, *J*= 1.7 Hz, 1H), 5.12 (d, *J*= 1.7 Hz, 1H), 4.20 (q, *J*= 7.0 Hz, 2H), 4.14 (dd, *J*= 13.4, 7.1 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.63 (s, 3H), 3.48 (q, *J*= 7.0 Hz, 1H), 1.30 (t, *J*= 7.1 Hz, 2H).

6-(Hydroxymethyl)cycloheptane-1,3,5-trione (22)

Lithium aluminum hydride (474 mg, 12.5 mmol, 1.2 equiv) is added portion wise to a solution of **25** (2.66 g, 10.4 mmol, 1 equiv) in diethyl ether (100 mL) at 0 °C. After stirring for 5 h, the reaction is quenched by the careful addition of water and stirring is continued for another 30 minutes. The mixture is extracted with diethyl ether. Flash chromatography (SiO_2, 20-50% EtOAc in c-hexane) yielded **31** instead of the desired **32**.

^{1}H NMR (300 MHz, Chloroform-d) δ 4.20 (dd, *J*= 8.8, 4.9 Hz, 1H), 4.12 (t, *J*= 7.5 Hz, 1H), 3.82 (d, *J*= 2.0 Hz, 1H), 3.67 (d, *J*= 6.0 Hz, 1H), 3.58 – 3.45 (m, 2H), 3.19 – 3.12 (m, 1H), 2.99 (d, *J*= 18.1 Hz, 1H), 2.78 (d, *J*= 18.2 Hz, 1H), 2.46 – 2.30 (m, 2H).

(2,4,6-Trimethoxycyclohepta-2,4,6-trien-1-yl)methanol (23)

To a solution of **25** (455 µL, 2 mmol, 1 equiv) in dry THF (10 mL) at -78 °C is added DIBAL (6 mL, 1M, 6 mmol, 3 equiv) drop wise. The cooling is removed and stirring is continued for another 12 h before Rochelle salt and EtOAc are added and stirred for another 30 minutes. Extraction followed by flash chromatography (SiO_2, 20-50% EtOAc in c-hexane) yielded 297 mg (70%) of a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.49 – 5.44 (d, 1H), 5.09 (d, *J*= 1.2 Hz, 1H), 4.28 (d, *J*= 4.6 Hz, 2H), 3.71 (s, *J*= 0.5 Hz, 3H), 3.68 (dd, *J*= 7.5, 2.8 Hz, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 1.73 (q, *J*= 4.9 Hz, 1H).

Standard conditions for the Buchner reaction of methoxyarenes

A solution of methoxyarene (24.0 mmol, 1 equiv) and $Rh_2(OAc)_4$ (13 mg, 0.03 mmol, 0.25 mol%) in CH_2Cl_2 at room temperature is degassed by bubbling argon through for 30 minutes and ethyl diazoacetate (3.8 mL, 87% in CH_2Cl_2, 28.8 mmol, 1.2 equiv) is added over 4 h. The reaction is left to stir for an additional 10 h before it is evaporated to dryness.

Ethyl 3,5-dimethoxycyclohepta-1,3,5-triene-1-carboxylate (27a):

From 1,3-dimethoxybenzene 1.61 g (30%) of a colorless oil was obtained by flash chromatography (SiO_2, 10-50% Et_2O in c-hexane)..

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.07 (dd, *J*= 6.7, 2.3 Hz, 1H), 6.45 (dd, *J*= 6.9, 2.3 Hz, 2H), 4.14 (q, *J*= 7.1 Hz, 2H), 3.79 (d, *J*= 3.0 Hz, 6H), 3.54 (s, 2H), 1.24 (t, *J*= 7.1 Hz, 2H).

Ethyl 2,4-dimethoxycyclohepta-2,4,6-triene-1-carboxylate (27b):

From 1,3-dimethoxybenzene 686 mg (13%) of a colorless oil was obtained by flash chromatography (SiO_2, 10-50% Et_2O in c-hexane).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.21 (dd, *J*= 9.4, 6.5 Hz, 1H), 5.60 (dd, *J*= 6.5, 1.6 Hz, 1H), 5.50 (dd, *J*= 9.4, 7.0 Hz, 1H), 5.32 (d, *J*= 1.6 Hz, 1H), 4.23 − 4.16 (m, 2H), 3.64 (s, 3H), 3.62 (s, 3H), 3.38 (d, *J*= 7.0 Hz, 1H), 1.24 (t, *J*= 7.1 Hz, 3H).

Ethyl 3,4-dimethoxybicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (29a):

From 1,2-dimethoxybenzene obtained as a mixture with **29b** and **29c** through distillation (0.2 mbar 230-240 °C); 27% (67% overall) yield estimated by ^{1}H NMR. Data matched that of the literature.[354]

Ethyl 2,3-dimethoxybicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (29b):

From 1,2-dimethoxybenzene obtained as a mixture with **29a** and **29c** through distillation (0.2 mbar 230-240 °C); 20% yield estimated by 1H NMR. Data matched that of the literature.[354]

354 a) Matsumoto, M.; Shiono, T.; Mutoh, H.; Amano, M.; Arimitsu, S. *J. Chem. Soc., Chem. Commun.* **1995**, 101-102. b) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873-876.

Ethyl 2,3-dimethoxycyclohepta-2,4,6-triene-1-carboxylate (29c):

From 1,2-dimethoxybenzene obtained as a mixture with **29a** and **29b** through distillation (0.2 mbar 230-240 °C); 19% yield estimated by 1H NMR. Can be removed from the mixture by subsequent flash chromatography (SiO_2, 30-50% Et2O in c-hexane).

Ethyl 2,3,4-trimethoxycyclohepta-2,4,6-triene-1-carboxylate (31a), ethyl 3,4,5-trimethoxycyclohepta-2,4,6-triene-1-carboxylate (31b), and ethyl 2,3,7-trimethoxycyclohepta-2,4,6-triene-1-carboxylate (31c):

Obtained as a complex mixture of the three products, starting material, and some decomposition product.

GC-MS (ESI)**:** R.T: 7.393 min. MS: calculated: 254.1, found 254.1.

GC-MS (ESI)**:** R.T: 7.375 min. MS: calculated: 254.1, found 254.1.

GC-MS (ESI)**:** R.T: 7.726 min. MS: calculated: 254.1, found 254.1

(2,4-Dimethoxycyclohepta-2,4,6-trien-1-yl)methanol (32)

To a solution of **31b** (670 mg, 3.0 mmol, 1 equiv) in diethyl ether (12 mL) at 0 °C is added lithium aluminum hydride (137 mg, 3.6 mg, 1.2 equiv) portion wise. The mixture is left to stir for an additional 4 h at 0 °C before it is carefully quenched with water and stirred for another 30 minutes. The mixture is extracted with diethyl ether and dried. Flash chromatography (SiO_2, 50% Et_2O in c-hexane) yielded 313 mg (57%) of a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.19 (dd, *J*= 9.5, 6.5 Hz, 1H), 5.61 (dd, *J*= 6.5, 1.7 Hz, 1H), 5.32 (d, *J*= 1.6 Hz, 1H), 5.10 (dd, *J*= 9.5, 6.5 Hz, 1H), 3.93 – 3.76 (m, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 2.69 – 2.58 (m, 1H), 1.96 (t, *J*= 6.5 Hz, 1H).

(4,5-Dimethoxycyclohepta-2,4,6-trien-1-yl)methanol (34a) + (3,4-dimethoxycyclo-hepta-2,4,6-trien-1-yl)methanol (34b)

To a solution of the mixture of **29a** and **29b** (1.45 g, 7.15 mmol, 1 equiv) in diethyl ether (30 mL) at 0 °C is added lithium aluminum hydride (326 mg, 8.6 mmol, 1.2 equiv) portion wise. A solid ball of material forms in the flask and a second portion of diethyl ether (100 mL) is added. The mixture is stirred for an

additional 5 h before water is carefully added. The mixture is extracted and flash chromatography (SiO_2, 30-60% Et_2O in pentane) yields 1.21 g (quantitative) of a colorless oil (3:2 mixture of **34a**/**34b**).

34a: **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 6.21 (d, *J*= 9.6 Hz, 2H), 5.15 (dd, *J*= 9.3, 5.8 Hz, 2H), 3.99 – 3.92 (m, 2H), 3.73 (d, *J*= 0.6 Hz, 6H), 1.83 (qd, *J*= 6.7, 1.4 Hz, 1H).

34b: **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 6.07 (ddd, *J*= 9.3, 6.5, 1.2 Hz, 1H), 5.83 (d, *J*= 6.4 Hz, 1H), 5.42 (dd, *J*= 9.4, 5.4 Hz, 1H), 4.67 (d, *J*= 6.4 Hz, 1H), 3.87 (d, *J*= 4.7 Hz, 2H), 3.73 (s, 3H), 3.63 (s, 3H), 2.30 – 2.18 (m, 1H).

2-(3,4-Dimethoxyphenyl)ethan-1-ol (37)

To a solution of the mixture of **33a** and **33b** (2.0 g, 9.0 mmol, 1 equiv) in dry THF (50 mL) at -78 °C was added DIBAL (27 mL, 1M, 27 mmol, 3 equiv) and the cooling was removed. After stirring for 14 h the mixture was quenched with Rochelle salt and extracted with EtOAc. Flash chromatography (SiO_2, 50-80% EtOAc in c-hexane) yields alcohol **37** instead of the desired **29a** and **29b**. The spectroscopic data matched with the literature.[355]

5-(((3,4-Dimethoxycyclohepta-2,4,6-trien-1-yl)methyl)thio)-1-phenyl-1*H*-tetrazole (38)

To a solution of 2-mercaptophenyl tetrazole (1.16 g, 6.5 mmol), a mixture of **29a** and **29b** (1.06 g, 6.5 mmol, *ca.* 3:2), and triphenylphosphine (1.70 g, 6.5 mmol) in dry THF (26 mL) was added DEAD (2.83 mL, 40%, 6.5 mmol) over 3 h and the reaction was left to stir for an additional 9 h. The mixture was concentrated and flash chromatography (SiO_2, 0-100% Et_2O in c-hexane) yielded 976 mg (44%) of a waxy solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.97 (d, *J*= 7.5 Hz, 1H), 7.60 – 7.53 (m, 4H), 6.82 – 6.73 (m, 1H), 6.16 (d, *J*= 9.9 Hz, 1H), 5.00 (dd, *J*= 9.0, 6.1 Hz, 1H), 3.87 (d, *J*= 1.1 Hz, 2H), 3.73 (s, 6H), 3.71 – 3.61 (m, 2H), 3.09 (t, *J*= 7.6 Hz, 1H).

355 Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362-2366.

5-(((3,4-Dimethoxycyclohepta-2,4,6-trien-1-yl)methyl)sulfonyl)-1-phenyl-1*H*-tetrazole (39)

Thioether **38** (976 mg, 2.85 mmol, 1 equiv) is dissolved in THF (12 mL) and ethanol (20 mL) is added. In another flask, ammonium heptamolybdate (528 mg, 0.43 mmol, 15 mol%) is dissolved in hydrogen peroxide (16 mL, 30%, 36 mmol, 12.5 equiv) and added drop wise to the thioether solution at 0°C. The mixture is left to stir for 14 h before water and CH_2Cl_2 are added and the compounds are extracted. Flash chromatography (SiO_2, 20-40% Et_2O in c-hexane) affords 228 mg (21%) of a white solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.74 – 7.58 (m, 5H), 6.13 – 6.05 (m, 1H), 5.85 (d, *J*= 6.6 Hz, 1H), 5.48 (dd, *J*= 9.4, 6.3 Hz, 1H), 4.74 (d, *J*= 7.5 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H), 3.27 – 3.19 (m, 2H), 2.96 (p, *J*= 7.1 Hz, 1H).

(*E*)-2,3-Dimethoxy-7-styrylcyclohepta-1,3,5-triene (44)

A solution of **41** (114 mg, 0.3 mmol, 1 equiv) in dry THF (2.4 mL) is cooled to -78 °C and a solution of LiHMDS (0.6 mL, 1M, 0.6 mmol, 2 equiv) is added. After stirring for 5 minutes, benzaldehyde (123 µL, 1.2 mmol, 4 equiv) is added and the cooling is removed after 10 minutes. The mixture is stirred for an additional 12 h before water is added and the mixture extracted. Flash chromatography (SiO_2, 0-50% Et_2O in pentane) yielded 25 mg (33%) of a colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.41 (m, 2H), 7.37 – 7.33 (m, 2H), 7.28 – 7.24 (m, 1H), 6.60 – 6.44 (m, 2H), 6.08 (ddd, *J*= 9.3, 6.3, 1.5 Hz, 1H), 5.93 (d, *J*= 6.3 Hz, 1H), 5.55 (dd, *J*= 9.3, 5.5 Hz, 1H), 4.79 (d, *J*= 6.5 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 2.84 – 2.75 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 149.7, 137.4, 131.6, 130.3, 128.6, 127.4, 127.3, 126.2, 122.6, 105.5, 102.3, 55.9, 55.3, 38.2.

GC-MS (ESI)**:** R.T: 9.956 min. MS: calculated: 254.1, found 254.1.

(*E*)-4-(2-Styrylcyclopropyl)-1,1'-biphenyl (46)

An NMR tube is charged with a solution of **44** (12.8 mg, 0.05 mmol, 1 equiv) and 4-vinylbiphenyl (9 mg, 0.05 mmol, 1 equiv) in *d2*-dichloromethane (5 mL). To the mixture was added [(JohnPhos)Au(MeCN)]SbF_6 (1.9 mg, 2.5 µmol, 5 mol%)

and the tube is left standing at 26 °C while measurements are taken 4 h. The reaction stops after 14 h and the conversion is estimated to be 50% by ^{1}H NMR. The spectroscopic data matches that of what is reported in *chapter 2*.

Ethyl 2,3,4,5,6,7-hexamethylcyclohepta-2,4,6-triene-1-carboxylate (49)

small scale: A solution of hexamethylbenzene (514 mg, 3.0 mmol, 2 equiv) and $Rh_2(TFA)_4$ (9.9 mg, 0.015 mmol, 1.0 mol%) in CH_2Cl_2 (10 mL) at room temperature is degassed by bubbling argon through for 30 minutes and ethyl diazoacetate (200 µL, 87% in CH_2Cl_2, 1.5 mmol, 1.0 equiv) is added over 4 h. The reaction is left to stir for an additional 4 h before it is evaporated to dryness. Flash chromatography (SiO_2, 10-50% Et2O in pentane) yielded 102 mg (27%) of a colorless oil.

Larger scale: A solution of hexamethylbenzene (1.0 g, 6.2 mmol, 1 equiv) and $Rh_2(TFA)_4$ (40 mg, 0.062 mmol, 1.0 mol%) in CH_2Cl_2 (10 mL) at room temperature is degassed by bubbling argon through for 30 minutes and ethyl diazoacetate (1.6 mL, 87% in CH_2Cl_2, 12.3 mmol, 2.0 equiv) is added over 4 h. The reaction is left to stir for an additional 4 h before it is evaporated to dryness. Flash chromatography (SiO_2, 10-50% Et2O in pentane) yielded 291 mg (19%) of a colorless oil. The spectroscopic data matches that of the literature.[356]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.28 (q, *J*= 7.1 Hz, 2H), 3.24 (s, 1H), 1.95 (d, *J*= 0.9 Hz, 6H), 1.79 (s, 6H), 1.78 (d, *J*= 1.0 Hz, 6H), 1.34 (t, *J*= 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 133.6, 129.1, 128.2, 60.0, 57.4, 21.4, 16.8, 16.4, 14.3.

GC-MS (ESI)**:** R.T: 6.869 min. MS: calculated: 248.2, found 248.1.

(2,3,4,5,6,7-Hexamethylcyclohepta-2,4,6-trien-1-yl)methanol (50)

To a solution of the mixture of **49** (270 mg, 1.1 mmol, 1 equiv) in dry THF (5.5 mL) at -78 °C was added DIBAL (3.3 mL, 1M, 3.3 mmol, 3 equiv) and the cooling was removed. After stirring for 6 h the mixture was quenched with Rochelle salt and extracted with EtOAc. Flash chromatography (SiO_2, 50-80% EtOAc in c-

356 a) Knoche, H. *Chem. Ber.* **1966**, *99*, 1097-1105. b) Komine, N.; Flores, J. A.; Pal, K.; Caulton, K. G.; Mindiola, D. J. *Organometallics* **2013**, *32*, 3185-3191.

hexane) yielded 161 mg (72%) of a colorless oil. No spectroscopic data has been reported for this compound.[356a]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.05 (d, *J*= 8.1 Hz, 2H), 2.10 (t, *J*= 8.0 Hz, 1H), 1.95 (s, 6H), 1.77 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 128.4, 128.1, 62.1, 48.3, 17.7, 15.9, 14.1.

GC-MS (ESI)**:** R.T: 10.262 min. MS: calculated: 206.3, found 207.0.

Standard conditions for the Buchner reaction of poly-methylarenes

A solution of poly-methylarene (1.0 mmol, 1 equiv) and $Rh_2(OAc)_4$ (22 mg, 0.05 mmol, 5 mol%) in CH_2Cl_2 (4 mL) at room temperature is degassed by bubbling argon through for 30 minutes and ethyl diazoacetate (260 μL, 87% in CH_2Cl_2, 2 mmol, 2 equiv) is added over 3 h. The reaction is left to stir for an additional 10 h before it is evaporated to dryness. The mixture is filtered and the yield estimated by ^{1}H NMR spectroscopy of the crude.

Ethyl 2,4,6-trimethylcyclohepta-2,4,6-triene-1-carboxylate (58)

A solution of mesitylene (500 mg, 4.16 mmol, 1 equiv) and $Rh_2(TFA)_4$ (136 mg, 0.21 mmol, 5 mol%) in CH_2Cl_2 (17 mL) at room temperature is degassed by bubbling argon through for 30 minutes and ethyl diazoacetate (532 μL, 87% in CH_2Cl_2, 8.3 mmol, 2 equiv) is added over 3 h. The reaction is left to stir for an additional 10 h before it is evaporated to dryness. Flash chromatography (SiO_2, 10-50% Et2O in pentane) yields 506 mg (59%) of a colorless oil. The spectroscopic data matches that of the literature.[357]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.25 (d, *J*= 1.9 Hz, 1H), 5.85 (t, *J*= 1.5 Hz, 1H), 5.38 (d, *J*= 6.5 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.02 (d, *J*= 1.3 Hz, 3H), 1.93 (d, *J*= 1.4 Hz, 3H), 1.90 (t, *J*= 1.1 Hz, 3H), 1.31 (t, *J*= 7.1 Hz, 3H).

(2,4,6-Trimethylcyclohepta-2,4,6-trien-1-yl)methanol (59)

To a solution of the mixture of **58** (154 mg, 0.74 mmol, 1 equiv) in diethyl ether (13 mL) at 0 °C is added lithium aluminum hydride (67 mg, 0.96 mmol, 1.3

357 Komine, N.; Flores, J. A.; Pal, K.; Caulton, K. G.; Mindiola, D. J. *Organometallics* **2013**, *32*, 3185-3191.

equiv) at once. The mixture is stirred for an additional 12 h whilst warming to room temperature before water is carefully added. The mixture is extracted and flash chromatography (SiO_2, 10-60% Et_2O in pentane) yielded 107 mg (88%) of a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.16 (d, *J*= 2.0 Hz, 1H), 5.87 – 5.84 (m, 1H), 5.02 (d, *J*= 7.3 Hz, 1H), 3.73 – 3.67 (m, 2H), 2.53 (q, *J*= 7.7 Hz, 1H), 2.00 (d, *J*= 1.6 Hz, 3H), 1.99 (d, *J*= 1.4 Hz, 3H), 1.89 (d, *J*= 1.3 Hz, 3H).

1-Phenyl-5-(((2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methyl)thio)-1*H*-tetrazole (60)

To a solution of 2-mercaptophenyl tetrazole (151 mg, 0.85 mmol), **59** (138 mg, 0.85 mmol,), and triphenylphosphine (224 mg, 0.85 mmol) in dry THF (3.5 mL) was added DEAD (385 µL, 40%, 0.85 mmol) over 3 h and the reaction was left to stir for an additional 9 h. The mixture was concentrated and flash chromatography (SiO_2, 5% Et_2O in c-hexane) yielded 86 mg (31%) of a colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.54 (m, 5H), 6.18 (d, *J*= 1.7 Hz, 1H), 5.89 (s, 1H), 5.16 (d, *J*= 7.9 Hz, 1H), 3.50 – 3.39 (m, 2H), 2.96 (q, *J*= 8.0 Hz, 1H), 2.01 (d, *J*= 1.4 Hz, 3H), 2.00 (d, *J*= 1.3 Hz, 3H), 1.89 (d, *J*= 1.3 Hz, 3H).

1-Phenyl-5-(((2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methyl)sulfonyl)-1*H*-tetrazole (61)

Thioether **60** (86 mg, 0.26 mmol, 1 equiv) is dissolved in THF (1 mL) and ethanol (2 mL) is added. In another flask, ammonium heptamolybdate (49 mg, 0.04 mmol, 15 mol%) is dissolved in hydrogen peroxide (1 mL, 30%, 2.2 mmol, 12.5 equiv) and added drop wise to the thioether solution at 0°C. The mixture is left to stir for 14 h before water and CH_2Cl_2 are added and the compounds are extracted. Flash chromatography (SiO_2, 5% Et_2O in c-hexane) affords 47 mg (49%) of a white solid.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 – 7.59 (m, 5H), 6.20 (s, 1H), 5.87 (d, *J*= 1.8 Hz, 1H), 5.15 (d, *J*= 8.4 Hz, 1H), 3.78 – 3.68 (m, 2H), 3.43 – 3.32 (m, 1H), 2.01 (s, 6H), 1.83 (d, *J*= 1.3 Hz, 3H).

(*E*)-1,3,5-Trimethyl-7-styrylcyclohepta-1,3,5-triene (62)

A solution of **61** (45 mg, 0.13 mmol, 1 equiv) in dry THF (0.6 mL) is cooled to -78 °C and a solution of LiHMDS (25 µL, 1M, 0.6 mmol, 1 equiv) is added. After stirring for 5 minutes, benzaldehyde (16 µL, 1.2 mmol, 2 equiv) is added and the cooling is removed after 10 minutes. The mixture is stirred for an additional 12 h before water is added and the mixture extracted. Flash chromatography (SiO_2, pentane) yielded 22 mg (70%) of a colorless oil.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 4H), 7.25 – 7.19 (m, 1H), 6.44 (d, *J*= 1.9 Hz, 1H), 6.42 (s, 1H), 6.23 (d, *J*= 1.7 Hz, 1H), 5.85 – 5.80 (m, 1H), 5.09 (d, *J*= 6.7 Hz, 1H), 2.86 – 2.79 (m, 1H), 2.03 (d, *J*= 1.3 Hz, 3H), 1.98 (d, *J*= 1.4 Hz, 3H), 1.90 (t, *J*= 1.0 Hz, 3H).

(*E*)-1-Methyl-3-(2-styrylcyclopropyl)benzene (63)

To a mixture of **62** (5.0 mg, 2.1 µmol, 1 equiv) and 3-methylstyrene (4 µL, 3.2 µmol, 1.5 equiv) in EtOAc (0.1 mL) was added [(JohnPhos)Au(MeCN)]SbF_6 (0.8 mg, 0.1 µmol, 5 mol%) and the mixture was stirred at 24 °C for 24 h. Flash chromatography (SiO_2, pentane) yielded 3.3 mg (68%) of a colorless oil. The spectroscopic data matches that of what is reported in *chapter 2*.

General Conclusions

A variety of dibenzonorcaradiene derivatives have been synthesized as cycloheptatriene surrogates in the attempt to facilitate the gold(I)-catalyzed retro-Buchner reaction. Derivatives can be obtained through functionalization of a common 1,1-dibromo intermediate, or through an intramolecular cyclopropanation reaction. However, the dibenzonorcaradienes did not offer an advantage over the existing cycloheptatriene derivatives in terms of reactivity, as the alkyl-substituted derivatives were unreactive, and the aryl substituted derivatives only led to modest yields. The challenging formation of 1-phenyl dibenzonorcaradiene has been achieved through a nickel-catalyzed Stille coupling. However, only the *exo*-isomer was obtained, which might be too sterically encumbered for gold to efficiently undergo the retro-Buchner reaction. Nevertheless, the synthetic approach towards the derivatives and the compounds themselves could offer an interesting entry in the light-mediated carbene formation.

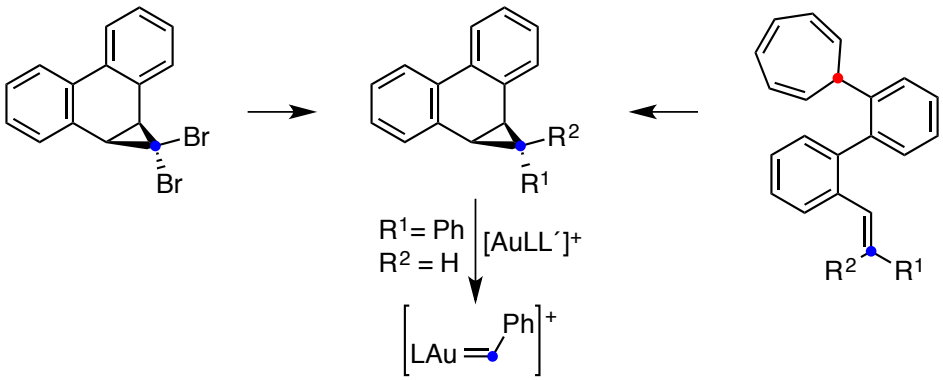


Figure 49. Synthesis of dibenzonorcaradiene derivatives and formation of gold(I) carbenes.

Vinyl gold(I) carbenes on the other hand are efficiently formed at 75 °C by the retro-Buchner reaction. The subsequent cyclopropanation takes place with excellent diastereoselectivity for aryl alkenes to form aryl-vinylcyclopropanes, while the selectivity in the formation of vinyl-aminocyclopropanes is lower. A Julia-Kocienski reagent was developed to obtain the required 7-alkenyl cycloheptatriene derivatives in a single step from readily available aldehydes and ketones.

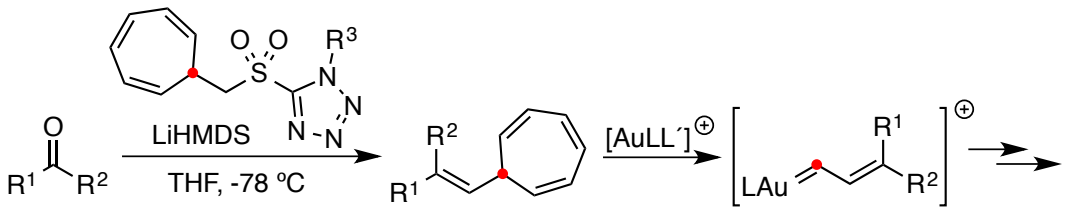


Figure 50. Synthesis of 7-alkenyl cycloheptatriene derivatives from aldehydes or ketones for the formation of allylic gold(I) carbenes via the retro-Buchner reaction.

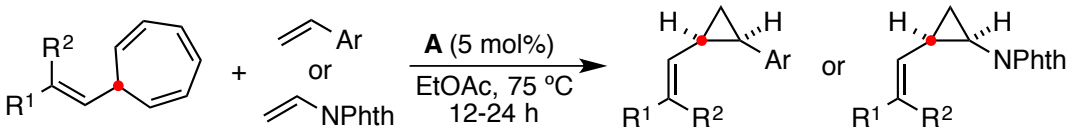


Figure 51. Stereoselective *cis*-vinylcyclopropanation via a gold(I)-catalyzed retro-Buchner reaction under mild conditions.

The mechanism for the retro-Buchner reaction for the formation of allylic gold(I) carbenes was investigated experimentally and computationally. In agreement with previous work, the first C-C bond cleavage of norcaradiene was found to be the rate-determining step and the calculated values are in close agreement with the experimental ones. An elaborated stereochemical model for the cyclopropanation could be generated where stabilizing π-π interactions in the *cis*-transition state lead to the excellent *cis*-selectivity of the reaction. In addition, the mechanism of an unprecedented gold(I)-mediated cyclopropane isomerization was elucidated, where a cationic structure is formed through opening of the cyclopropane by gold(I).

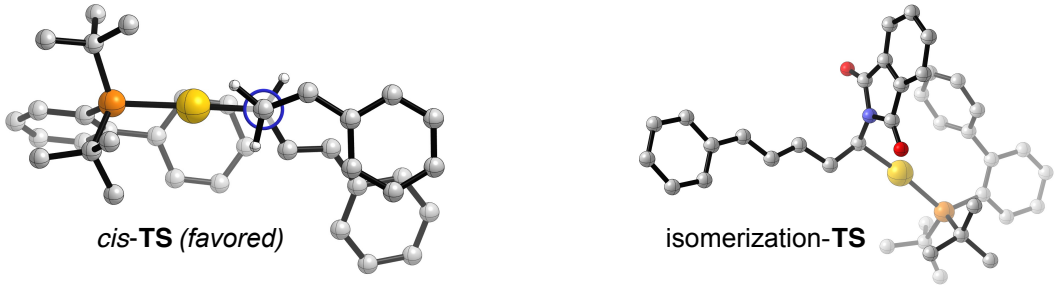


Figure 52. Transition state leading to the *cis*-product stabilized by π-π interactions (left), linear cationic transition state for the gold(I) catalyzed cyclopropane isomerization (right).

Although the barriers of the retro-Buchner reaction for copper(I) and silver(I) complexes were calculated to be very similar in energy to the barrier for gold(I), the formation of copper(I) or silver(I) carbenes from cycloheptatriene derivatives was not observed.

Based on the new mechanistic understanding and the synthetic strategy to obtain 7-alkenyl cycloheptatriene derivatives, two new classes of cycloheptatriene derivatives were developed as carbene precursors, bearing additional electron-donating groups. Although the results should still be considered preliminary, the gold(I)-catalyzed retro-Buchner reaction and subsequent cyclopropanation took place at 24 – 26 °C. Especially the 7-alkenyl-1,3,5-trimethyl-1,3,5-cycloheptatriene reagents derived from mesitylene can be considered an important increment, as the reaction took place with nearly identical results as previously obtained.

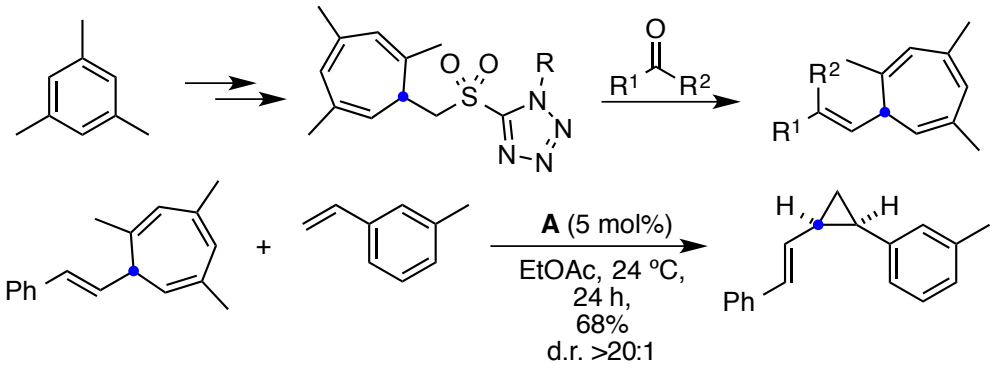


Figure 53. Synthesis of trimethyl-cycloheptatriene derivatives with the Julia-Kocienski strategy (top), and the room-temperature gold(I)-catalyzed retro-Buchner and cyclopropanation reaction (bottom).

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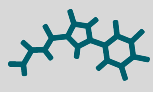

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Stereoselective Cyclopropanations via Gold(I)-Catalyzed Retro-Buchner Reactions

Bart Herlé