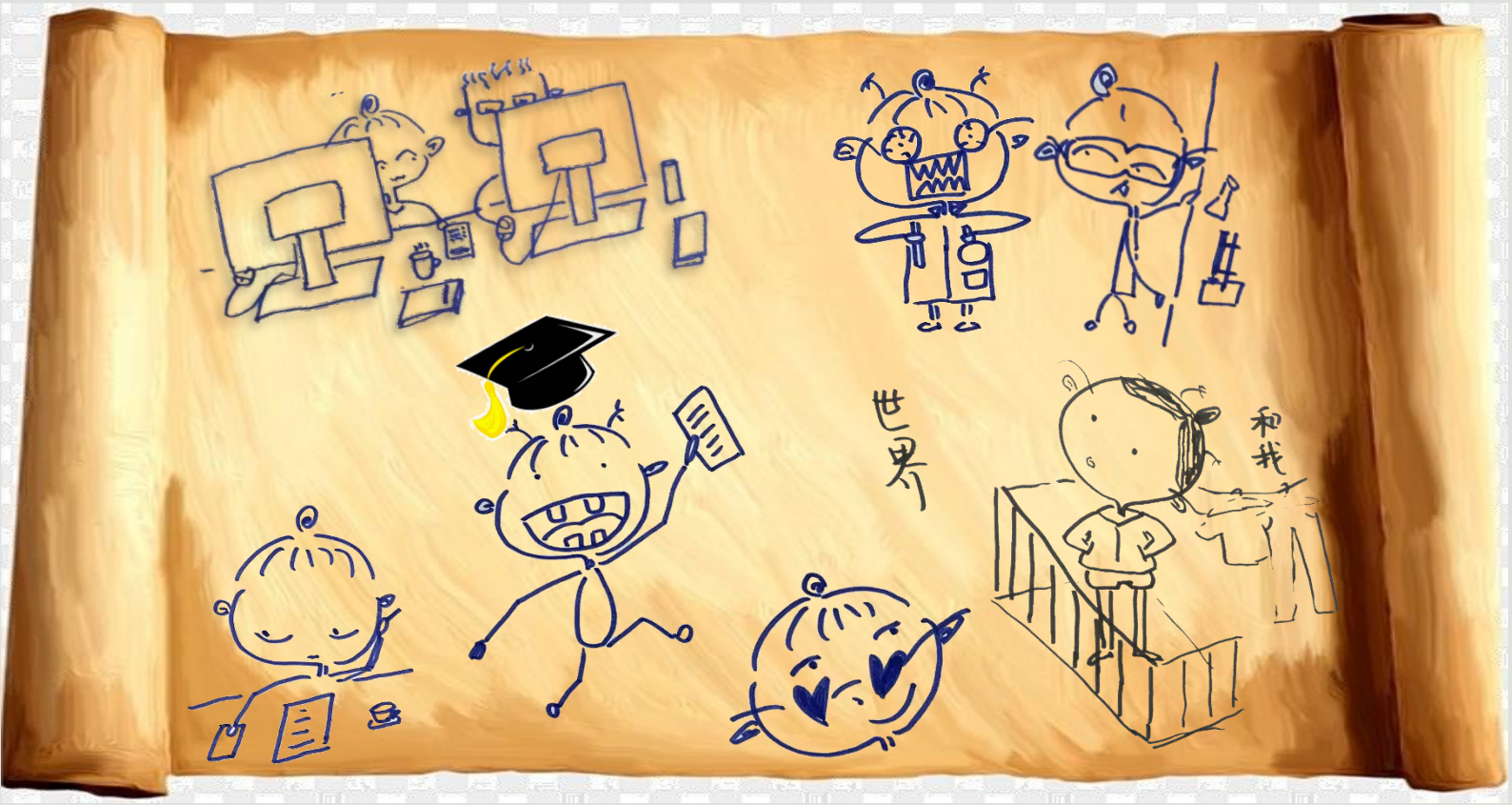
CATALYTIC FORMATION OF HETEROCYCLES FROM - AND -EPOXY ALCOHOLS

Chang Qiao

UNIVERSITAT ROVIRA i VIRGILI

Catalytic Formation of Heterocycles from α- and β-Epoxy Alcohols

CHANG QIAO



DOCTORAL THESIS

2022

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PhD Thesis

"Catalytic Formation of Heterocycles from α- and β-Epoxy Alcohols"

Chang Qiao

Supervised by Prof. Dr. Arjan W. Kleij

Tarragona

June 2022

UNIVERSITAT ROVIRA I VIRGILI
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Prof. Dr. Arjan W. Kleij, Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor at the Catalan Institution for Research and Advanced Studies (ICREA):

I STATE that the present Doctoral Thesis, entitled "**Catalytic Formation of Heterocycles from α- and β-Epoxy Alcohols**" presented by Chang Qiao to receive the degree of Doctor, has been carried out under my supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, June 2022

Doctoral Thesis Supervisor

Prof. Dr. Arjan W. Kleij

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CATALYTIC FORMATION OF HETEROCYCLES FROM - AND -EPOXY ALCOHOLS
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Curriculum Vitae

Chang Qiao was born on June 6 in 1992 in Hebei, China. She obtained her BSc degree in July 2015 at Langfang Normal University, majoring in chemistry. Then she started her MSc degree in the State Key Laboratory of Elemento-Organic Chemistry (SKLEOC, Nankai University, Tianjin), under the supervision of Prof. Liangnian He, during which she was working on carboxylic acids as alkylating agents in coupling reactions with different nucleophiles. In July 2018, she obtained her MSc degree and then she joined the Institute of Chemical Research of Catalonia (ICIQ, Tarragona) to pursue her doctoral studies under the supervision of Prof. Arjan W. Kleij. Her PhD research was financially supported by Chinese Scholarship Council (CSC). and focused on the catalytic formation of heterocycles from α- and β-epoxy, and these results are presented in this thesis. Part of this PhD research was communicated as a poster and oral presentation at the 14th CaRLa Winter School in Heidelberg in 2022, and at the 5th International Symposium on Green Chemistry in La Rochelle in 2022.

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Acknowledgments

Every year when June arrives, I feel that this month comes faster than the others. Especially this year, as I am about to turn 30 years old, I feel that youth is passing away so easily. Fortunately, this June not only brings me my 30th birthday, but also my doctorate degree, which makes me less sad and more grateful. This is a very special moment for me to look back and think over my 11 years of chemistry-related experience. Today, let´s just focus on my Ph.D. I would like to take this precious opportunity to express my deepest gratitude to those who gave me all the support over the last four years.

First and foremost, I would like to thank Prof. **Arjan Kleij** for giving me the opportunity to join his group. I first met Arjan in Shanghai at a conference (2017), and at that time I noticed how much he liked to talk about chemistry. Shortly after, Arjan gave a speech at my university in Tianjin, where I had the opportunity to talk with him in person. However, what attracted my attention was that he mentioned he had a handsome son who did not have a girlfriend. One year later (2018), when I arrived in Tarragona for my PhD, I found out his son was only 12. So, I had to devote all my passion and energy to Mr. Chemistry instead. During the past four years, my relationship with Mr. Chemistry provoked several difficult moments. Arjan's patience, optimism, kindness and faith always cheered me up and encouraged me to conquer these difficulties. And undoubtedly, these moments will always be a guide to me for the near and distant future.

I think my whole Ph.D. career can be divided into two parts, pre-pandemic time and during the pandemic time. **José Enrique Gómez (Kike)**, **Aijie Cai**, **Jianing Xie**, **Sijing Xue**, **Àlex Cristòfol**, **Cristina Maquilón**, **Josefine Sprachmann**, **Alèria García**, **Francesco Della Monica and Nicola Zanda**. I really appreciate I spent time with you guys without COVID and masks. The food we ate, the beer we drank and the games we played together are my cherished memories and the happiest time I had in Tarragona. I would particularly like to thank my co-authors **Alba Villar**, **Josefine Sprachmann**, **Arianna Brandolese**, **Diego Garay-Ruiz**, **Jordi Benet-Buchholz**, **Carles Bo**, **Eduardo C. Escudero-Adán** and **Wangyu Shi**. Their substantial contributions to the work presented in this thesis is really appreciated. During the pandemic time, we all had hard times, and I want to thank **Sijing**, **Cristina**, **Alèria** and **Qian** for not only being my colleagues but also friends, who stood by me and let me know I am not alone. **Jianing**, we have known each other since we were in China, thank you for introducing Arjan and ICIQ to me. You provided me with this opportunity, helped me fit in the lab when I

started my Ph.D. abroad, and I appreciated all the help and knowledge you transferred to me. **Sijing**, the moment when I eavesdropped on your talking to someone about you just having learned how to make a cake, I made my decision to be your friend. The next three years, you brought me three cakes, more and more like a car accident scene than the other, but I never regret my decision. After you finished your Ph.D. and left, I learned to make glorious cakes by myself. This change made me deeply realize that my own happiness depends on me. Being trustable and reliable friends to each other is the luck of my life.

I would like to express my gratitude to the ICIQ's IT department, human resources unit, maintenance unit, SHEQ unit and research support units. Especially, I would like to express my gratitude to **Gabriel**, **Israel** and **Germán** from the NMR unit for helping me with the NMR analyses; **Jordi** from the X-ray unit for being patient with my elusive molecules, and **Noemí** from the Mass unit. Many thanks to our secretaries/administrative support including **Ingrid, Núria, Eva, Elena** and **Cristina**. There are also lots of people who helped me during my Ph.D. who I did not mention yet. I would like to give them my sincere gratitude. I could not have done it without your help.

I would like to express my gratitude for the financial support from the CSC (China Scholarship Council), as well as the meticulous work of the education group in Spain. With your kind support, for the first time in my life, I have lived a financially independent life.

Last but not least, I would like to express my deepest gratitude to my family for all their love and encouragement. Especially, to my parents, 你们家产的年纪已经不小了的小妖精就要带着她的博士学位回来了 (you homemade, not little mischievous darling is coming back with her doctorate).

The experience of living in Spain and working at ICIQ is a precious fortune that I will carry for my entire life. Although the 30-year-old thing will still be difficult for me to accept for a while, the successful experience I have had here allows me to be calmer in my life in the future.

Chang, 2022

List of Publications

The results described in this doctoral thesis are based on the following publications:

- **C. Qiao**, A. Villar-Yanez, J. Sprachmann, B. Limburg, C. Bo, A. W. Kleij, *Angew. Chem. Int. Ed*. **2020**, *59*, 18446–18451.
- **C. Qiao**, W. Shi, A. Brandolese, J. Benet-Buchholz, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed*. **2022**, *61*, e202205053.
- **C. Qiao**, A. Villar-Yanez, D. Garay-Ruiz, J. B. Buchholz, C. Bo, A. W. Kleij, *ACS. Catal.* **2022**, *12*, 5464–5469.

Other contribution during the Ph.D:

- J. Xie, **C. Qiao**, M. Martínez Belmonte, E. C. Escudero-Adán, A. W. Kleij, *ChemSusChem* **2019**, *12*, 3152-3158.

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List of Abbreviations

In this doctoral thesis, the abbreviations and acronyms most commonly used in organic chemistry are based on the recommendations of the ACS "Guidelines for authors" which can be found and consulted at *https://www.cas.org/support/documentation/references/cas-standard-abbreviations#listinga*.

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Chapter 1.

Introduction

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1.1 Epoxides

1.1.1 Structure and properties

Cyclic ethers with a three-membered ring are known as epoxides or oxiranes. The large family of ethers comprise of both cyclic and acyclic members with the latter being typically stable and difficult to activate. Epoxides are, however, easily activated and constitute therefore useful intermediates in synthetic chemistry. What makes epoxides so reactive and interesting? The bond angles in oxiranes are about 60°. This contrast with the "ideal" bond angle of 109.5° for tetrahedral carbon centers, and the severe ring strain present in an epoxide ring (about 13 kcal/mol) provides a thermodynamic driving force for their ring-opening (Figure 1.1) usually promoted by nucleophiles.[1]

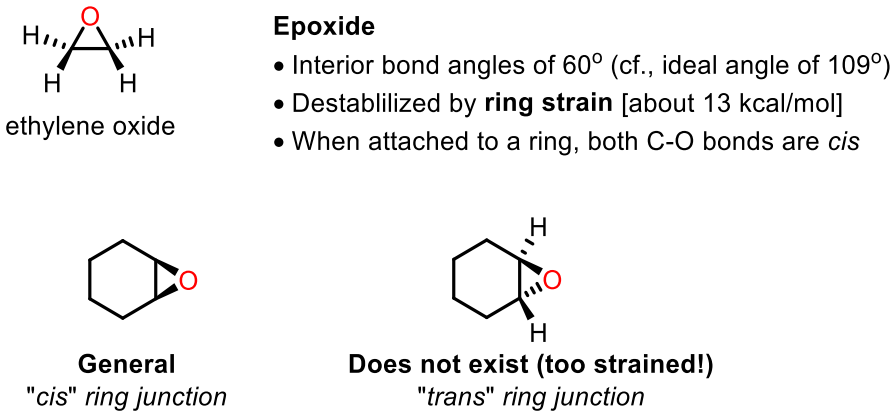

Figure 1.1 Epoxide ring strain and stereochemistry.

1.1.2 Epoxide utilization

The most commonly prepared epoxides in industry are ethylene oxide and propylene oxide. These are produced on a scale of 30[2] and 130[3] million tons (2019), respectively, and are used as precursors for many consumer products as well as non-consumer chemicals and intermediates. The epoxide-derived products include detergents, thickeners, solvents, plastics, and various organic chemicals such as ethylene glycol, ethanol amines, simple and complex glycols, polyglycol ethers, and other compounds.[4] In organic synthesis, research mainly

[1] The image has been extracted from: https://www.masterorganicchemistry.com/2015/01/26/.
[2] https://www.statista.com/statistics/1245260/ethylene-oxide-market-volume-worldwide/.
[3] https://www.statista.com/statistics/1065879/global-propylene-production-capacity/.
[4] Rebsdat, S.; Mayer, D. Ethylene Oxide. In *Ullmann's Encyclopedia of Industrial Chemistry*.

focuses on ring-opening polymerization[5] and nucleophilic ring-opening of the strained oxirane with the most widely studied nucleophiles being water,[6] alcohols,[7] amines,[8] halides and several types of carbanions.[9]

Vinyl epoxides, a sub-class of oxiranes, are unique building blocks with rich functionalization chemistry. The strained oxirane is a reactive moiety itself, and the combination of a proximal carbon−carbon double bond allows to take advantage over the conjugated nature of these two functional groups. In addition to the specific properties of each of these two functional groups, vinyl epoxides also participate in various metal-mediated reactions acting as an allylic surrogate.[10]

1.1.3 Epoxy alcohols

Epoxy alcohols also have two different functional groups, and combine both a nucleophilic and electrophilic site in their molecular structure. Unlike vinyl epoxides, these two groups can have different relative positions such as in α-epoxy, β-epoxy and γ-epoxy alcohols. The relatively positioning of the functional groups may alter their reactivity and control the chemo-selective formation of a particular product (*vide infra*).

One well-known example of epoxy alcohol versatility is the Payne rearrangement/isomerization under basic conditions of 2,3-epoxy alcohols (i.e., α-epoxy alcohols) to isomeric 1,2-epoxy alcohols with inversion of configuration (Scheme 1.1).[11] The difference in thermodynamic stability between the two epoxide isomers and the kinetic differences associated with their trapping offer synthetic to obtain a single isomer in good yields.[12] However, unlike α-epoxy alcohols, β-epoxy alcohols and higher homologues had been rarely studied until 2016 (see section **1.3.1.2**).

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[5] A. L. Brocas, C. Mantzaridis, D. Tunc, S. Carlotti, *Prog. Polym. Sci.* **2013**, *38*, 845–873; (b) O. Nuyken, S. D. Pask, *Polymers* **2013**, *5*, 361–403; (c) Y. Sarazin, J. F. Carpentier, *Chem. Rev.* **2015**, *115*, 3564–3614.

[6] L. P. C. Nielsen, C. P. Stevenson, D. G. Blackmond, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362.

[7] G. D. Yadav, S. Singh, *Tetrahedron Lett.* **2014**, *55*, 3979–3983.

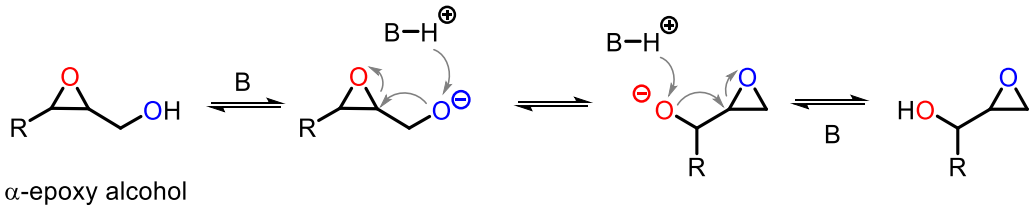
[8] F. A. Saddique, A. F. Zahoor, S. Faiz, S. A. R. Naqvi, M. Usman, Ahmad, M. *Synth. Commun.* **2016**, *46*, 831–868.

[9] S. Gil, M. Torres, N. Ortúzar, R. Wincewicz, M. Parra, *Eur. J. Org. Chem.* **2004**, 2160–2165.

[10] J. He, J. Ling, P. Chiu, *Chem. Rev.* **2014**, *114*, 8037–8128.

[11] G. B. Payne, *J. Org. Chem.* **1962**, *27*, 3819–3822.

[12] R. M. Hanson, Epoxide Migration (Payne Rearrangement) and Related Reactions. In *Organic Reactions*; pp 1–156.



Scheme 1.1 Payne rearrangement of α-epoxy alcohols. B stands for a base.

1.2 Carbon dioxide

Photosynthesis is a process used by plants and other organisms to convert light energy into chemical energy that, through cellular respiration, is later released as fuel in organisms to power activities. Some of this chemical energy is stored in carbohydrate molecules, such as sugars and starches, which are synthesized from carbon dioxide and water – hence the name photosynthesis.[13] For a long time, photosynthesis was regarded as an important bridge connecting the inorganic and organic worlds, and it provided the material basis for the development of human civilization. Carbon dioxide as a raw material for photosynthesis undoubtedly has an important impact on human life. However, with the dramatic rise in atmospheric carbon dioxide levels in the recent decades, carbon dioxide emissions have become synonymous to climate change, expressed as sea-level rise, the melting of glaciers and ice shelves, desertification and increasingly frequent severe climate extremes. According to Mauna Loa Observatory's records (that started in 1960), the atmospheric carbon dioxide level has risen from 316 to 416 ppm (on February 2022) in the past 62 years,[14] while over the past 800.000 years, this number never exceeded 300 ppm (Figure 1.2).[15]

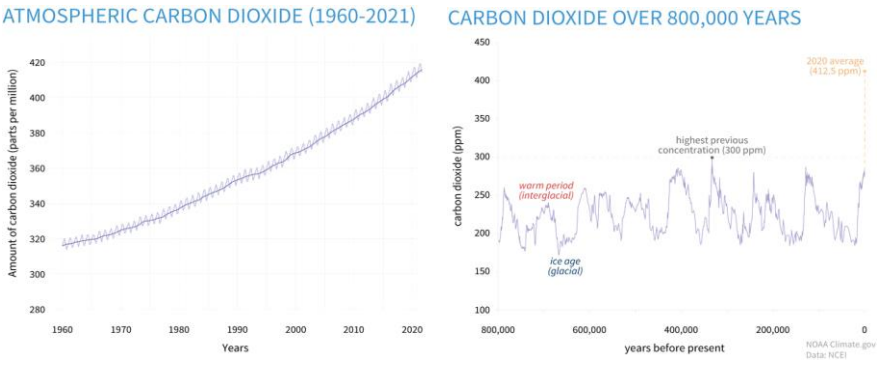


Figure 1.2 Evolution of the concentration of carbon dioxide present in the atmosphere.

[13] See: https://en.wikipedia.org/wiki/Photosynthesis.
[14] Global Monitoring Laboratory: https://gml.noaa.gov/ccgg/.
[15] The image has been extracted from: https://www.climate.gov/.

Unlike society who regards CO_2 as a greenhouse gas and a main cause of climate change, contemporary chemists consider CO_2 as a nontoxic, feasible, and sustainable C1 resource.[16] Currently, there are two available approaches to process waste carbon dioxide beside emitting it to the atmosphere: carbon capture and storage (CCS) and carbon capture and utilization (CCU).[17] Especially, in CCU carbon dioxide is not treated as waste, but as a valuable resource for the chemical or biological synthesis of commercially important chemicals and fuels (Figure 1.3).

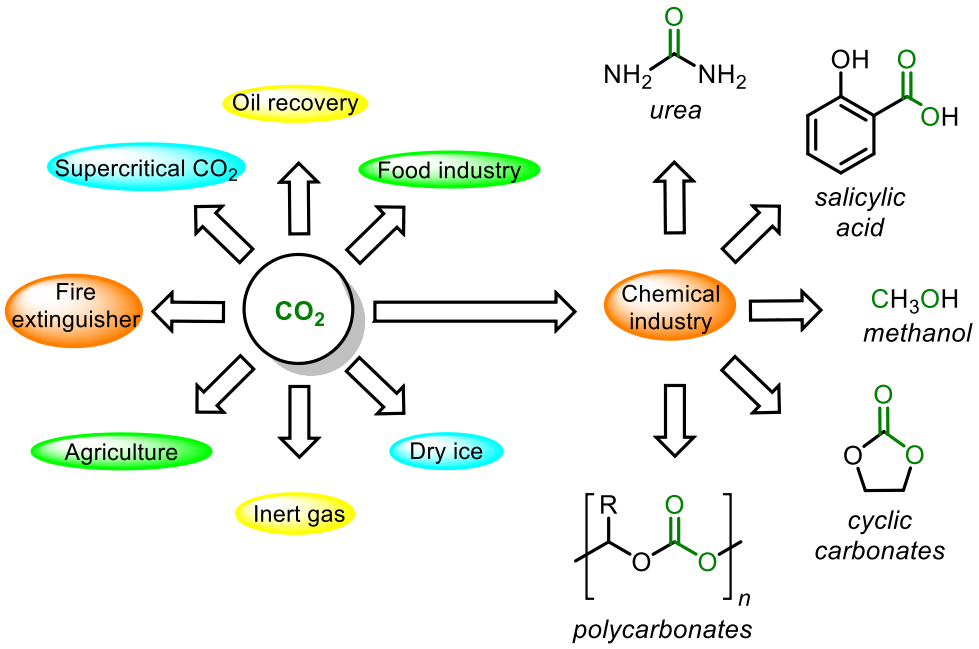


Figure 1.3 Utilization of CO_2 in a variety of applications.

Up to now, several strategies have been developed to overcome both the thermodynamic stability and kinetic inertness of CO_2. It is common knowledge that CO_2 is a non-polar molecule with a delocalized π bond containing three centers and four electrons, which stabilizes the CO_2 molecule. To realize CO_2 transformations, the utilization of high-energy substrates[18] such as organometallic reagents and strained cyclic ethers is a productive approach, while the addition of high-energy additives to trigger the reaction and provide energy for a catalytic cycle

[16] (a) A. Mustafa, B. G. Lougou, Y. Shuai, Z. Wang, H. Tan, *J. Energy Chem.* **2020**, *49*, 96–123; (b) S. Valluri, V. Claremboux, S. Kawatra, *J. Environ. Sci.* **2022**, *113*, 322–344.
[17] (a) S. Valluri, V. Claremboux, S. Kawatra, *J. Environ. Sci.* **2022**, *113*, 322–344; (b) F. M. Baena-Moreno, M. Rodríguez-Galán, F. Vega, B. Alonso-Fariñas, L. F. V. Arenas, B. Navarrete, *Energy Sources, Part A Recover. Util. Environ. Eff.* **2019**, *41*, 1403–1433.
[18] A. K. Yudin, *Aziridines and Epoxides in Organic Synthesis*; Wiley, **2006**.

is also effective. Moreover, the use of catalysts[19] that activate CO_2 or its reaction partners and accelerate the reaction by lowering the activation barrier of the process is key to achieve favorable kinetics.

1.3 Heterocyclic compounds

Heterocyclic compounds are cyclic organic compounds that contain at least one hetero atom, and the most common heteroatoms are nitrogen, oxygen and sulfur but heterocyclic rings containing other heteroatoms are also widely known.[20] A variety of well-known life-related biological compounds such as DNA and RNA, chlorophyll, hemoglobin, vitamins and many others contain a heterocyclic ring in their skeleton. Therefore, heterocyclic compounds are considered to play a major role in medicinal chemistry and biochemistry.[21] According to the database analysis of U.S. FDA-approved drugs, 59% of unique small-molecule drugs contain a nitrogen heterocycle.[22] In addition, compounds derived from heterocyclic rings have also been widely applied in agriculture, plastic production, new polymer developments and in other fields.[23] Considering the content and focus of this doctoral thesis, two oxygen-containing heterocyclic compounds will be introduced in more detail (vide infra).

1.3.1 CO_2-based cyclic carbonates

1.3.1.1 Synthesis of cyclic carbonates from CO_2 and epoxides

Cyclic carbonates are valuable heterocycles and have been widely applied as polar aprotic solvents, electrolytes in batteries, monomers in the preparation of polycarbonates and as intermediates in the manufacture of fine chemicals.[24] Currently, the most common and

[19] (a) T. Sakakura, J.-C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365–2387; (b) Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933; (c) J. Artz, T. E. Müller, K. Thenert, J. Kleinekorte, R. Meys, A. Sternberg, A. Bardow, W. Leitner, *Chem. Rev.* **2018**, *118*, 434–504.

[20] (a) T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*; Wiley, **2013**; (b) J. A. Joule, K. Mills, *Heterocyclic Chemistry At A Glance*; Wiley, **2012**; (c) V. A. Petrov, *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Wiley, **2009**.

[21] (a) Q. Jin, X. Wang, S. Li, H. Mikulčić, T. Bešenić, S. Deng, M. Vujanović, H. Tan, B. M. Kumfer, *J. Energy Inst.* **2019**, *92*, 108–117; (b) P. N. Kalaria, S. C. Karad, D. K. Raval, *Eur. J. Med. Chem.* **2018**, *158*, 917–936; (c) M. Kidwai, R. Venktaramanan, R. Mohan, P. Sapra, *Curr. Med. Chem.* **2002**, *9*, 1209–1228.

[22] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.

[23] R. Merten, Synthesis of Heterocyclic Ring Systems for Heat-Resistant Plastics from Polyisocyanates. *Angew. Chem. Int. Ed.* **1971**, *10*, 294–301; (b) A. F. Pozharskii, A. R. Katritzky, A. T. Soldatenkov, *Heterocycles in Life and Society*; Wiley Chichester, **2011**.

[24] For selected reviews on CO_2-related cyclic carbonate synthesis and utilization, see: (a) L. Guo, K. J. Lamb, M. North, *Green Chem.* **2021**, *23*, 77–118; (b) P. P. Pescarmona, *Curr. Opin. Green Sustain.*

effective route to prepare cyclic carbonates is the [3+2] cycloaddition of CO_2 to epoxides. This reaction has several advantages in the context of green and sustainable chemistry, as it uses a renewable, nontoxic and widely available reactant and displays 100% atom efficiency as all reactants are incorporated in the product (Figure1.4).

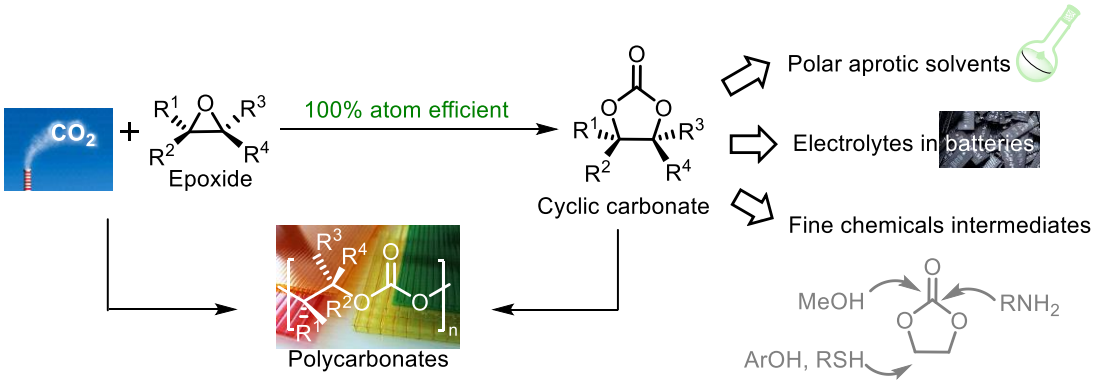


Figure 1.4 Some applications of cyclic carbonates.

Over the past few decades, catalysts have emerged that are able to efficiently mediate the addition of CO_2 to epoxides. The most prominent systems are based on alkali metal,[25] metal oxides,[26] organo-catalysts,[27] ionic liquids[28] and transition metals.[29] Currently the use of alkali metals and metal oxides has been almost completely been replaced by organo-catalysts and metal-based catalysts, due to the much better performance of the latter two catalyst categories in this area. Especially (transition)metal-based catalysts have a stronger potential for epoxide activation, allowing the processes to be operated at lower catalyst loading and reaction

Chem. **2021**, *29*, 100457; (c) P. Rollin, L. K. Soares, A. M. Barcellos, D. R. Araujo, E. J. Lenardão, R. G. Jacob, G. Perin, *Appl. Sci.* **2021**, *11*, 5024; (d) M. Ghasemlou, F. Daver, E. P. Ivanova, B. Adhikari, *Eur. Polym. J.* **2019**, *118*, 668–684; (e) A. J. Kamphuis, F. Picchioni, P. P. Pescarmona, *Green Chem.* **2019**, *21*, 406–448; (f) S. Wang, C. Xi, *Chem. Soc. Rev.* **2019**, *48*, 382–404.

[25] (a) J. Song, B. Zhang, P. Zhang, *Catal. Today*. **2012**, *183*, 130–135; (b) S. Kaneko, S. Shirakawa, *ACS Sustain. Chem. Eng.* **2017**, *5*, 2836–2840.

[26] (a) A. Barbarini, R. Maggi, A. Mazzacani, G. Mori, G. Sartori, R. Sartorio, *Tetrahedron Lett.* **2003**, *44*, 2931–2934; (b) K. Yamaguchi, K. Ebitani, T. Yoshida, H. Yoshida, K. Kaneda, *J. Am. Chem. Soc.* **1999**, *121*, 4526–4527.

[27] (a) C. J. Whiteoak, A. Nova, F. Maseras, A. W. Kleij, *ChemSusChem* **2012**, *5*, 2032–2038; (b) G. Fiorani, W. Guo, A. W. Kleij, *Green Chem.* **2015**, *17*, 1375–1389; (c) V. Laserna, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *ACS Catal.* **2017**, *7*, 5478–5482.

[28] (a) Z. Zhang, F. Fan, H. Xing, Q. Yang, Z. Bao, Q. Ren, *ACS Sustain. Chem. Eng.* **2017**, *5*, 2841–2846; (b) B.-H. Xu, J.-Q. Wang, J. Sun, Y. Huang, J.-P. Zhang, X.-P. Zhang, S.-J. Zhang, *Green Chem.* **2015**, *17*, 108–122.

[29] For selected reviews on transition metal catalysts in the synthesis of cyclic carbonates (a) C. Martín, G. Fiorani, A. W. Kleij, *ACS Catal.* **2015**, *5*, 1353–1370; (b) J. W. Comerford, I. D. V. Ingram, M. North, X. Wu, *Green Chem.* **2015**, *17*, 1966–1987.

temperatures/pressures, while giving access to a wider scope of organic carbonates. The current main approach for metal-catalyzed formation of cyclic carbonates focuses on the use of binary systems consisting of Lewis acid (LA) and a nucleophilic (Nu) additive. A widely accepted mechanism for the addition of CO_2 to epoxides catalyzed by binary catalysts is depicted in Figure 1.5A.

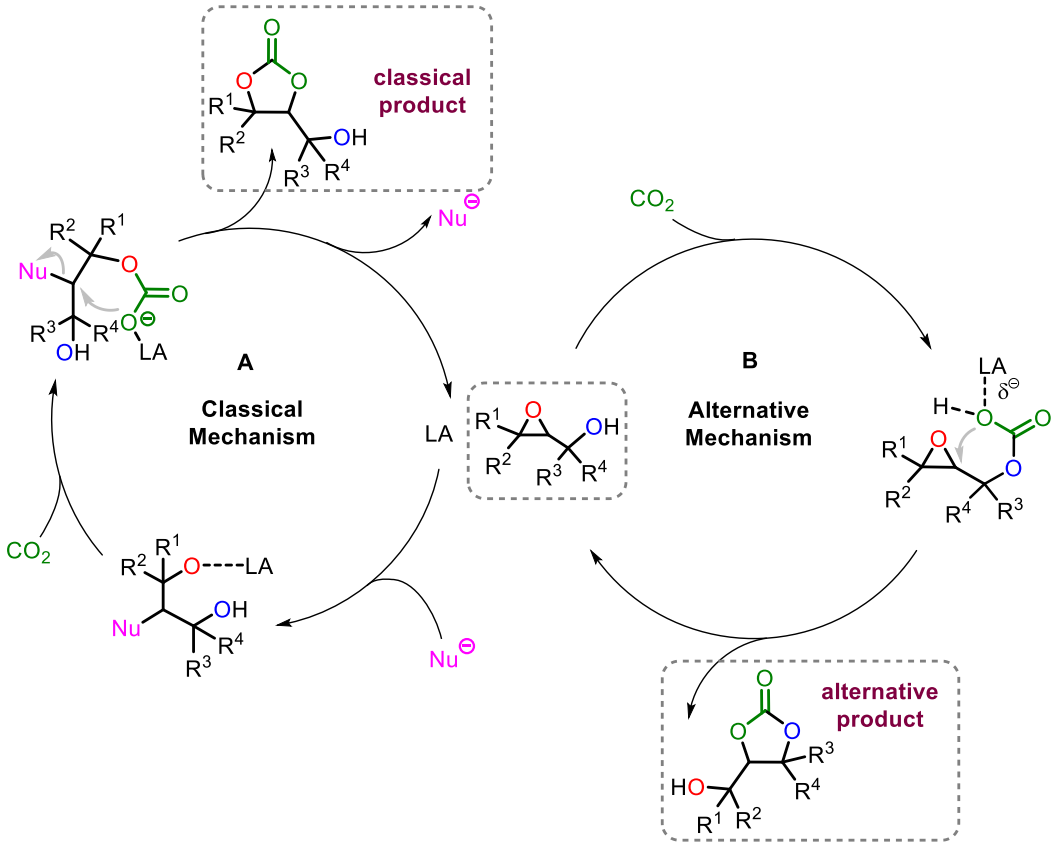


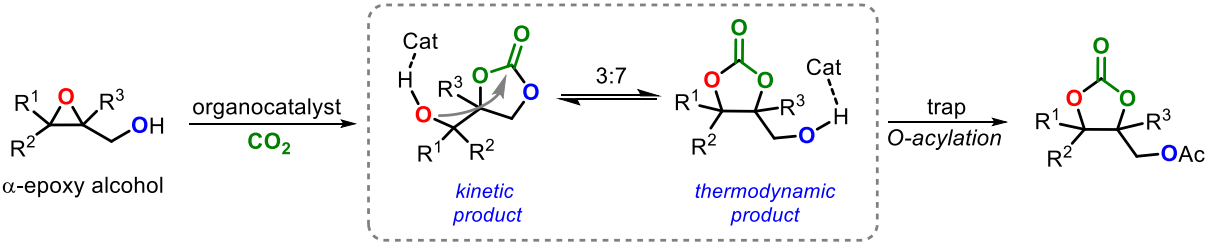
Figure 1.5 Mechanistic divergence in the coupling between CO_2 and epoxy alcohols leading to product diversity.

1.3.1.2 Synthesis of cyclic carbonates from CO_2 and epoxy alcohols

Unlike in the classical mechanism involved in the cycloaddition of CO_2 to epoxides that builds on the presence of an external (halide) nucleophile, in 2016 our group developed a new catalytic process that operates via an alternative reaction pathway and involves α-epoxy alcohols.[30] In this catalytic process, CO_2 is initially activated by the alcohol unit, thus providing in situ a requisite nucleophile for intramolecular epoxy ring-opening under mild reaction conditions (Figure 1.5B).

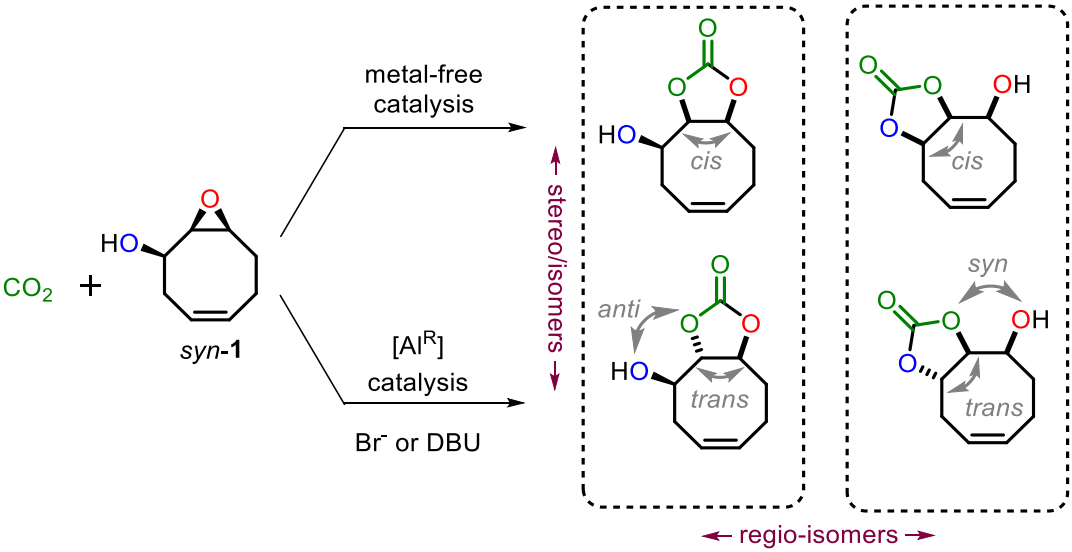
[30] J. Rintjema, R. Epping, G. Fiorani, E. Martín, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed.* **2016**, *55*, 3972–3976.

Inspired by Payne rearrangement of epoxy alcohols, a simple and cheap superbase-assisted approach has been developed towards highly substituted cyclic carbonates by reaction between α-epoxy alcohols and carbon dioxide.[31] Though a less substituted carbonate product formed initially, a thermodynamic equilibrium at the carbonate level allows for the formation and in situ trapping of tri- and even tetra-substituted cyclic carbonates by *O*-acylation.



Scheme 1.2 A new strategy for the synthesis of highly substituted cyclic carbonates.

Compared to acyclic epoxy alcohols, cyclic epoxy alcohols show additionally complex regio- and stereochemical diversity posed by their rigid nature. Distinct bicyclic carbonate products can be produced from a single starting material depending on the catalytic conditions (Scheme 1.3),[32,33c] with both *cis*/*trans* and *syn*/*anti* isomeric structures being feasible.

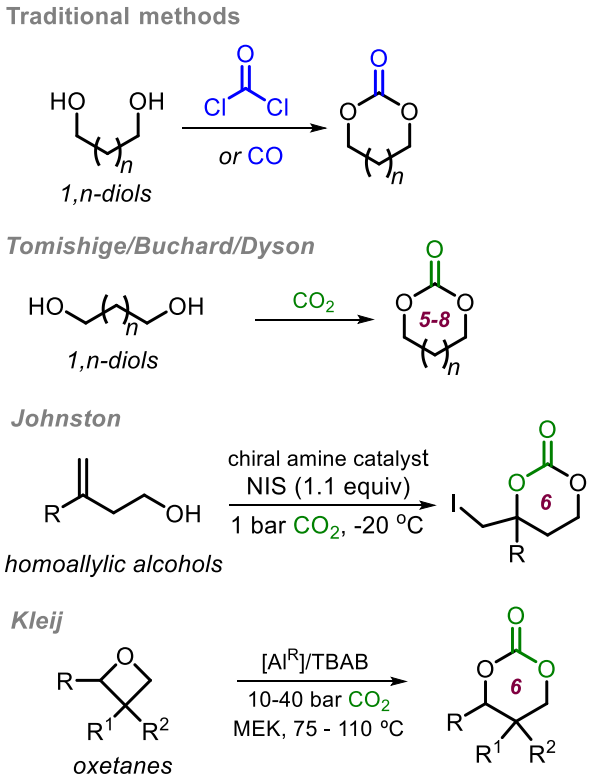


Scheme 1.3 Regio- and diastereo-divergent synthesis of bicyclic carbonates

[31] S. Sopeña, M. Cozzolino, C. Maquilón, E. C. Escudero-Adán, M. Martínez Belmonte, A. W. Kleij, *Angew. Chem. Int. Ed.* **2018**, *57*, 11203–11207.
[32] C. Maquilón, B. Limburg, V. Laserna, D. Garay-Ruiz, J. González-Fabra, C. Bo, M. Martínez Belmonte, E. C. Escudero-Adán, A. W. Kleij, *Organometallics* **2020**, *39*, 1642–1651.

1.3.1.3 Synthesis of larger ring cyclic carbonates from CO_2

Opposed to the well-studied catalytic formation of 5-membered cyclic carbonates, catalytic procedures for the preparation of larger-ring homologues are scarce. Conventional preparation of 6-membered or even larger cyclic carbonates involves phosgene[33] or CO[34] which are highly toxic reagents. In the past few years, alternative methods to generate 6-membered heterocycles from CO_2 have been developed, however, these methodologies are often relying on stoichiometric approaches[35] or on synthetically elaborate substrates (Scheme 1.4).[36]



Scheme 1.4 Methods for the synthesis of larger ring cyclic carbonates. Note that Al^R stands for an Al-centered aminotriphenolate complex, TBAB = tetrabutylammonium bromide.

[33] (a) G. Rokicki, *Prog. Polym. Sci*. **2000**, *25*, 259–342; (b) A. G. Shaikh, S. Sivaram, *Chem. Rev*. **1996**, *96*, 951–976.

[34] (a) B. Gabriele, R. Mancuso, G. Salerno, L. Veltri, M.; Costa. A. Dibenedetto, *ChemSusChem* **2011**, *4*, 1778–1786; (b) D. M. Pearson, N. R.; Conley. R. M. Waymouth, *Adv. Synth. Catal*. **2011**, *353*, 3007–3013.

[35] (a) G. L. Gregory, M. Ulmann, A. Buchard, *RSC Adv.* **2015**, *5*, 39404–39408; (b) T. M. McGuire, E. M. López-Vidal, G. L. Gregory, A. Buchard, *J. CO_2 Util.* **2018**, *27*, 283–288; (c) B. A. Vara, T. J. Struble, W. Wang, M. C. Dobish, J. N. Johnston, *J. Am. Chem. Soc.* **2015**, *137*, 7302–7305; (d) M. Honda, M. Tamura, K. Nakao, K. Suzuki, Y. Nakagawa, K. Tomishige, *ACS Catal*. **2014**, *4*, 1893–1896.

[36] J. Rintjema, W. Guo, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *Chem. Eur. J.* **2015**, *21*, 10754–10762.

Therefore, new concepts are highly required to advance the access to these larger ring targets and preferably through catalytic approaches. New methods may also provide access to previously inaccessible larger ring carbonates with potential in new polycarbonate development through ring-opening polymerization techniques.

1.3.2 Polycyclic ethers

Polycyclic ether based natural products represent formidable and challenging synthetic molecules due to their structural complexity, though their exceptionally potent biological activities make them interesting targets. Examples include the family of Brevetoxins, which are neurotoxins that bind to voltage-gated sodium channels in nerve cells, leading to disruption of normal neurological processes.[37] Tremendous progress has been made over the past decade toward the total synthesis of marine polycyclic ether natural products. In this area, a convergent strategy for assembling small fragments into an entire molecule always plays a key role in successful total synthesis.[38] More specifically, the use of epoxide ring-opening cascades has played and continues to represent a powerful approach for the single-pot construction of polycyclic ether compounds, with in some cases a key role for catalyst design and application.[39]

Recently xylose-derived tricyclic compounds (a relatively simple example of a polycyclic ether compound) have emerged as potent monomers in polymer science creating new impetus for the design of bio-based polyether and polyester macromolecules with tunable properties (Scheme 1.5).[40] However, this naturally based monomer limits the structural diversity of the resultant polymers, and hence their properties. New synthetic methodologies that lead to similar types of bicyclic ether derivatives though amplifying the structural diversity by virtue of the precursors used can provide more opportunities for these intriguing compounds as novel types of monomers. In addition, this example of small molecule synthesis allows more easily to study the mechanistic implications of epoxide ring-opening cascade thereby giving new

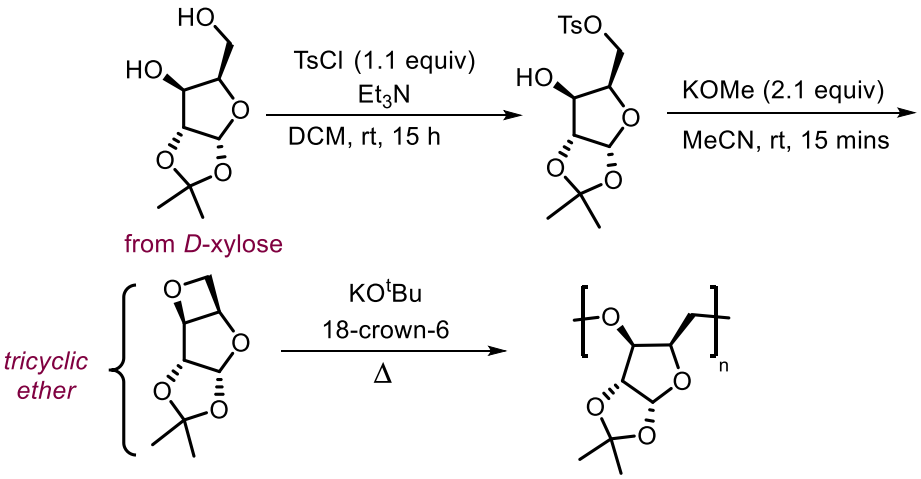
[37] See for instance: K. C. Nicolaou, Z. Yang, G. Shi, J. L. Gunzner, K. A. Agrios, P. Gärtner, *Nature* **1998**, *392*, 264–269.

[38] (a) C. M. M. Santos, A. M. S. Silva, *Comprehensive Heterocyclic Chemistry IV*; D. S. Black, J. Cossy, C. V. Stevens, Eds.; Elsevier: Oxford, **2022**; pp 44–84; (b) M. Sasaki, H. Fuwa, *Nat. Prod. Rep.* **2008**, *25*, 401–426; (c) T. Nakata, *Chem. Rev.* **2005**, *105*, 4314–4347.

[39] For instance: G. L. Simpson, T. P. Heffron, E. Merino, T. F. Jamison, *J. Am. Chem. Soc*. **2006**, *128*, 1056–1057.

[40] (a) T. M. McGuire, J. Bowles, E. Deane, E. H. E. Farrar, M. N. Grayson, A. Buchard, *Angew. Chem. Int. Ed*. **2021**, *60*, 4524–4528; (b) T. M. McGuire, E. F. Clark, A. Buchard, *Macromolecules* **2021**, *54*, 5094–5105; (c) T. M. McGuire, A. Buchard, *Polym. Chem*. **2021**, *12*, 4253–4261; (d) M. Piccini, J. Lightfoot, B. Castro Dominguez, A. Buchard, *ACS Appl. Polym. Mater*. **2021**, *3*, 5870–5881; (e) D. K. Tran, A. Z. Rashad, D. J. Darensbourg, K. L. Wooley, *Polym. Chem*. **2021**, *12*, 5271–5278.

incentives for a better understanding of the biogenesis of much larger polycyclic ether structures.



Scheme 1.5 Example of a ring-opening polymerization of an anhydro *D*-xylose-based monomer.[40]

1.4 Aluminum aminotriphenolate complexes

Among all the metal complexes that have been employed for epoxide conversion, aluminum centered complexes represent an attractive alternative. Not only is aluminum the most abundant metal in the Earth´s crust, it also has a highly oxophilic nature making it especially suitable for activation of oxygen-containing compounds such as epoxides. In the past, most catalytic systems employed either porphyrins or salen type complexes, either incorporating aluminum (Figure 1.6, selected examples are shown from various research groups) or other sustainable/cheap metals such as Fe or Zn.[41] A relatively new class of ligands introduced in the field of CO_2 valorization is represented by aminotriphenolates, which are potentially tetradentate ligands with a flexible C_3-symmetry (Figure 1.6).[42] These complexes have significantly contributed to the area of cyclic carbonates in various ways, expanding greatly the portfolio of functional carbonates, the development of new synthetic concepts and, to some extent, the access to larger ring carbonates.

[41] Q.-W. Song, Z.-H. Zhou, L.-N. He, *Green Chem.* **2017**, *19*, 3707–3728.
[42] B. Limburg, À. Cristòfol, F. Della Monica, A. W. Kleij, *ChemSusChem* **2020**, 13, 6056-6065.

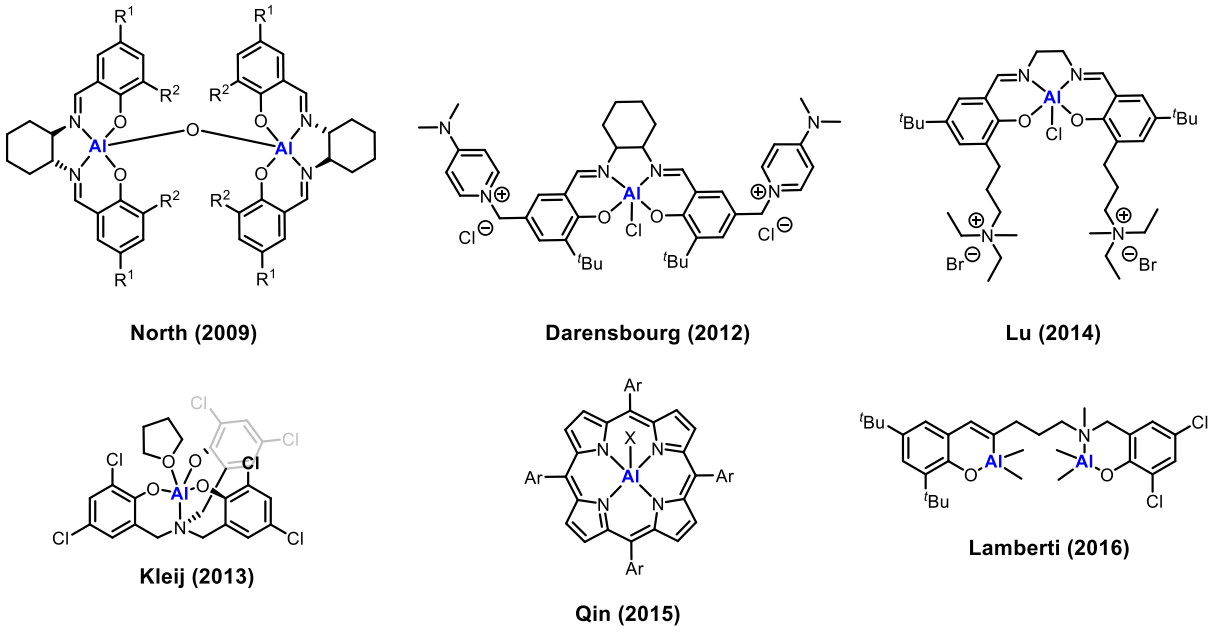


Figure 1.6 Aluminum based complexes utilized for highly efficient catalytic conversion of CO_2 to cyclic carbonates.

As reported for previously developed salen and porphyrin ligand systems, the aminotriphenolate ligand also allows for facile steric and electronic modulation. A distinct difference between these three types of the ligands is that salen and porphyrin structures (once their metal complexes are formed) adopt a relatively planar conformation, while the aminotriphenolate ligand enforces a rather flexible trigonal bipyramidal coordination geometry around the metal center, which provides it adaptivity upon binding epoxide substrates. This is key for the activation of sterically encumbered epoxy compounds, and the aminotriphenolate complexes allow for some degree of geometrical distortion without reaching to high free energy levels. As such, these complexes have proven over the last decade to efficiently activate and convert sterically challenging epoxides and their transformation into highly substituted cyclic carbonates and derivatives.[42,43]

[43] (a) C. J. Whiteoak, N. Kielland, V. Laserna, E. C. Escudero-Adán, E. Martin, A. W. Kleij, *J. Am. Chem. Soc.* **2013**, *135*, 1228–1231; (b) C. J. Whiteoak, N. Kielland, V. Laserna, F. Castro-Gómez, E. Martin, E. C. Escudero-Adán, C. Bo, A. W. Kleij, *Chem. Eur. J.* **2014**, *20*, 2264–2275.

1.5 Objectives and outline of this thesis

The previous sections have shown the importance of heterocyclic compounds in both industrial applications and academic research, and their reliance on the availability and diversity of epoxy precursors. Considering our long-standing interest in the formation of cyclic carbonates, the use of metal aminotriphenolate complexes as binary catalyst components and the lack of general catalytic procedures for both **larger-ring carbonates** and **multicyclic ether compounds**, this thesis will focus on advancing these targets using Al(III) aminotriphenolate complexes as key components. These *de novo* catalysis approaches need to provide not only a wider diversity of carbonate derivatives, but preferably also new types of monomers for ring-opening polymerization thereby producing new CO_2-derived polymers. To achieve these goals, we have selected as principal substrates alcohol-substituted epoxides, *viz*. **α- and β-epoxy alcohols**.

The main objective is thus to realize the development of new catalysis procedures for the creation of new types of six-membered cyclic carbonates from β-epoxy alcohols with CO_2 under Al-catalysis and bicyclic ether compounds from α-bisepoxy alcohols under Al-catalysis.

This thesis, apart from the brief introduction, consists of the following chapters: **Chapter 2** reports a conceptually novel catalytic approach towards larger-ring cyclic carbonates using acyclic β-epoxy alcohols as newly applied substrates. After initial formation of five-membered cyclic carbonates, the latter are conveniently converted into their six-membered analogues and trapped by an acylation agent. This procedure is unique in the sense that a thermodynamically less stable cyclic carbonates can be easily prepared, and the mechanistic reasons for the accessibility under the experimental conditions is also detailed.

In **Chapter 3**, a further advancement of the catalytic synthesis of six-membered cyclic carbonates is presented. Binary catalysis based on the use of Al-aminotriphenolates allows for the direct conversion of β-epoxy alcohols and CO_2 into bicyclic six-membered carbonates with ample variety in the substitution degree and functionality. Control experiments point out that the stereochemical configuration of the substrate plays a dominant role in the chemo-selectivity of these reactions, while a set of initial experiments demonstrate the use of these larger-ring carbonate in ring-opening polymerization.

In the final experimental chapter (**Chapter 4**), bis-epoxy alcohol precursors (with the OH group in the α-position) are shown as versatile substrates toward the formation of a range of

[4+5] bicycles under Al-catalysis. A detailed mechanistic analysis shows that proton relay steps are important to control the delicate steps forming part of this cascade manifold, allowing to produce the bicyclic derivatives in good yield and scope. Preliminary experiments demonstrate that this epoxide ring-opening cascade process can be extended to other structures such as bicyclic [5+6] scaffolds. The [4+5] bicycles are essentially 3,5-anhydro furanose mimics and potentially useful as monomers in ring-opening polymerization.

In the final **Chapter 5**, a short summary of the thesis is provided together with the main overall conclusions of the thesis work including an outlook how the results may be of value to future protocols that build on the rich chemistry of epoxy alcohols and the flexible/adaptive nature of the Al-aminotriphenolate complexes.

Chapter 2.

Organocatalytic Trapping of Elusive Carbon Dioxide based Heterocycles through a Kinetically Controlled Cascade Process

The results described in this chapter have been published in:

C. Qiao, A. Villar-Yanez, J. Sprachmann, B. Limburg, C. Bo, A. W. Kleij, *Angew. Chem. Int. Ed*. **2020**, *59*, 18446–18451.

UNIVERSITAT ROVIRA I VIRGILI
CATALYTIC FORMATION OF HETEROCYCLES FROM - AND -EPOXY ALCOHOLS
Chang Qiao

2.1 Introduction

The last decade has witnessed a spectacular development of a plethora of new catalytic processes that focus on the valorization of carbon dioxide (CO_2)[1] affording organic molecules of use as precursors in fine chemical,[2] pharmaceutical[3] and polymer chemistry.[4] One of the most widely applied valorization routes is undoubtedly the non-reductive transformation of CO_2. Catalyst engineering in this area has been mainly focusing on using both metal-[5] and organo-catalysts[6] for the activation of the requisite co-reactant (often cyclic ethers) to produce a nucleophilic intermediate species that activates CO_2 followed by the formation of the desired product. The preparation of heterocyclic targets such as cyclic carbonates,[7] carbamates[8] and ureas[9] has greatly advanced as testified by the growing complexity of these CO_2-based products.

Larger-ring, typically difficult to prepare CO_2 based heterocycles remain challenging targets (Scheme 2.1, top). In the area of organic carbonate synthesis, methods to generate six-

[1] a) J. Artz, T. E. Müller, K. Thenert, J. Kleinekorte, R. Meys, A. Sternberg, A. Bardow, W. Leitner, *Chem. Rev*. **2018**, *118*, 434–504; b) S. Liu, L. R. Winter, J. G. Chen, *ACS Catal*. **2020**, *10*, 2855–2871; c) M. B. Ross, P. de Luna, Y. Li, C.-T. Dinh, D. Kim, P. Yang, E. H. Sargent, *Nat. Catal*. **2019**, *2*, 648–658; d) A. Goeppert, M. Czaun, J.-P. Jones, G. K. Surya Prakash, G. A. Olah, *Chem. Soc. Rev*. **2014**, *43*, 7995–8048.

[2] a) Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun*. **2015**, *6*, 5933; b) W. Guo, J. E. Gómez, À. Cristòfol, J. Xie, A. W. Kleij, *Angew. Chem. Int. Ed*. **2018**, *57*, 13735–13747; c) L. Song, Y.-X. Jiang, Z. Zhang, Y.-Y. Gui, X.-Y. Zhou, D.-G. Yu, *Chem. Commun*. **2020**, *56*, 8355–8367.

[3] a) A. Tortajada, F. Juliá-Hernández, M. Börjesson, T. Moragas, R. Martin, *Angew. Chem. Int. Ed*. **2018**, *57*, 15948–15982; b) W. Guo, V. Laserna, J. Rintjema, A. W. Kleij, *Adv. Synth. Catal*. **2016**, *358*, 1602–1607; c) D. U. Nielsen, X.-M. Hu, K. Daasbjerg, T. Skrydstrup, *Nat. Catal*. **2018**, *1*, 244–254.

[4] For some selected examples: a) A. J. Kamphuis, F. Picchioni, P. P. Pescarmona, *Green Chem*. **2019**, *21*, 406–448; b) B. Grignard, S. Gennen, C. Jérôme, A. W. Kleij, C. Detrembleur, *Chem. Soc. Rev*. **2019**, *48*, 4466–4514; c) S. J. Poland, D. J. Darensbourg, *Green Chem*. **2017**, *19*, 4990–5011; d) S. Paul, Y. Zhu, C. Romain, R. Brooks, P. K. Saini, C. K. Williams, *Chem. Commun*. **2015**, 51, 6459–6479.

[5] a) R. Rajjak Shaikh, S. Pornpraprom, V. D'Elia, *ACS Catal*. **2018**, *8*, 419–450; b) J. W. Comerford, I. D. V. Ingram, M. North, X. Wu, *Green Chem*. **2015**, *17*, 1966–1987; c) C. Martín, G. Fiorani, A. W. Kleij, *ACS Catal*. **2015**, *5*, 1353–1370.

[6] a) G. Fiorani, W. Guo, A. W. Kleij, *Green Chem*. **2015**, *17*, 1375–1389; b) M. Alves, B. Grignard, R. Mereau, C. Jerome, T. Tassaing, C. Detrembleur, *Catal. Sci. Technol*. **2017**, *7*, 2651-2684; for recent original work: c) N. Liu, Y.-F. Xie, C. Wang, S.-J. Li, D. Wei, M. Li, B. Dai, *ACS Catal*. **2018**, *8*, 9945–9957.

[7] For some illustrative, recent examples: a) G. Fiorani, M. Stuck, C. Martín, M. Martínez-Belmonte, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *ChemSusChem* **2016**, *9*, 1304–1311; b) H. Zhou, H. Zhang, S. Mu, W.-Z. Zhang, W.-M. Ren, X.-B. Lu, *Green Chem*. **2019**, *21*, 6335–6341; c) L. Longwitz, J. Steinbauer, A. Spannenberg, T. Werner, *ACS Catal*. **2018**, *8*, 665–672.

[8] a) B. Yu, L.-N. He, *ChemSusChem* **2015**, *8*, 52–62; for some recent original examples: b) R. Yousefi, R. Yousefi, T. J. Struble, J. L. Payne, M. Vishe, N. D. Schley, J. N. Johnston, *J. Am. Chem. Soc*. **2019**, *141*, 618–625; c) J. K. Mannisto, A. Sahari, K. Lagerblom, T. Niemi, M. Nieger, G. Sztanó, T. Repo, *Chem. Eur. J*. **2019**, *25*, 10284–10289.

[9] a) M. Tamura, K. Noro, M. Honda, Y. Nakagawa, K. Tomishige, *Green Chem*. **2013**, *15*, 1567–1577; b) J. Hwang, D. Han, J. J. Oh, M. Cheong, H.-J. Koo, J. S. Lee, H. S. Kim, *Adv. Synth. Catal*. **2019**, *361*, 297–306.

membered heterocycles are scarce and often rely on stoichiometric approaches.[10] An exception is presented by the coupling reaction between oxetanes and CO_2, although to date very few catalysts have been shown to be effective for these substrates,[11] and oxetanes are much less ubiquitous than epoxides. Therefore, new concepts are required to empower the potential of such novel, functionalized heterocyclic scaffolds and widen their prospective as synthetic intermediates[12] and polymerizable monomers.[13] With this challenge in mind, we set out to design a new conceptual route towards the synthesis of six-membered cyclic carbonates from simple and accessible building blocks (Scheme 2.1, below).

2.2 Aims and objectives

Homoallylic alcohols of type **2.A** are ubiquitous precursors and play a significant role in organic synthesis.[14] Their epoxidation directly affords substrates of type **2.B** that should be easily converted into intermediate 5-membered cyclic carbonate products **2.1**. Inspired by our previous work on substrate-controlled synthesis of organic carbonates,[15] we envisioned that the

[10] a) T. M. McGuire, E. M. López-Vidal, G. L. Gregory, A. Buchard, *J. CO_2 Util.* **2018**, *27*, 283–288; b) G. L. Gregory, M. Ulmann, A. Buchard, *RSC Adv.* **2015**, *5*, 39404–39408; c) M. Honda, M. Tamura, K. Nakao, K. Suzuki, Y. Nakagawa, K. Tomishige, *ACS Catal.* **2014**, *4*, 1893–1896; d) T. Hirose, S. Shimizu, S. Qu, H. Shitara, K. Kodama, L. Wang, *RSC Adv.* **2016**, *6*, 69040–69044; using a stoichiometric iodine source: e) B. A. Vara, T. J. Struble, W. Wang, M. C. Dobish, J. N. Johnston, *J. Am. Chem. Soc.* **2015**, *137*, 7302–7305. See also: f) A. Hosseinian, S. Farshbaf, R. Mohammadi, A. Monfaredc, E. Vessally, *RSC Adv*. **2018**, *8*, 17976–17988.

[11] a) C. J. Whiteoak, E. Martin, M. Martínez Belmonte, J. Benet-Buchholz, A. W. Kleij, *Adv. Synth. Catal*. **2012**, *354*, 469–476; b) J. Rintjema, W. Guo, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *Chem. Eur. J*. **2015**, *21*, 10754–10762; c) B. R. Buckley, A. P. Patel, K. G. Upul Wijayantha, *Eur. J. Org. Chem*. **2014**, 474–478; d) D. J. Darensbourg, A. Horn, Jr; A. I. Moncada, *Green Chem*. **2010**, *12*, 1376–1379.

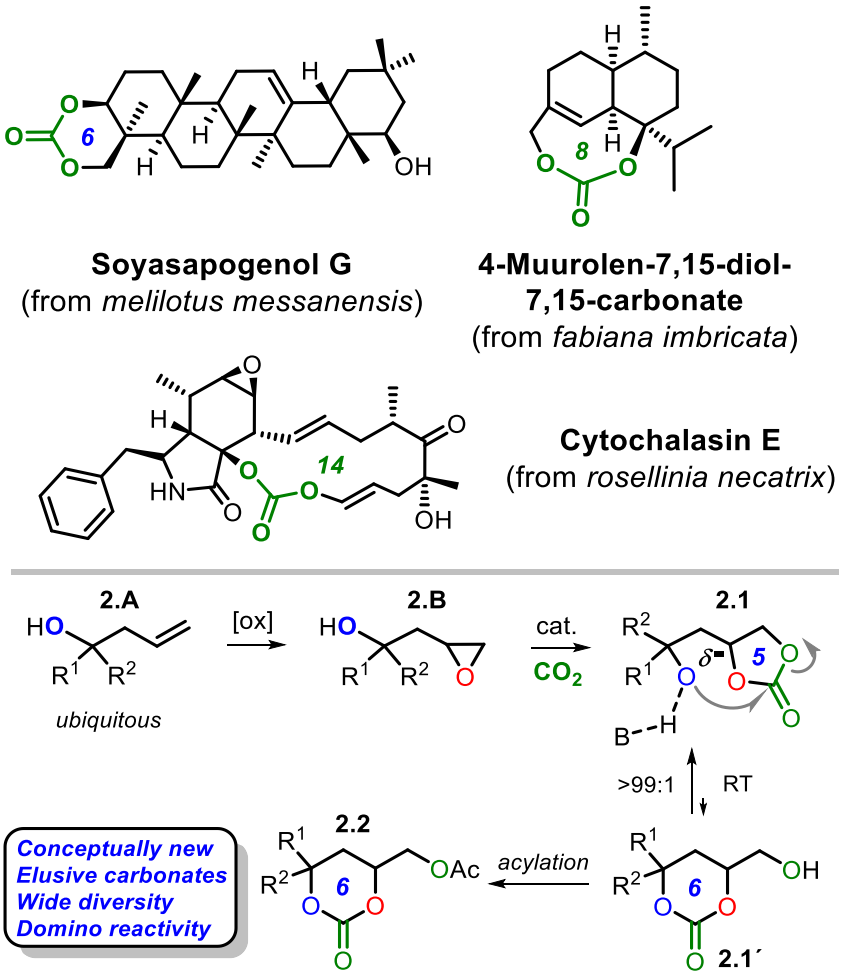
[12] a) J. Vaitla, Y. Guttormsen, J. K. Mannisto, A. Nova, T. Repo, A. Bayer, K. H. Hopmann, *ACS Catal*. **2017**, *7*, 7231–7244; b) B. D. W. Allen, C. P. Lakeland, J. P. A. Harrity, *Chem. Eur. J*. **2017**, *23*, 13830–13857. See also ref. 2b.

[13] For selected examples: a) G. L. Gregory, G. Kociok-Köhn, A. Buchard, *Polym. Chem*. **2017**, *8*, 2093–2104; b) G. L. Gregory, L. M. Jenisch, B. Charles, G. Kociok-Köhn, A. Buchard, *Macromolecules* **2016**, *49*, 7165–7169; c) P. Brignou, J.-F. Carpentier, S. M. Guillaume, *Macromolecules* **2011**, *44*, 5127–5135; d) D. J. Darensbourg, A. I. Moncada, S.-H. Wei, *Macromolecules* **2011**, 44, 2568–2576; e) D. J. Darensbourg, A. I. Moncada, *Macromolecules* **2010**, *43*, 5996–6003.

[14] For some recently developed procedures: a) M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc*. **2005**, *127*, 14556–14557; b) G.-L. Chai, B. Zhu, J. Chang, *J. Org. Chem*. **2019**, *84*, 120–127; c) Y. Zhang, N. Li, N. Goyal, G. Li, H. Lee, B. Z. Lu, C. H. Senanayake, *J. Org. Chem*. **2013**, *78*, 5775–5781.

[15] a) J. Rintjema, R. Epping, G. Fiorani, E. Martín, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed*. **2016**, *55*, 3972–3976; b) V. Laserna, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *ACS Catal*. **2017**, *7*, 5478–5482; c) S. Sopeña, M. Cozzolino, C. Maquilón, E. C. Escudero-Adán, M. Martínez Belmonte, A. W. Kleij, *Angew Chem Int Ed*. **2018**, *57*, 11203–11207; d) R. Huang, J. Rintjema, J. González-Fabra, E. Martín, E. C. Escudero-Adán, C. Bo, A. Urakawa, A. W. Kleij, *Nat. Catal*. **2019**, *2*, 62–70; e) C. Maquilón, B. Limburg, V. Laserna, D. Garay-Ruiz, J. González-Fabra, C. Bo, M. Martínez Belmonte, E. C. Escudero-Adán, A. W. Kleij, *Organometallics* **2020**, *39*, 1642–1651.

presence of a suitable organocatalyst (base) should be able to induce isomerization between carbonates **2.1** and **2.1´** with the latter being thermodynamically less stable. Selective acylation of the primary alcohol in **2.1´** offers then a tangible route to isolate the more elusive cyclic carbonate product **2.2**.



Scheme 2.1 Top: larger-ring, naturally occurring cyclic organic carbonates. Bottom: new conceptual approach towards six-membered cyclic carbonates. B represents a base.

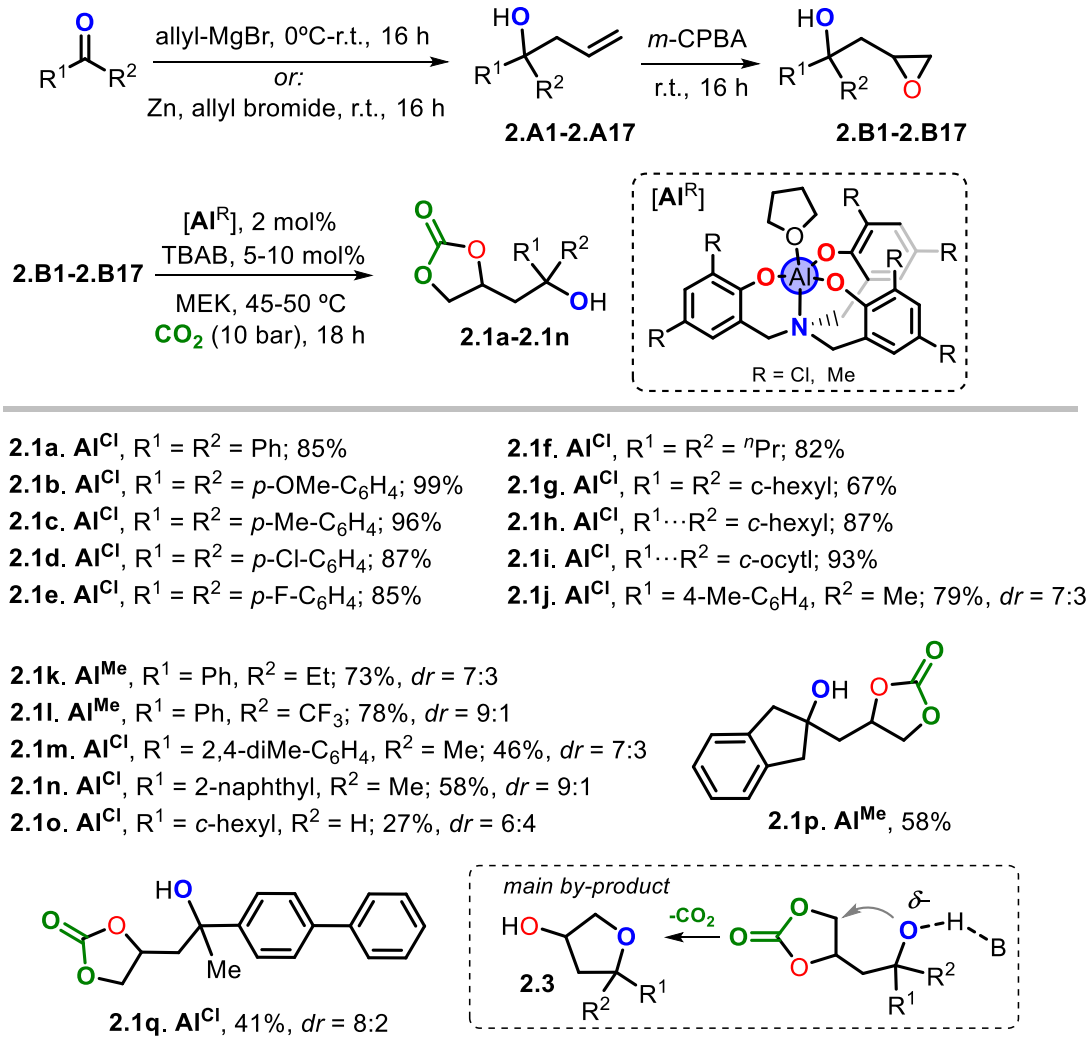
In this chapter, we describe a successful, new and generally high-yielding route towards highly substituted six-membered carbonates of type **2.2** creating a superior diversity of such valuable heterocycles. Both control experiments and DFT studies were performed to gain insight into the selective interconversion between five- and six-membered free alcohol based cyclic carbonates. A kinetically controlled protecting step, and a thermodynamically disfavored 6-membered carbonate structure are documented as highlights.

2.3 Results and discussion

We first prepared a series of 5-membered cyclic carbonates of type **2.1** by employing various homoallylic alcohols (**2.A1**-**2.A17**) as precursors that are conveniently prepared from readily available ketones and allyl magnesium bromide. Epoxidation of these homoallylic compounds using *m*-CPBA at room temperature (r.t.) afforded the oxiranes **2.B1**-**2.B17** with a β-hydroxy group. The oxiranes **2.B1**-**2.B17** (Scheme 2.2) were then used as reagents to furnish the cyclic carbonates **2.1a**-**2.1q** typically in good yields (with some exceptions) in the presence of CO_2 and suitable binary catalysts derived from Al-aminotriphenolate complexes $\mathbf{Al^{Cl}}$ and $\mathbf{Al^{Me}}$.[16] In some cases, significant byproduct formation occurred, and these products were identified as substituted tetrahydrofuran derivatives. The observed *dr* values for some of the 5-membered cyclic carbonates are similar to the ones of their respective precursors **2.B**, and hence supports the view that the formation of these five-membered carbonates is diastereospecific.

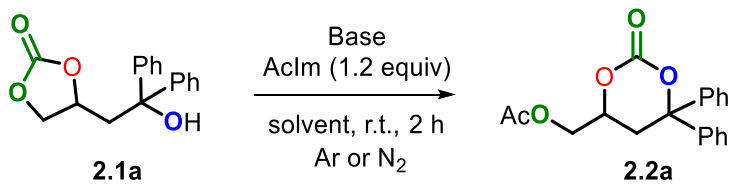
For the screening studies focusing on the preparation of six-membered cyclic carbonate **2.2a** (Table 2.1), we chose carbonate **2.1a** as a benchmark substrate. Various *N*-heterocyclic compounds and standard bases were examined and acetyl imidazole was used as acylation reagent.[15c] The nature of the base had a significant effect on both the yield of **2.2a** and the overall chemo-selectivity. Among the eight bases tested, the *N*-heterocyclic ones (Table 2.1, entries 1, 2 and 4–6) gave the best results, with TBD (entry 1, 64%) providing comparatively the best yield of **2.2a**. By further variation of the solvent and the amount of TBD (entries 9–17), the best considered conditions (entry 15; 30 mol% TBD) offered an easy access to **2.2a** in high yield. In the absence of AcIm and by using a high loading of TBD, only tetrahydrofuran derivative **2.3a** could be identified (entry 17). In the absence of TBD (entry 18), no conversion of **2.1a** could be observed. This r.t. catalytic conversion of a 5- into a 6-membered cyclic carbonate is rather unique as the latter type of product is typically difficult to prepare under such mild conditions.

[16] For the first use of the Al-complexes in cyclic carbonate synthesis: a) C. J. Whiteoak, N. Kielland, V. Laserna, E. C. Escudero-Adán, E. Martin, A. W. Kleij, *J. Am. Chem. Soc*. **2013**, *135*, 1228–1231; b) C. J. Whiteoak, N. Kielland, V. Laserna, F. Castro-Gómez, E. Martin, E. C. Escudero-Adán, C. Bo, A. W. Kleij, *Chem. Eur. J*. **2014**, *20*, 2264–2275.



Scheme 2.2 Preparation of 5-membered carbonates **2.1a-2.1q** from precursors **2.B1-2.B17** that are prepared from homoallylic alkenes **2.A1-2.A17** using either **Al^{Cl}** or **Al^{Me}**.

Table 2.1 Screening conditions for the conversion of cyclic carbonate **2.1a** into its 6-membered congener **2.2a** under various conditions.[a]



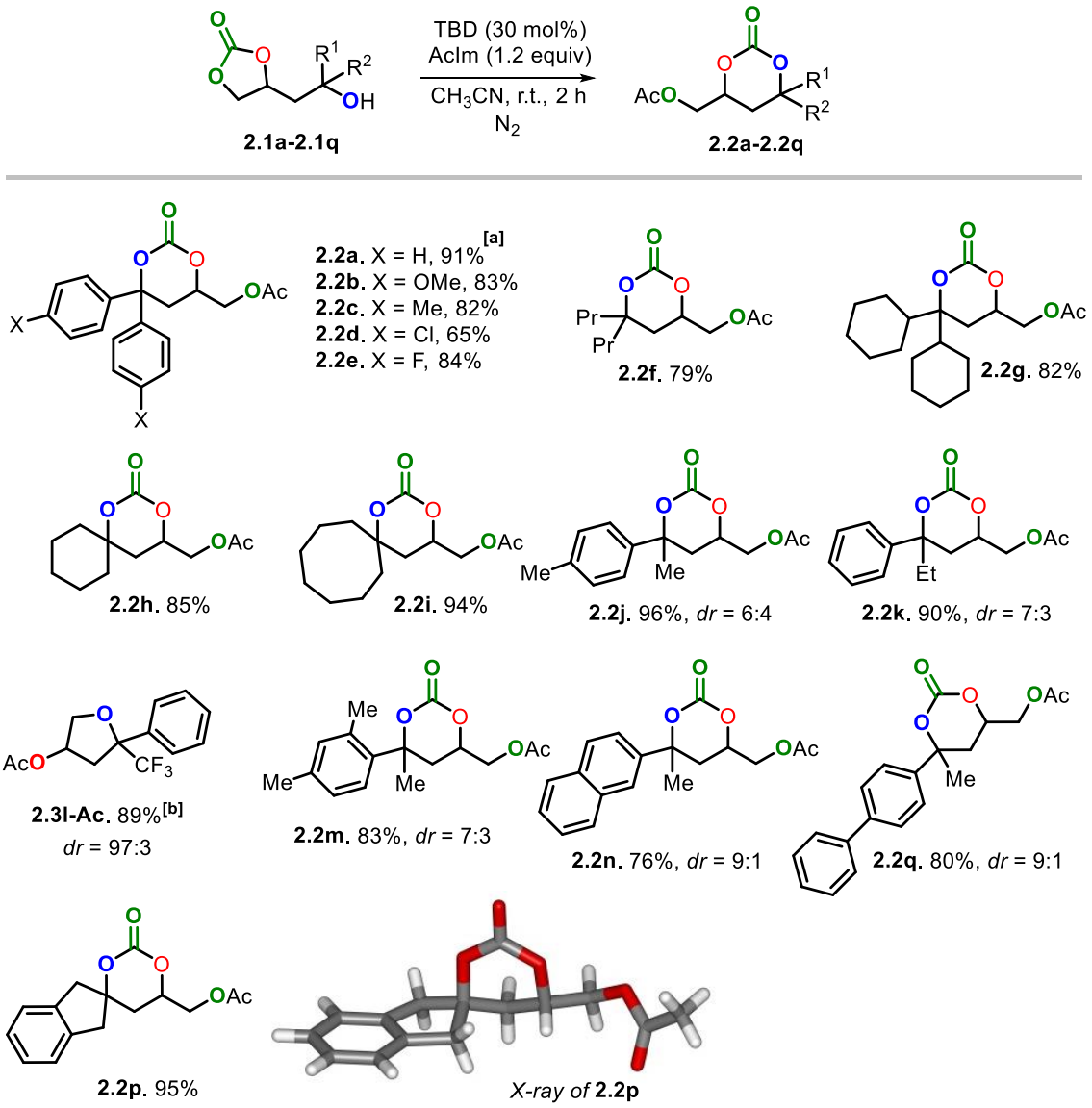
2.1a **2.2a**

Entry	Base [mol%]	Solvent	Conv. of **2.1a** [%][b]	Yield of **2.2a** [%][c]
1	TBD (20)	CH_3CN	64	64
2	DBU (20)	CH_3CN	49	49
3	KOH (20)	CH_3CN	100	0[d]
4	DMAP (20)	CH_3CN	8	2
5	DBN (20)	CH_3CN	43	18
6	DABCO (20)	CH_3CN	6	0
7	TEA (20)	CH_3CN	6	0
8	K_2CO_3 (20)	CH_3CN	16	0
9	TBD (20)	THF	31	31
10[e]	TBD (20)	Et_2O	46	32
11	TBD (20)	Toluene	63	59
12	TBD (20)	DMF	15	15
13	TBD (20)	EtOH	21	3
14	TBD (20)	DCM	53	53
15	TBD (30)	CH_3CN	94	93 (91)[f]
16	TBD (50)	CH_3CN	97	97 (96)[f]
17[g]	TBD (100)	CH_3CN	>99	0[h]
18	–	CH_3CN	<1	0

[a] Reaction conditions: substrate **2.1a** (0.10 mmol), solvent (0.20 mL), 2 h, under Ar or N_2. [b] Conversions measured by ^1H NMR ($CDCl_3$). [c] Determined by ^1H NMR using mesitylene as internal standard. [d] An unidentified byproduct was formed. [e] Heterogeneous mixture; two duplicate experiments gave 21 (10) and 42 (32)% substrate conversion. Note: in brackets the isolated yield of **2.2a**. [f] In brackets the isolated yield of **2.2a**. [g] In the absence of acetyl imidazole. [h] Note that 5,5-diphenyl-tetrahydrofuran-3-ol (**2.3a**) was isolated in 14% yield (see also **2.3** in Scheme 2.2). Abbreviations: TBD = triazabicyclodecene, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, TEA = triethyl amine.

We then investigated the scope of this novel approach towards the formation of a wider diversity of 6-membered cyclic carbonate products (Scheme 2.3) by varying the R^1 and R^2 substituents. The presence of substituted aryl groups in the carbonate substrates **2.1a**-**2.1e** was well tolerated and provided smooth access to six-membered cyclic carbonates **2.2a**-**2.2e** in good to excellent yields (65-91%; a gram-scale synthesis of **2.2a** provided 1.24 g of product). The introduction of alkyl groups such as those present in the carbonate products **2.2f**-**2.2i** also did not pose any significant issue. Apart from the combination of two equal groups, carbonate substrates with distinct R^1 and R^2 substituents (**2.1j-2.1n**) were also probed. Whereas six-membered cyclic carbonates **2.2j**, **2.2k**, **2.2m** and **2.2n** were synthesized in good yields, the presence of a strongly electron-withdrawing CF_3 group (cf., attempted preparation of **2.2l**) changed the chemo-selectivity in favor of the decarboxylated, *O*-acetyl protected tetrahydrofuran product **2.3l-Ac** which was isolated in 89% (see Experimental section **2.6.13**). Finally, the *spiro*-derivative **2.2p** (95%) and biphenyl-based carbonate **2.2q** (80%) were prepared in good yields, and the identity of **2.2p** was further substantiated by X-ray analysis (Scheme 2.3).[17]

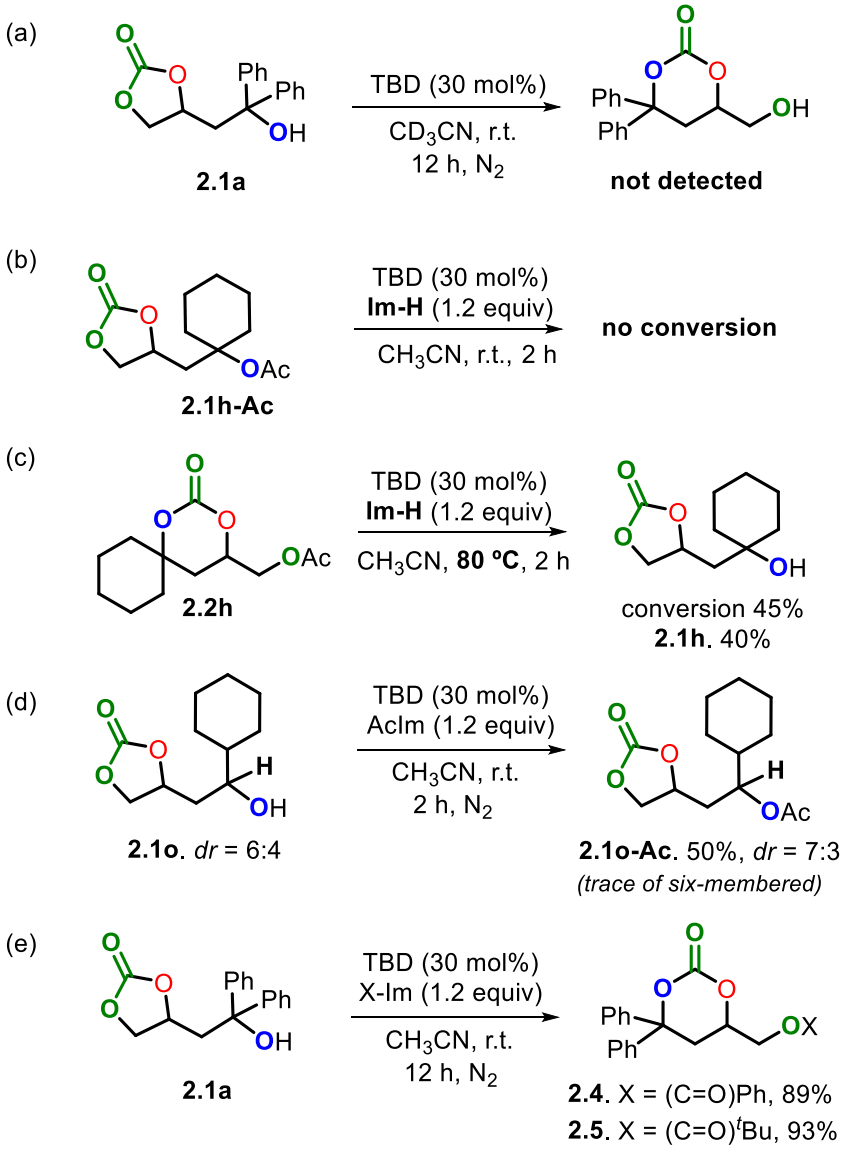
[17] For details of the structure of **2.2p**, please consult CCDC-1997736 and the Experimental section **2.6.8**.



Scheme 2.3 Scope of six-membered cyclic carbonates **2.2a-2.2q** using **2.1a-2.1q** as precursors and the reaction conditions of entry 15 in Table 2.1. [a] Gram-scale synthesis of **2.2a** using 5 mmol **2.1a**: yield 1.24 g, 76%. [b] The desired six-membered cyclic carbonate **2.2l** was not formed.

Next, a series of control experiments were conducted to investigate the proposed role of the pendent alcohol group in substrate **2.1a** and the relative stability of the free alcohol carbonates (Scheme 2.4). In the presence of TBD only, there is no observable conversion of the 5-membered carbonate **2.1a** into a 6-membered one suggesting indeed that **2.1a** is thermodynamically significantly more stable (Scheme 2.4a). We separately prepared acylated **2.1h**-Ac and subjected this compound to the conditions that are present at the end of the cascade process (Scheme 2.4b). No conversion was observed pointing at the crucial role of a free

alcohol group in carbonate **2.1h** *prior to* equilibration of the 5- to a 6-membered cyclic carbonate.



Scheme 2.4 Various control experiments.

Whereas 6-membered cyclic carbonate **2.2h** is stable at lower temperatures, at elevated ones deprotection of the O-Ac group occurs giving the free alcohol, 5-membered cyclic carbonate **2.1h** as the sole carbonate product in 40% isolated yield.[18] Deprotection of **2.2h** therefore leads to equilibration to 5-membered cyclic carbonate **2.1h** reinforcing the view that the free alcohol cyclic carbonate equilibrium is under thermodynamic control. To further probe the role of the

[18] Note that beside the 5-membered carbonate product **2.1h** also substantial amounts of a tetrahydrofuran by-product (cf., Scheme 2.2) was noted. At 110 ºC, the ratio (~ 4:1) between these products further changed in favour of the latter.

alcohol group, 5-membered cyclic carbonate **2.1o** comprising a secondary (instead of tertiary) OH was examined. By following the optimized conditions (Table 2.1, entry 15), acetylated **2.1o-Ac** (50%) was isolated as the major carbonate product and only a trace amount of the 6-membered carbonate was noted. This result can be anticipated as secondary alcohols should be much more susceptible towards protection largely precluding competitive carbonate equilibration to the unprotected 6-membered carbonate (cf., Scheme 2.1: **2.1** $\rightarrow$**2.1´**) and subsequent acylation. Finally, we used other protecting agents (compounds **2.4** and **2.5**, Scheme 2.4e) to illustrate that also variations in the ester group are feasible.

2.4 DFT studies

To further shed light on the mechanism, density functional theory (DFT) calculations were carried out (Figure 2.1).[19] DFT calculations were performed using ωB97X-D functional and the 6-311G** basis set. All structures in this study were calculated with the Gaussian16 program. In order to obtain results as close as possible to reality, all calculations were performed at 298 K (room temperature) and an acetonitrile solvent model SMD was used. Further details are provided in Figures 2.2-2.6 (see the Experimental section **2.6.9**-**2.6.12**). The conversion of **2.1a** into **2.2a** was examined as a representative case.

The overall cascade process (Figure 2.1) can be best described as two consecutive reactions. The first one is the conversion of the five-membered carbonate **5MCC-OH** (**2.1a**) into the six-membered one designated as **6MCC-OH**, while the second step involves the protection of the alcohol group of **6MCC-OH** using acetyl imidazole (AcIm) leading to the final product **2.2a**. The first part of the mechanism only involves **2.1a** and TBD with AcIm as spectator. First, the tertiary alcohol in **5MCC-OH** is deprotonated by TBD through **TS1** obtaining **5MCC-O** and TBD-H^+. The alkoxide group in **5MCC-O** subsequently approaches the carbonate carbon center and generates intermediate **5MCC-Int**. From here, an isomerization of **5MCC-Int** to **6MCC-Int1** takes place via **TS2**. This second step needs the presence of TBD-H^+ in order to induce a closer interaction between the alkoxide and the carbonyl carbon in **5MCC-Int** thus enabling the opening of the five-membered ring generating six-membered **6MCC-Int1**. This transformation has an energetic span of 17.6 kcal·mol^{-1} and supports the feasibility of all steps at room temperature. Then, the latter intermediate is converted into **6MCC-OH** through proton transfer from TBD-H^+ (**TS3**) and produces the six-membered carbonate which contains a primary alcohol. This is an important step since the conformational change while forming **TS3** positions the alkoxide group away from the carbonate carbon avoiding (to some extent) a back-reaction to **5MCC-Int1**. Importantly, **6MCC-OH** is computed to be thermodynamically significantly less stable than **5MCC-OH** (nearly 3 kcal·mol^{-1}, K_{eq} = 7.5 × 10^{-3}) and corroborates with the observation that an NMR mixture of **2.2a** and TBD (*cf.*, Scheme 2.4a and

[19] For fast scans in the potential energy surface the xTB program developed by Grimme was used, see ref. 20. This program allows the scanning of one or more distances, angles and dihedral angles at the same time or sequentially, giving a general idea of each structure. Furthermore, it performs meta-dynamics simulations using the root-mean-square deviation (RMSD) in Cartesian space as a collective variable. Full access to the computational data is provided through: http://dx.doi.org/10.19061/iochem-bd-1-171.

[20] a) S. Grimme, C. Bannwarth, P. Shushkov, *J. Chem. Theory Comput*. **2017**, *13*, 1989–2009. See also: b) J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys*. **2008**, *10*, 6615–6620.

c) did not show any sign of **6MCC-OH**. In order to be able to isolate the six-membered carbonate, *O*-protection by AcIm is thus crucial.

The second part of the cascade process describes the acylation of the primary alcohol in **6MCC-OH** (Figure 2.1). This *O*-protection using AcIm is catalyzed by TBD affording **6MCC-OAc** (**2.2a**) as a thermodynamically and kinetically stable product. The acylation process occurs in three steps. The first one is the deprotonation of the primary alcohol in **6MCC-OH** by TBD (via **TS4**) generating intermediate **6MCC-O-1** and TBD-H^+. Notably, **6MCC-Int1** is different from **6MCC-O-1** in that the alkoxide group is located nearer the carbonate carbon in **6MCC-Int1**. This larger separation present in ternary intermediate **6MCC-O-2** and facilitated by TBD-H^+ allows the nucleophilic alkoxide to attack the carbonyl fragment in AcIm through **TS5** and furnishes intermediate **6MCC-Int2**. As a consequence, the carbonyl carbon from AcIm undergoes a change from sp^2-to-sp^3 hybridization. Finally, TBD-H^+ transfers a proton to the outer nitrogen atom of the imidazole group (**TS6**) thus provoking an electronic rearrangement that allows for the generation of the final product **6MCC-OAc** (**2.2a**) and Im-H as by-product while regenerating TBD. The highest barrier (**TS6**) of the acylation process is located at 14.6 kcal·mol^{-1} and is substantially lower than the energetic requirement for the isomerization of **5MCC-OH** to **6MCC-OH**. This isomerization appears to be rate-limiting, and the final product **6MCC-OAc** (**2.2a**) is thermodynamically more stable than **2.1a** by 10.2 kcal·mol^{-1}.

Since all intermediates are in dynamic equilibrium, *O*-protection seems to make the overall cascade process irreversible at ambient temperature. To substantiate that hypothesis, we also computed the acylation of the starting carbonate **5MCC-OH** (**2.1a**) through the same pathway that leads to **6MCC-OAc** (**2.2a**). Interestingly, the acetylated carbonate **5MCC-OAc** has a substantially higher free energy than **6MCC-OAc** (1.8 and –10.2 kcal·mol^{-1}, respectively) but the difference in activation barrier ($\Delta\Delta G^{\ddagger}$) of both acylation processes is markedly different (see Figure 2.2, Experimental section **2.6.9**). At r.t., the *O*-protection in **5MCC-OH** (having a tertiary alcohol) is energetically not competitive with the 5-to-6 carbonate isomerization/acylation cascade with a $\Delta\Delta G^{\ddagger}$ of 7.2 kcal·mol^{-1}. Therefore, key to formation of the protected product **6MCC-OAc** is a kinetic differentiation between both alcohol protection pathways allowing to selectively trap the acylated six-membered carbonate **2.2a** in high isolated yield.

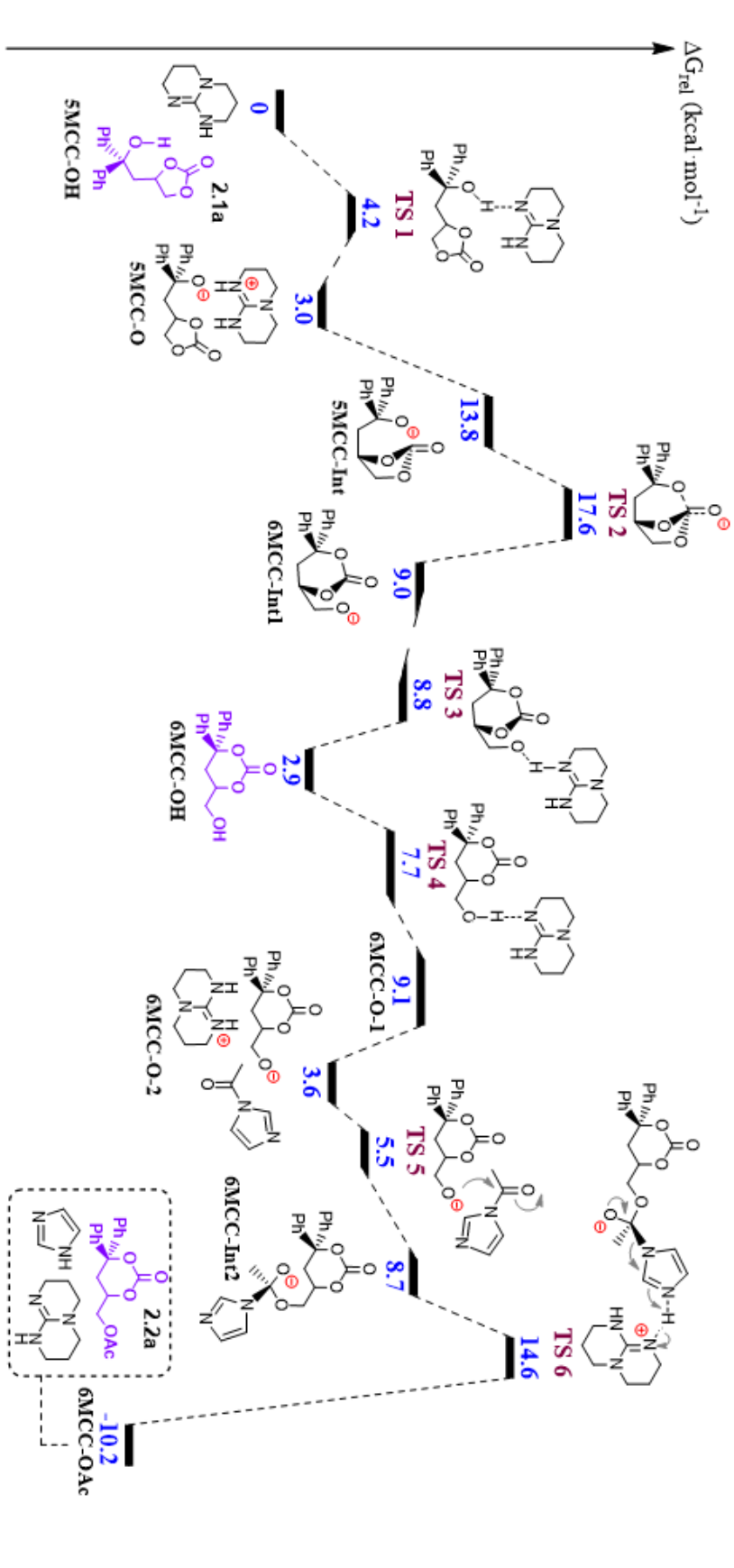


Figure 2.1 Relative Gibbs free energy profile in kcal·mol^{-1} for the formation of acylated six-membered cyclic carbonate **2.2a** from five-membered **2.1a** using TBD as catalyst and acetyl imidazole as acylating agent.

2.5 Conclusions

In summary, we here present a unique organocatalytic manifold for the formation of elusive 6-membered heterocycles at room temperature. The six-membered cyclic carbonates that are attained this way are highly versatile and allow for the presence of several alkyl and aryl ring substituents. Computational analysis complemented by control experiments emphasize the importance of kinetic differentiation in pendent alcohol protection as a way to isolate otherwise difficult to prepare CO_2 based heterocycles through a unique cascade process.

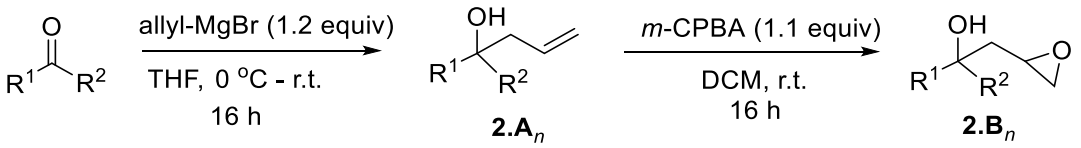
2.6 Experimental section

2.6.1 General comments

All reagents were used as received from commercial suppliers (Aldrich, Acros or TCI) unless stated otherwise. Carbon dioxide was purchased from PRAXAIR and used without further purification. Solvents were dried using an Innovative Technology PURE SOLV solvent purification system. NMR spectra were recorded on Bruker AV-300, AV-400 or AV-500 spectrometers. The residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm, CD_3CN: δ_H = 1.94 ppm, δ_C = 1.32 ppm). ^{19}F NMR spectra were not calibrated by an internal reference. FT-IR measurements were carried out on a Bruker Optics FTIR-ATR TR0 spectrometer. Exact mass analyses and X-ray diffraction studies were performed by the Research Support Area (RSA) at ICIQ.

2.6.2 Experimental procedures for the synthesis of the homoallylic epoxides

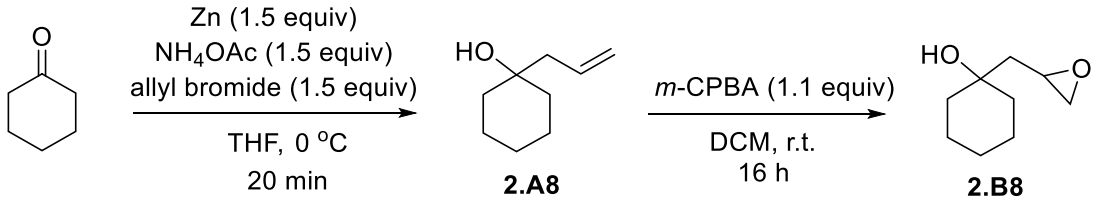
Method A



Step 1: The starting ketone or aldehyde (10 mmol) was added in a 50 mL oven-dried Schleck flask under nitrogen, and then 10 mL of dry THF was added via a syringe. Allyl magnesium bromide (12 mL, 1.2 equiv, 1.0 M Et_2O solution) was added dropwise at 0 °C using an ice bath. The reaction was stirred at room temperature for 16 h, then quenched with saturated NH_4Cl (aq) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated to obtain the corresponding homoallylic alcohol.

Step 2: The homoallylic alcohols were used without further purification unless stated otherwise. The latter were dissolved in DCM (50 mL) at 0 °C and *m*-CPBA (1.1 equiv, 11 mmol, 2.5 g) was added. The mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was washed with $NaHCO_3$ (4 × 30 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography employing 5% - 25% EA in hexane as eluent. **Note**: EA stands for ethyl acetate.

Method B

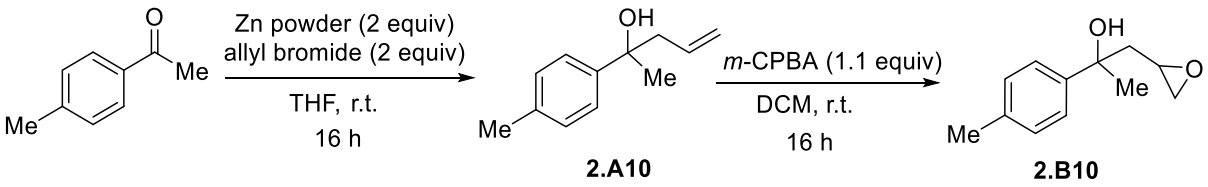


Step 1: To a stirred suspension of cyclohexanone (0.98 g, 10 mmol, 1.0 equiv), zinc powder (976 mg, 15 mmol, 1.5 equiv), and ammonium acetate (1.156 g, 15 mmol, 1.5 equiv) in THF (40.0 mL, 0.25 M) at 0 °C was added allyl bromide (1.3 mL, 15 mmol, 1.5 equiv) dropwise over 1 min.[20] After stirring for 10 min, the reaction mixture was quenched at 0 °C by addition of 20 mL of saturated aqueous $NaHCO_3$ and allowed to warm to room temperature over 20 min. The mixture was then transferred to a separation funnel together with Et_2O (30 mL) and H_2O (30 mL). After separation of the organic layer, the aqueous one was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure to yield homoallylic alcohol **2.A8** as a colorless oil.

Step 2: The homoallylic alcohol **2.A8** was used without further purification. The following epoxidation process was similar to the one described in **Method A**. The product **2.B8**, was isolated as a light-yellow oil using as eluent 10% - 25% EA in hexane. Yield: 86%.

[20] N. A. Weires, Y. Slutskyy, L. E. Overman, *Angew. Chem. Int. Ed*. **2019**, *58*, 8561–8565.

Method C

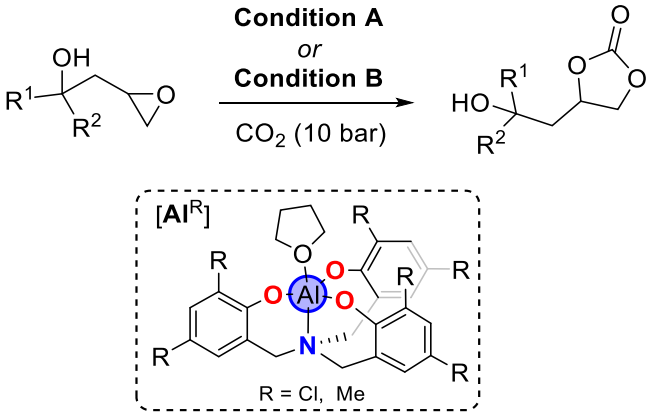


To a suspension of zinc powder (1.3 g, 20 mmol, 2 equiv) in dry THF (40.0 mL) at r.t. under nitrogen was added allyl bromide (2.42 g, 20 mmol, 2 equiv).[21] The reaction mixture was refluxed for 2 min, and then cooled to r.t. The ketone (1.34 g, 10 mmol, 1 equiv) was added dropwise to the mixture via a syringe. The mixture was stirred for 16 h, quenched with saturated NH_4Cl (aq) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and then purified by flash chromatography employing 3 % - 10% EA in hexane as eluent to obtain homoallylic alcohol **2.A10**. The following epoxidation process was similar to the one described in **Method A**. The product **2.B10** was isolated as a light-yellow oil using as eluent 5% - 10% EA in hexane. Yield: 89%.

[21] Y. Zhang, X. Jia, J.-X. Wang, *Eur. J. Org. Chem.* **2009**, 2983–2986.

2.6.3 Synthesis of the 5-membered cyclic carbonates 2.1a-2.1q

The non-commercial cyclic carbonates[15a,15c] and Al(III) aminotriphenolate complexes **Al^{Cl}** and **Al^{Me}** [16b] were prepared according to literature procedures.



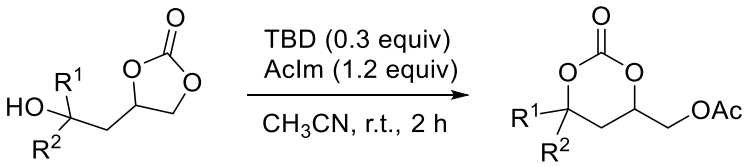
Condition A

In a 30 mL stainless steel reactor, the epoxide (1 mmol) was dissolved in MEK (3 mL) and **Al^{Cl}** (0.02 mmol, 2 mol%, 12.8 mg) and TBAB (0.05 mmol 5 mol%, 16.0 mg) were added. Three cycles of pressurization and depressurization of the reactor with 10 bars of CO_2 were carried out before finally stabilizing at 10 bars. The mixture was stirred at 45 °C for 18 h, then cooled in an ice bath and carefully depressurized. The solvent was removed *in vacuo* and the resulting product was purified by flash chromatography. Unless stated otherwise, the eluent was 10% - 25% EA in hexane.

Condition B

In a stainless-steel HEL multi-reactor, the epoxide (0.5 mmol) was dissolved in MEK (400 μL) and **Al^{Me}** (0.01 mmol 2 mol%, 5.1 mg) and TBAB (0.05 mmol 10 mol%, 8.0 mg) were added. The reactor was purged twice with CO_2 (10 bars) and then charged with CO_2 (10 bars). The mixture was stirred at 50 °C for 18 h, then cooled in an ice bath and carefully depressurized. The solvent was removed *in vacuo* and the resulting product was purified by flash chromatography employing 10% - 25% EA in hexane as eluent.

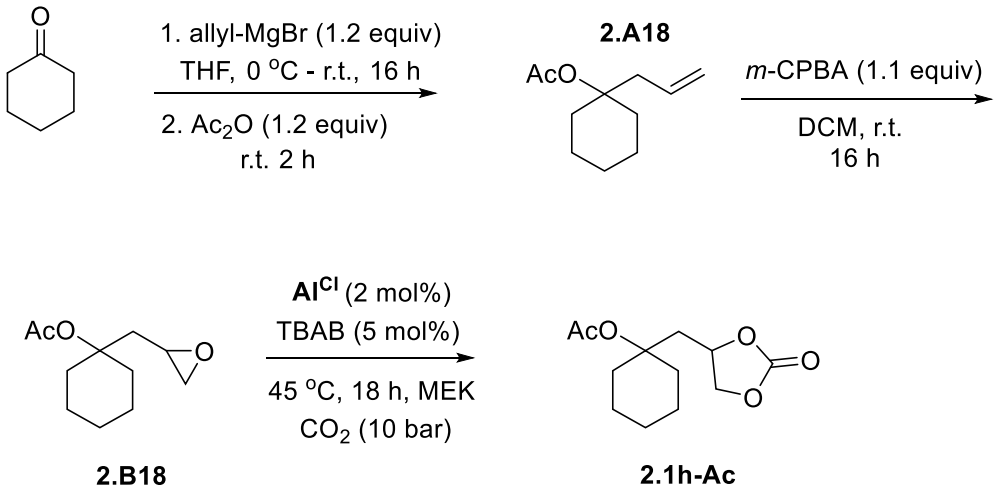
2.6.4 Synthesis of 6-membered cyclic carbonates 2.2a-2.2q



2.1a-2.1q **2.2a-2.2q**

The respective 5-membered cyclic carbonate (0.1 mmol), TBD (0.3 equiv, 0.03 mmol, 4.2 mg) and 1-acetylimidazole (AcIm, 1.2 equiv, 0.12 mmol, 13.2 mg) were added in an oven-dried glassware glass vial under argon, and then 0.2 mL of CH_3CN was added via a syringe. The reaction mixture was stirred at room temperature. After 2 h, the mixture was transferred to a round-bottom flask, concentrated and purified by flash column chromatography with 10% - 25% EA in hexane as eluent. In some cases, preparative TLC were used to purify the product mixtures.

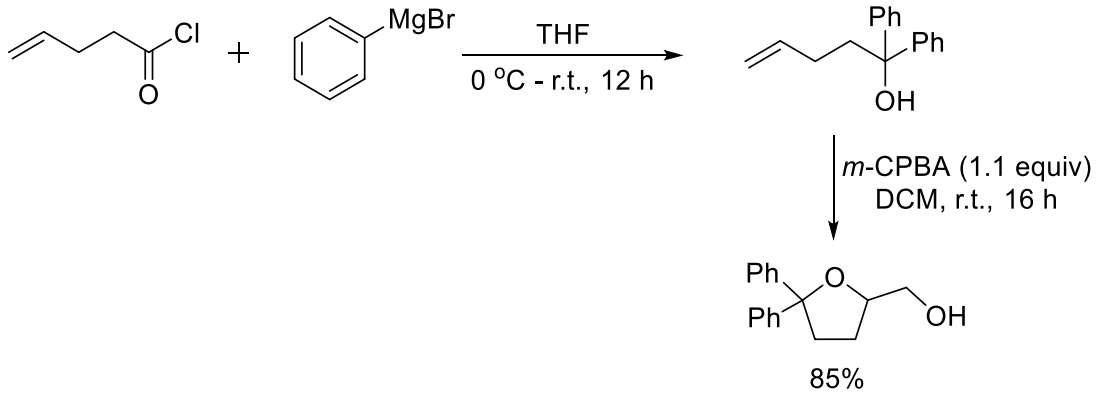
2.6.5 Experimental procedure for the synthesis of 2.1h-Ac (*cf.*, *Scheme 4.4b*)



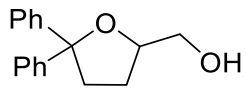
Cyclohexanone (10 mmol) was added to a 50 mL oven-dried Schleck flask under nitrogen, and then 10 mL of dry THF was added via a syringe. Allyl magnesium bromide (12 mL, 1.2 equiv, 1.0 M Et_2O solution) was added dropwise at 0 °C using an ice bath. The reaction mixture was stirred at room temperature for 16 h, quenched with Ac_2O (1.2 equiv, 12 mmol, 1.23 g). The mixture was stirred for another 2 h, and then extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography using 1% - 5 % EA in hexane as eluent. The first product **2.A18** (the acetyl-protected homo-allylic alcohols) was isolated as a yellow liquid. Yield: 50% (0.91 g). The following epoxidation and cycloaddition reactions were similar to the procedures described under **Method A** and **Condition A**. The epoxide intermediate **2.B18** (scale: 5 mmol) was isolated as a light-yellow oil. Yield: 13%, 130.2 mg. The final product **2.1h-Ac** (scale: 0.5 mmol) was isolated as an orange oil. Yield: 77%, 92.8 mg.

2.6.6 Attempted synthesis of larger-ring carbonates

By using the same synthetic approach for the beta-hydroxy-epoxides, we intended to prepare the y-analogues using the synthetic scheme below. We tried two different targets but, in both cases, we found that the major product was an undesired furan derivative. Experimental and analytical details are provided below:

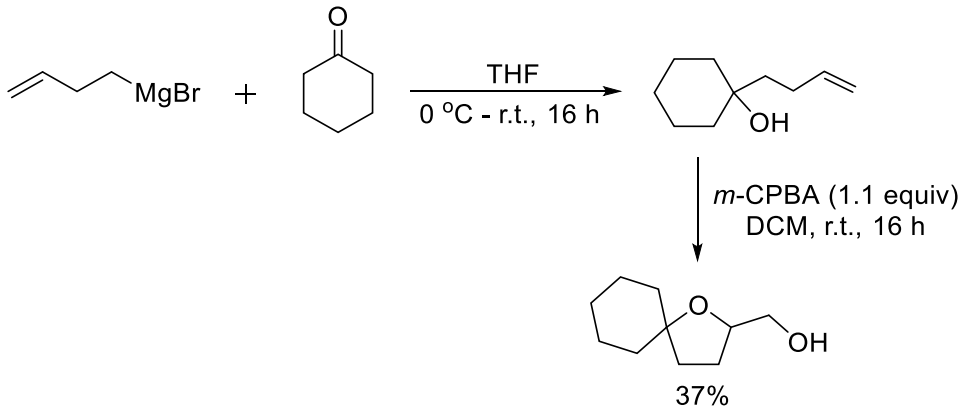


4-Pentenoyl chloride (5 mmol, 0.55 mL) and THF (20 mL) were added in an oven-dried Schleck flask under nitrogen. The mixture was cooled to 0 °C in an ice bath for five min and then phenyl magnesium bromide (20 mL, 20 mmol, 1 M in THF) was added dropwise to the flask. The resulting mixture was warmed to r.t. and stirred for 12 h, then quenched with saturated NH_4Cl (aq) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated to obtain the crude 1,1-diphenylpent-4-en-1-ol.[22] This crude 1,1-diphenylpent-4-en-1-ol was directly used for the next step without purification. The following epoxidation process was similar to the one described in **Method A**. The product was isolated as a white solid using as eluent 10% - 25% EA in hexane. Yield after 2 steps: 85%.



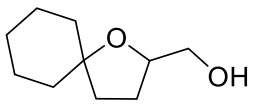
The product was isolated as a white solid. Yield: 85%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 4H), 7.33 – 7.26 (m, 4H), 7.24 – 7.16 (m, 2H), 4.35 – 4.26 (m, 1H), 3.77 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.57 (dd, *J* = 11.5, 5.8 Hz, 1H), 2.68 (ddd, *J* = 12.5, 7.6, 5.7 Hz, 1H), 2.56 (dt, *J* = 12.5, 8.0 Hz, 1H), 2.02 – 1.80 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.59, 146.20, 128.37, 128.36, 127.02, 126.88, 125.90, 125.84, 88.86, 79.36, 65.67, 38.79, 27.50; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{18}NaO_2$) 277.1199 $(M+Na)^+$: found: 227.1203.

[22] B. A. Hopkins, Z. J. Garlets, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2015**, *54*,13390–13392.



Step 1: The Grignard reagent (homo-allylic magnesium bromide, 1.0 M in THF) was prepared following the procedure described as below.[23] Magnesium turnings (15.0 mmol, 1.5 equiv) and I_2 (0.025 equiv) were introduced into an oven-dried Schlenk flask equipped with a stirring bar; the mixture was subjected to three cycles of vacuum/filling with N_2. After that, under protection of N_2, the flask was gently heated with a heat gun until the iodine melted completely. The resultant mixture was stirred for 30 min at room temperature. Then dry THF (15 mL) was added affording a brown solution, to which 4-bromobut-1-ene (15.0 mmol, 1.5 equiv) was added in one portion. Upon stirring for 30 min at room temperature until all the magnesium turnings were consumed, the required Grignard reagent was obtained.

Step 2: Cyclohexanone (0.98 g, 10 mmol, 1.0 equiv) was added dropwise to the Grignard reagent solution at 0 ºC. The resulting mixture was warmed to r.t. and stirred for 16 h, then quenched with saturated NH_4Cl (aq) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and then concentrated to obtain the crude1-(but-3-en-1-yl)cyclohexan-1-ol. 1-(but-3-en-1-yl)cyclohexan-1-ol was directly used for the next step without purification. The following epoxidation process was similar to the one described in Method A. The product was isolated as a white solid using as eluent 10% - 25% EA in hexane. Yield after 2 steps: 37%.

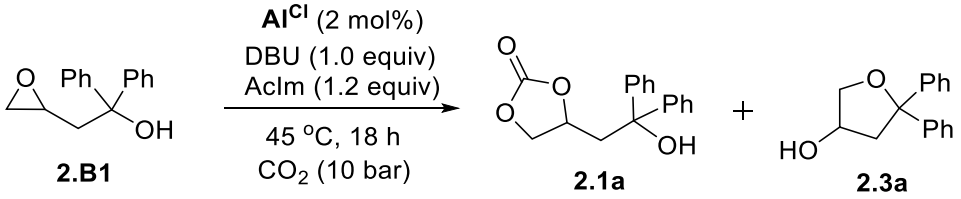


The product was isolated as a colorless oil. Yield: 37%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.08 (tdd, *J* = 6.8, 5.4, 3.3 Hz, 1H), 3.67 (dt, *J* = 11.4, 4.1 Hz, 1H), 3.45 (dt, *J* = 10.9, 5.1 Hz, 1H), 2.10– 2.06 (m, 1H), 1.98 – 1.88 (m, 1H), 1.79 – 1.62 (m, 6H), 1.58– 1.46 (m, 4H), 1.40 – 1.31 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.53, 78.24, 65.40, 38.48, 37.46, 36.14, 27.23, 25.77, 24.19, 23.87; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{18}NaO_2$) 193.1199 $(M+Na)^+$: found: 193.1198.

[23] J. E. Gómez, W. Guo, S. Gaspa, A. W. Kleij. *Angew. Chem. Int. Ed.* **2017**, *56*, 15035–15038.

2.6.7 Further screening data

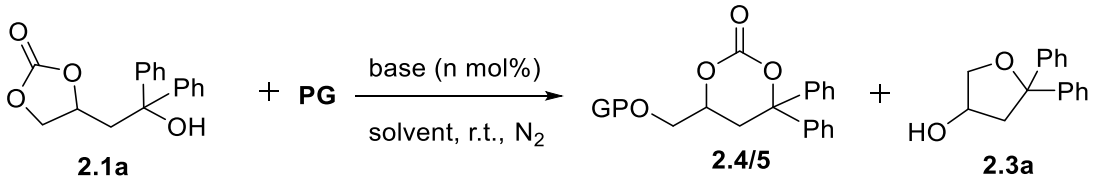
Table 2.2 Qualitative reactions between **Al^{Cl}** and epoxy alcohol **2.B1**.



Entry[a]	Cat.	DBU	CO_2	AcIm	Conv.	2.1a/2.3a
1	✓	✓	✓	✓	high	**2.1a+2.3a**
2	✓	×	✓	✓	high	**2.1a**
3	×	✓	✓	✓	low	**2.1a+2.3a**
4	✓	✓	×	✓	0	–
5[b]	×	✓	×	×	low	**2.3a**

[a] Reaction conditions: substrate (0.25 mmol), butanone (3 mL), 45 °C, 18 h. [b] Using **2.1a** as starting material.

Table 2.3 Installation of other protecting groups.

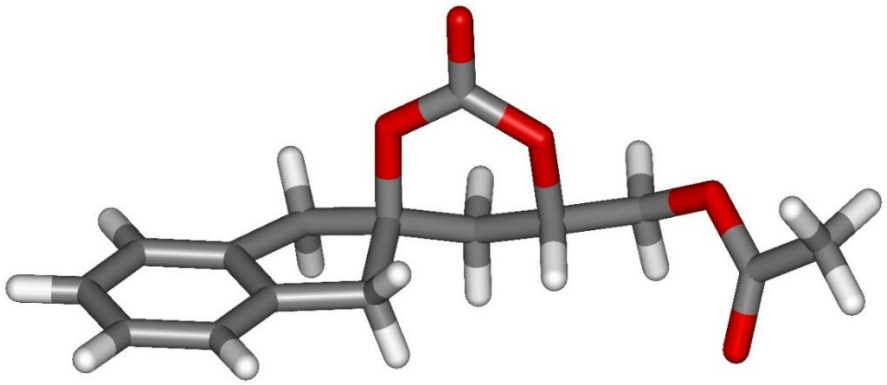


PG (1.2 equiv)	Base (mol equiv)	T/h	Solvent	Results[b, c]
Benzoylimidazole[e]	TBD (0.3)	2 h/12 h	CH_3CN	86%/89% of **2.4**[d]
Pivoylimidazole[e]	TBD (0.3)	2 h/12 h	CH_3CN	79%/93% of **2.5**[d]
TMSIm	TBD (0.3)	2 h	CH_3CN	Trace of **2.3a**
TBDMSIm	TBD (0.3)	2 h	CH_3CN	no conversion
TMSCl	DBU (1.2)	16 h	DCM	13% of **2.3a**
TMSCl	TBD (0.3)	2 h	CH_3CN	no conversion
TBDMSCl	TBD (0.3)	2 h	CH_3CN	no conversion
TBDMSCl	Imidazole (1.2)	2 h	CH_3CN	no conversion

[a] Reaction conditions: substrate **2.1a** (0.10 mmol), solvent (0.20 mL), under N_2. [b] Conversions measured by ^{1}H NMR ($CDCl_3$). [c] Determined by ^{1}H NMR using mesitylene as internal standard. [d] Yield of isolated product, [e] freshly prepared, see reference.[24]

[24] J. Zhuo, Y. Zhang, Z. Li, C. Li, *ACS Catal.* **2020**, *10*, 3895–3903.

2.6.8 X-ray crystallographic studies of 2.2p



Crystallized with DCM and pentane.

General experimental procedure for X-ray analysis: The measured crystals of carbonate **2.2p** were stable under atmospheric conditions; nevertheless, they were treated under inert conditions immersed in perfluoro-polyether as protecting oil for manipulation. Data Collection: measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX II 4K CCD area detector, a FR591 rotating anode with MoKα radiation, Montel mirrors and a Kryoflex low temperature device (T = −173 °C). Full-sphere data collection was used with ω and φ scans. Programs used: Data collection Apex2 V2011.3 (Bruker-Nonius 2008), data reduction Saint+Version 7.60A (Bruker AXS 2008) and absorption correction SADABS V. 2008−1 (2008). Structure Solution: SHELXTL Version 6.10 (Sheldrick, 2000)[25] was used. Structure Refinement: SHELXTL-97-UNIX VERSION.

Crystallographic details for 2.2p: $C_{15}H_{16}O_5$, M_r = 276.28, orthorhombic, $P2_12_12_1$, a = 12.7976(2) Å, b = 10.50753(14) Å, c = 11.1906(2) Å, $\alpha = \gamma = 90^o$, β = 115.914(2)°, V = 1353.51(4) Å^3, Z = 4, ρ = 1.356 mg·M^{-3}, μ = 0.102 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 584, crystal size = 0.15 × 0.10 × 0.10 mm, θ(min) = 2.625°, θ(max) = 40.759°, 114539 reflections collected, 8744 reflections unique (R_{int} = 0.0268), GoF = 1.198, R_1 = 0.0357 and wR_2 = 0.1370 [$I > 2\sigma(I)$], R_1 = 0.0421 and wR_2 = 0.1432 (all indices), min/max residual density = −0.225/0.625 [e·Å^{-3}]. Completeness to θ(40.759°) = 99.2%. CCDC number 1997736.

[25] G. M. Sheldrick, SHELXTL Crystallographic System, version 6.10; Bruker AXS, Inc.: Madison, WI, 2000.

2.6.9 Computational acylation of 5MCC-OH (2.1a)

The acylation of the **5MCC-OH** (**2.1a**) having a tertiary OH group was calculated using the same acylation method/steps as reported in Figure 2.1 for **6MCC-OH**. These additional studies were performed to elucidate why under the optimized experimental conditions for the preparation of **6MCC-OAc** (**2.2a**), no acylated 5-membered carbonate could be detected (Figure 2.2).

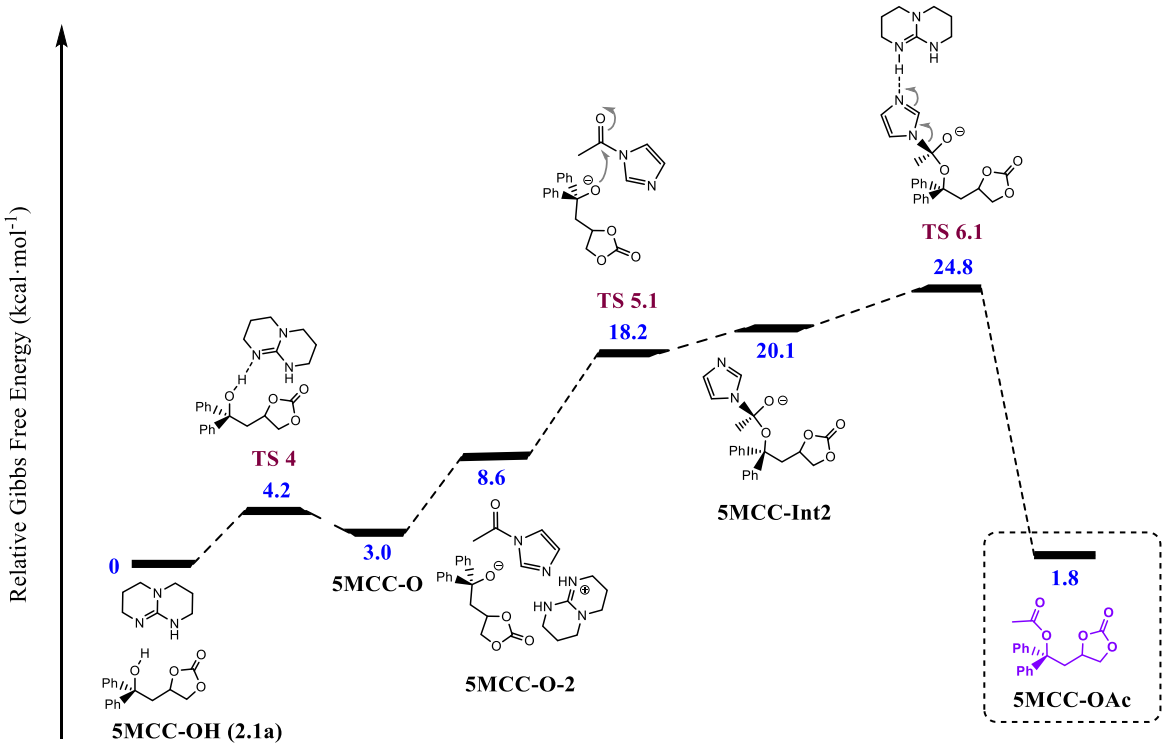


Figure 2.2 Relative Gibbs free energy profile in kcal·mol^{-1} for the acylation of **5MCC-OH** (**2.1a**). Note that the acylation pathway for 6MCC-OH is provided in the main text.

The $\Delta\Delta G^{\ddagger}$ between the two pathways leading to either **5MCC-OAc** and **6MCC-OAc** (**2.2a**) were compared. Both pathways begin with the same reactant **5MCC-OH** (**2.1a**). Note that the acylation of 6MCC-OH involves *first* the isomerization of **5MCC-OH** (**2.1a**) to **6MCC-OH**:

Figure 2.1: $\Delta G^{\ddagger}$ = 17.6 kcal·mol^{-1}

Figure 2.2: $\Delta G^{\ddagger}$ = 24.8 kcal·mol^{-1}

Thus, the acylation of **6MCC-OH** (starting from **5MCC-OH**) is **7.2 kcal·mol^{-1}** more favored, and provides a rationale for the exclusive observation and formation of **6MCC-OAc** at r.t.

2.6.10 Relative Gibbs free energy and potential energy profiles

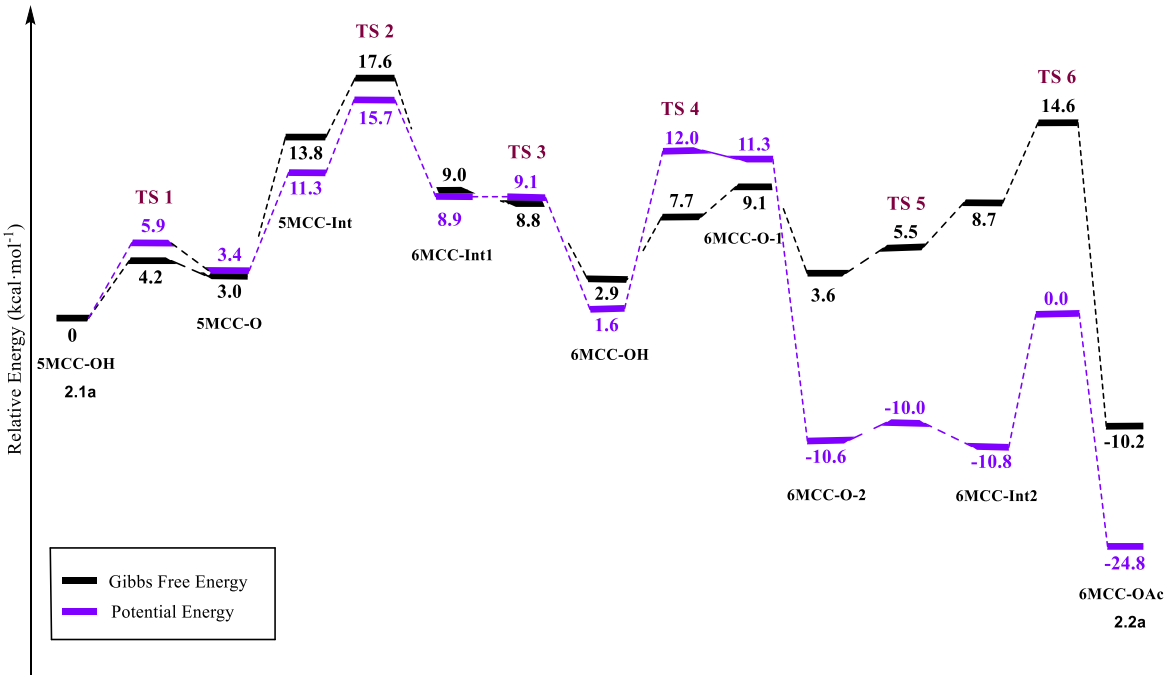


Figure 2.3 Relative Gibbs free energy (black) and potential energy (purple) profiles in kcal·mol^{-1}. This is the entire mechanism that involves both the isomerization of **2.1a** and acylation towards the formation of **2.2a**.

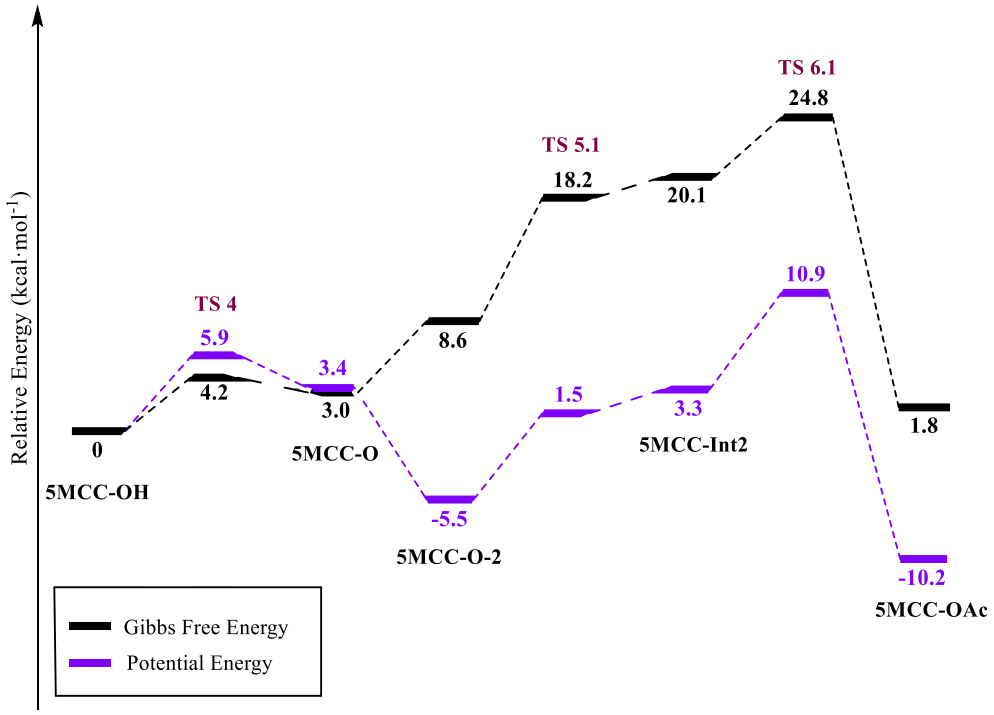


Figure 2.4 Relative Gibbs free energy (black) and potential energy (purple) profiles in kcal·mol^{-1}. This is the acylation mechanism for **5MCC-OH** (**2.1a**).

2.6.11 Visual description of the mechanism leading to 6MCC-OAc

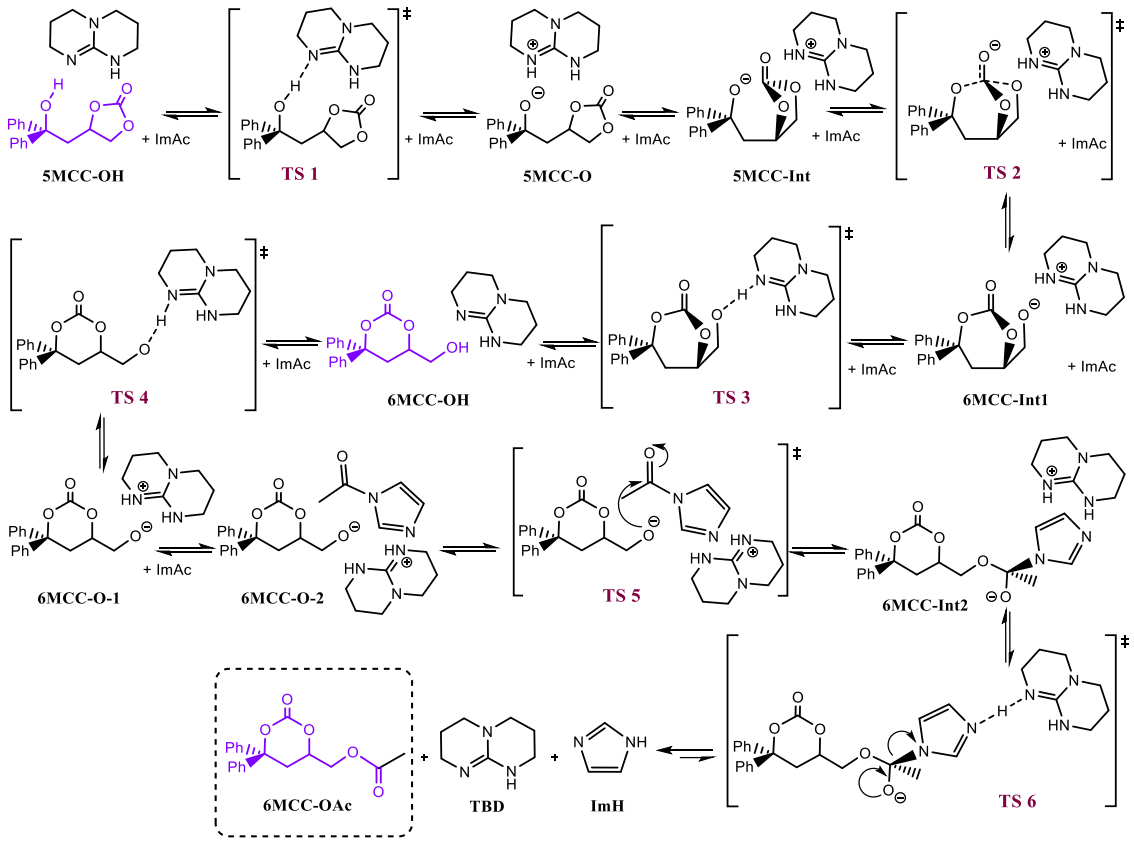


Figure 2.5 Detailed scheme of the reaction mechanism from the reactant (**5MCC-OH**) to the product (**6MCC-OAc**).

Full access to the computational data can be achieved through the following link:

http://dx.doi.org/10.19061/iochem-bd-1-171

2.6.12 Comparison of thermodynamic stability of the different carbonates

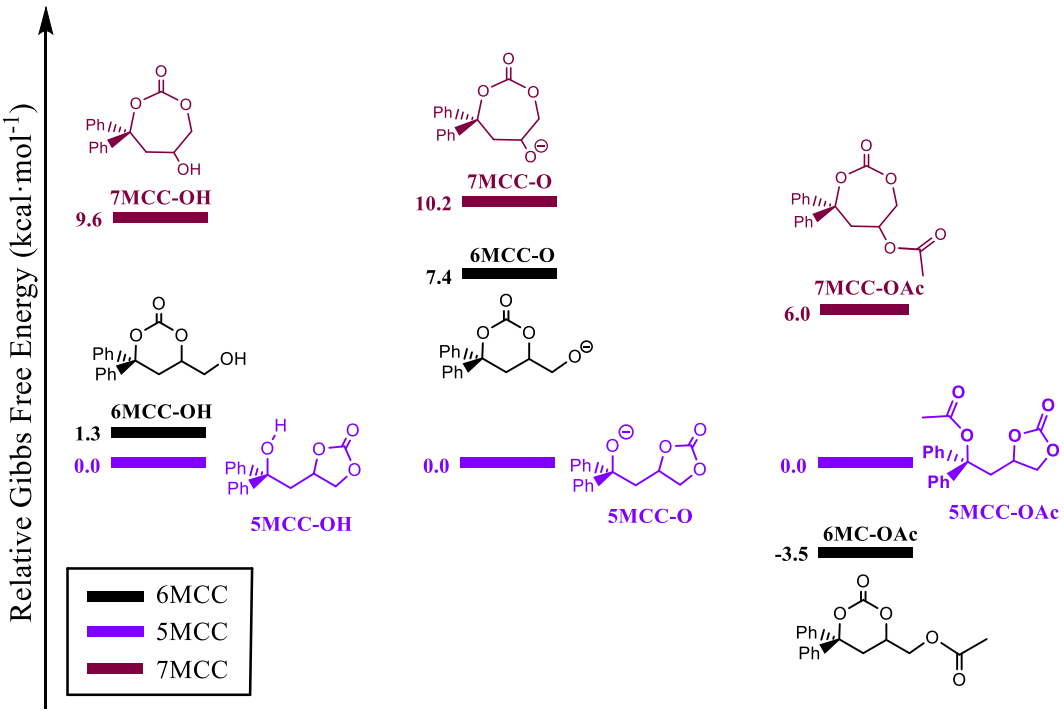


Figure 2.6 Gibbs free energy (in kcal·mol^{-1}) relative to **5MCC**. The first, second, and third columns compare the alcohol, alkoxide and acetate derivatives, respectively.

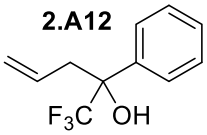
Figure 2.6 shows a comparison between substrates with different functional groups/substituents relative to the five-membered carbonate ring structures. Note that here we compare the stability of the "isolated" five-, six- and seven-membered carbonates (based on **2.1a**), without any additional stabilization provided by interactions with TBD and/or imidazole.

The **7MMC** shows a tendency to be thermodynamically less stable than the other carbonate structures. The **6MCC´s** display the same trend except for the acetate structure. This general behavior is consistent with the experimental results.

2.6.13 Characterization data for all new and relevant compounds

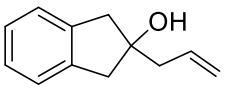
Homoallylic alcohols

2.A12



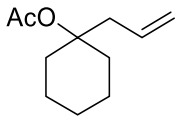
See reference[26]. The product was isolated as colorless oil, eluent: 1% - 2% EA in hexane. Yield: 27%, 95:5 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.3, 1.9 Hz, 2H), 7.47 – 7.34 (m, 3H), 5.63 – 5.49 (m, 1H), 5.32 – 5.17 (m, 2H), 2.99 (dd, *J* = 14.3, 6.7 Hz, 1H), 2.85 (dd, *J* = 14.2, 8.1 Hz, 1H), 2.61 (s, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.98, 130.53, 129.70, 128.69, 128.49, 128.37, 126.87, 126.59, 126.58, 124.03, 122.16, 76.06, 75.78, 75.50, 40.46 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.91, -79.16 ppm.

2.A16



See reference[27]. The product was isolated as a light-yellow solid, eluent: 2% - 3% EA in hexane, yield: 37%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.13 (m, 4H), 6.13 – 5.89 (m, 1H), 5.26 – 5.16 (m, 2H), 3.57 (s, 1H), 3.09 (d, *J* = 16.2 Hz, 2H), 2.96 (d, *J* = 16.2 Hz, 2H), 2.52 (dt, *J* = 7.3, 1.2 Hz, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.30, 134.10, 126.76, 125.12, 119.18, 81.61, 46.64, 45.16 ppm.

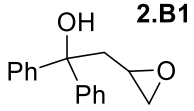
2.A18



The product was isolated as light-yellow oil, eluent: 2%-3% EA in hexane. Yield: 50%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 – 5.66 (m, 1H), 5.11 – 4.93 (m, 2H), 2.64 (dt, *J* = 7.4, 1.2 Hz, 2H), 2.25 – 2.11 (m, 2H), 2.00 (s, 3H), 1.66 – 1.30 (m, 8H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.52, 133.25, 118.15, 83.45, 42.07, 34.60, 25.63, 22.38, 21.94 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{18}O_2$) 123.1168 $(M–CH_3COO)^+$: found: 123.1169.

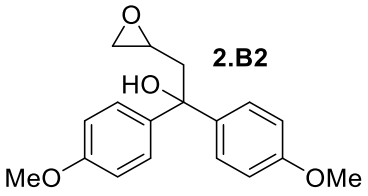
Expoxy alcohols 2.B1-2.B18

2.B1

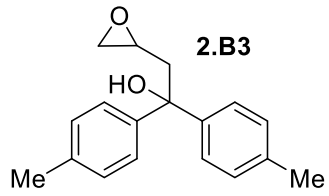


The product was isolated as a white solid, yield: 98%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 4H), 7.36 – 7.22 (m, 6H), 3.21 (s, 1H), 2.98 (dtd, *J* = 7.0, 4.2, 2.7 Hz, 1H), 2.78 – 2.64 (m, 2H), 2.47 (dd, *J* = 4.9, 2.8 Hz, 1H), 2.35 (dd, *J* = 14.4, 7.2 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.91, 146.27, 128.43, 128.42, 127.31, 127.14, 126.16, 125.95, 78.24, 49.80, 47.18, 44.27 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{16}H_{16}NaO_2$) 236.1043 $(M+Na)^+$: found: 263.1046.

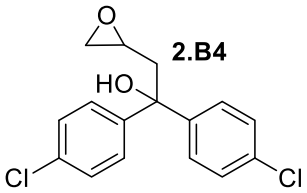
[26] Z. Xie, G. Li, G. Zhao, J. Wang, *Chin. J. Chem.* **2010**, *28*, 1212-1216.
[27] S. Silver, A. Leppänen, R. Sjöholm, A. Penninkangas, R. Leino, *Eur. J. Org. Chem.* **2005**, 1058–1081.



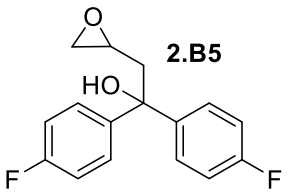
The product was isolated as an orange oil, yield: 56%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 4H), 6.89 – 6.81 (m, 4H), 3.80 (s, 3H), 3.78 (s, 3H), 3.08 (s, 1H), 2.97 (dtd, *J* = 7.1, 4.3, 2.8 Hz, 1H), 2.68 (dd, *J* = 4.9, 4.0 Hz, 1H), 2.61 (dd, *J* = 14.3, 4.4 Hz, 1H), 2.45 (dd, *J* = 4.9, 2.8 Hz, 1H), 2.34 (dd, *J* = 14.3, 7.0 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.68, 158.58, 139.46, 138.73, 127.37, 127.23, 113.65, 113.63, 77.68, 55.37, 49.85, 47.23, 44.59 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{18}H_{20}NaO_4$) 323.1254; $(M+Na)^+$: found: 323.1246.



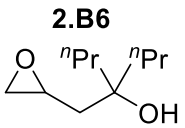
The product was isolated as a pale-colored oil, eluent: 5% - 10% EA in hexane, yield: 73%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.18 – 7.10 (m, 4H), 3.11 (s, 1H), 2.98 (dtd, *J* = 7.0, 4.2, 2.7 Hz, 1H), 2.70 – 2.62 (m, 2H), 2.45 (dd, *J* = 4.9, 2.8 Hz, 1H), 2.40 – 2.30 (m, 7H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.18, 143.58, 136.78, 136.61, 129.04, 129.02, 126.02, 125.83, 77.91, 49.82, 47.19, 44.36, 21.09; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{18}H_{20}NaO_2$) 291.1356 $(M+Na)^+$: found: 291.1358.



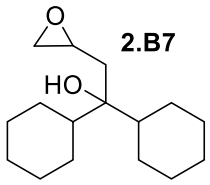
The product was isolated as a white solid, yield: 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.36 – 7.26 (m, 6H), 3.47 (s, 1H), 2.94 (dtd, *J* = 7.8, 3.9, 2.7 Hz, 1H), 2.77 – 2.69 (m, 2H), 2.49 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.20 (dd, *J* = 14.5, 7.7 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.06, 144.36, 133.38, 133.27, 128.69, 128.61, 127.59, 127.32, 77.67, 49.58, 47.08, 43.87 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{16}H_{14}Cl_2NaO_2$) 331.0263 $(M+Na)^+$: found: 331.0258.



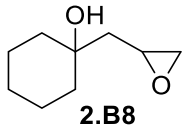
The product was isolated as a white solid, yield: 79%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.39 – 7.34 (m, 2H), 7.07 – 6.94 (m, 4H), 3.43 (s, 1H), 2.95 (dtd, *J* = 7.8, 4.0, 2.7 Hz, 1H), 2.74 – 2.66 (m, 2H), 2.48 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.25 (dd, *J* = 14.4, 7.5 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.98, 162.93, 161.02, 160.97, 142.66, 142.63, 141.87, 141.85, 127.91, 127.85, 127.72, 127.66, 115.36, 115.28, 115.19, 115.11, 77.64, 49.65, 47.09, 44.32 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.55, -115.82 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{16}H_{13}F_2O$) 259.0929 $(M–OH)^+$: found: 259.0929.



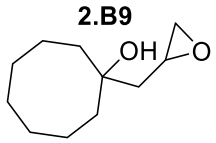
The product was isolated as a light-yellow oil, yield: 76%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.10 (dtd, *J* = 7.0, 4.1, 2.7 Hz, 1H), 2.78 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.79 (dd, *J* = 14.5, 4.2 Hz, 2H), 1.59 – 1.46 (m, 5H), 1.40 – 1.26 (m, 4H), 0.93 (td, *J* = 7.3, 2.6 Hz, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 74.63, 49.24, 46.99, 42.15, 42.11, 42.03, 17.05, 16.94, 14.80, 14.77 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{19}O$) 155.1430 $(M–OH)^+$: found: 155.1428.



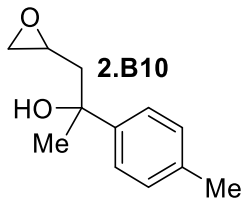
The product was isolated as a colorless oil, yield: 83%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.04 (dtd, *J* = 7.0, 4.2, 2.7 Hz, 1H), 2.80 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.49 (dd, *J* = 5.0, 2.8 Hz, 1H), 1.89 – 1.72 (m, 10H), 1.64 – 1.52 (m, 4H), 1.33 – 0.95 (m, 10H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 77.37, 49.61, 48.10, 45.29, 44.91, 37.15, 27.58, 27.39, 27.32, 27.22, 27.18, 27.16, 27.12, 27.09, 26.81 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{16}H_{27}O$) 235.2056 $(M\text{-}OH)^+$: found: 235.2057.



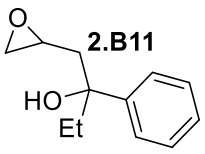
The product was isolated as a light-yellow oil, yield: 86%.[20] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.15 (dtd, *J* = 7.1, 4.2, 2.8 Hz, 1H), 2.79 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.80 (dd, *J* = 14.4, 4.3 Hz, 2H), 1.70 – 1.41 (m, 11H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 71.70, 49.05, 46.93, 44.67, 38.13, 37.84, 25.78, 22.30, 22.21 ppm.



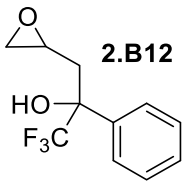
The product was isolated as a colorless oil, yield: 59%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.21 – 3.11 (m, 1H), 2.80 (t, *J* = 4.5 Hz, 1H), 2.48 (dd, *J* = 5.1, 2.8 Hz, 1H), 1.95 – 1.77 (m, 4H), 1.71 – 1.37 (m, 14H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 75.22, 49.25, 47.03, 44.04, 36.79, 36.68, 28.35, 28.28, 25.06, 22.34, 22.30 ppm. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{20}NaO_2$) 207.1356 $(M+Na)^+$: found: 207.1357.



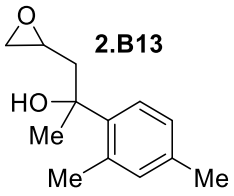
The product was isolated as a light-yellow oil, yield: 89%, 63:37 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 5.57H), 7.22 – 7.11 (m, 5.51H), 3.00 – 2.95 (m, 1H), 2.87 (dtd, *J* = 8.1, 3.8, 2.8 Hz, 1.73H), 2.77 (s, 1.29H), 2.72 (dd, *J* = 5.0, 4.0 Hz, 1.09H), 2.66 (dd, *J* = 4.9, 4.1 Hz, 1.76H), 2.44 (dd, *J* = 5.0, 2.7 Hz, 1.09H), 2.41 (dd, *J* = 4.9, 2.7 Hz, 1.99H), 2.35 (s, 8.26H), 2.29 (dd, *J* = 14.5, 3.5 Hz, 1.82H), 2.07 (dd, *J* = 14.3, 4.8 Hz, 1.09H), 1.98 (dd, *J* = 14.3, 6.7 Hz, 1.09H), 1.75 (dd, *J* = 14.5, 8.3 Hz, 1.99H), 1.66 (s, 3.43H), 1.59 (s, 5.74H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.77, 144.56, 136.64, 136.43, 129.13, 129.11, 124.77, 124.71, 74.81, 74.17, 49.72, 49.51, 47.07, 46.65, 46.42, 46.18, 31.02, 29.87, 21.09, 21.07 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{16}NaO_2$) 215.1043 $(M+Na)^+$: found: 215.1047.



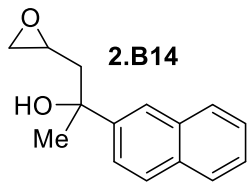
The product was isolated as a colorless oil, yield: 85%, 69:31 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (ddt, *J* = 8.4, 6.3, 1.2 Hz, 2.87H), 7.36 (td, *J* = 7.7, 1.6 Hz, 2.86H), 7.28 – 7.22 (m, 1.69H), 2.97 (tdd, J = 5.8, 4.0, 2.7 Hz, 0.45H), 2.87 (s, 0.93H), 2.81 (dddd, *J* = 8.5, 4.1, 3.4, 2.8 Hz, 1H), 2.71 (dd, J = 5.0, 4.0 Hz, 0.46H), 2.63 (dd, *J* = 4.9, 4.1 Hz, 1.01H), 2.45 (dd, *J* = 5.0, 2.8 Hz, 0.46H), 2.40 (dd, *J* = 4.9, 2.8 Hz, 1.01H), 2.34 (d, *J* = 3.3 Hz, 0.91 H), 2.30 (d, J = 3.4 Hz, 0.53H), 2.06 (d, *J* = 5.7 Hz, 0.86H), 1.97 (qd, *J* = 7.4, 1.1 Hz, 0.86H), 1.87 (qd, *J* = 7.4, 2.4 Hz, 1.95H), 1.76 (dd, *J* = 14.5, 8.4 Hz, 0.98H), 0.78 (td, *J* = 7.4, 1.8 Hz, 4.47H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.67, 128.35, 126.84, 126.69, 125.49, 125.33, 76.76, 49.71, 49.37, 47.27, 46.73, 44.98, 44.72, 36.20, 34.94, 7.79, 7.65 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{15}O$) 175.1117 $(M–OH)^+$: found: 175.1115.



Scale: 1.85 mmol. The product was isolated as white solid, eluent: 3% - 10% EA in hexane. Yield: 42%, 97:3 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.49 – 7.34 (m, 3H), 3.78 (s, 1H), 2.87 – 2.77 (m, 2H), 2.70 (dd, *J* = 4.7, 3.9 Hz, 1H), 2.51 (dd, *J* = 4.6, 2.6 Hz, 1H), 1.92 (dd, *J* = 15.3, 9.4 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.55, 128.87, 128.65, 128.56, 126.80, 126.18, 123.91, 121.64, 48.56, 46.40, 37.77 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.45, -80.95; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{11}F_3NaO_2$) 255.0603 $(M+Na)^+$: found: 255.0605.

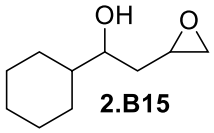


The product was isolated as a yellow oil. Yield: 63%, 57:43 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 0.43H), 7.41 – 7.32 (m, 0.57H), 7.04 – 6.92 (m, 2H), 3.01 – 2.85 (m, 0.99H), 2.77 – 2.67 (m, 1.46H), 2.56 – 2.50 (m, 3.50), 2.45 (td, *J* = 4.8, 2.8 Hz, 1.04H), 2.30 – 2.28 (m, 3.59H), 2.21 (dd, *J* = 14.4, 4.7 Hz, 0.62H), 2.08 (dd, *J* = 14.4, 6.7 Hz, 0.56H), 1.80 – 1.72 (m, 2.20H), 1.66 (s, 1.28H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.80, 141.56, 136.90, 136.74, 135.41, 134.52, 133.72, 133.58, 126.76, 126.52, 126.22, 126.04, 75.80, 75.39, 49.91, 49.66, 47.00, 46.71, 44.40, 29.78, 29.67, 22.47, 22.38, 20.80 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{17}O$) 189.1274 $(M–OH)^+$: found: 189.1279.



2.B14

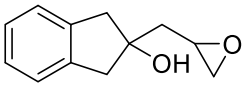
The product was isolated as a brown oil. Yield: 42%, 74:26 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.79 (m, 6.35H), 7.64 – 7.43 (m, 4.94H), 3.10 (s, 0.95H), 3.00 (dddd, *J* = 6.7, 4.9, 3.1, 2.0 Hz, 1H), 2.87 (dddd, *J* = 8.3, 4.1, 3.5, 2.8 Hz, 0.35H), 2.72 (dd, *J* = 4.9, 4.0 Hz, 0.62H), 2.64 (dd, *J* = 4.9, 4.1 Hz, 1.15H), 2.45 – 2.39 (m, 2.16H), 2.18 (dd, *J* = 14.4, 4.9 Hz, 0.36H), 2.09 (dd, *J* = 14.3, 6.7 Hz, 0.38H), 1.84 (dd, *J* = 14.5, 8.3 Hz, 1.1H), 1.77 (s, 1.08H), 1.69 (s, 3.11H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.03, 144.79, 133.40, 133.31, 132.52, 132.44, 128.43, 128.34, 128.20, 128.18, 127.63, 127.61, 126.46, 126.30, 126.00, 125.94, 123.51, 123.49, 123.47, 123.23, 75.17, 74.47, 49.73, 49.52, 47.11, 46.63, 46.16, 45.94, 31.08, 29.85 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{15}O$) 211.1117 $(M–OH)^+$: found: 211.1119.



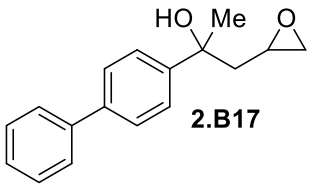
2.B15

The product was isolated as colorless oil, eluent: 3% - 10% EA in hexane. Yield: 47%, 58:42 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.64 (ddd, *J* = 9.4, 5.6, 2.8 Hz, 1H), 3.58 (ddd, *J* = 9.7, 5.7, 2.7 Hz, 0.71H), 3.19 – 3.13 (m, 0.73H), 3.10 (dtd, *J* = 7.1, 4.2, 2.7 Hz, 0.91H), 2.82 (dd, *J* = 4.9, 4.0 Hz, 0.75H), 2.78 (dd, *J* = 4.9, 4.0 Hz, 0.98H), 2.61 (dd, *J* = 4.9, 2.8 Hz, 0.7H), 2.49 (dd, *J* = 4.9, 2.7 Hz, 1.01H), 2.14 (s, 1.39H), 1.92 – 0.95 (m, 25.75H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 74.98, 73.48, 51.32, 50.74, 47.23, 46.70, 43.91, 43.81, 36.72, 36.10, 29.13, 28.99, 28.04, 28.03, 26.61, 26.59, 26.35, 26.23, 26.21 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{19}O_2$) 171.1380 $(M+H)^+$: found: 171.1379.

2.B16

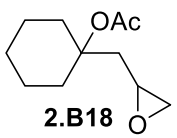


Scale: 3.6 mmol. The product was isolated as a light-yellow solid, eluent: 2% - 3% EA in hexane. Yield: 64%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 4H), 3.24 (dtd, *J* = 6.8, 4.1, 2.7 Hz, 1H), 3.16 (d, *J* = 16.2 Hz, 2H), 3.06 (d, *J* = 16.2 Hz, 2H), 2.84 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.55 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.14 (dd, *J* = 14.3, 4.1 Hz, 1H), 1.81 (dd, *J* = 14.3, 7.5 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.17, 140.94, 126.90, 126.85, 125.24, 125.17, 81.90, 49.69, 47.14, 47.13, 46.93, 42.76 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{13}O$) 173.0961 $(M–OH)^+$: found: 173.0962.



2.B17

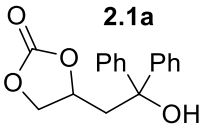
The product was isolated as a light-yellow oil. Yield: 66%, 67:33 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.51 (m, 18H), 7.50 – 7.41 (m, 6H), 7.38 – 7.31 (m, 3H), 3.04 (dddd, *J* = 6.8, 4.8, 4.0, 2.7 Hz, 1H), 2.97 – 2.88 (m, 2H), 2.76 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.70 (dd, *J* = 4.9, 4.1 Hz, 2H), 2.49 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.45 (dd, *J* = 4.9, 2.8 Hz, 2H), 2.37 (dd, *J* = 14.5, 3.4 Hz, 2H), 2.15 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.02 (dd, *J* = 14.4, 6.8 Hz, 1H), 1.79 (dd, *J* = 14.5, 8.4 Hz, 2H), 1.72 (s, 3H), 1.65 (s, 6H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.76, 146.55, 140.88, 140.85, 139.95, 139.78, 128.93, 128.90, 127.40, 127.38, 127.18, 127.15, 125.36, 125.29, 74.94, 74.26, 49.74, 49.51, 47.12, 46.69, 46.34, 46.10, 31.06, 29.82 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{17}O$) 237.1274 $(M–OH)^+$: found: 237.1281.



2.B18

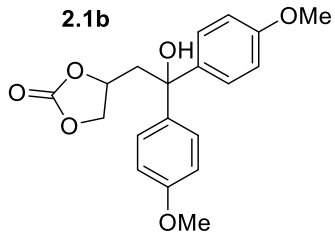
Scale: 5 mmol. The product was isolated as light-yellow oil, eluent: 5% EA in hexane. Yield: 13%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.97 (dtd, *J* = 7.0, 4.1, 2.7 Hz, 1H), 2.73 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.42 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.34 – 2.24 (m, 3H), 2.04 (s, 3H), 1.91 (dd, *J* = 14.7, 7.3 Hz, 1H), 1.60 – 1.39 (m, 7H), 1.33 – 1.20 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.74, 83.09, 48.51, 46.34, 40.58, 35.14, 34.98, 25.52, 22.40, 21.89, 21.79 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{18}NaO_3$) 221.1148 $(M+Na)^+$: found: 221.1142.

5-Membered cyclic carbonates 2.1a-2.1g



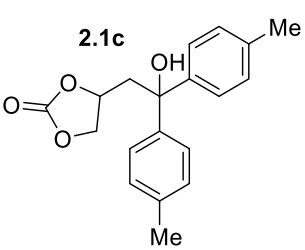
2.1a

Condition A. The product was isolated as a white solid. Yield: 85%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 10H), 4.68 (dddd, *J* = 9.3, 8.5, 7.6, 3.6 Hz, 1H), 4.30 (dd, *J* = 9.0, 7.6 Hz, 1H), 4.05 (t, *J* = 8.8 Hz, 1H), 2.99 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.73 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.34 (s, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.00, 145.99, 145.10, 128.78, 128.70, 127.93, 127.72, 125.80, 125.79, 76.83, 75.34, 71.01, 45.49 ppm. **IR** (neat): *v* = 1777 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{16}NaO_4$) 307.0941 $(M+Na)^+$: found: 307.0941.



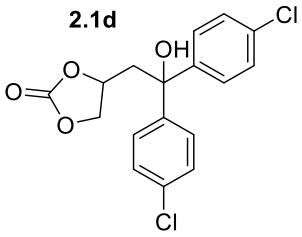
2.1b

Condition A. The product was isolated as a light-yellow solid. Yield: 99%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 13.1, 8.8 Hz, 4H), 6.84 (dd, *J* = 12.4, 8.6 Hz, 4H), 4.64 (qd, *J* = 8.4, 3.3 Hz, 1H), 4.24 (t, *J* = 8.1 Hz, 1H), 4.00 (t, *J* = 8.7 Hz, 1H), 3.77 (d, *J* = 6.3 Hz, 6H), 2.88 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.73 (s, 1H), 2.63 (dd, *J* = 13.6, 9.4 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.22, 159.07, 154.97, 138.35, 137.47, 131.13, 129.42, 127.18, 127.12, 114.06, 114.01, 76.45, 75.41, 71.07, 55.45, 45.90 ppm; **IR** (neat): *v* = 1769 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{20}NaO_6$) 367.1152 $(M+Na)^+$: found: 367.1146.

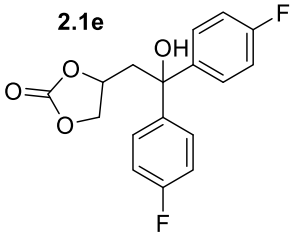


2.1c

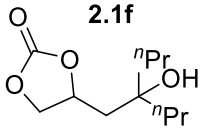
Condition A. The product was isolated as a white solid. Yield: 95%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 4H), 7.12 (dd, *J* = 11.0, 8.1 Hz, 4H), 4.64 (dddd, *J* = 9.5, 8.6, 7.6, 3.4 Hz, 1H), 4.25 (dd, *J* = 9.1, 7.6 Hz, 1H), 4.02 (t, *J* = 8.8 Hz, 1H), 2.92 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.65 (dd, *J* = 13.7, 9.5 Hz, 1H), 2.37 (s, 1H), 2.31 (d, *J* = 6.6 Hz, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.02, 143.28, 142.33, 137.73, 137.44, 129.44, 129.38, 125.71, 76.71, 75.44, 71.09, 45.60, 21.10 ppm; **IR** (neat): *v* = 1786 cm^{-1}; HRMS (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{20}NaO_4$) 335.1254 $(M+Na)^+$: found: 335.1265.



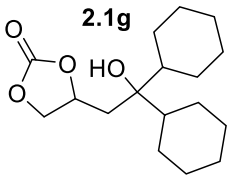
Condition A. The product was isolated as a white solid. Yield: 87%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 8H), 4.62 (tdd, *J* = 8.5, 7.6, 4.1 Hz, 1H), 4.34 (dd, *J* = 9.0, 7.6 Hz, 1H), 4.07 (t, *J* = 8.7 Hz, 1H), 2.90 (dd, *J* = 13.9, 4.1 Hz, 1H), 2.79 (s, 1H), 2.66 (dd, *J* = 13.9, 8.6 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.83, 144.06, 143.27, 134.12, 133.91, 129.04, 128.97, 127.29, 127.22, 76.26, 74.94, 70.87, 45.36 ppm; **IR** (neat): *v* = 1776 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{14}Cl_2NaO_4$) 375.0161 $(M+Na)^+$: found: 375.0160.



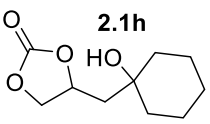
Condition A. The product was isolated as a white solid. Yield: 85%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (tdd, *J* = 9.1, 5.2, 2.1 Hz, 4H), 7.04 (td, *J* = 8.7, 7.5 Hz, 4H), 4.64 (tdd, *J* = 8.5, 7.6, 4.0 Hz, 1H), 4.34 (dd, *J* = 9.0, 7.6 Hz, 1H), 4.07 (t, *J* = 8.7 Hz, 1H), 2.92 (dd, *J* = 13.8, 4.0 Hz, 1H), 2.69 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.54 (s, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.31, 163.22, 161.34, 161.25, 154.79, 141.63, 141.60, 140.79, 140.77, 127.76, 127.70, 127.66, 127.60, 115.87, 115.77, 115.70, 115.61, 77.41, 74.98, 70.88, 45.81 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.76, -114.32 ppm; **IR** (neat): *v* = 1772 cm^{-1}; HRMS (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{14}F_2NaO_4$) 343.0752 $(M+Na)^+$: found: 343.0756.



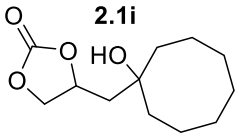
Condition A. The product was isolated as a light-yellow oil. Yield: 82%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.97 – 4.92 (m, 1H), 4.58 (dd, *J* = 8.8, 7.7 Hz, 1H), 4.14 (t, *J* = 8.6 Hz, 1H), 2.05 (dd, *J* = 14.5, 6.1 Hz, 1H), 1.79 (dd, *J* = 14.5, 6.7 Hz, 1H), 1.54 – 1.24 (m, 10H), 0.93 (td, *J* = 7.2, 5.1 Hz, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.20, 74.78, 73.62, 71.07, 43.06, 42.98, 41.26, 17.24, 16.72, 14.63, 14.61 ppm; **IR** (neat): *v* = 1775 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{20}NaO_4$) 239.1254 $(M+Na)^+$: found: 239.1252.



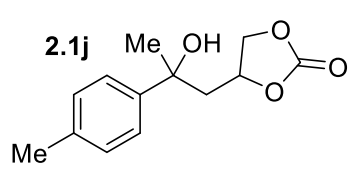
Condition A. The product was isolated as a white solid. Yield: 67%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.93 (qd, *J* = 8.0, 4.7 Hz, 1H), 4.53 (t, *J* = 8.3 Hz, 1H), 4.13 (t, *J* = 8.4 Hz, 1H), 2.06 – 1.89 (m, 2H), 1.87 – 1.59 (m, 11H), 1.44 (qt, *J* = 11.7, 2.9 Hz, 2H), 1.23 – 0.90 (m, 10H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.28, 76.06, 76.00, 71.43, 46.35, 45.31, 37.21, 27.22, 27.05, 26.79, 26.72, 26.62, 26.52, 26.48 ppm; **IR** (neat): *v* = 1789 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{28}NaO_4$) 319.1880 $(M+Na)^+$: found: 319.1864.



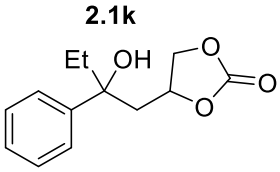
Condition A. The product was isolated as a light-yellow solid. Yield: 87%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.99 (tt, *J* = 8.1, 6.4 Hz, 1H), 4.58 (dd, *J* = 8.8, 7.7 Hz, 1H), 4.14 (t, *J* = 8.6 Hz, 1H), 2.10 (dd, *J* = 14.5, 6.3 Hz, 1H), 1.80 – 1.74 (m, 2H), 1.64 – 1.28 (m, 10H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.30, 74.60, 71.01, 70.52, 45.49, 39.37, 36.96, 25.45, 22.14, 22.07 ppm; **IR** (neat): *v* = 1787 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{16}NaO_4$) 223.0941 $(M+Na)^+$: found: 223.0941.



Condition A. The product was isolated as a white solid. Yield: 93%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.02 – 4.95 (m, 1H), 4.59 (dd, *J* = 8.8, 7.7 Hz, 1H), 4.15 (t, *J* = 8.6 Hz, 1H), 2.15 (dd, *J* = 14.5, 6.2 Hz, 1H), 1.85 – 1.40 (m, 16H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.34, 74.89, 73.93, 71.05, 44.56, 38.49, 34.99, 28.16, 27.91, 24.96, 22.24, 22.05 ppm; **IR** (neat): *v* = 1776 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{20}NaO_4$) 251.1254 $(M+Na)^+$: found: 251.1258.

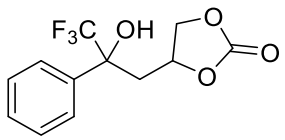


Condition A. The product was isolated as a white solid. Yield: 79%, 73:27 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2.78H), 7.20 – 7.15 (m, 2.72H), 4.87 (tt, *J* = 8.1, 6.4 Hz, 1H), 4.47 (dd, J = 8.7, 7.5 Hz, 0.38H), 4.38 (dddd, J = 9.3, 8.4, 7.5, 4.0 Hz, 0.37H), 4.25 (t, J = 8.5 Hz, 0.38H), 4.21 (dd, *J* = 8.8, 7.8 Hz, 1H), 3.79 (t, *J* = 8.6 Hz, 1H), 2.49 – 2.33 (m, 5.75H), 2.22 – 2.10 (m, 1.44H), 1.64 (s, 4.34H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.13, 154.95, 143.80, 142.70, 137.25, 137.23, 129.47, 124.42, 124.32, 75.19, 74.81, 73.63, 73.17, 71.16, 70.35, 47.83, 47.29, 32.15, 30.72, 21.06 ppm; **IR** (neat): *v* = 1783 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{16}NaO_4$) 259.0941 $(M+Na)^+$: found: 259.0952.



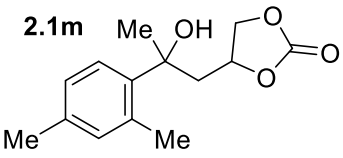
Condition B. The product was isolated as a pale-yellow oil. Yield: 73%, 7:3 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 5.68H), 7.29 – 7.25 (m, 1.42H), 4.82 (dddd, *J* = 8.3, 7.7, 6.8, 5.8 Hz, 1H), 4.48 (dd, J = 8.5, 7.2 Hz, 0.42H), 4.36 (dddd, J = 9.5, 8.4, 7.1, 3.4 Hz, 0.42H), 4.30 (t, J = 8.5 Hz, 0.42H), 4.03 (dd, *J* = 8.8, 7.7 Hz, 1H), 3.67 (t, *J* = 8.6 Hz, 1H), 2.50 – 2.40 (m, 1.42H), 2.37 – 2.10 (m, 2.46H), 2.01 – 1.82 (m, 2.94H), 0.74 (td, *J* = 7.4, 1.5 Hz, 4.40H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.24, 154.96, 144.38, 143.83, 128.71, 128.69, 127.32, 127.28, 125.02, 124.95, 76.16, 75.67, 75.28, 74.84, 71.34, 70.26, 46.77, 45.95, 36.47, 35.60, 7.46, 7.24 ppm; **IR** (neat): *v* = 1776 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{16}NaO_4$) 259.0941 $(M+Na)^+$: found: 259.0948.

2.1l



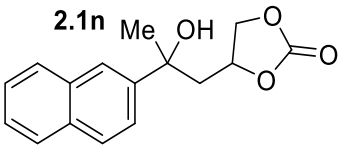
Condition B. Scale: 0.5 mmol. The product was isolated as white solid, eluent: 10% - 20% EA in hexane. Yield: 78%, 9:1 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H), 7.42 – 7.33 (m, 3H), 4.73 (qd, *J* = 7.5, 4.7 Hz, 1H), 3.97 (ddd, *J* = 8.8, 7.7, 1.0 Hz, 1H), 3.72 (td, *J* = 8.7, 1.0 Hz, 1H), 3.03 (s, 3H), 2.70 (ddd, *J* = 14.6, 5.2, 1.0 Hz, 1H), 2.42 (dd, *J* = 14.6, 7.3 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.23, 135.57, 129.53, 129.12, 128.50, 126.15, 126.10, 123.87, 121.60, 76.35, 76.12, 73.35, 69.75, 39.95 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –79.29, -80.21 ppm; **IR** (neat): *v* = 1786 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{13}F_3NaO_4$) 299.0502 $(M+Na)^+$: found: 299.0491.

2.1m

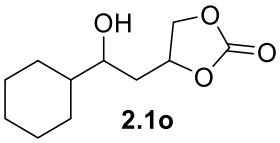


Condition A. The product was isolated as a colorless oil. Yield: 46%, 74:26 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 1.35H), 7.06 – 6.90 (m, 2.75H), 4.93 (tt, *J* = 8.1, 6.1 Hz, 1H), 4.46 – 4.35 (m, 0.72H), 4.31 (dd, *J* = 8.8, 7.7 Hz, 1H), 4.23 – 4.18 (m, 0.35H), 3.91 (t, *J* = 8.7 Hz, 1.01H), 2.68 (dd, J = 14.1, 3.8 Hz, 0.35H), 2.52 – 2.46 (m, 4.22H), 2.41 – 2.32 (m, 2.02H), 2.30 (s, 4.17H), 2.25 – 2.12 (m, 1.14H), 1.72 – 1.70 (m, 4.26H) ppm; **^{13}C** NMR (101 MHz, $CDCl_3$) δ 155.14, 155.03, 141.25, 139.80, 137.42, 137.41, 134.28, 134.26, 133.98, 133.86, 127.00, 126.92, 125.77, 125.54, 75.45, 75.07, 74.36, 74.04, 71.17, 70.52, 45.49, 45.12, 31.10, 29.67, 22.39, 22.34, 20.75 ppm; **IR** (neat): *v* = 1778 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{18}NaO_4$) 273.1097 $(M+Na)^+$: found: 273.1094.

2.1n

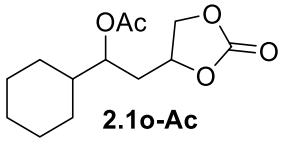


Condition A. The product was isolated as a pink solid employing 10 % - 70% Et_2O in hexane as eluent. Yield: 58%, 9:1 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 – 7.92 (m, 0.99H), 7.86 – 7.83 (m, 3.37H), 7.54 – 7.43 (m, 3.79H), 4.88 (tt, *J* = 8.1, 6.3 Hz, 1H), 4.48 (dd, J = 8.7, 7.4 Hz, 0.10H), 4.42 – 4.33 (m, 0.08H), 4.28 (t, J = 8.5 Hz, 0.07H), 4.19 (dd, *J* = 8.8, 7.8 Hz, 0.97H), 3.79 (t, *J* = 8.5 Hz, 1H), 2.68 – 2.55 (m, 0.14H), 2.44 (dd, *J* = 14.5, 6.4 Hz, 1.04H), 2.24 (dd, *J* = 14.5, 6.2 Hz, 0.99H), 1.74 (s, 3.43H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.05, 154.86, 144.01, 143.00, 133.28, 133.22, 132.61, 132.58, 128.79, 128.68, 128.30, 128.24, 127.72, 127.69, 126.70, 126.40, 126.25, 123.16, 123.06, 122.88, 122.84, 76.90, 75.08, 74.73, 73.88, 73.49, 71.11, 70.28, 47.57, 47.05, 32.10, 30.68 ppm; **IR** (neat): *v* = 1782 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{16}H_{16}NaO_4$) 295.0941 $(M+Na)^+$: found: 295.1043.



2.1o

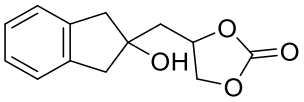
Condition A. The product was isolated as light-yellow solid, eluent: 10% - 25% EA in hexane. Yield: 27%, 58:42 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.99 – 4.91 (m, 1H), 4.61 – 4.54 (m, 1.02H), 4.25 – 4.21 (m, 0.42H), 4.15 (dd, *J* = 8.7, 7.7 Hz, 0.58H), 3.63 – 3.59 (m, 0.58H), 3.52 – 3.48 (m, 0.42H), 2.06 – 1.63 (m, 8.64H), 1.40 – 0. 93 (m, 6.46H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.26, 75.93, 75.66, 72.57, 72.43, 70.61, 69.67, 44.29, 43.82, 38.29, 37.21, 28.93, 28.88, 27.99, 27.87, 26.42, 26.40, 26.16, 26.13, 26.04, 26.01 ppm; **IR** (neat): *v* = 1791 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{18}NaO_4$) 237.1079 $(M+Na)^+$: found: 237.1089.



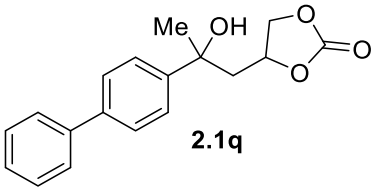
2.1o-Ac

The product was isolated as light-yellow solid, eluent: 5%-15% EA in hexane. Yield: 50%, 69:31 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.94 – 4.89 (ddd, *J* = 9.7, 5.5, 3.0 Hz, 0.31H), 4.78 – 4.66 (m, 1.69H), 4.58 – 4.48 (m, 1.02H), 4.13 – 4.06 (m, 1.02H), 2.21 – 2.10 (m, 0.98H), 2.08 – 2.07 (m, 3.12H), 1.93 – 1.84 (m, 1.15H), 1.78 – 1.66 (m, 5.32H), 1.57 – 1.48 (m, 1.14H), 1.27 – 1.10 (m, 3.80H), 1.05 – 0.93 (m, 2.24H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.27, 170.62, 154.85, 154.65, 74.85, 74.82, 74.35, 73.65, 69.69, 69.58, 41.80, 41.58, 36.03, 35.87, 28.97, 28.62, 28.26, 28.11, 26.35, 26.28, 26.05, 25.96, 25.90, 21.18, 21.12 ppm; **IR** (neat): *v* = 1729, 1798 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{20}NaO_5$) 279.1210 $(M+Na)^+$: found: 279.1203.

2.1p

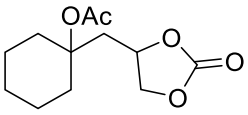


Condition B. The product was isolated as a colorless oil. Yield: 58%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 4H), 5.06 (tt, *J* = 8.0, 6.4 Hz, 1H), 4.61 (dd, *J* = 8.8, 7.8 Hz, 1H), 4.20 (t, *J* = 8.5 Hz, 1H), 3.21 – 2.93 (m, 4H), 2.28 – 2.18 (m, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.19, 140.65, 140.05, 127.16, 127.12, 125.43, 125.27, 80.54, 75.08, 70.68, 48.34, 46.67, 43.66 ppm; **IR** (neat): *v* = 1779 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{14}NaO_4$) 257.0784 $(M+Na)^+$: found: 257.0792.



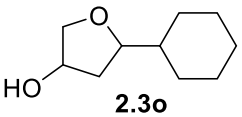
2.1q

Condition A. The product was isolated as a white solid. Yield: 41%, 83:17 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 4.06H), 7.51 – 7.43 (m, 4.11H), 7.40 – 7.34 (m, 1.07H), 4.92 (tt, *J* = 8.0, 6.3 Hz, 0.83H), 4.54 – 4.41 (m, 0.37H), 4.31 – 4.24 (m, 1H), 3.85 (t, *J* = 8.6 Hz, 0.84H), 2.58 – 2.28 (m, 1.93H), 2.27 – 2.13 (m, 1.23H), 1.68 (s, 3.12H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.18, 155.02, 145.85, 144.72, 140.41, 140.29, 128.95, 128.90, 127.60, 127.57, 127.39, 127.36, 127.12, 127.10, 125.03, 124.93, 75.19, 74.81, 73.51, 73.13, 71.18, 70.36, 47.66, 47.23, 32.00, 30.50 ppm; **IR** (neat): *v* = 1768 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{18}H_{18}NaO_4$) 321.1097 $(M+Na)^+$: found: 321.1102.



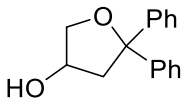
2.1h-Ac

Condition A. Scale: 0.5 mmol. The product was isolated as orange oil, eluent: 10% - 25% EA in hexane. Yield: 77%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.84 (tdd, *J* = 8.5, 7.8, 3.5 Hz, 1H), 4.52 (dd, *J* = 8.5, 7.8 Hz, 1H), 4.00 (t, *J* = 8.4 Hz, 1H), 2.46 – 2.21 (m, 4H), 2.05 (s, 3H), 1.64 – 1.26 (m, 8H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.96, 154.90, 81.91, 73.74, 70.02, 41.87, 35.12, 34.95, 25.28, 22.37, 21.84, 21.61 ppm; **IR** (neat): *v* = 1725, 1794 cm^{-1}; **HRMS (**ESI+; MeOH): *m/z* calcd. ($C_{12}H_{18}NaO_5$) 265.1046 $(M+Na)^+$: found: 265.1045.

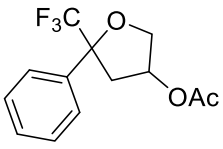


2.3o

Note: the tetrahydrofuran derivative **2.3o** was isolated in the attempted synthesis of cyclic carbonate **2.1o**. **Condition A**. The product was isolated as colorless oil, eluent: 10% - 25% EA in hexane. Yield: 48%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.46 – 4.38 (m, 1H), 3.92 (dd, *J* = 9.8, 4.3 Hz, 0.52H), 3.86 – 3.74 (m, 1H), 3.70 – 3.58 (m, 1H), 3.46 (q, *J* = 7.7 Hz, 0.5H), 2.29 – 2.20 (m, 1.44H), 1.98 – 1.87 (m, 1.62H), 1.81 – 0.87 (m, 12.09H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.77, 82.66, 75.41, 75.24, 72.56, 72.28, 43.14, 42.98, 39.33, 39.29, 29.92, 29.85, 29.22, 28.97, 26.58, 26.11, 26.06, 25.94, 25.88 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{19}O_2$) 171.1380 $(M+H)^+$: found: 171.1380.

2.3a


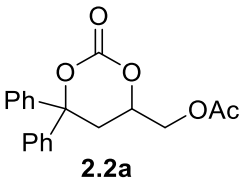
Note: product **2.3a** was isolated when using the conditions of Table 2.1, entry 17.[28] The product was isolated as white solid, eluent: 10% - 25% EA in hexane. Yield: 15%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.44 – 7.39 (m, 2H), 7.35 – 7.27 (m, 4H), 7.25 – 7.17 (m, 2H), 4.55 (s, 1H), 4.16 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.96 (ddd, *J* = 9.9, 2.6, 0.9 Hz, 1H), 2.87 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.78 (ddd, *J* = 13.5, 3.0, 0.9 Hz, 1H), 1.53 (s, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.22, 146.18, 128.57, 128.43, 127.18, 127.06, 125.87, 125.75, 87.89, 75.29, 73.40, 48.49 ppm.

2.3l-Ac


Note: the tetrahydrofuran product (**2.3l-Ac**) was the only product isolated while attempting the synthesis of cyclic carbonate **2.2l**. The product was isolated as white solid, eluent: 2% - 5% EA in hexane. Yield: 89%, 97:3 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 2H), 7.41 – 7.32 (m, 3H), 5.38 (ddt, *J* = 6.8, 4.4, 2.3 Hz, 1H), 4.34 (dd, *J* = 10.2, 4.6 Hz, 1H), 4.13 (ddq, *J* = 10.2, 2.3, 1.1 Hz, 1H), 2.97 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.58 (ddt, *J* = 14.4, 2.5, 1.1 Hz, 1H), 1.77 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.63, 137.82, 128.93, 128.60, 128.23, 126.66, 126.57, 126.56, 124.39, 122.13, 85.85, 85.62, 85.38, 85.15, 74.46, 74.30, 40.44, 20.75 ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -78.80, -79.10 ppm; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{13}F_3NaO_3$) 297.0709 $(M+Na)^+$: found: 297.0719.

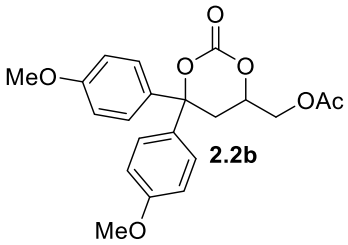
[28]M. Gamedze, C. Nkambule, *Tetrahedron Lett.* **2015**, *56*, 1825–1829.

6-Membered cyclic carbonates 2.2a-2.2q



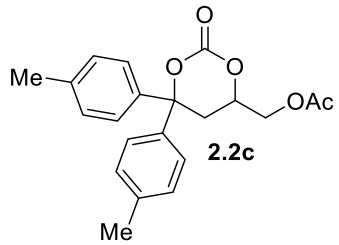
2.2a

The product was isolated as a white solid. Yield: 91%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 7H), 7.37 – 7.25 (m, 4H), 4.51 – 4.43 (m, 1H), 4.28 (dd, *J* = 12.3, 3.3 Hz, 1H), 4.24 – 4.16 (m, 1H), 2.93 (dd, *J* = 14.3, 3.2 Hz, 1H), 2.58 (dd, *J* = 14.4, 12.2 Hz, 1H), 2.08 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.58, 148.12, 142.42, 141.07, 129.37, 128.76, 128.56, 128.55, 125.37, 125.20, 86.31, 74.10, 64.68, 34.21, 20.74 ppm; **IR** (neat): *v* = 1737 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{18}NaO_5$) 349.1046 $(M+Na)^+$: found: 349.1039.



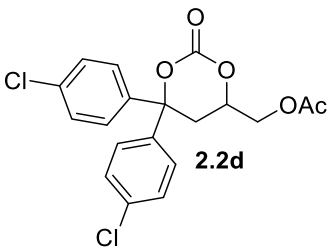
2.2b

The product was isolated as a colorless oil. Yield: 83%. **^{1}H NMR** (500 MHz, CD_3CN) δ 7.33 – 7.26 (m, 4H), 7.00 – 6.95 (m, 2H), 6.93 – 6.87 (m, 2H), 4.42 (ddt, *J* = 12.0, 5.4, 3.2 Hz, 1H), 4.26 (dd, *J* = 12.4, 3.0 Hz, 1H), 4.16 (dd, *J* = 12.4, 5.6 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.99 (dd, *J* = 14.5, 3.4 Hz, 1H), 2.58 (dd, *J* = 14.5, 12.1 Hz, 1H), 2.03 (s, 3H) ppm; **^{13}C NMR** (126 MHz, CD_3CN) δ 171.38, 160.51, 160.45, 149.07, 136.42, 134.66, 127.88, 127.54, 115.33, 114.77, 87.02, 75.89, 65.50, 56.06, 56.00, 34.03, 20.87 ppm; **IR** (neat): *v* = 1742 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{21}H_{23}O_7$) 387.1423 $(M+H)^+$: found: 387.1438.



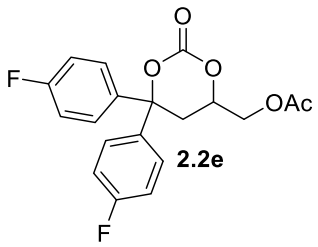
2.2c

The product was isolated as a colorless oil. Yield: 82%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.5, 0.8 Hz, 4H), 7.23 – 7.17 (m, 2H), 7.16 – 7.12 (m, 2H), 4.52 – 4.43 (m, 1H), 4.28 (dd, *J* = 12.3, 3.3 Hz, 1H), 4.20 (dd, *J* = 12.3, 5.0 Hz, 1H), 2.86 (dd, *J* = 14.3, 3.2 Hz, 1H), 2.54 (dd, *J* = 14.3, 12.2 Hz, 1H), 2.33 (d, *J* = 10.8 Hz, 6H), 2.09 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) **δ** 170.66, 148.33, 139.83, 138.45, 138.40, 138.33, 130.01, 129.40, 125.37, 125.14, 86.39, 77.48, 77.16, 76.84, 74.13, 64.80, 34.36, 21.13, 21.11, 20.80 ppm; **IR** (neat): *v* = 1741 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{21}H_{22}NaO_5$) 377.1359 $(M+Na)^+$: found: 377.1370.



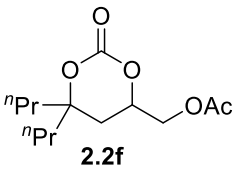
2.2d

The product was isolated as a colorless oil. Yield: 65%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.36 – 7.28 (m, 6H), 4.46 (ddt, *J* = 12.2, 4.9, 3.3 Hz, 1H), 4.29 (dd, *J* = 12.4, 3.4 Hz, 1H), 4.22 (dd, *J* = 12.4, 4.9 Hz, 1H), 2.86 (dd, *J* = 14.4, 3.2 Hz, 1H), 2.54 (dd, *J* = 14.4, 12.2 Hz, 1H), 2.10 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.60, 147.54, 140.60, 139.25, 135.08, 134.96, 129.80, 129.15, 126.80, 126.69, 85.46, 74.04, 64.56, 34.21, 20.80 ppm; **IR** (neat): *v* = 1738 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{16}Cl_2NaO_5$) 417.0267 $(M+Na)^+$: found: 417.0270.



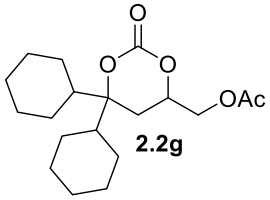
2.2e

The product was isolated as a white solid. Yield: 84%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.15 – 7.09 (m, 2H), 7.07 – 7.01 (m, 2H), 4.47 (ddt, *J* = 12.2, 4.9, 3.3 Hz, 1H), 4.30 (dd, *J* = 12.3, 3.4 Hz, 1H), 4.22 (dd, *J* = 12.4, 4.9 Hz, 1H), 2.85 (dd, *J* = 14.4, 3.1 Hz, 1H), 2.56 (dd, *J* = 14.4, 12.2 Hz, 1H), 2.10 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.62, 163.68, 163.67, 161.70, 161.69, 147.74, 138.31, 138.28, 136.77, 136.75, 127.48, 127.41, 127.28, 127.21, 116.66, 116.49, 115.94, 115.77, 85.63, 74.07, 64.63, 34.56, 20.80 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.70, -112.85 ppm; **IR** (neat): *v* = 1741 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{16}F_2NaO_5$) 385.0858 $(M+Na)^+$: found: 385.0855.



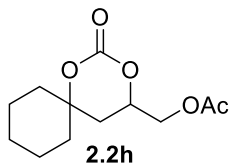
2.2f

The product was isolated as a white solid. Yield: 79%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.72 – 4.62 (m, 1H), 4.26 (dd, *J* = 12.1, 3.5 Hz, 1H), 4.16 (dd, *J* = 12.2, 5.5 Hz, 1H), 2.11 (s, 3H), 1.96 – 1.74 (m, 3H), 1.70 – 1.56 (m, 4H), 1.48 – 1.28 (m, 4H), 0.95 (td, *J* = 7.3, 4.1 Hz, 6H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.73, 149.11, 85.26, 73.12, 65.09, 41.49, 39.36, 31.64, 20.83, 16.97, 16.31, 14.43, 14.28 ppm; **IR** (neat): *v* = 1737 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{22}NaO_5$) 281.1359 $(M+Na)^+$: found: 281.1362.



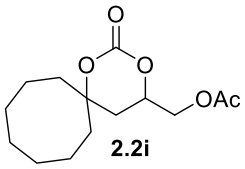
2.2g

The product was isolated as a colorless oil. Yield: 82%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.48 (ddt, *J* = 12.2, 6.1, 3.6 Hz, 1H), 4.25 (dd, *J* = 12.2, 3.3 Hz, 1H), 4.15 (dd, *J* = 12.1, 6.1 Hz, 1H), 2.11 (s, 3H), 2.01 – 1.68 (m, 15H), 1.27 – 1.08 (m, 10H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.77, 151.16, 89.96, 73.86, 64.82, 45.47, 45.00, 27.51, 26.96, 26.87, 26.84, 26.66, 26.57, 26.53, 26.29, 26.28, 26.04, 20.87 ppm; **IR** (neat): *v* = 1744 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{30}NaO_5$) 361.1985 $(M+Na)^+$: found: 361.1981.



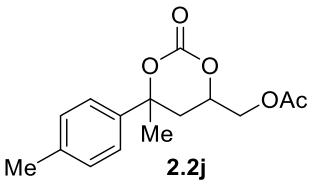
2.2h

The product was isolated as a white solid. Yield: 85%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.71 (ddt, *J* = 12.4, 5.5, 3.5 Hz, 1H), 4.27 (dd, *J* = 12.2, 3.5 Hz, 1H), 4.16 (dd, *J* = 12.2, 5.4 Hz, 1H), 2.10– 2.09 (m, 3H), 2.02 – 1.94 (m, 2H), 1.84 – 1.72 (m, 4H), 1.62 – 1.49 (m, 5H), 1.51 – 1.32 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.74, 148.85, 82.03, 72.91, 65.06, 38.72, 35.04, 33.74, 25.14, 21.78, 21.45, 20.83 ppm; **IR** (neat): *v* = 1736 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{18}NaO_5$) 256.1046 $(M+Na)^+$: found: 256.1052.



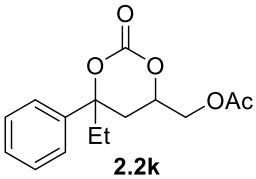
2.2i

The product was isolated as a brown oil. Yield: 94%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.68 (ddt, *J* = 12.4, 5.4, 3.5 Hz, 1H), 4.26 (dd, *J* = 12.1, 3.4 Hz, 1H), 4.16 (dd, *J* = 12.1, 5.5 Hz, 1H), 2.19 – 1.99 (m, 6H), 1.80 – 1.32 (m, 13H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.73, 148.81, 86.10, 73.20, 65.09, 37.98, 33.17, 32.78, 28.10, 27.69, 24.95, 21.88, 21.42, 20.83 ppm; **IR** (neat): *v* = 1738 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{22}NaO_5$) 293.1359 $(M+Na)^+$: found: 293.1362.



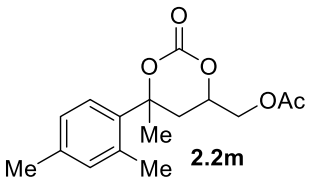
2.2j

The product was isolated as a colorless oil. Yield: 96%, 63:37 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 0.8H), 7.24 – 7.15 (m, 3.17H), 4.86 (ddt, *J* = 11.9, 5.4, 3.5 Hz, 0.37H), 4.32 – 4.08 (m, 2.63H), 2.47 – 2.28 (m, 4.09H), 2.23 – 2.12 (m, 1.02H), 2.09– 2.08 (m, 2.83H), 1.78 (s, 1.08H), 1.71 (s, 1.86H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.68, 170.65, 148.59, 148.53, 140.96, 139.07, 138.26, 138.11, 129.99, 129.54, 124.00, 123.76, 84.08, 83.14, 74.06, 73.75, 64.86, 64.69, 35.73, 35.50, 31.26, 27.66, 21.11, 21.07, 20.80, 20.78 ppm; **IR** (neat): *v* = 1743 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{18}NaO_5$) 301.1046 $(M+Na)^+$: found: 301.1050.



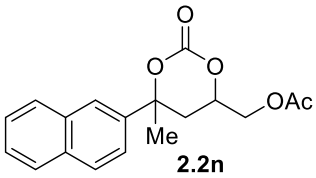
2.2k

The product was isolated as a colorless oil. Yield: 90%, 7:3 *dr*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 3.53H), 7.30 – 7.24 (m, 1.51H), 4.84 (ddt, *J* = 11.7, 5.5, 3.6 Hz, 1H), 4.30 – 4.08 (m, 2.7H), 2.49 – 2.35 (m, 0.99H), 2.26 – 2.13 (m, 1.34H), 2.10 – 2.04 (m, 2.54H), 2.03 – 1.95 (m, 1.73H), 0.84 (t, *J* = 7.4 Hz, 2.10H), 0.79 (t, *J* = 7.4 Hz, 0.9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.64, 170.60, 148.68, 148.47, 141.82, 140.50, 129.25, 128.80, 128.32, 128.07, 124.74, 124.42, 86.60, 85.88, 73.87, 73.53, 64.84, 64.74, 36.32, 34.46, 33.87, 33.47, 20.78, 20.76, 7.76, 7.33 ppm; **IR** (neat): *v* = 1735 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{18}NaO_5$) 301.1046 $(M+Na)^+$: found: 301.1045.



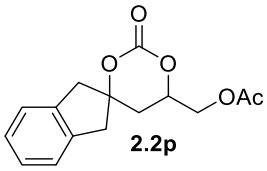
2.2m

The product was isolated as a colorless oil. Yield: 83%, 72:28 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.30 (d, *J* = 8.6 Hz, 0.29H), 7.19 – 7.14 (m, 0.71H), 7.05 – 7.01 (m, 2H), 4.84 (ddt, *J* = 12.1, 5.3, 3.5 Hz, 0.28H), 4.35 – 4.29 (m, 1.03H), 4.24 – 4.19 (m, 1.04H), 4.14 (dd, *J* = 12.2, 5.0 Hz, 0.72H), 2.76 (dd, *J* = 14.6, 3.2 Hz, 0.71H), 2.53 – 2.36 (m, 3.63H), 2.34 – 2.26 (m, 3.45H), 2.17 – 2.06 (m, 3.81H), 1.86 (s, 0.89H), 1.77 (s, 2.16H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.68, 170.65, 148.60, 148.49, 138.40, 138.29, 138.25, 136.12, 134.50, 134.08, 133.84, 127.50, 127.00, 125.31, 124.77, 85.11, 84.51, 74.14, 73.47, 64.85, 64.82, 34.75, 34.49, 29.43, 26.89, 22.11, 22.04, 20.82, 20.79 ppm; **IR** (neat): *v* = 1736 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{16}H_{20}NaO_5$) 315.1197 $(M+Na)^+$: found: 315.1203.



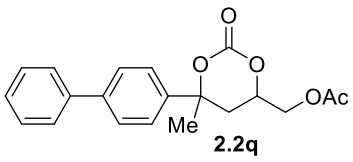
2.2n

The product was isolated preparative TLC, white solid, eluent: 25% EA in hexane. Yield: 76%, 91:9 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 3.85H), 7.56 – 7.50 (m, 1.99H), 7.33 (dd, *J* = 8.6, 2.1 Hz, 0.90H), 4.92 (ddt, *J* = 12.2, 5.3, 3.5 Hz, 0.09H), 4.33 (dd, *J* = 12.2, 3.6 Hz, 0.08H), 4.26 – 4.10 (m, 2.83H), 2.58 (dd, *J* = 14.4, 3.0 Hz, 0.90H), 2.27 (dd, *J* = 14.3, 12.1 Hz, 0.97H), 2.09 – 2.04 (m, 2.86H), 1.89 (s, 0.24H), 1.82 (s, 2.7H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.57, 148.54, 141.00, 139.16, 133.20, 133.11, 132.86, 132.84, 129.53, 128.92, 128.44, 128.41, 127.70, 127.12, 126.96, 126.85, 126.75, 123.53, 122.69, 121.80, 121.53, 84.20, 83.25, 74.10, 73.76, 64.81, 64.61, 35.63, 35.41, 31.04, 27.63, 20.78, 20.74 ppm; **IR** (neat): *v* = 1735 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{18}H_{18}NaO_5$) 337.1046 $(M+Na)^+$: found: 337.1055.



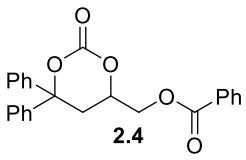
2.2p

The product was isolated as a white solid. Yield: 95%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 4H), 4.83 (dtd, *J* = 10.8, 5.0, 3.6 Hz, 1H), 4.33 (dd, *J* = 12.2, 3.6 Hz, 1H), 4.23 (dd, *J* = 12.2, 5.3 Hz, 1H), 3.39 (dd, *J* = 19.3, 16.6 Hz, 2H), 3.19 (dd, *J* = 16.5, 2.9 Hz, 2H), 2.26 – 2.08 (m, 5H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.69, 148.27, 138.84, 138.42, 127.63, 127.47, 124.88, 124.82, 89.72, 74.38, 64.88, 46.39, 44.53, 32.83, 20.83 ppm; **IR** (neat): *v* = 1734 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{16}NaO_5$) 299.0890 $(M+Na)^+$: found: 299.0882.



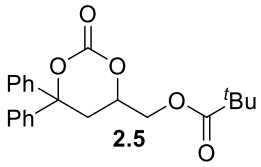
2.2q

The product was isolated by preparative TLC, light yellow oil, eluent: 25% EA in hexane. Yield: 80%, 94:6 *dr*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 1.97H), 7.61 – 7.55 (m, 1.97H), 7.48 – 7.43 (m, 1.97H), 7.41 – 7.34 (m, 2.79H), 4.92 – 4.87 (m, 0.06H), 4.37 – 4.13 (m, 2.94H), 2.50 (dd, *J* = 14.3, 3.1 Hz, 0.93H), 2.24 (dd, *J* = 14.3, 12.3 Hz, 0.99H), 2.09 (s, 2.43H), 1.78 (s, 2.76H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.64, 148.47, 141.43, 140.94, 140.10, 129.05, 128.05, 127.89, 127.20, 124.63, 84.00, 74.09, 64.68, 35.52, 31.26, 20.80 ppm; **IR** (neat): *v* = 1736 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{20}H_{20}NaO_5$) 363.1203 $(M+Na)^+$: found: 363.1201.



2.4

The product was isolated as a white solid. Yield: 79% (93% for 12 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.59 – 7.55 (m, 1H), 7.46 – 7.38 (m, 8H), 7.36 – 7.26 (m, 4H), 4.65 – 4.55 (m, 1H), 4.55 – 4.45 (m, 2H), 2.99 (dd, *J* = 14.3, 3.1 Hz, 1H), 2.64 (dd, *J* = 14.3, 12.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.21, 148.17, 142.50, 141.16, 133.64, 129.95, 129.45, 129.29, 128.83, 128.66, 128.61, 128.60, 125.43, 125.28, 86.39, 74.38, 65.15, 34.49; **IR** (neat): *v* = 1719 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{24}H_{20}NaO_5$) 411.1203 $(M+Na)^+$: found: 411.1208.



2.5

The product was isolated as a white solid. Yield: 86% (89% for 12 h). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 10H), 4.52 – 4.43 (m, 1H), 4.31 – 4.21 (m, 2H), 2.92 (dd, *J* = 14.3, 3.1 Hz, 1H), 2.56 (dd, *J* = 14.3, 12.0 Hz, 1H), 1.22 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.12, 148.19, 142.59, 141.10, 129.42, 128.84, 128.61, 128.60, 125.44, 125.33, 86.33, 74.25, 64.51, 39.06, 34.58, 27.28; **IR** (neat): *v* = 1731 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{22}H_{24}NaO_5$) 391.1516 $(M+Na)^+$: found: 391.1531.

Chapter 2

Chapter 3.

A Novel Catalytic Route to Polymerizable Bicyclic Cyclic Carbonate Monomers from Carbon Dioxide

The results described in this chapter have been published in:

C. Qiao, W. Shi, A. Brandolese, J. Benet-Buchholz, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed*. **2022**, e202205053.

UNIVERSITAT ROVIRA I VIRGILI
CATALYTIC FORMATION OF HETEROCYCLES FROM - AND -EPOXY ALCOHOLS
Chang Qiao

3.1 Introduction

The catalytic recycling of carbon dioxide into valuable chemicals useful as intermediates in synthetic chemistry[1] and polymer science[2] represents a seminal approach within the context of a circular economy.[3] The synthesis of cyclic carbonates through non-reductive coupling methods embodies a valuable carbon dioxide reutilization approach and has advanced greatly in the last decade. In this regard, modern methods build on the [3+2] cycloaddition between readily available cyclic ethers and carbon dioxide (CO_2) under attractive process conditions.[4] Unlike for this well-established catalytic formation of 5-membered cyclic carbonates, traditional methods that allow for larger ring carbonate formation rely on the use of CO or $COCl_2$, which are extremely toxic.[5] (Semi)stoichiometric methods (Scheme 3.1a) include the use of homoallylic alcohols reported by Johnston[6] or diols as established by Buchard,[7a,b] Dyson[7c] and Tomishige.[7d] However, these entries to larger-ring cyclic carbonates typically

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[1] a) Z. Zhang, J.-H. Ye, T. Ju, L.-L. Liao, H. Huang, Y.-Y. Gui, W.-J. Zhou, D.-G. Yu, *ACS Catal*. **2020**, *10*, 10871–10885; b) Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun*. **2015**, *6*, 5933; c) Y. Zhang, T. Zhang, S. Das, *Green Chem*. **2020**, *22*, 1800–1820; d) M. Aresta, A. Dibenedetto, A. Angelini, *Chem. Rev*. **2014**, *114*, 1709–1742; e) B. Limburg, À. Cristòfol, F. Della Monica, A. W. Kleij, *ChemSusChem* **2020**, *13*, 6056–6065.

[2] a) B. Grignard, S. Gennen, C. Jérôme, A. W. Kleij, C. Detrembleur, *Chem. Soc. Rev*. **2019**, *48*, 4466–4514; b) W. Yu, E. Maynard, V. Chiaradia, M. C. Arno, A. P. Dove, *Chem. Rev*. **2021**, *121*, 10865–10907; c) B. Song, A. Qin, B. Z. Tang, *Cell Rep. Phys. Sci*. **2022**, *3*, 100719; d) M. Scharfenberg, J. Hilf, H. Frey, *Adv. Funct. Mater*. **2018**, *28*, 1704302.

[3] T. Keijer, V. Bakker, J. C. Slootweg, *Nat. Chem*. **2019**, *11*, 190–195.

[4] a) J. W. Comerford, I. D. V. Ingram, M. North, X. Wu, *Green Chem*. **2015**, *17*, 1966–1987; b) M. Alves, B. Grignard, R. Mereau, C. Jérôme, T. Tassaing, C. Detrembleur, *Catal. Sci. Technol*. **2017**, *7*, 2651–2684; c) R. Rajjak Shaikh, S. Pornpraprom, V. D'Elia, *ACS Catal*. **2018**, *8*, 419–450; d) A. J. Kamphuis, F. Picchioni, P. P. Pescarmona, *Green Chem*. **2019**, *21*, 406–448; e) P. P. Pescarmona, *Curr. Opin. Green Sustain. Chem*. **2021**, 29, 100457; f) P. Rollin, L. K. Soares, A. M. Barcellos, D. R. Araujo, E. J. Lenardão, R. G. Jacob, G. Perin, *Appl. Sci*. **2021**, *11*, 5024; g) L. Guo, K. J. Lamb, M. North, *Green Chem*. **2021**, ***23***, 77**–**118; h) F. Della Monica, A. W. Kleij, *Catal. Sci. Technol*. **2020**, *10*, 3483-3501; i) Y.-Y. Zhang, G.-W. Yang, R. Xie, L. Yang, B. Li, G.-P. Wu, *Angew. Chem. Int. Ed*. **2020**, *59*, 23921**–**23298.

[5] a) G. Rokicki, *Prog. Polym. Sci*. **2000**, *25*, 259–342; b) A. G. Shaikh, S. Sivaram, *Chem. Rev*. **1996**, *96*, 951–976; c) B. Gabriele, R. Mancuso, G. Salerno, L. Veltri, M. Costa, A. Dibenedetto, *ChemSusChem* **2011**, *4*, 1778–1786; d) D. M. Pearson, N. R.; Conley. R. M. Waymouth, *Adv. Synth. Catal*. **2011**, *353*, 3007–3013.

[6] B. A. Vara, T. J. Struble, W. Wang, M. C. Dobish, J. N. Johnston, *J. Am. Chem. Soc.* **2015**, *137*, 7302–7305.

[7] For methods utilizing diols as principal reagents see a) G. L. Gregory, M. Ulmann, A. Buchard, *RSC Adv*. **2015**, *5*, 39404–39408; b) T. M. McGuire, E. M. López-Vidal, G. L. Gregory, A. Buchard, *J. CO_2 Utiliz*. **2018**, *27*, 283–288; c) F. D. Bobbink, W. Gruszka, M. Hulla, S. Das, P. J. Dyson *Chem. Commun.* **2016**, *52*, 10787–10790; d) M. Honda, M. Tamura, K. Nakao, K. Suzuki, Y. Nakagawa, K. Tomishige, *ACS Catal*. **2014**, *4*, 1893–1896. For an example that does not require sacrificial reagents, see: e) Z.-F. Diao, Z.-H. Zhou, C.-X. Guo, B. Yu, L.-N. He, *RSC Adv*. **2016**, *6*, 32400–32404.

require the presence of sacrificial reagents such as alkyl halides, tosyl chloride or cyano pyridines. Transesterification of polyols with activated forms of CO_2[8] and the direct coupling of oxetanes and CO_2 (Scheme 3.1a)[9] also have shown potential to access larger carbonate heterocycles.

Larger ring-carbonates have important incentives in the area of polymer chemistry for the design of new types of functional macromolecules with tunable mechanical and thermal properties.[10] Therefore, conceptually new catalytic methods that enable a wider scope of such monomers while being created from a renewable carbon source can create important incentives for future low-carbon emission polymers.

3.2 Aims and objectives

Recently we disclosed an unusual isomerization of five- to six-membered cyclic carbonates (Scheme 3.1b).[11a] A tertiary, β-positioned alcohol group in the smaller-sized heterocycles plays a crucial role as it acts as a pro-nucleophile able to attack the carbonate carbon center thereby forming a larger-ring cyclic carbonate. Key to the success of this ring-expanding approach is the higher kinetic feasibility to intercept the primary alcohol present in the six-membered compound. These protected six-membered carbonates were examined under standard ring-opening polymerization (ROP) conditions but failed to deliver a polycarbonate product as *O*-deprotection and back-isomerization to the thermodynamically more stable five-membered

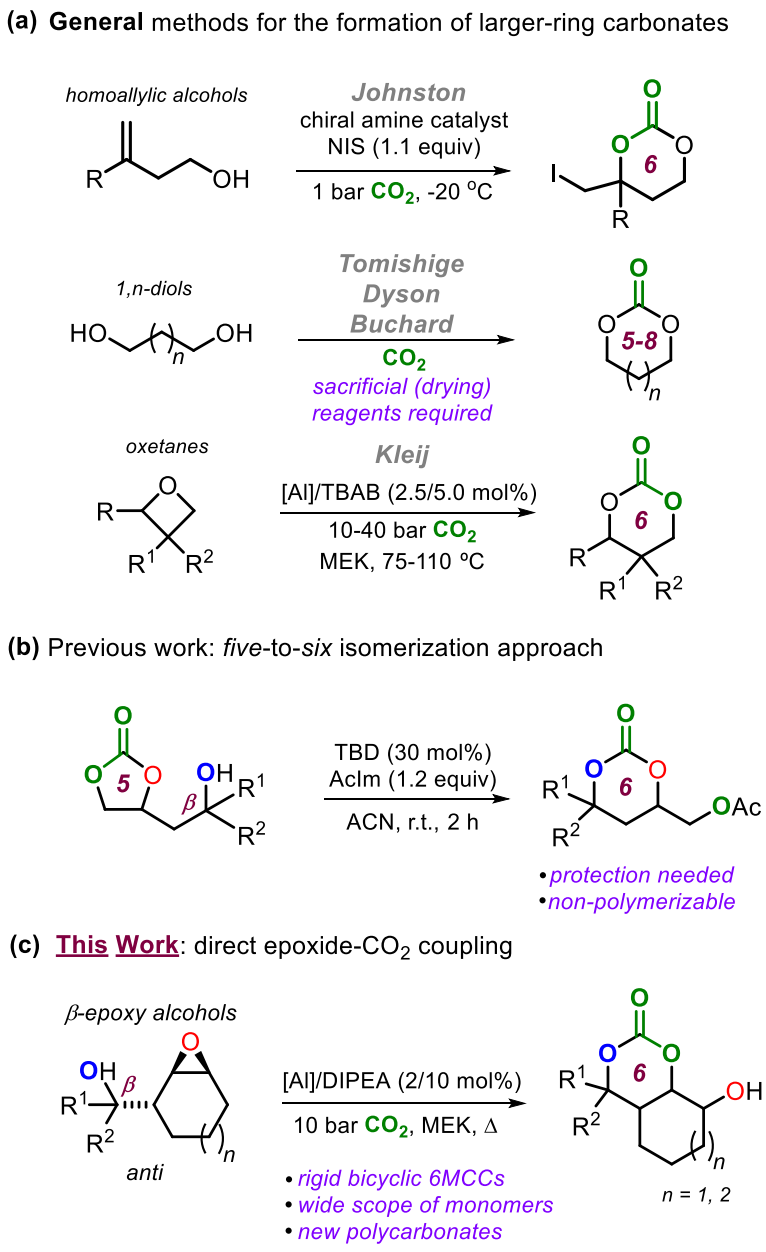
[8] a) P. Furtwengler, L. Avérous, *Sci. Rep.* **2018**, *8*, 9134; b) E. R. Baral, J. H. Lee, J. G. Kim, *J. Org. Chem.* **2018**, *83*, 11768–11776; c) M. Selva, A. Perosa, S. Guidi, L. Cattelan, *Beilstein J. Org. Chem.* **2016**, *12*, 1911–1924.

[9] a) J. Rintjema, W. Guo, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *Chem. Eur. J.* **2015**, *21*, 10754−10762; b) D. J. Darensbourg; Adolfo Horn, Jr; Adriana I. Moncada, *Green Chem.* **2010**, *12*, 1376−1379.

[10] a) T. M. McGuire, C. Pérale, R. Castaing, G. Kociok-Köhn, A. Buchard, *J. Am. Chem. Soc.* **2019**, *141*, 13301−13305; b) J. Huang, P. Olsén, E. Svensson Grape, A. K. Inge, K. Odelius, *Macromolecules* **2022**, *55*, 608−614; c) S. Tempelaar, L. Mespouille, O. Coulembier, P. Dubois, A. P. Dove, *Chem. Soc. Rev.* **2013**, *42*, 1312−1336; d) W. Guerin, A. K. Diallo, E. Kirilov, M. Helou, M. Slawinski, J.-M. Brusson, J.-F. Carpentier, S. M. Guillaume, *Macromolecules* **2014**, *47*, 4230−4235; e) Y. Song, X. Yang, Y. Shen, M. Dong, Y.-N. Lin, M. B. Hall, K. L. Wooley, *J. Am. Chem. Soc.* **2020**, *142*, 16974−16981; f) W. Zhang, J. Dai, Y.-C. Wu, J.-X. Chen, S.-Y. Shan, Z. Cai, J.-B. Zhu, *ACS Macro Lett.* **2022**, *11*, 173–178.

[11] a) C. Qiao, A. Villar-Yanez, J. Sprachmann, B. Limburg, C. Bo, A. W. Kleij, *Angew. Chem. Int. Ed.* **2020**, *59*, 18446−18451; b) J. Rintjema, R. Epping, G. Fiorani, E. Martín, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed.* **2016**, *55*, 3972–3976; c) S. Sopeña, M. Cozzolino, C. Maquilón, E. C. Escudero-Adán, M. Martínez Belmonte, A. W. Kleij, *Angew. Chem. Int. Ed.* **2018**, *57*, 11203−11207; d) R. Huang, J. Rintjema, J. González-Fabra, E. Martin, E. C. Escudero-Adán, C. Bo, A. Urakawa, A. W. Kleij, *Nat. Catal.* **2019**, *2*, 62−70.

carbonate occurs. This lack of polymerization potential motivated us to design a different strategy that could build on our previously established substrate-directed CO_2 activation manifold.[11b-d]



Scheme 3.1 (a) General approaches for six-membered cyclic carbonate synthesis. (b) Our previously reported synthesis of *O*-protected six-membered carbonates (Chapter 2). (c) A new and challenging direct coupling of an epoxide and CO_2 providing bicyclic carbonate heterocycles (Chapter 3).

By rigidifying the substrate scaffold though preserving the presence of a β-positioned alcohol, we discovered a salient difference between *syn*- and *anti*-configured β-epoxy alcohols in their coupling with CO_2 leading to cyclic carbonates (Scheme 3.1c). The *anti* substrates deliver in one step six-membered bicyclic carbonates in good yield and selectivity under binary catalysis. The mechanistic pathway towards the observed chemo-selectivity is discussed and supported through X-ray structural studies, and diversification studies show that these heterocycles have both utility and stability upon modification. ROP of representative bicyclic six-membered carbonates is successfully demonstrated, illustrating the importance of backbone rigidity to substantially increase the thermal resistance of the resultant polycarbonate.

3.3 Results and discussion

At the onset of our screening studies, we examined various conditions for the conversion of both *syn*- and *anti*-**3.1a** (Table 3.1).[12] Based on our previous experience,[11] various combinations of Al-complexes **3.A** and **3.B** and additives (DBU, DIPEA and TBAB) were scrutinized to examine their effect on the chemo-selectivity of this benchmark conversion.[13] First, a low-temperature approach was chosen (entry 1) with **3.A** and DIPEA as binary catalyst at relatively high CO_2 pressure but this proved to be unproductive. By increasing the reaction temperature and lowering the pressure to 10 bar, low conversion of **3.1a** was noted but no carbonate products were detected (entry 2). We found that a reaction temperature of 100 ºC was key towards carbonate formation (see Table 3.3). In the presence of TBAB (entries 3 and 4), the five-membered ring carbonate *syn*-**3.P1^{a}** was formed suggesting the occurrence of a standard double inversion pathway.[14] Interestingly, in the presence of base catalyst (entry 5), a configurationally different five-membered cyclic carbonate (*anti*-**3.P1^{b}**) was produced as the major reaction

[12] a) T. Itoh, K. Jitsukawa, K. Kaneda, S. Teranishi, *J. Am. Chem. Soc.* **1979**, *101*, 159–169; b) K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.

[13] For a full description of the chemo-selectivity of these screening reactions, please refer to the Experimental section **3.6.4**, Table 3.3.

[14] For a review on catalytic mechanisms leading to cyclic carbonates, see: F. Della Monica, A. W. Kleij, *Catal. Sci. Technol*. **2020**, *10*, 3483–3501.

component as supported by X-ray crystallography.[15,16] The presence of both TBAB and DBU (entry 6) leads to a mixture of five-membered cyclic carbonates *syn*-**3.P1**$^{\mathbf{a}}$ and *anti*-**3.P1**$^{\mathbf{b}}$.

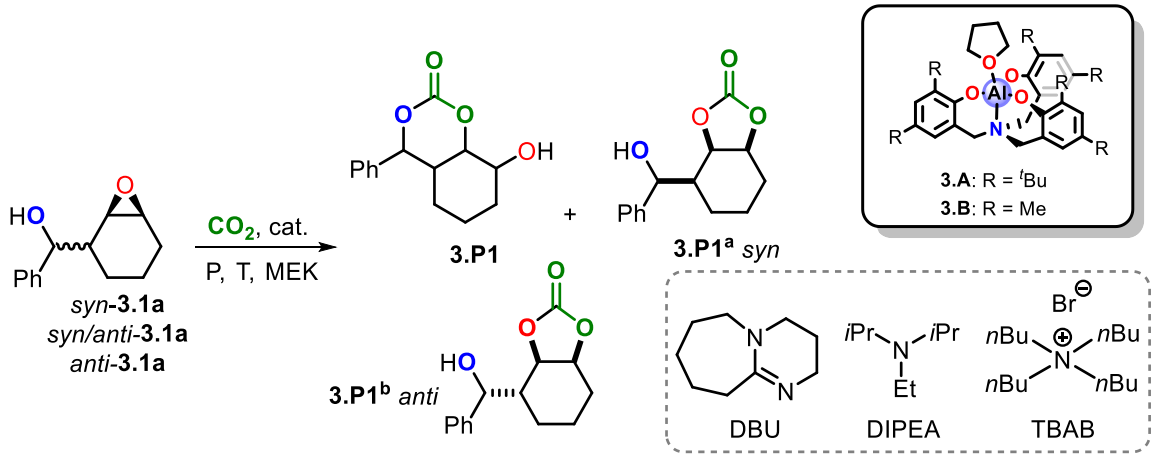
An important lead result was accomplished in the conversion of a 3:1 *syn*/*anti*-substrate mixture (entries 7 and 8) leading to substantial formation (20%, close to the amount of the *anti*-isomer in *syn*/*anti*-**3.1a**) of the target six-membered cyclic carbonate **3.P1** (see also Table 3.3). The selectivity towards **3.P1** could be further increased by using *anti*-**1a** (entries 9-13). Compared to the presence of TBAB, the use of DIPEA shows slightly higher selectivity for **3.P1** (entries 9 and 10, see Tables 3.3 and 3.4 in the Experimental section **3.6.5** and **3.6.6** for further details) but, more importantly does not necessitate the use of halide-containing additives.[17] In the presence of only the Al- complex **3.A**, the reaction had low efficiency (entry 11; 11% yield of **3.P1**) while DIPEA individually did not show any selectivity towards the formation of **3.P1** (entry 12). It therefore appears that a cooperative action of both catalyst components is required for efficient and selective substrate conversion. Though Al-complex **3.B** also showed good potential towards the formation of the desired product (entry 13), a somewhat lower yield of **3.P1** was noted. In a full screening studies (Table 3.3, Experimental section **3.6.5**), we found that other products may also be formed.

[15] The formation of configurationally distinct, though constitutional rather similar five-membered bicyclic carbonates has been previously been studied, see: C. Maquilón, B. Limburg, V. Laserna, D. Garay-Ruiz, J. González-Fabra, C. Bo, M. Martínez Belmonte, E. C. Escudero-Adán, A. W. Kleij, *Organometallics* **2020**, *39*, 1642–1651.

[16] For full details regarding the X-ray molecular structures of this work, see CCDC 2157244–2157247 and the Experimental section **3.6.8**.

[17] Halide-free synthesis of cyclic carbonates is considered to be more sustainable, see: a) A. W. Kleij, *Curr. Opin. Green Sust. Chem*. **2020**, *24*, 72–81; b) I. D. V. Ingram, M. North, X. Wu, *Halide-Free Synthesis of Cyclic and Polycarbonates*. In: P. Tundo, L.-N. He, E. Lokteva, C. Mota, (eds.) Chemistry Beyond Chlorine, Springer, Cham **2016**.

Table 3.1 Trials conducted with epoxy alcohol substrate **3.1a** using various catalysts under different reaction conditions.[a]



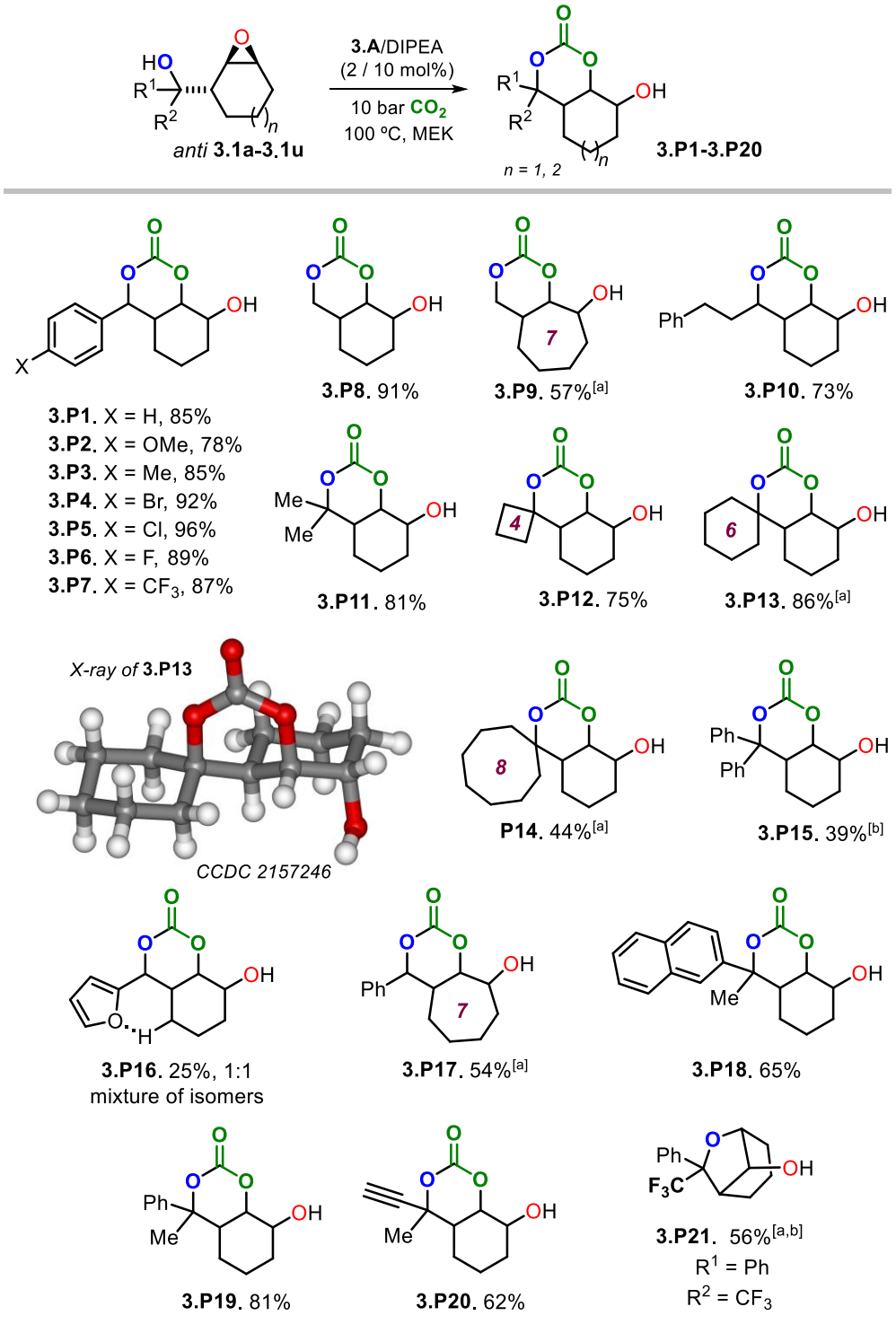
Entry	**3.1a**	Cat. [mol%]	P/T [bar/ºC]	Conv [%]	**3.P1** [%]	**3.P1**[a] [%]	**3.P1**[b] [%]
1	*syn*	**3.A**/DIPEA, 10	30/50	<1	–	–	–
2	*syn*	**3.A**/DIPEA, 10	10/100	18	0	0	0
3	*syn*	**3.A**/TBAB, 5	10/100	84	0	35	0
4	*syn*	TBAB, 5	10/100	74	0	**37**	0
5	*syn*	DBU, 10	10/100	94	0	0	26
6[b]	*syn*	TBAB/DBU	10/100	95	0	12	29
7[d]	[c]	**3.A**/DIPEA, 10	10/100	61	20	0	0
8[d]	[c]	**3.A**/TBAB, 5	10/100	>99	20	18	0
9[d]	*anti*	**3.A**/TBAB, 5	10/100	>99	83	0	0
10[d]	*anti*	**3.A**/DIPEA, 10	10/100	95	**85**	0	0
11	*anti*	**3.A**	10/100	36	11	0	0
12	*anti*	DIPEA, 10	10/100	14	0	0	0
13[d]	*anti*	**3.B**/DIPEA, 10	10/100	>99	77	0	0

[a] Reaction performed under the indicated pressure and temperature, MEK as solvent (0.4 mL), *syn*-**3.1a** or **3.1a** (0.5 mmol) or *anti*-**3.1a** (0.2 mmol), Al-complex **3.A** or **3.B** (2 mol%), additive (indicated), 22 h. The amount of **3.P1**, **3.P1**[a] and **3.P1**[b] and the overall conversion of **3.1a** was determined by ^{1}H NMR ($CDCl_3$). [b] TBAB (5 mol%) and DBU (10 mol%). [c] A 3:1 mixture of s*yn/anti*-**3.1a** was used. [d] Yields of the isolated product are reported for these entries.

The scope of this new CO_2 transformative process (Scheme 3.2) was then examined using the conditions reported in entry 10 of Table 2.1. Aryl-substituted bicyclic carbonates **3.P2**-**3.P7** could be prepared in good yields from their β-epoxy alcohols precursors (**3.1b**-**3.1g**; having secondary alcohol groups) providing, in some cases, useful functional groups for post-synthetic modifications. Then we also examined precursors comprising primary alcohol groups and this allowed us to prepare **3.P8** (91%) and **3.P9** (57%) in excellent and moderately high yield, respectively. The lower yield for **3.P9** is ascribed to the more flexible nature of the cycloheptyl ring and a higher energy requirement to produce a reactive conformation. In order to widen the scope, epoxy alcohol substrates with groups other than aryls were also tested, providing access to bicyclic carbonates **3.P10**-**3.P14** in good yields (except for **3.P14**: 44%). In some of these cases, a longer reaction time was needed to reach higher substrate conversion such as for spiranes **3.P13** and **3.P14**. In the latter case, the twisted nature of the cyclo-octyl ring likely increases the steric impediment around the alcohol group, leading to slower intramolecular attack on the oxirane unit. A similar "steric" effect probably holds for the synthesis of **3.P15** (39%), whereas the low yield of the furan derivative **3.P16** (25%) is ascribed to (thermal) decomposition over time, which likely involves the reactive furan group.[18] **3.P16** was isolated as a mixture of rotamers as suggested by molecular modelling studies. The isomers relate to the relative positioning of the furan group with respect to the bicyclic scaffold with CH···O interactions being competitive to HO···OC(O)O hydrogen bonding. Finally, we examined the use of an aryl-substituted cycloheptane oxide and "mixed" substituted epoxy alcohols, which allowed to prepare the carbonate products **3.P17**-**3.P20** in appreciable yields. Notably, **3.P20** (62% yield) featuring a terminal alkyne offers a synthetic handle while building up molecular complexity. Substrate **3.1u** having a strongly electron-withdrawing CF_3 group changed the chemo-selectivity drastically. Only a trace amount of the desired carbonate could be detected in the crude product by ^{1}H NMR. From the reaction mixture we were able to isolate and characterize bicycle **3.P21** (see Table 3.5 in the Experimental section **3.6.6** for details).[19]

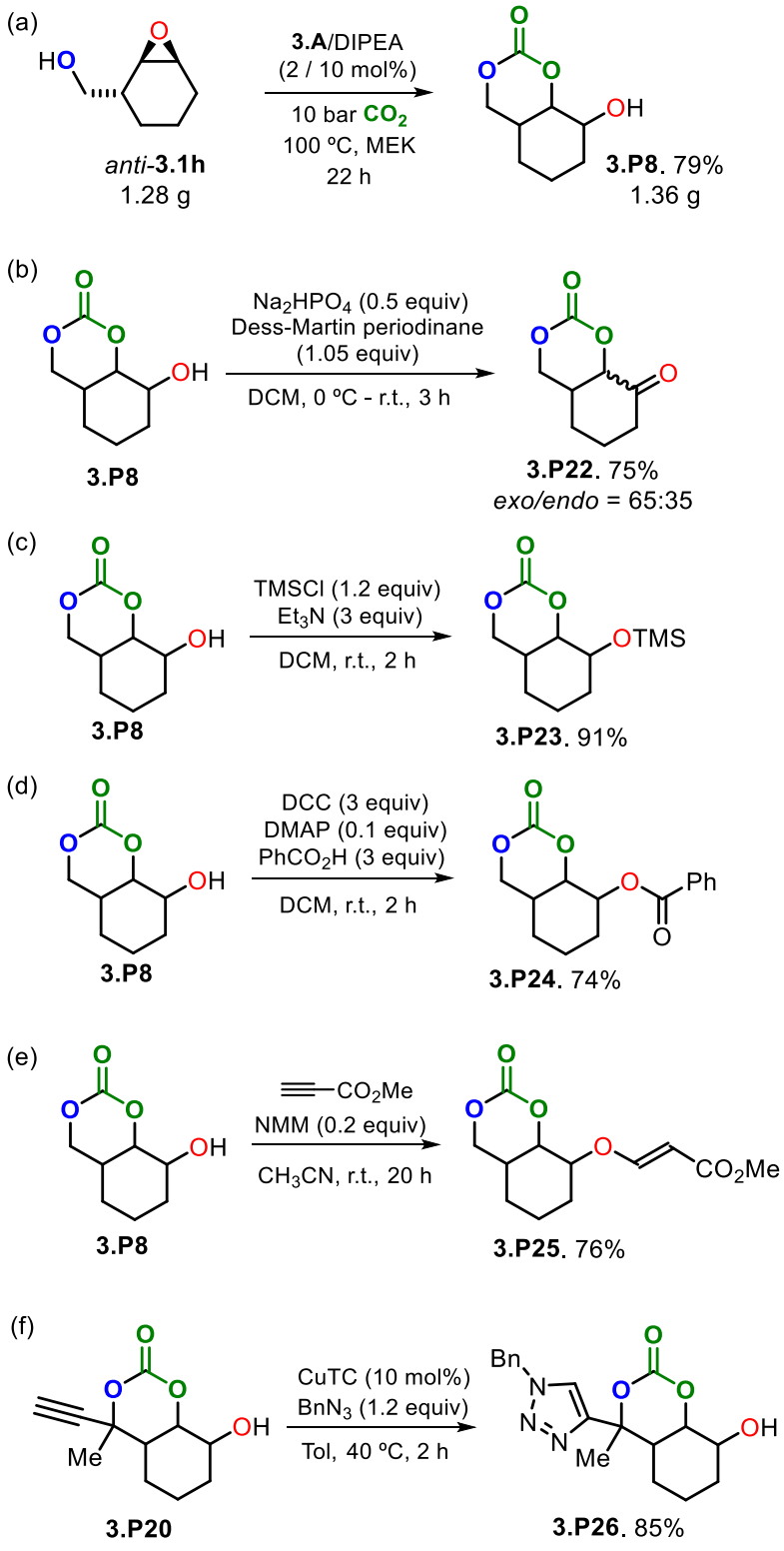
[18] Ring-opening and isomerization reactions may occur at elevated temperatures and in the presence of a Lewis acid, see: M. Clerc, F. Stricker, S. Ulrich, M. Sroda, N. Bruns, L. F. Boesel, J. Read de Alaniz, *Angew. Chem. Int. Ed*. **2021**, *60*, 10219–10227.

[19] Under the optimized reaction condition, substrates **4.1o**, **4.2p** and **4.3q** display relatively low conversion under the catalytic conditions though high chemo-selectivity was observed toward their products.



Scheme 3.2 Scope of six-membered bicyclic carbonates (**3.P1-3.P20**) by coupling of epoxy alcohols **3.1a-3.1u** and CO_2 in the presence of Al-complex **3.A** and DIPEA. [a] Reaction time was 72 h. [b] Using TBAB (5 mol%) instead of DIPEA.

The synthetic potential and stability of bicyclic carbonates **3.P8** and **3.P20** was then examined (Scheme 3.3). Scaling up the synthesis of **3.P8** (79%) was straightforward providing gram-quantity of this bicyclic carbonate (Scheme 3.3a) without significant influence on the reaction outcomr. Dess-Martin oxidation of **3.P8** (Scheme 3.3b) gave access to the ketone product **3.P22** in 75% yield as a mixture of isomers as the carbonyl fragment can have two relative orientations (*exo* and *endo*) with respect to the cyclic carbonate ring. *O*-protection in **3.P8** was simple and straightforward (Scheme 3.3c and 3.3d) with both silylated **3.P23** (91%) and phenyl ester **3.P24** (75%) isolated in good yields. Acrylic ester derivative **3.P25** (76%, Scheme 3.3e) was produced by coupling of **3.P8** with a propargylic ester, giving thus access to a bifunctional monomer. A Cu-catalyzed azide-alkyne "click" coupling of **3.P20** resulted cleanly into the formation of 1,2,3-triazole derivative **3.P26** (Scheme 3.3f, 85%) showcasing the synthetic use of the terminal alkyne present in the starting material.



Scheme 3.3 Scale up of **3.P8** and product diversification studies using both **3.P8** and **3.P20**.

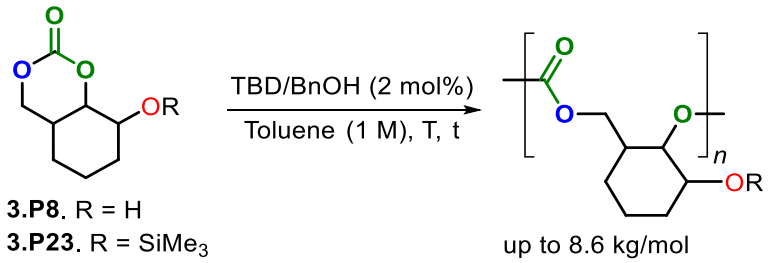
3.4 Ring-opening polymerization studies

Finally, we used monomers **3.P8** and **3.P23** to examine their ring-opening polymerization (ROP) potential under standard conditions (Table 3.2).[10a,10e, 20] Monomer **3.P8** could be oligomerized (entry 1, M_n = 1.7 kg/mol, $Đ$ = 1.47) at incomplete conversion, and extension of the reaction time to 48 h (entry 2) led to (partial) degradation of this oligo-carbonate. These data indicated that the free alcohol present in **3.P8** might interfere with the ROP process. We therefore then examined silyl-protected **3.P23** (entry 3) and found that nearly full monomer conversion was achieved at r.t. after 20 h, with the polycarbonate having improved features (M_n = 5.9 kg/mol, $Đ$ = 1.34). Scale up of this process (entry 4) further improved the efficiency (M_n = 7.8 kg/mol, $Đ$ = 1.32) and the new polycarbonate could be isolated as a white solid in 80%. Performing the ROP of **3.P23** at higher temperature (entry 5 versus 3) did not provoke any significant change in the polymer properties, which is in line with the non-innocent nature of the free alcohol in **3.P8** during the polymerization process. A slightly higher molecular weight polymer was produced in DCM (entry 6 versus 3). Finally, we found that a slightly higher M_n value for the polycarbonate could be secured when performing the reaction with less catalyst/initiator (entry 7; M_n = 8.6 kg/mol).

The isolated polycarbonate from entry 4 was subjected to thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). The T_g of this new polycarbonate is substantially higher (52 ºC) than the unsubstituted polycarbonate that is generated from the ROP of trimethylenecarbonate (T_g = –26 ºC for a sample having a molecular weight of around 7 kg/mol).[21] This more rigid polycarbonate also exhibits a high T_d^5 of 234 ºC favorable to process the polymer beyond its glass transition.

[20] a) M. Helou, O. Miserque, J.-M. Brusson, J.-F. Carpentier, S. M. Guillaume, *Chem. Eur. J.* **2010**, *16*, 13805–13813; b) C. Maquilón, F. Della Monica, B. Limburg, A. W. Kleij, *Adv. Synth. Catal.* **2021**, *363*, 4033–4040.
[21] K. J. Zhu, R. W. Hendren, K. Jensen, C. G. Pitt, *Macromolecules* **1991**, *24*, 1736–1740.

Table 3.2 ROP studies using **3.P8** and **3.P23** as monomers, and TBD/BnOH as catalyst/initiator.[a]



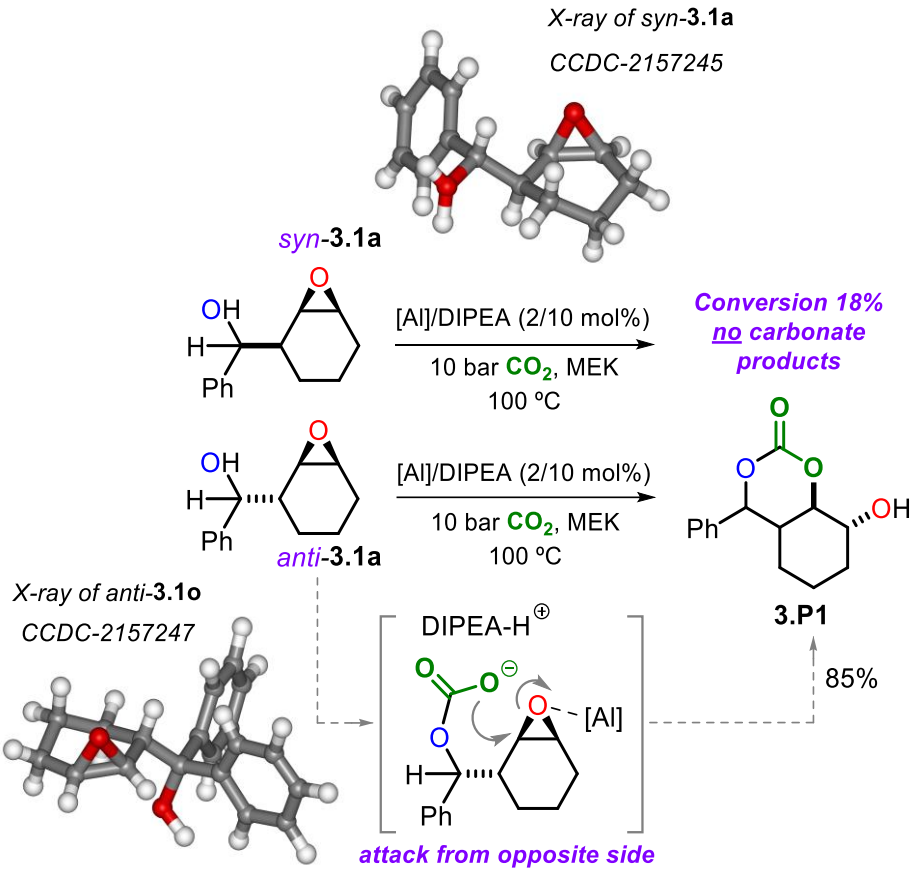
Entry	Monomer	Solvent	t/T [h]/ [° C]	Conv.[b] [%]	M_n [c] [kg/mol]	$Đ$[c]
1[d]	**3.P8**	toluene	20, r.t.	–	1.7	1.47
2[d]	**3.P8**	toluene	48, r.t.	–	0.5	3.83
3	**3.P23**	toluene	20, r.t.	96	5.9	1.34
4[e]	**3.P23**	toluene	20, r.t.	>99[f]	7.8	1.32
5	**3.P23**	toluene	20, 100	94	5.5	1.20
6	**3.P23**	DCM	20, r.t.	88	6.4	1.27
7[e,g]	**3.P23**	toluene	20, r.t.	>99	8.6	1.27

[a] For monomer **3.P8**: 20 mg ($1.17\cdot10^{-4}$ mol), TBD/BnOH = 1:1, 2 mol%, 117 µL of solvent. For monomer **3.P23**: 20 mg ($8.2\cdot10^{-5}$ mol), TBD/BnOH = 1:1, 2 mol%, 82 µL of solvent. For both monomers: time and temperature indicated. Note that only one of the two possible regio-isomers is shown. [b] Conversion determined by ^{1}H NMR ($CDCl_3$). [c] M_n and $Đ$ values obtained through GPC analysis in THF using PS standards. [d] Incomplete conversion, accurate determination of monomer conversion not possible due to too much signal overlap. [e] **3.P23** (200 mg, $8.2\cdot10^{-4}$ mol), TBD/BnOH = 1:1, 2 mol%, 820 µL of solvent. [f] Yield of the isolated polycarbonate: 80%. [g] TBD/BnOH = 1:1, 1 mol%.

The marked difference in reactivity between the *syn* and *anti*-isomer of **3.1a** can be rationalized by a stereochemical model where the Al-complex activates the oxirane at one side of the *anti*-configured cyclic epoxide. The alcohol (in the presence of a suitable base) enables the activation of CO_2 from the other face (Scheme 3.4, lower part; note, molecular structure of *anti*-**3.1o** as a structural model)[22] allowing for ring-opening and straightforward formation of bicyclic product **3.P1**. Such reactivity would not be possible with the *syn* isomer of **3.1a** (cf.,

[22] Note that *anti*-**3.1a** is a viscous liquid and therefore *anti*-**3.1o** was selected as a closely related structural model for *anti*-**3.1a** demonstrating the favorable relative positioning of the alcohol and the oxirane towards the formation of the six-membered bicyclic carbonate **3.P1**.

X-ray of *syn*-**3.1a** and Table 3.1, entry 2) though a double inversion process is feasible in the presence of TBAB leading to the five-membered cyclic carbonate **3.P1**[a].



Scheme 3.4 Reactivity comparison between both stereoisomers of **3.1a** under similar conditions, and stereochemical model for the conversion of β-epoxy alcohol *anti*-**3.1a** in the presence of binary catalyst **3.A**/DIPEA.

3.5 Conclusions

In this chapter, we describe a novel catalytic approach that allows the coupling between β-epoxy alcohols and CO_2 leading to the direct formation of an unusual scope of larger-ring bicyclic carbonates in good yields. Crucial in this manifold is the stereochemical configuration of the substrate with the *anti*-isomer leading exclusively to a six-membered bicyclic carbonate while the corresponding *syn*-isomer only provides access to five-membered ring carbonates. The potential of these bicyclic carbonates has been further illustrated in ROP experiments, and the substitution degree and functionality thus hold promise for the design and preparation of a whole new range of (functional) and above all rigidified polycarbonates obtained from CO_2-based monomers.

3.6 Experimental section

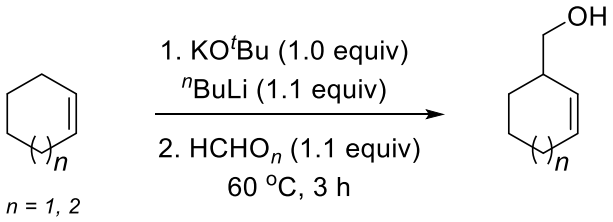
3.6.1 General comments

All reagents were used as received from commercial suppliers (Aldrich, Acros or TCI) unless otherwise stated. Carbon dioxide was purchased from PRAXAIR and used without further purification. NMR-spectra were recorded on Bruker AV-400 or AV-500 spectrometers. The residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra ($CDCl_3$: δ^H = 7.26 ppm, δ^C = 77.16 ppm, $(CD_3)_2SO$: δ^H = 2.5 ppm, δ^C = 39.52 ppm). ^{19}F NMR spectra were not calibrated by an internal reference. FT-IR measurements were carried out on a Bruker Optics FTIR-ATR TR0 spectrometer. Exact mass analyses and X-ray diffraction studies were performed by the Research Support Area (RSA) at ICIQ. Solvents were dried using an Innovative Technology PURE SOLV solvent purification system.

3.6.2 Experimental procedures for the synthesis of cycloalkenes

Non-commercial allyl bromides were synthesized using literature procedures.[22] These allyl bromides are thermally unstable and become brownish while decomposing when exposed to air and/or under light. They were therefore freshly prepared and directly used in further transformations.

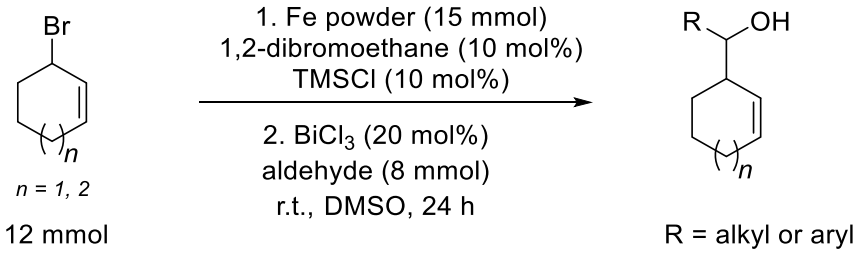
Method A: cycloalkenes with a primary alcohol group[23]



^{n}BuLi (1.6 M in hexanes, 20 mL, 32 mmol) was added to a degassed suspension of KO^{t}Bu (3.39 g, 30.2 mmol) in cyclohexene (27 mL) or cycloheptene (30 mmol in 25 mL cyclohexane) under a nitrogen atmosphere. The reaction mixture was kept below 15 ºC over a period of 2 h, and then allowed to warm to r.t. over 16 h. The resultant suspension was cooled to 0 °C and $(HCHO)_n$ (1 g, 33.2 mmol) was added (**Caution**: exothermic reaction!). The reaction mixture was heated to 60 ºC for 3 h, then cooled to 0 °C and quenched with a saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed sequentially with a saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried and concentrated in vacuo to give the desired product. All the cycloalkenes with primary alcohol groups synthesized using this method were used directly for the next step without further purification.

[23] C. W. Bond, A. J. Cresswell, S. G. Davies, A. M. Fletcher, W. Kurosawa, J. A. Lee, P. M. Roberts, A. J. Russell, A. D. Smith, J. E. Thomson, *J. Org. Chem.* **2009**, *74*, 6735–6748.

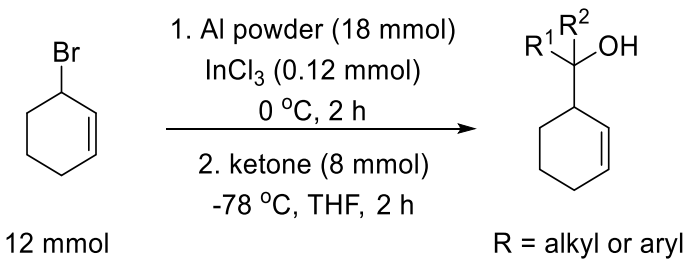
Method B: cycloalkenes with a secondary alcohol group[24]



To a 10 mL Schlenk flask was sequentially added iron powder (838 mg, 15 mmol) and DMSO (10 mL). Then the iron was activated by the addition of 1,2-dibromoethane (282 mg, 10 mol%) and TMSCl (162 mg, 10 mol%). After stirring for 30 min, $BiCl_3$ (504 mg, 1.6 mmol), the cyclic allyl bromide (12 mmol) and aldehyde (8 mmol) were sequentially added to the reaction mixture. The suspension was vigorously stirred at r.t. for 24 h before quenching it with a saturated aqueous $NaHCO_3$ solution (30 mL) following extraction with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using ethyl acetate (EA)/hexane as eluent to give the pure products.

[24] X.-Y. Liu, B.-Q. Cheng, Y.-C. Guo, X.-Q. Chu, W. Rao, T.-P. Loh, Z.-L. Shen, *Org. Chem. Front.* **2019**, *6*, 1581–1586.

Method C: cycloalkenes with a tertiary alcohol group[25]

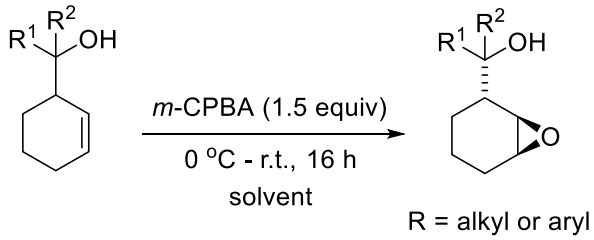


Al-powder (486 mg, 18 mmol) and $InCl_3$ (26.4 mg, 0.12 mmol) were placed in an argon-flushed dry flask. After THF (15 mL) was added, a solution of a cyclic allyl bromide (12 mmol) in THF (15 mL) was added with a syringe pump over 1 h at 0 ºC and the resulting solution was stirred at 0 ºC for another hour. A solution of the ketone reagent (8 mmol) in THF (5 mL) was added to the mixture at -78 ºC via a syringe and the resulting mixture was stirred at -78 ºC for 2 h. Standard work-up as described under **methods A** and **B**, and purification by flash chromatography over silica was carried out to isolate the target compounds.

[25] Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8516−8519.

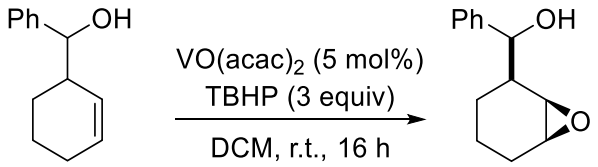
3.6.3 Experimental procedures for the synthesis of cyclic epoxy alcohols

<u>*Anti*-isomers</u>



The respective cycloalkene alcohol (3 mmol) was dissolved in DCM/MeOH (15 mL) at 0 °C and *m*-CPBA (1.5 equiv., 4.5 mmol, 1.0 g) was added. The mixture was allowed to warm to r.t. and was stirred for 16 h. The reaction mixture was washed with Na_2CO_3 (2 × 30 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography. Note: under these conditions, syn and anti-isomers were obtained at the same time, and in most cases, they could be separated by flash chromatography.

<u>*Syn*-isomers</u>[26]

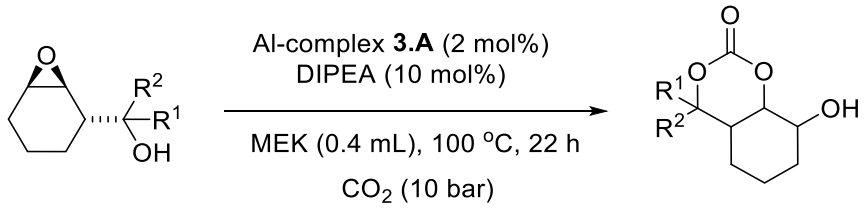


The respective epoxy alcohol (5 mmol, 1.0 equiv) and $VO(acac)_2$ (5 mol%, 32 mg) were dissolved in DCM (50 mL) at 0 °C, then TBHP (tert-butyl hydroperoxide solution, 5.0-6.0 M in decane, 3 mL) was added. The mixture was stirred at r.t. for 16 h. After the reaction, the solvent was removed under vacuum and the crude product was purified by flash chromatography employing 10% EA in hexane as eluent.

[26] T. Itoh, K. Jitsukawa, K. Kaneda, S. Teranishi, *J. Am. Chem. Soc.* **1979**, *101*, 159–169.

3.6.4 Experimental procedure for the 6-membered cyclic carbonates

The Al(III) aminotriphenolate complexes **3.A**, **3.B** and **3.C** were prepared according to a literature procedure.[27]



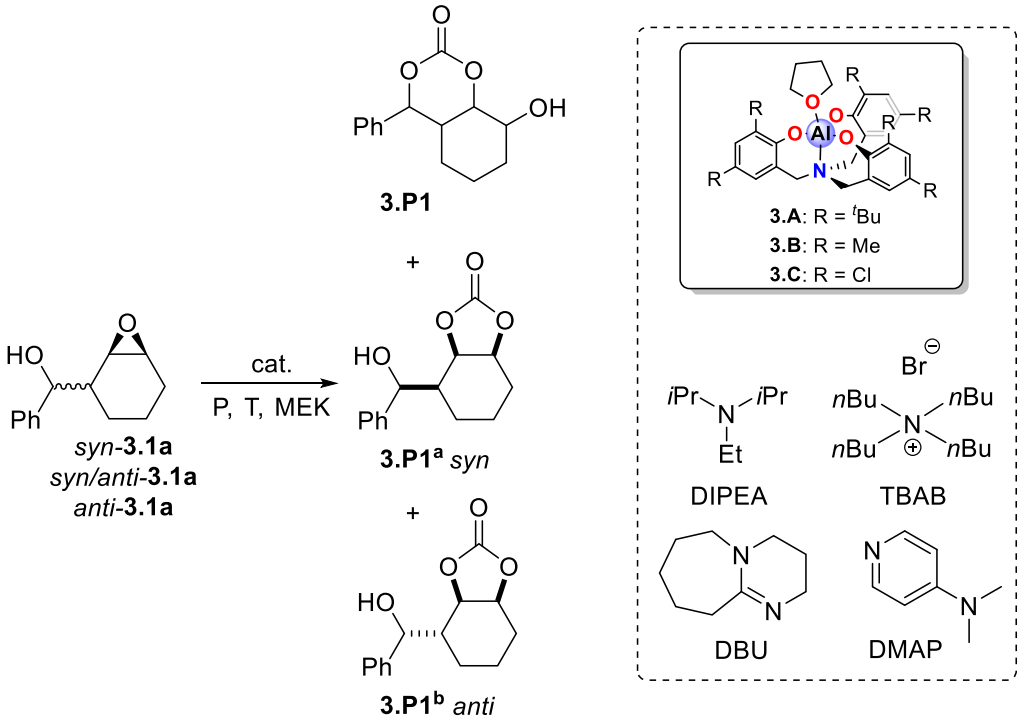
Typical experiment: a stainless-steel HEL multi-reactor was charged with the epoxide (0.1 mmol) dissolved in MEK (400 μL) and Al-complex **3.A** (0.002 mmol 2 mol%, 1.6 mg) and DIPEA (0.01 mmol 10 mol%, 1.3 mg) were added. The reactor was purged twice with CO_2 (10 bar) and then charged with CO_2 (10 bar). The mixture was stirred at 100 °C for 22 h, then cooled with an ice/water bath and carefully depressurized. The solvent was removed in vacuo and the resulting product was purified by flash chromatography employing 30% - 70% EA in hexane as a gradient eluent.

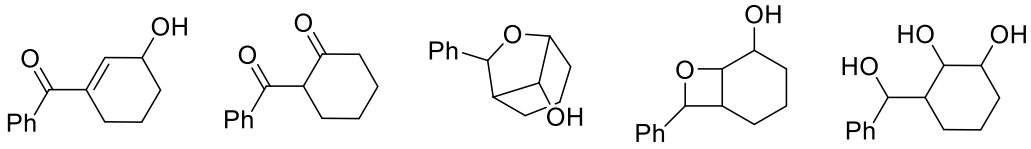
NB: A scale-up of the synthesis of product **3.P8** was also performed (10 mmol scale, substrate-based) in 5 mL of MEK in a 30 mL stainless steel reactor. Yield 1.36 g (79%).

[27] C. J. Whiteoak, N. Kielland, V. Laserna, F. Castro-Gómez, E. Martin, E. C. Escudero-Adán, C. Bo, A. W. Kleij, *Chem. Eur. J.* **2014**, *20*, 2264–2275.

3.6.5 Full screening Table 3.3

Table 3.3 Full set of screening data obtained in the conversion of substrate **3.1**[a]





Entry	**3.1a**	Cat. [mol%]	P/T [bar/ºC]	Conv [%]	Yield [%][d]
1	*syn*	**3.A**/DIPEA, 10	30/50	<1	–
2	*syn*	**3.A**/DIPEA, 10	10/75	<5	–
3	*syn*	**3.A**/DIPEA, 10	10/100	18	**3.ByP1:** 5.4 **3.ByP5:** 8.6
4	*syn*	**3.A**/TBAB, 5	10/100	84	**3.P1a:** 35 (29) **3.ByP1:** 7 **3.ByP4:** 16 **3.ByP5:** 9
5	*syn*	TBAB, 5	10/100	74	**3.P1a:** 37 **3.ByP1:** 7 **3.ByP4:** 7 **3.ByP5:** 10

Continuation of Table 3.3

Entry	**3.1a**	Cat. [mol%]	P/T [bar/ºC]	Conv [%]	Yield [%][d]
6	*syn*	DBU, 10	10/100	94	**3.P1[b]:** 26 (21) **3.ByP1:** 3 **3.ByP5:** 13
7	*syn*	**3.B**/TBAB, 5	10/100	>99	**3.ByP1:** 5 **3.ByP4:** 22 **3.ByP5:** 10
8	*syn*	DMAP, 10	10/100	>99	**3.P1[b]:** 39 (37) **3.ByP1:** trace **3.ByP2:** trace **3.ByP5:** 10
9	*syn*	**3.A**/DBU, 10	10/100	>99	**3.ByP2:** trace **3.ByP3:** 46 (46) **3.ByP5:** 12
10[b]	*syn*	TBAB/DBU	10/100	95	**3.P1[a]:** 12 **3.P1[b]:** 29 **3.ByP2:** 7.3 **3.ByP5:** 7.3
11	[c]	**3.A**/DIPEA, 10	10/100	61	**3.P1:** (20) **3.ByP4:** (23)
12	[c]	**3.A**/TBAB, 5	10/100	>99	**3.P1:** (20) **3.P1[a]:** 18 **3.ByP4:** 61
13	*anti*	**3.A**/TBAB, 5	10/100	>99	**3.P1:** (83) **3.ByP5:** trace
14	*anti*	**3.A**/DIPEA, 10	10/75	70	**3.P1:** 65
15	*anti*	**3.B**/DIPEA, 2	10/100	83	**3.P1:** 75 **3.ByP5:** trace
16	*anti*	**3.C**/DIPEA, 6	10/100	93	**3.P1:** 76 **3.ByP5:** 9

Continuation of Table 3.3

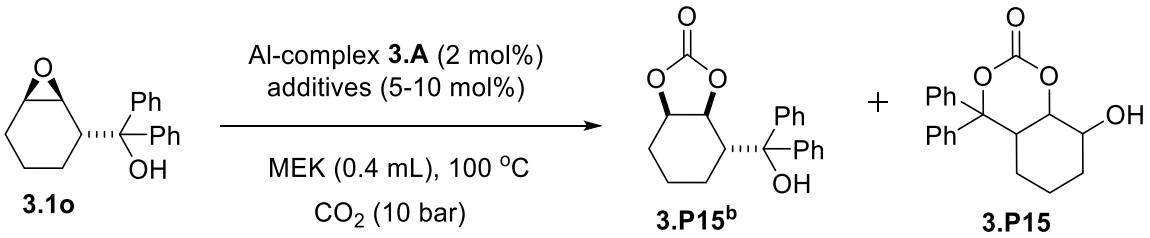
Entry	**3.1a**	Cat. [mol%]	P/T [bar/ºC]	Conv [%]	Yield [%][d]
17	*anti*	**3.A**/DIPEA, 10	10/100	95	**3.P1:** (85)
18	*anti*	**3.B**/DIPEA, 10	10/100	>99	**3.P1:** (77)
19	*anti*	**3.C**/DIPEA, 10	10/100	>99	**3.P1:** trace **3.ByP5:** 8
20	*anti*	TBAB, 5	10/100	74	**3.P1[b]:** 21 **3.ByP5:** 11
21	*anti*	DMAP, 10	10/100	14	0
22	*anti*	DBU, 10	10/100	>99	**3.ByP5:** 74
23	*anti*	**3.A**	10/100	36	**3.P1:** 11 **3.ByP5:** trace
24	*anti*	DIPEA, 10	10/100	14	0

[a] Reaction was performed under the indicated pressure and temperature, MEK as solvent (0.4 mL), *syn*-**3.1a** or **3.1a** (0.5 mmol) or *anti*-**3.1a** (0.2 mmol), Al-complex **3.A**, **3.B** or **3.C** (2 mol%), additive (indicated), 22 h. The amount of **3.P1**, **3.P1[a]** and **3.P1[b]** and the overall conversion of **3.1a** was determined by ^{1}H NMR ($CDCl_3$). [b] TBAB (5 mol%) and DBU (10 mol%). [c] *Syn/anti* (3:1 mixture) **3.1a** was used. [d] In brackets, the yield of the isolated product.

Note: all the by-products (**3.ByP1** to **3.ByP5**) reported in Table 3.3 were isolated and fully characterized/identified by ^{1}H NMR, ^{13}C NMR, IR and HRMS. These data are provided below in the respective Experimental section **3.6.10** onwards.

3.6.6 Further screening results with substrates 3.1o and 3.1u

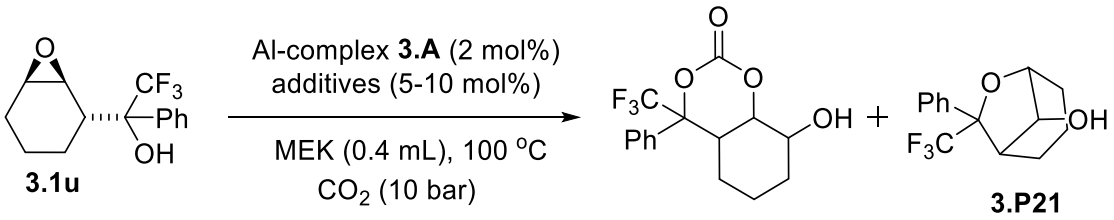
Table 3.4 Further screening results with substrate **3.1o** [a]



Entry	Additives (mol%)	t (h)	Yield of **3.P15**[b,b,c] [%]	Yield of **3.P15**[c] [%]
1	DIPEA (10)	22	–	trace
2	DIPEA (10)	72	–	19
3	TBAB (5)	22	18[b]	39[b]
4	TBAB (5)	72	63	35

[a] Substrate **3.1o** (0.1 mmol), CO_2 (10 bar), Al-complex **3.A** (2 mol%), additive (5-10 mol%), MEK (0.4 mL). [b] Yield of the isolated product. [c] All reported yields and conversions are based on ^1H NMR ($CDCl_3$) measurements using mesitylene as an internal standard.

Table 3.5 Further screening results with substrate **3.1u** [a]

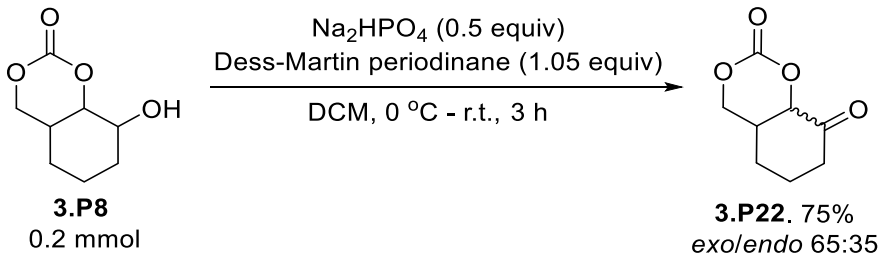


Entry	Additives (mol%)	t (h)	Yield of 6MCC[b] [%]	Yield of **3.P21**[b] [%]
1	DIPEA (10)	22	*trace*	18 [c]
2	DIPEA (10)	72	*trace*	22
3	TBAB (5)	72	*trace*	56 [c]

[a] Substrate **3.1u** (0.1 mmol), CO_2 (10 bar), Al-complex **3.A** (2 mol%), additives (5-10 mol%), MEK (0.4 mL). [b] All reported yields and conversions are based on ^{1}H NMR ($CDCl_3$) measurements using mesitylene as an internal standard. [c] Yield of the isolated product.

3.6.7 Experimental procedures for the product diversification studies

Synthesis of 3.P22

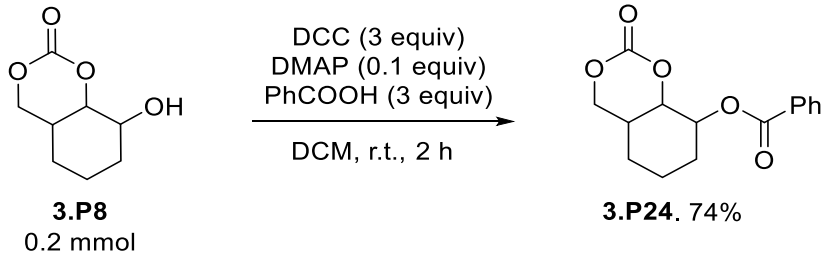


In a 10 mL oven-dried glass vial, **3.P8** (0.2 mmol, 34.4 mg, 1.0 equiv) was dissolved in 1 mL of dry DCM under argon. The solution was cooled to 0 °C, and anhydrous Na_2HPO_4 (15.7 mg, 0.1 mmol, 0.5 equiv) was added. Dess-Martin periodinane (90 mg, 0.21 mmol, 1.05 equiv) was then added at once at 0 °C, and the resulting suspension was warmed to r.t. and stirred for 3 h. The reaction mixture was then quenched by successive addition of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 solutions (1.5 mL in both cases), extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EA= 10:1) to afford the desired **3.P22** (25.5 mg, 75%) as a white solid.

Synthesis of 3.P23

In a 10 mL oven-dried glass vial, a mixture of **3.P8** (34.4 mg, 0.20 mmol, 1.0 equiv) and triethyl amine (84 μL, 0.6 mmol 3.0 equiv) in anhydrous DCM (2 mL) under N_2 was prepared. Subsequently, Me_3SiCl (31.0 μL, 0.24 mmol, 1.2 equiv) was added slowly. After stirring for 2 h at r.t., the mixture was concentrated to dryness and directly purified by column chromatography (hexane/EA = 10:1) to give the product **3.P23** in 91% yield (44.5 mg) as white solid.

Synthesis of 3.P24

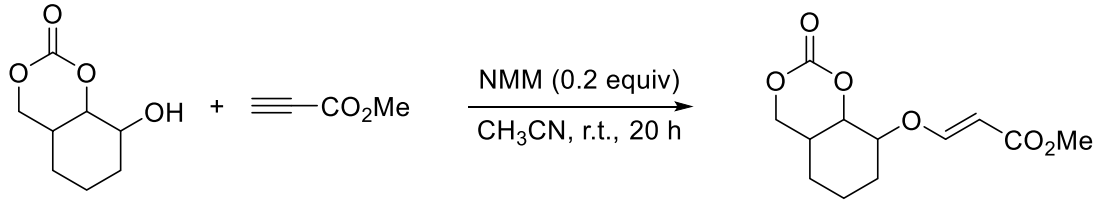


3.P8
0.2 mmol

3.P24. 74%

To a stirred solution of **3.P8** (34.4 mg, 0.2 mmol, 1 equiv) in 1 mL of DCM was successively added DMAP (2.4 mg, 0.02 mmol, 0.1 equiv), benzoic acid (73.2 mg, 0.6 mmol, 3 equiv) and DCC (123.7 mg, 0.6 mmol, 3 equiv). After stirring for 2 h at r.t., the mixture was diluted with 2 mL of diethyl ether, and then filtered. The filtrate was concentrated to dryness and purified by column chromatography (hexane/EA = 4:1 to 2:1) to give the esterification product **3.P24** in 74% yield (41.0 mg) as a white solid.

Synthesis of 3.P25

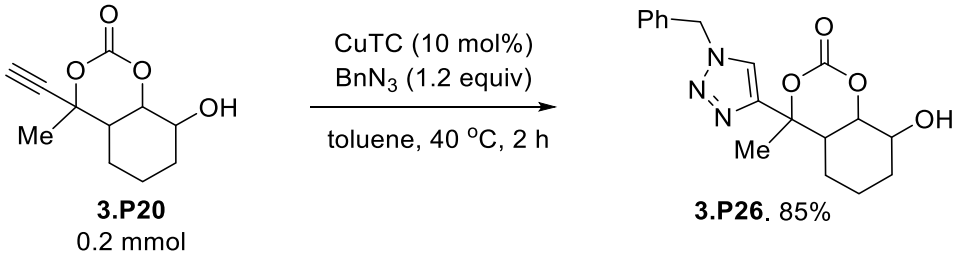


3.P8
0.2 mmol

3.P25. 76%

To a stirred solution of **3.P8** (34.4 mg, 0.2 mmol, 1 equiv) in 1 mL of CH_3CN was successively added NMM (4.0 mg, 0.04 mmol, 0.2 equiv) and methyl propiolate (20.2 mg, 0.24 mmol, 1.2 equiv). After stirring for 20 h at r.t., the mixture was concentrated to dryness and directly purified by column chromatography (hexane/EA = 2:1) to give the ether product **3.P25** in 76% yield (38.9 mg) as a colorless oil.

Synthesis of 3.P26



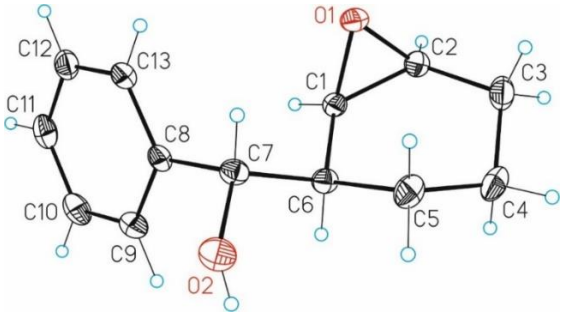
3.P20
0.2 mmol

3.P26. 85%

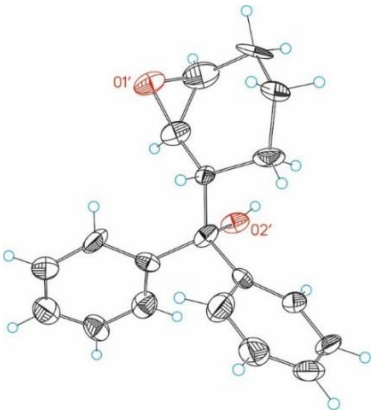
In a 10 mL oven-dried glass vial, a mixture of **3.P20** (43.2 mg, 0.20 mmol, 1.0 equiv) and copper(I) thiophene-2-carboxylate (CuTC) (3.8 mg, 0.02 mmol, 0.1 equiv) in anhydrous toluene (1 mL) was cooled with an ice-water bath. Subsequently, benzyl azide (30.0 μL, 0.24 mmol, 1.2 equiv) was added slowly, and the reaction mixture was heated to 40 °C and stirred for 2 h while monitored by TLC. The reaction mixture was quenched by a saturated aqueous NH_4Cl solution, extracted with DCM (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EA= 1:1) to afford the desired triazole **3.P26** (58.4 mg, 85%) as a white solid.

3.6.8 X-ray molecular structures

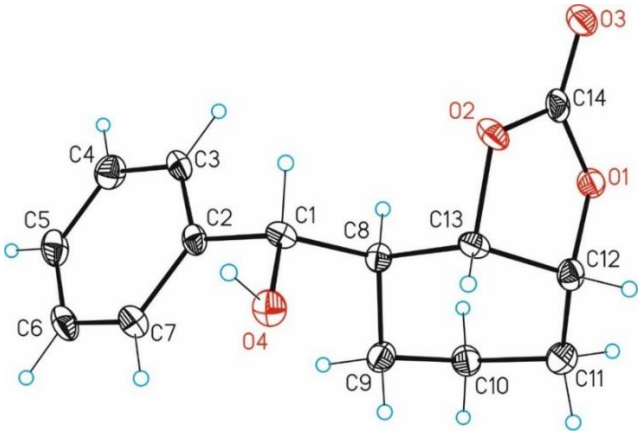
For the experimental procedure of the X-ray crystallographic analysis, please refer to Chapter 2.



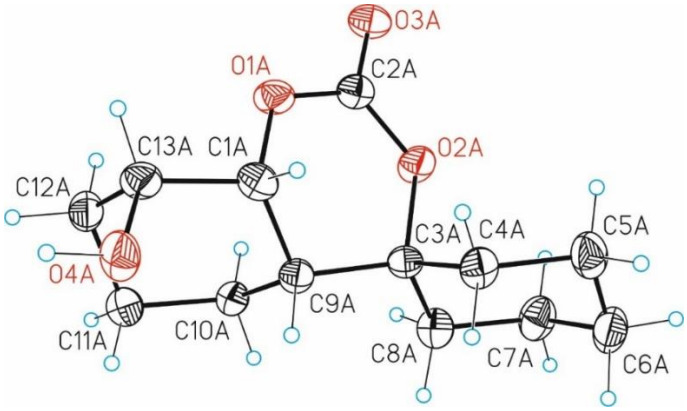
Crystallographic data for syn-3.1a: $C_{13}H_{16}O_2$, M_r = 204.26, T = 100(2)K, monoclinic, C 2/c, a = 21.648(2)Å, b = 9.2058(9)Å, c = 10.7785(10)Å, $\alpha = \gamma = 90°$, β = 93.321(3)°, V = 2144.4(4) Å^3, Z =8, λ = 0.71073 Å, ρ = 1.265 Mg/m^3, μ = 0.084 mm^{-1}, F(000) = 880, crystal size = 0.200 x 0.100 x 0.020 mm^3, θ(min) = 1.885° θ(max) =30.551°, 13045 reflections collected, 3245 reflections unique (R_{int} = 0.0408), GoF = 1.047, R_1 = 0.0484, wR_2 = 0.1344 [I>2σ(I)], R_1 = 0.0627, wR_2 = 0.1447 (all indices), max/min residual density = 0.549/-0.266 [e.Å^{-3}]. Completeness to θ(30.551°) = 98.9%. CCDC-2157245.



Crystallographic data for anti-3.1o: $C_{38}H_{40}O_4$, M_r = 560.70, T = 100(2)K, monoclinic, P 21/c, a = 18.4631(4)Å, b = 10.33078(17)Å, c = 17.5044(4)Å, $\alpha = \gamma = 90°$, β = 118.196(3)°, V = 2942.58(13) Å^3, Z =4, λ = 0.71073 Å, ρ = 1.266 Mg/m^3, μ = 0.080 mm^{-1}, F(000) = 1200, crystal size = 0.200 x 0.050 x 0.050 mm^3, θ(min) = 2.335° θ(max) =29.566°, 44545 reflections collected, 7163 reflections unique (R_{int} = 0.0286), GoF = 1.787, R_1 = 0.0489, wR_2 = 0.2012 [I>2σ(I)], R_1 = 0.0555, wR_2 = 0.2053 (all indices), max/min residual density = 0.241/-0.309 [e.Å^{-3}]. Completeness to θ(29.566°) = 86.5%. CCDC-2157247.



Crystallographic data for 3.P1[b]: $C_{14}H_{16}O_4$, M_r = 248.27, T = 100(2)K, monoclinic, C 2/c, a = 25.391(8)Å, b = 5.6252(19)Å, c = 17.103(5)Å, $\alpha = \gamma = 90°$, β = 96.863(10)°, V = 2425.3(14) Å^3, Z =8, λ = 0.71073 Å, ρ = 1.360 Mg/m^3, μ = 0.099 mm^{-1}, F(000) = 1056, crystal size = 0.400 x 0.040 x 0.030 mm^3, θ(min) = 1.616 ° θ(max) =24.133°, 12088 reflections collected, 1932 reflections unique (R_{int} = 0.1037), GoF = 1.057, R_1 = 0.0538, wR_2 = 0.1211 [I>2σ(I)], R_1 = 0.0916, wR_2 = 0.1373 (all indices), max/min residual density = 0.231/-0.366 [e.Å^{-3}]. Completeness to θ(24.133°) = 99.6%. CCDC-2157244.



Crystallographic data for 3.P13: $C_{52}H_{81.82}O_{17.18}$, M_r = 981.81, T = 100(2)K, triclinic, P -1, a = 11.3607(17)Å, b = 11.9291(18)Å, c = 18.900(3)Å, α= 88.466(3)°, β = 76.159(3)°, γ = 89.416(3), V = 2486.2(6) Å^3, Z =2, λ = 0.71073 Å, ρ = 1.312 Mg/m^3, μ = 0.097 mm^{-1}, F(000) = 1062, crystal size = 0.400 x 0.040 x 0.010 mm^3, θ(min) = 1.110 ° θ(max) =26.730°, 36623 reflections collected, 10474 reflections unique (R_{int} = 0.0638), GoF = 1.087, R_1 = 0.0860, wR_2 = 0.2262 [I>2σ(I)], R_1 = 0.1119, wR_2 = 0.2423 (all indices), max/min residual density = 1.035/-0.573 [e.Å^{-3}]. Completeness to θ(26.730°) = 99.2%. CCDC-2157246.

3.6.9 General information on the ring-opening polymerization studies

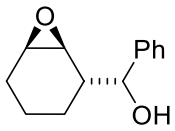
General considerations: All water-sensitive operations were carried out under a nitrogen atmosphere using an MBraun glovebox, standard vacuum line, and Schlenk techniques. Solvents were purchased from Sigma-Aldrich (HPLC grade) and dried using an MBraun MBSPS800 purification system. Benzyl alcohol was dried over CaH_2 and distilled under reduced pressure. TBD and the 6-membered cyclic carbonate monomer were dissolved in DCM and THF separately, stirred over calcium hydride, filtered and dried in vacuum prior to use. Differential scanning calorimetry (DSC) analyses for determination of the glass transition temperatures (T_g) were measured under a N_2 atmosphere using a Mettler Toledo equipment (model DSC822e). Samples were weighed into 40 μL aluminum crucibles and subjected to two heating cycles at a heating rate of 10 °C/min. Thermogravimetric analyses (TGA) were recorded under air atmosphere using Mettler Toledo equipment (model TGA/SDTA851). Samples were weighed into 40 μL aluminum crucibles and heated to 600 ºC at a heating rate of 10 °C/min. Gel permeation chromatography (GPC) measurements were performed using an Agilent 1200 series HPLC system, equipped with PSS SDV Analytical linear M GPC column (8 × 300 mm; 5 μm particle size) in tetrahydrofuran at 30 °C at a flow rate of 1 mL/min. Samples were analyzed at a concentration of 1 mg/mL after filtration through a 0.45 μm pore-size membrane. M_n, M_w, and $Đ$ data were derived from the RI signal by a calibration curve based on polystyrene standards (PS from Polymer Standards Service) for the analysis of the polymers. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) was performed using a BRUKER Autoflex spectrometer under the following sample preparation conditions: 1 mg of polymer was dissolved in 1 mL of CH_2Cl_2 (1 mg/mL). 5 μL of this solution was added to a solution of dithranol in CH_2Cl_2 as a matrix (25 μL, 10 mg/mL) and CF_3COONa in THF as an additive (1 μL, 1 mg/mL).

Typical ring-opening polymerization procedure

In a glovebox, monomer **3.P23** (20 mg, 82 μmol) was introduced into a vial equipped with a magnetic stirrer. Then, benzyl alcohol (27 μL from a 59.2 mM stock solution in toluene, 1.62 μmol, 2.0 mol%) and TBD (55 μL of a 29.5 mM stock solution in toluene, 1.62 μmol, 2 mol%) were added in this sequence. Once out of the glovebox, the vial was sealed with electric insulator tape. After stirring for 20 h, the reaction mixture was quenched with benzoic acid (30 μL of a 83.5 mM stock solution in toluene, 1.22 μmol) and a sample was analyzed by ^{1}H NMR ($CDCl_3$) to determine the monomer conversion. The polymer product was collected by precipitation of the crude reaction mixture from DCM/MeOH following filtration. The measured conversion of **3.P23** of this example preparation was 96%. M_n (GPC) = 5.9 kDa, $Đ$ = 1.32 (Table 3.2, entry 3).

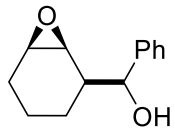
3.6.10 Characterization data for all new and relevant compounds

Cyclic epoxy alcohols



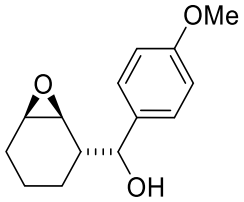
3.1a (*anti*)

Using methanol as solvent. The product was isolated as a colorless oil, eluent: 10% EA in hexane. Yield: 60%, 367.3 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.32 – 7.26 (m, 1H), 4.87 (d, *J* = 5.8 Hz, 1H), 3.18 (dt, *J* = 4.0, 2.0 Hz, 1H), 3.07 (d, *J* = 3.9 Hz, 1H), 2.22 (dt, *J* = 11.3, 5.6 Hz, 1H), 2.11 – 2.04 (m, 1H), 1.89 (s, 1H), 1.68 (dddd, *J* = 14.9, 11.6, 5.3, 2.0 Hz, 1H), 1.45 – 1.37 (m, 2H), 1.34 – 1.23 (m, 1H), 1.19 – 1.11 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.73, 128.62, 127.87, 126.39, 76.53, 54.85, 53.08, 41.92, 24.95, 21.52, 17.13; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{16}NaO_2$) 227.1043 $(M+Na)^+$: found: 227.1036.



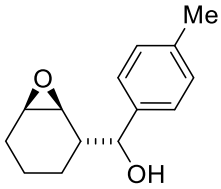
3.1a (*syn*)

The product was isolated as a white solid, eluent: 10% EA in hexane. Yield: 92%, 563 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.41 – 7.36 (m, 2H), 7.33 – 7.29 (m, 1H), 4.89 (dt, *J* = 6.7, 1.1 Hz, 1H), 3.15 (tdd, *J* = 4.1, 1.4, 0.6 Hz, 1H), 2.91 (dd, *J* = 4.1, 2.6 Hz, 1H), 2.45 (d, *J* = 2.2 Hz, 1H), 2.16 (dtd, *J* = 8.0, 6.6, 2.5 Hz, 1H), 1.93 – 1.81 (m, 2H), 1.65 – 1.58 (m, 1H), 1.50 – 1.44 (m, 2H), 1.30 – 1.17 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.03, 128.47, 127.68, 126.51, 76.54, 54.37, 52.48, 42.43, 23.83, 20.44, 19.73; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{16}NaO_2$) 227.1043 $(M+Na)^+$: found: 227.1038.



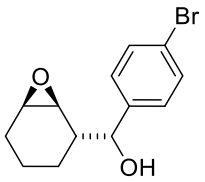
3.1b

Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 13%, 91.5 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.92 – 6.86 (m, 2H), 4.77 (d, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 3.19 – 3.11 (m, 1H), 3.04 – 2.95 (m, 1H), 2.18 (dt, *J* = 11.6, 6.0 Hz, 1H), 2.06 (ddd, *J* = 15.3, 3.4, 1.9 Hz, 1H), 1.91 (s, 1H), 1.71 – 1.63 (m, 1H), 1.54 – 1.37 (m, 2H), 1.31 (dddd, *J* = 15.0, 6.4, 4.6, 2.2 Hz, 1H), 1.12 (tdd, *J* = 12.5, 11.0, 2.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.30, 134.88, 127.66, 114.00, 76.18, 55.43, 54.68, 53.07, 41.97, 24.95, 21.97, 17.16; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{18}NaO_3$) 257.1148 $(M+Na)^+$: found: 257.1149.



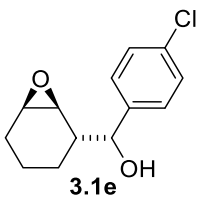
3.1c

Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 16%, 104.8 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 4.81 (d, *J* = 6.0 Hz, 1H), 3.16 (dt, *J* = 4.1, 2.0 Hz, 1H), 3.04 (d, *J* = 3.9 Hz, 1H), 2.35 (s, 3H), 2.19 (dt, *J* = 11.6, 5.9 Hz, 1H), 1.94 (s, 1H), 1.72 – 1.58 (m, 2H), 1.49 – 1.37 (m, 2H), 1.34 – 1.23 (m, 1H), 1.18 – 1.08 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.76, 137.53, 129.27, 126.35, 76.39, 54.82, 53.08, 41.90, 24.95, 21.71, 21.23, 17.15; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{18}NaO_2$) 241.1199 $(M+Na)^+$: found: 241.1199.



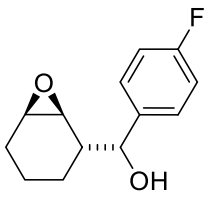
3.1d

Using dichloromethane as solvent. The product was isolated as a white solid, eluent: 30% EA in hexane. Yield: 15%, 127.5 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.24 – 7.20 (m, 2H), 4.82 (d, *J* = 5.4 Hz, 1H), 3.16 (dt, *J* = 4.1, 1.9 Hz, 1H), 3.05 – 3.02 (m, 1H), 2.22 (s, 1H), 2.13 (dt, *J* = 11.2, 5.6 Hz, 1H), 2.05 (dqd, *J* = 14.6, 2.9, 1.4 Hz, 1H), 1.65 (dddd, *J* = 14.9, 11.8, 5.4, 2.0 Hz, 1H), 1.41 – 1.19 (m, 3H), 1.09 (tdd, *J* = 12.8, 11.2, 2.7 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.73, 131.62, 128.05, 121.54, 75.70, 54.77, 53.10, 41.86, 24.84, 21.21, 17.05; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{15}BrNaO_2$) 305.1048 $(M+Na)^+$: found: 305.1049.



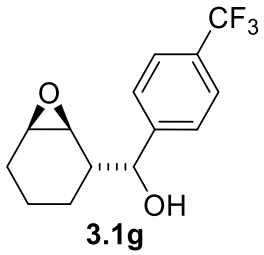
3.1e

Using dichloromethane as solvent. The product was isolated as a white solid, eluent: 30% EA in hexane. Yield: 13%, 93.1 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 4.87 (d, *J* = 5.5 Hz, 1H), 3.18 (dd, *J* = 3.9, 2.0 Hz, 1H), 3.05 (d, *J* = 3.7 Hz, 1H), 2.17 (dt, *J* = 10.9, 5.5 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.66 (dddd, *J* = 14.9, 11.5, 5.4, 1.9 Hz, 1H), 1.45 – 1.24 (m, 3H), 1.18 – 1.06 (m, 1H**)**; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.19, 133.53, 128.74, 127.72, 75.80, 54.73, 53.07, 41.96, 24.89, 21.29, 17.08; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{15}ClNaO_2$) 261.0653 $(M+Na)^+$: found: 261.0649.



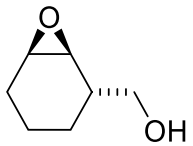
3.1f

Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 10%, 66.7 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.07 – 7.02 (m, 2H), 4.84 (d, *J* = 5.8 Hz, 1H), 3.16 (dt, *J* = 4.2, 1.9 Hz, 1H), 3.03 (d, *J* = 3.9 Hz, 1H), 2.16 (dt, *J* = 11.2, 5.6 Hz, 1H), 2.09 – 2.00 (m, 2H), 1.66 (dddd, *J* = 14.9, 11.8, 5.3, 2.0 Hz, 1H), 1.45 – 1.37 (m, 2H), 1.33 – 1.23 (m, 1H), 1.16 – 1.07 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.37 (d, *J* = 245.9 Hz), 138.47 (d, *J* = 3.2 Hz), 128.00 (d, *J* = 7.9 Hz), 115.43 (d, *J* = 21.5 Hz), 75.83, 54.69, 53.06, 42.01, 24.90, 21.51, 17.09; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -114.79; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{15}FNaO_2$) 245.0948 $(M+Na)^+$: found: 245.0940.



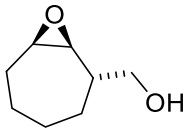
3.1g

Using dichloromethane as solvent. The product was isolated as a white solid, eluent: 30% EA in hexane. Yield: 25%, 204.2 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 2H), 7.48 (dq, *J* = 8.2, 0.9 Hz, 2H), 4.97 (d, *J* = 5.1 Hz, 1H), 3.20 (dd, *J* = 3.8, 2.0 Hz, 1H), 3.10 (dt, *J* = 4.0, 0.7 Hz, 1H), 2.20 (dt, *J* = 11.0, 5.4 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.67 (dddd, *J* = 14.9, 11.5, 5.5, 1.9 Hz, 1H), 1.39 (dtd, *J* = 9.8, 5.2, 4.7, 2.6 Hz, 1H), 1.33 – 1.20 (m, 2H), 1.19 – 1.07 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.72, 133.70, 130.49, 130.31, 130.17, 129.94, 129.85, 129.53, 128.34, 128.28, 126.61, 125.57, 125.53, 125.49, 125.45, 122.87, 120.17, 75.78, 54.87, 53.12, 41.95, 24.84, 20.94, 17.04; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.61; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{15}F_3NaO_2$) 295.0916 $(M+Na)^+$: found: 295.0916.



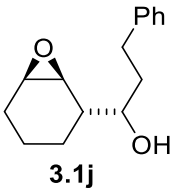
3.1h

Using methanol as solvent. The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 17%, 65.4 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.73 (dd, *J* = 10.7, 5.7 Hz, 1H), 3.64 (dd, *J* = 10.7, 7.0 Hz, 1H), 3.18 (dt, *J* = 4.1, 2.0 Hz, 1H), 3.09 (dd, *J* = 4.0, 1.0 Hz, 1H), 2.13 – 2.00 (m, 2H), 1.69 (dddd, *J* = 15.0, 10.4, 6.3, 2.1 Hz, 2H), 1.60 – 1.53 (m, 1H), 1.43 – 1.35 (m, 2H), 0.95 (dtd, *J* = 13.2, 11.1, 4.3 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 65.43, 54.16, 52.83, 37.61, 24.93, 23.97, 17.20. **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_7H_{13}O_2$) 129.0910 $(M+H)^+$: found: 129.0905.



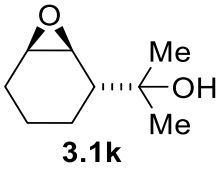
3.1i

Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 46%, 196.2 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 (qd, *J* = 10.5, 6.6 Hz, 2H), 3.04 (ddd, *J* = 7.3, 5.5, 4.5 Hz, 1H), 2.87 (dd, *J* = 7.1, 4.7 Hz, 1H), 2.21 (ddd, *J* = 11.7, 7.5, 5.6 Hz, 1H), 1.86 – 1.72 (m, 2H), 1.71 – 1.64 (m, 1H), 1.59 (dq, *J* = 5.6, 3.1, 2.2 Hz, 2H), 1.46 – 1.33 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 66.18, 57.81, 54.76, 43.90, 30.16, 29.92, 28.19, 24.59; **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_8H_{13}O$) 125.0961 $(M-OH)^+$: found: 125.0955.



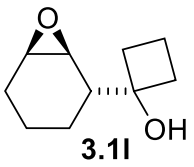
3.1j

Using methanol as solvent. The product was isolated as a colorless oil, eluent: 15% EA in hexane. Yield: 27%, 188.2 mg, *anti*: *syn* = 3:1. Only the data for the *anti* isomer is reported here. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.8, 6.8 Hz, 3H), 7.24 – 7.16 (m, 4H), 3.80 (dt, *J* = 8.4, 4.2 Hz, 1H), 3.20 (ddd, *J* = 10.5, 4.1, 1.6 Hz, 1H), 3.06 (dd, *J* = 4.0, 1.1 Hz, 1H), 2.83 (ddd, *J* = 13.6, 9.4, 5.9 Hz, 1H), 2.69 (tdd, *J* = 13.7, 9.5, 6.7 Hz, 1H), 2.09 (ddq, *J* = 14.8, 4.2, 2.2 Hz, 1H), 1.98 – 1.76 (m, 6H), 1.69 – 1.62 (m, 1H), 1.58 – 1.48 (m, 2H), 1.44 (dtt, *J* = 12.9, 5.2, 2.9 Hz, 1H), 1.40 – 1.23 (m, 2H), 1.08 (qd, *J* = 12.9, 3.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.31, 141.79, 128.61, 128.57, 128.53, 128.50, 126.12, 125.91, 74.26, 73.50, 55.30, 53.36, 53.01, 52.48, 40.36, 40.16, 37.02, 36.22, 32.63, 32.30, 24.99, 23.79, 22.41, 20.87, 19.86, 17.14; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{20}NaO_2$) 255.1356 $(M+Na)^+$: found: 255.1347.



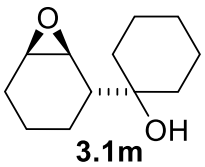
3.1k

Using methanol as solvent. The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 46%, 215.6 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.23 (dd, *J* = 4.0, 1.3 Hz, 1H), 3.18 (q, *J* = 2.0 Hz, 1H), 2.11 (ddq, *J* = 14.8, 3.8, 1.9 Hz, 1H), 1.79 (dd, *J* = 12.2, 6.0 Hz, 1H), 1.67 – 1.61 (m, 2H), 1.48 – 1.41 (m, 1H), 1.35 (ddd, *J* = 12.9, 4.6, 2.6 Hz, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 0.93 (qd, *J* = 12.9, 3.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 72.55, 53.54, 53.07, 46.17, 28.70, 26.34, 25.02, 23.33, 17.54; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_9H_{16}NaO_2$) 179.1043 $(M+Na)^+$: found: 179.1042.



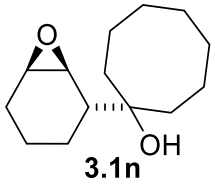
3.1l

Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 20% EA in hexane. Yield: 21%, 106.0 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.20 (dt, *J* = 4.1, 1.9 Hz, 1H), 3.07 (dd, *J* = 4.0, 1.3 Hz, 1H), 2.38 (dddd, *J* = 12.5, 9.6, 4.3, 3.5 Hz, 1H), 2.22 (dddd, *J* = 13.1, 8.4, 4.4, 3.5 Hz, 1H), 2.14 – 2.08 (m, 2H), 1.99 (dd, *J* = 12.2, 6.0 Hz, 1H), 1.96 – 1.90 (m, 1H), 1.89 – 1.80 (m, 1H), 1.72 – 1.57 (m, 5H), 1.49 (dtt, *J* = 12.7, 5.1, 2.6 Hz, 1H), 1.35 (qdd, *J* = 13.1, 4.6, 2.7 Hz, 1H), 1.12 – 1.02 (m, 1H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 77.08, 53.57, 52.98, 42.21, 35.69, 34.78, 24.98, 20.82, 17.51, 12.20; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{16}NaO_2$) 191.1043 $(M+Na)^+$: found: 191.1037.



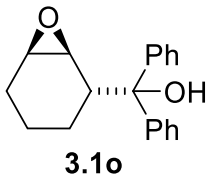
3.1m

Using methanol as solvent. The product was isolated as a colorless oil, eluent: 10% EA in hexane. Yield: 60%, 353.3 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.24 (dd, *J* = 4.1, 1.3 Hz, 1H), 3.15 (dt, *J* = 4.0, 1.9 Hz, 1H), 2.09 (ddt, *J* = 14.8, 4.2, 1.9 Hz, 1H), 1.77 (dd, *J* = 12.3, 6.0 Hz, 1H), 1.70 – 1.48 (m, 12H), 1.45 (ddp, *J* = 12.7, 5.1, 2.5 Hz, 1H), 1.39 – 1.28 (m, 2H), 0.99 (qd, *J* = 12.8, 3.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 73.11, 53.56, 53.09, 44.73, 35.55, 34.22, 25.79, 25.03, 22.03, 22.02, 21.94, 17.62; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{20}NaO_2$) 219.1356 $(M+Na)^+$: found: 219.1348.



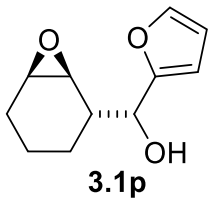
3.1n

Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 15% EA in hexane. Yield: 28%, 188.5 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.28 (dd, *J* = 4.1, 1.3 Hz, 1H), 3.18 – 3.14 (m, 1H), 2.14 – 2.07 (m, 1H), 1.99 – 1.92 (m, 1H), 1.85 – 1.75 (m, 3H), 1.71 – 1.59 (m, 9H), 1.55 – 1.28 (m, 7H), 1.05 (dtd, *J* = 13.3, 12.5, 2.9 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 76.24, 53.78, 53.15, 44.30, 34.98, 34.44, 28.31, 25.15, 24.98, 22.30, 22.29, 22.21, 17.88; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{24}NaO_2$) 247.1669 $(M+Na)^+$: found: 247.1670.



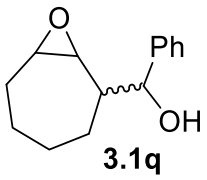
3.1o

Using methanol as solvent. The product was isolated as a white solid, eluent: 10% EA in hexane. Yield: 30%, 252.3 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.42 – 7.39 (m, 2H), 7.38 – 7.33 (m, 2H), 7.29 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.25 – 7.21 (m, 1H), 7.20 – 7.14 (m, 1H), 3.17 – 3.14 (m, 2H), 2.98 (dd, *J* = 12.2, 5.6 Hz, 1H), 2.12 (ddq, *J* = 15.0, 3.7, 1.6 Hz, 1H), 1.67 (dddd, *J* = 15.0, 12.3, 5.9, 1.6 Hz, 1H), 1.46 – 1.31 (m, 2H), 1.26 – 1.19 (m, 1H), 1.08 (qd, *J* = 12.8, 3.5 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.94, 145.85, 128.76, 128.36, 127.14, 126.70, 126.15, 125.47, 80.39, 54.53, 53.58, 43.49, 24.93, 22.47, 17.72; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{20}NaO_2$) 303.1356 (M+Na)+: found: 303.1346.



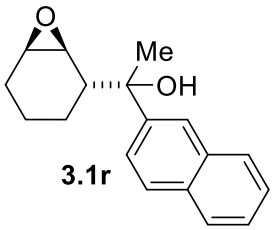
3.1p

Using dichloromethane as solvent. The product was isolated as colorless oil, eluent: 30% Et_2O in hexane. Yield: 21%, 122.4 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (dt, *J* = 1.9, 1.0 Hz, 1H), 6.35 (td, *J* = 2.4, 1.9, 1.2 Hz, 1H), 6.30 (dq, *J* = 3.2, 0.8 Hz, 1H), 4.81 – 4.75 (m, 1H), 3.16 (q, *J* = 2.1 Hz, 1H), 3.08 (dd, *J* = 3.9, 1.1 Hz, 1H), 2.36 (ddd, *J* = 12.4, 7.1, 5.3 Hz, 1H), 2.11 – 2.05 (m, 1H), 1.70 – 1.55 (m, 2H), 1.43 – 1.31 (m, 2H), 1.12 – 1.02 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.17, 142.32, 110.38, 107.27, 70.18, 70.16, 54.05, 54.04, 52.98, 52.97, 40.00, 24.87, 22.68, 17.07; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{14}NaO_3$) 217.0835 $(M+Na)^+$: found: 217.0830.



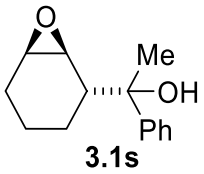
3.1q

Using dichloromethane as solvent. The product was isolated as colorless oil, eluent: 30% EA in hexane. Yield: 61%, 399.5 mg, *anti*: *syn* = 1:1. The NMR data for both *anti* and *syn* isomers are reported here. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 4H), 7.31 (dddd, *J* = 8.0, 4.3, 3.1, 1.7 Hz, 0.97H), 4.91 (dd, *J* = 5.6, 1.9 Hz, 0.52H), 4.79 (dd, *J* = 6.5, 2.9 Hz, 0.48H), 3.19 (dd, *J* = 4.8, 1.1 Hz, 0.52H), 3.10 (t, *J* = 5.2 Hz, 0.52H), 2.99 (tdd, *J* = 5.6, 4.7, 1.6 Hz, 0.48H), 2.89 (dd, *J* = 7.4, 4.8 Hz, 0.48H), 2.30 (dtdd, *J* = 15.0, 5.3, 2.7, 1.2 Hz, 0.55H), 2.25 – 2.16 (m, 1.54H), 2.05 (d, *J* = 3.7 Hz, 0.42H), 2.00 – 1.84 (m, 1.51H), 1.81 – 1.71 (m, 1.16H), 1.70 – 1.65 (m, 0.81H), 1.56 (d, *J* = 14.1 Hz, 0.59H), 1.47 – 1.26 (m, 2.63H), 1.20 (dtd, *J* = 14.0, 12.1, 2.1 Hz, 0.57H), 0.83 (dtt, *J* = 14.3, 12.2, 2.2 Hz, 0.57H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.92, 142.89, 128.57, 128.49, 127.89, 127.74, 126.62, 78.28, 76.34, 58.19, 56.93, 55.21, 55.05, 48.24, 46.87, 30.25, 29.86, 28.97, 28.35, 26.86, 25.06, 24.66, 24.32; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{18}NaO_2$) 241.1199 $(M+Na)^+$: found: 241.1197.



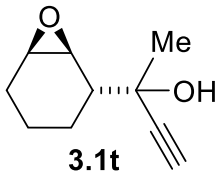
3.1r

Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 16%, 128.8 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.9 Hz, 1H), 7.88 – 7.80 (m, 3H), 7.54 – 7.42 (m, 3H), 3.42 (dd, *J* = 4.1, 1.3 Hz, 1H), 3.18 (dd, *J* = 3.9, 2.0 Hz, 1H), 2.30 – 2.23 (m, 1H), 2.10 – 2.01 (m, 1H), 1.96 (s, 1H), 1.80 (s, 3H), 1.61 – 1.53 (m, 1H), 1.34 – 1.11 (m, 3H), 0.92 (dq, *J* = 12.8, 3.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.42, 133.21, 132.40, 128.27, 128.17, 127.62, 126.33, 126.00, 123.74, 123.5076.45, 53.68, 53.18, 45.60, 28.56, 24.84, 23.17, 17.67; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{18}H_{20}NaO_2$) 291.1356 $(M+Na)^+$: found: 291.1355.



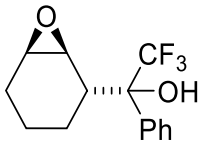
3.1s

Using methanol as solvent. The product was isolated as a colorless oil, eluent: 10% EA in hexane. Yield: 51%, 334.0 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.38 – 7.31 (m, 2H), 7.26 – 7.22 (m, 1H), 3.35 (dd, *J* = 4.1, 1.3 Hz, 1H), 3.16 (dt, *J* = 3.5, 1.8 Hz, 1H), 2.15 (dd, *J* = 12.4, 5.7 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.79 (s, 1H), 1.72 (s, 3H), 1.60 – 1.51 (m, 1H), 1.36 – 1.12 (m, 3H), 0.88 (dq, *J* = 13.0, 3.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.94, 128.36, 126.90, 125.10, 76.26, 53.66, 53.14, 45.86, 28.52, 24.86, 23.07, 17.69; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{18}NaO_2$) 241.1199 $(M+Na)^+$: found: 241.1187.



3.1t

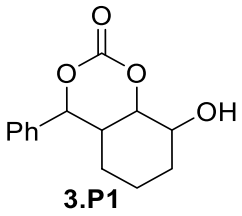
Using dichloromethane as solvent. The product was isolated as a white solid, eluent: 10% EA in hexane. Yield: 70%, 349.1 mg, *anti*: *syn* = 10:1. Only the NMR data for the *anti* isomer is reported here. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.37 (dd, J = 4.0, 1.3 Hz, 1H), 3.20 (dt, J = 4.1, 1.9 Hz, 1H), 2.47 (s, 1H), 2.15 – 2.07 (m, 2H), 1.97 (dd, J = 12.1, 6.2 Hz, 1H), 1.73 – 1.63 (m, 2H), 1.55 (s, 3H), 1.41 (dddd, J = 25.7, 12.8, 5.3, 2.7 Hz, 2H), 1.17 – 1.05 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 86.27, 72.77, 69.97, 53.25, 53.01, 45.77, 28.70, 24.81, 23.62, 17.20; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{14}NaO_2$) 189.0886 $(M+H)^+$: found: 189.0882.



3.1u

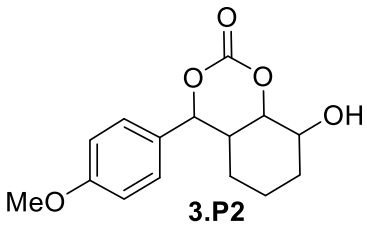
Using dichloromethane as solvent. The product was isolated as a colorless oil, eluent: 13% EA in hexane. Yield: 31%, 235.21 mg, *dr* >20:1 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.43 – 7.36 (m, 3H), 3.53 (d, *J* = 4.0 Hz, 1H), 3.13 (dt, *J* = 4.0, 2.0 Hz, 1H), 3.12 – 3.07 (m, 1H), 2.59 (dd, *J* = 12.2, 5.5 Hz, 1H), 2.06 (ddd, *J* = 15.0, 3.9, 2.1 Hz, 1H), 1.63 – 1.53 (m, 1H), 1.42 – 1.20 (m, 3H), 0.97 (qd, *J* = 12.8, 3.4 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.12; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.94, 130.42, 128.64, 128.58, 127.56, 125.92 (q, *J* = 2.0 Hz), 124.70, 121.84, 79.37 (q, *J* = 27.3 Hz), 53.02, 52.25 (q, *J* = 3.5 Hz), 41.56, 24.42, 22.78, 17.41; **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_{14}H_{14}F_3O$) 255.0991 $(M–OH)^+$: found: 255.0986.

6-Membered cyclic carbonates



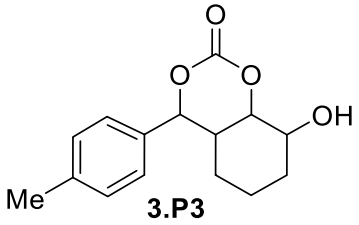
3.P1

The product was isolated as a white solid, eluent: 30% EA in hexane. Yield: 85%, 21.1 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.28 (m, 3H), 5.63 (d, *J* = 3.0 Hz, 1H), 4.71 (t, *J* = 3.1 Hz, 1H), 4.19 (q, *J* = 3.0 Hz, 1H), 2.51 – 2.43 (m, 1H), 1.83 – 1.66 (m, 3H), 1.63 – 1.46 (m, 2H), 1.28 – 1.17 (m, 1H), 1.14 (dt, *J* = 13.8, 4.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.75, 135.96, 128.68, 128.37, 125.22, 82.99, 79.33, 66.64, 33.45, 27.25, 18.22, 17.54; **IR** (neat, C=O, cm^{-1}): *ν* = 1731; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{16}NaO_4$) 217.0941 $(M+Na)^+$: found: 217.0938.



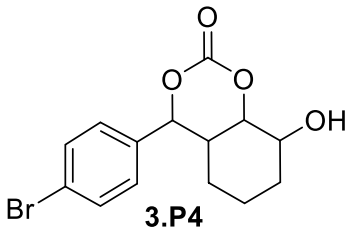
3.P2

The product was isolated as a white solid, eluent: 70% EA in hexane. Yield: 78%, 21.7 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 2H), 6.93 – 6.89 (m, 2H), 5.58 (d, *J* = 3.1 Hz, 1H), 4.68 (t, *J* = 3.0 Hz, 1H), 4.17 (q, *J* = 3.0 Hz, 1H), 3.81 (s, 3H), 2.41 (ddt, *J* = 11.8, 5.8, 2.9 Hz, 1H), 2.08 (s, 1H), 1.80 – 1.66 (m, 2H), 1.62 – 1.48 (m, 2H), 1.26 – 1.15 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.60, 148.90, 127.98, 126.58, 114.05, 82.98, 79.36, 77.41, 77.16, 76.91, 66.63, 55.45, 33.60, 27.27, 18.23, 17.58; **IR** (neat, C=O, cm^{-1}): *v* = 1728; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{18}NaO_5$) 301.1046 $(M+Na)^+$: found: 301.1051.



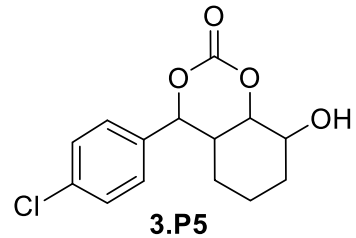
3.P3

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 85%, 22.3 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 (s, 4H), 5.60 (d, *J* = 3.1 Hz, 1H), 4.69 (t, *J* = 3.1 Hz, 1H), 4.18 (q, *J* = 3.0 Hz, 1H), 2.43 (ddt, *J* = 12.7, 5.5, 2.9 Hz, 1H), 2.35 (s, 3H), 1.91 (s, 1H), 1.82 – 1.69 (m, 2H), 1.62 – 1.47 (m, 2H), 1.27 – 1.12 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.80, 138.16, 132.99, 129.33, 125.19, 83.05, 79.32, 66.70, 33.53, 27.30, 21.26, 18.23, 17.57; **IR** (neat, C=O, cm^{-1}): *v* = 1734; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{18}NaO_4$) 285.1097 $(M+Na)^+$: found: 285.1102.



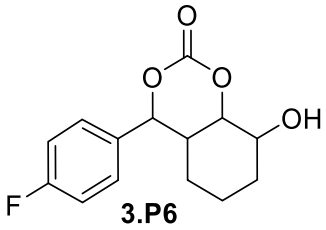
3.P4

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 92%, 30.1 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 5.59 (d, *J* = 3.1 Hz, 1H), 4.69 (t, *J* = 3.1 Hz, 1H), 4.19 (q, *J* = 3.1 Hz, 1H), 2.48 – 2.40 (m, 1H), 1.81 – 1.67 (m, 3H), 1.62 – 1.50 (m, 2H), 1.23 – 1.07 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.28, 135.06, 131.92, 126.95, 122.40, 82.33, 79.17, 66.63, 33.30, 27.25, 18.17, 17.48; **IR** (neat, C=O, cm^{-1}): *v* = 1733; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{15}BrNaO_4$) 349.0046 $(M+Na)^+$: found: 349.0046.



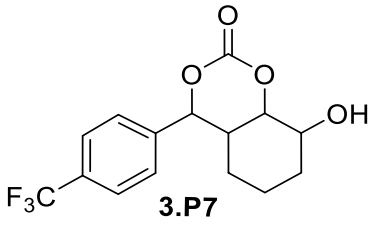
3.P5

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 96%, 27.1 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.27 – 7.24 (m, 2H), 5.61 (d, *J* = 3.1 Hz, 1H), 4.69 (t, *J* = 3.2 Hz, 1H), 4.19 (s, 1H), 2.44 (ddt, *J* = 12.9, 5.6, 2.9 Hz, 1H), 1.82 – 1.67 (m, 3H), 1.63 – 1.49 (m, 3H), 1.24 – 1.16 (m, 1H), 1.12 (dd, *J* = 13.7, 4.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.28, 134.52, 134.32, 128.97, 126.65, 82.32, 79.17, 66.65, 33.36, 27.27, 18.18, 17.49; **IR** (neat, C=O, cm^{-1}): *v* = 1733; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{15}ClNaO_4$) 305.0551 $(M+Na)^+$: found: 305.0553.



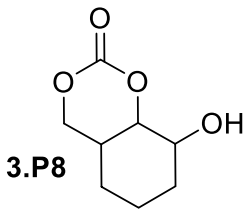
3.P6

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 89%, 23.7 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.11 – 7.05 (m, 2H), 5.61 (d, *J* = 3.1 Hz, 1H), 4.70 (t, *J* = 3.1 Hz, 1H), 4.19 (s, 1H), 2.44 (ddt, *J* = 12.9, 4.8, 2.9 Hz, 1H), 1.95 (s, 1H), 1.81 – 1.68 (m, 2H), 1.55 (ddt, *J* = 27.7, 10.6, 4.1 Hz, 2H), 1.21 (qd, *J* = 13.0, 4.2 Hz, 1H), 1.13 (dd, *J* = 13.6, 4.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.62 (d, *J* = 247.3 Hz), 148.49, 131.76 (d, *J* = 3.2 Hz), 127.05 (d, *J* = 8.2 Hz), 115.73 (d, *J* = 21.7 Hz), 82.48, 79.25, 66.61, 33.46, 27.25, 18.17, 17.50; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -113.54; **IR** (neat, C=O, cm^{-1}): *v* = 1735; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{15}FNaO_4$) 289.0847 $(M+Na)^+$: found: 289.0852.



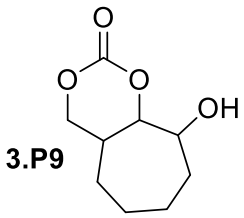
3.P7

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 87%, 27.5 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 2H), 7.49 – 7.43 (m, 2H), 5.69 (d, *J* = 3.1 Hz, 1H), 4.73 (t, *J* = 3.0 Hz, 1H), 4.21 (d, *J* = 3.0 Hz, 1H), 2.51 (ddt, *J* = 13.1, 4.6, 2.9 Hz, 1H), 1.83 (s, 1H), 1.82 – 1.68 (m, 2H), 1.64 – 1.51 (m, 2H), 1.22 (qd, *J* = 13.2, 4.4 Hz, 1H), 1.07 (dd, *J* = 13.8, 4.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.12, 140.00, 139.99, 131.15, 130.89, 130.63, 130.37, 127.24, 125.83, 125.80, 125.77, 125.74, 125.65, 125.08, 122.91, 120.75, 82.20, 79.17, 66.61, 33.28, 27.22, 18.20, 17.44; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.67; **IR** (neat, C=O, cm^{-1}): *v* = 1737; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{15}F_3NaO_4$) 339.0815 $(M+Na)^+$: found: 339.0812.



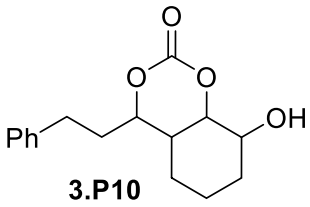
3.P8

The product was isolated as a white solid, eluent: 70% EA in hexane. Yield: 91%, 15.7 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.48 – 4.39 (m, 2H), 4.24 (dd, *J* = 11.0, 3.9 Hz, 1H), 4.07 (td, *J* = 4.8, 3.1 Hz, 1H), 2.39 – 2.33 (m, 1H), 2.19 (s, 1H), 1.87 – 1.79 (m, 1H), 1.78 – 1.53 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.37, 79.85, 72.13, 67.26, 28.37, 28.00, 23.13, 18.19; **IR** (neat, C=O, cm^{-1}): *v* = 1716 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_8H_{12}NaO_4$) 195.0628 $(M+Na)^+$: found: 195.0621.



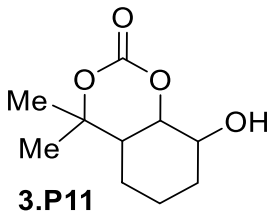
3.P9

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 57%, 10.6 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.57 (ddd, *J* = 7.2, 6.0, 0.9 Hz, 1H), 4.41 (dd, *J* = 11.0, 3.6 Hz, 1H), 4.13 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.88 (ddd, *J* = 10.5, 7.4, 1.4 Hz, 1H), 2.74 (s, 1H), 2.28 – 2.21 (m, 1H), 1.98 – 1.85 (m, 3H), 1.72 – 1.60 (m, 3H), 1.52 – 1.43 (m, 1H), 1.40 – 1.31 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.53, 88.40, 75.63, 72.57, 35.09, 32.05, 29.14, 26.87, 26.50; **IR** (neat, C=O, cm^{-1}): *v* = 1730; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_9H_{14}NaO_4$) 209.0748 $(M+Na)^+$: found: 209.0748.



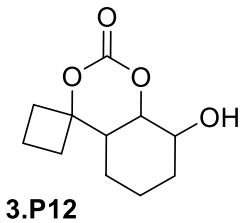
3.P10

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 73%, 20.2 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.24 – 7.17 (m, 3H), 4.43 – 4.38 (m, 2H), 4.11 – 4.07 (m, 1H), 2.86 (ddd, *J* = 14.3, 9.3, 5.4 Hz, 1H), 2.71 (dt, *J* = 13.9, 8.1 Hz, 1H), 2.16 (ddt, *J* = 10.1, 5.3, 3.2 Hz, 1H), 2.08 (dddd, *J* = 13.9, 9.7, 8.5, 5.4 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.77 – 1.57 (m, 6H), 1.35 – 1.29 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.02, 140.52, 128.76, 128.59, 126.47, 81.72, 79.35, 66.43, 33.28, 31.17, 30.91, 27.16, 18.16, 17.48; **IR** (neat, C=O, cm^{-1}): *v* = 1719; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{16}H_{20}NaO_4$) 299.1254 $(M+Na)^+$: found: 299.1249.



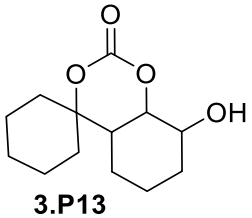
3.P11

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 81%, 16.2 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.67 (t, *J* = 3.2 Hz, 1H), 4.17 – 4.10 (m, 1H), 2.21 (s, 1H), 1.98 (ddd, *J* = 13.0, 4.7, 2.8 Hz, 1H), 1.79 – 1.71 (m, 2H), 1.70 – 1.57 (m, 3H), 1.51 (s, 3H), 1.38 (s, 3H), 1.32 – 1.23 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.35, 84.47, 75.67, 66.44, 35.36, 27.94, 26.87, 25.87, 20.75, 17.81; **IR** (neat, C=O, cm^{-1}): *v* = 1714; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{10}H_{16}NaO_4$) 223.0941 $(M+Na)^+$: found: 223.0938.



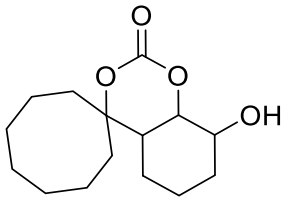
3.P12

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 75%, 15.9 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.49 (t, *J* = 3.1 Hz, 1H), 4.12 (q, *J* = 2.8 Hz, 1H), 2.43 (ddt, *J* = 10.1, 8.2, 5.7 Hz, 1H), 2.30 (td, *J* = 7.9, 7.3, 1.9 Hz, 2H), 2.19 (dddd, *J* = 15.6, 8.9, 6.6, 3.5 Hz, 2H), 2.00 – 1.90 (m, 1H), 1.77 – 1.57 (m, 6H), 1.22 – 1.10 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.84, 85.91, 75.01, 66.17, 34.98, 33.36, 31.06, 26.97, 18.91, 17.65, 12.25; **IR** (neat, C=O, cm^{-1}): *v* = 1717; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{16}NaO_4$) 235.0941 $(M+Na)^+$: found: 235.0933.



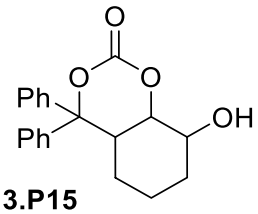
3.P13

The product was isolated as a white solid, eluent: 30% EA in hexane. Yield: 86%, 20.7 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.64 (t, *J* = 3.3 Hz, 1H), 4.12 (d, *J* = 3.5 Hz, 1H), 2.10 (ddd, *J* = 13.1, 4.5, 2.8 Hz, 2H), 1.96 (dt, *J* = 12.3, 4.0 Hz, 1H), 1.81 – 1.65 (m, 8H), 1.60 – 1.50 (m, 4H), 1.48 – 1.35 (m, 2H), 1.31 – 1.21 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.46, 85.56, 75.20, 66.48, 35.80, 33.82, 27.01, 25.10, 22.10, 21.59, 19.85, 17.89; **IR** (neat, C=O, cm^{-1}): *v* = 1719; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{20}NaO_4$) 263.1254 (M+Na)+: found: 263.1247.



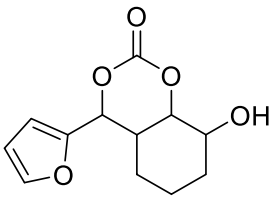
3.P14

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 44%, 12.6 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.65 (t, *J* = 3.3 Hz, 1H), 4.13 (q, *J* = 2.8 Hz, 1H), 2.23 (ddd, *J* = 15.2, 10.2, 2.6 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.78 – 1.71 (m, 6H), 1.69 – 1.51 (m, 9H), 1.44 – 1.29 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.27, 89.34, 75.76, 66.66, 33.95, 32.75, 31.90, 28.11, 27.94, 27.10, 25.41, 21.85, 21.62, 20.56, 17.93; **IR** (neat, C=O, cm^{-1}): *v* = 1718; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{24}NaO_4$) 291.1567 $(M+Na)^+$: found: 291.1562.



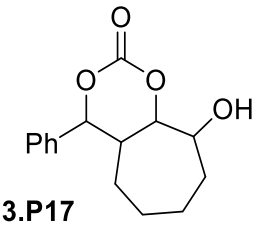
3.P15

The product was isolated as a white solid, eluent: 25% EA in hexane. Yield: 39%, 12.7 mg. **^{1}H NMR** (400 MHz, DMSO) δ 7.62 – 7.55 (m, 4H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.28 (m, 3H), 7.27 – 7.22 (m, 1H), 5.25 (d, *J* = 3.8 Hz, 1H), 4.22 (t, *J* = 3.2 Hz, 1H), 3.78 (t, *J* = 3.4 Hz, 1H), 3.50 (dt, *J* = 12.5, 3.8 Hz, 1H), 1.71 (q, *J* = 13.3, 11.1 Hz, 1H), 1.60 (d, *J* = 13.4 Hz, 1H), 1.50 – 1.39 (m, 2H), 1.33 (d, *J* = 13.7 Hz, 1H), 1.08 – 0.95 (m, 1H); **^{13}C NMR** (101 MHz, DMSO) δ 147.67, 143.58, 141.44, 129.73, 129.05, 128.31, 127.76, 124.89, 124.85, 89.35, 77.47, 65.28, 34.03, 27.00, 21.08, 17.95; **IR** (neat, C=O, cm^{-1}): *v* = 1710; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{20}H_{20}NaO_4$) 347.1254 $(M+Na)^+$: found: 347.1261.



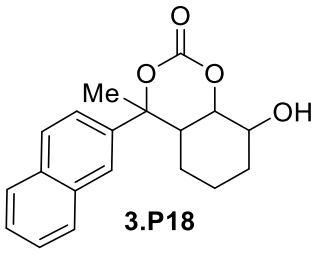
3.P16

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 25%, 6.0 mg, isomeric ratio is 56:44. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (ddd, *J* = 15.6, 1.8, 0.8 Hz, 0.92H), 6.43 (ddt, *J* = 8.1, 3.3, 0.8 Hz, 0.94H), 6.39 (td, *J* = 3.2, 1.8 Hz, 0.94H), 5.58 (d, *J* = 3.2 Hz, 0.55H), 5.35 (d, *J* = 6.0 Hz, 0.43H), 4.63 (t, *J* = 3.2 Hz, 0.56H), 4.50 (dd, *J* = 6.2, 4.2 Hz, 0.44H), 4.17 (t, *J* = 3.2 Hz, 0.56H), 4.08 (dt, *J* = 6.4, 3.2 Hz, 0.44H), 2.78 – 2.70 (m, 0.45H), 2.58 (ddt, *J* = 12.5, 5.5, 3.0 Hz, 0.58H), 2.21 (d, *J* = 3.2 Hz, 0.42H), 1.96 (ddd, *J* = 12.2, 7.8, 3.9 Hz, 0.47H), 1.84 – 1.67 (m, 3.03H), 1.67 – 1.61 (m, 0.7H), 1.59 – 1.51 (m, 1.53H), 1.45 – 1.31 (m, 1.27H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.42, 148.76, 147.94, 147.83, 143.74, 142.88, 110.77, 110.61, 110.08, 108.63, 79.42, 79.01, 78.20, 76.64, 67.99, 66.59, 32.61, 31.83, 29.25, 27.10, 24.44, 18.91, 18.47, 17.48; **IR** (neat, C=O, cm^{-1}): *v* = 1731; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_5$) 261.0733 $(M+Na)^+$: found: 261.0731.



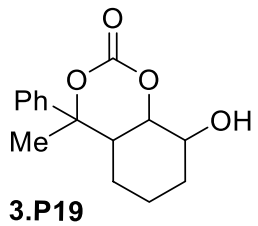
3.P17

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 54%, 14.2 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.36 – 7.32 (m, 3H), 5.60 (d, *J* = 2.5 Hz, 1H), 4.84 (ddd, *J* = 6.5, 5.0, 1.2 Hz, 1H), 3.95 (dd, *J* = 10.3, 6.7 Hz, 1H), 2.87 (s, 1H), 2.40 – 2.33 (m, 1H), 1.87 (d, *J* = 12.0 Hz, 2H), 1.82 – 1.67 (m, 2H), 1.44 (dtd, *J* = 27.6, 14.6, 13.7, 4.9 Hz, 2H), 1.32 – 1.24 (m, 1H), 1.11 – 1.01 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.27, 135.85, 128.86, 128.37, 125.33, 89.87, 81.15, 76.53, 40.52, 31.83, 29.50, 26.58, 19.75; **IR** (neat, C=O, cm^{-1}): *v* = 1742; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{18}NaO_4$) 285.1097 $(M+Na)^+$: found: 285.1095.



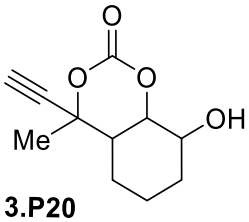
3.P18

The product was isolated as a light-yellow solid, eluent: 50% EA in hexane. Yield: 65%, 20.3 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 – 7.75 (m, 4H), 7.58 – 7.32 (m, 3H), 4.94 (t, *J* = 3.3 Hz, 1H), 4.25 (s, 1H), 2.51 (ddd, *J* = 12.3, 5.4, 2.9 Hz, 1H), 1.96 (s, 1H), 1.89 (s, 3H), 1.79 – 1.68 (m, 2H), 1.57 (ddt, *J* = 17.2, 8.7, 4.5 Hz, 1H), 1.40 (dt, *J* = 13.6, 3.5 Hz, 1H), 1.10 – 0.96 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.76, 140.65, 133.21, 132.58, 128.68, 128.48, 127.65, 126.77, 126.51, 123.27, 121.92, 86.91, 75.89, 66.74, 36.19, 28.45, 27.08, 21.47, 17.76; **IR** (neat, C=O, cm^{-1}): *v* = 1723; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{19}H_{20}NaO_4$) 335.1254 $(M+Na)^+$: found: 335.1252.



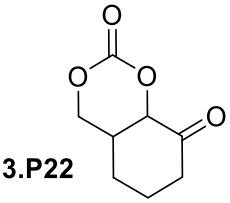
3.P19

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 81%, 21.3 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 3H), 7.34 – 7.27 (m, 2H), 4.88 (t, *J* = 3.2 Hz, 1H), 4.22 (q, *J* = 3.1 Hz, 1H), 2.38 (ddd, *J* = 11.5, 6.7, 2.8 Hz, 1H), 1.81 (s, 3H), 1.76 – 1.64 (m, 2H), 1.61 – 1.50 (m, 1H), 1.43 (dq, *J* = 13.6, 3.6 Hz, 1H), 1.02 – 0.96 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.74, 141.90, 128.73, 127.62, 124.12, 86.78, 75.91, 66.71, 36.39, 28.48, 27.07, 21.34, 17.78; **IR** (neat, C=O, cm^{-1}): *v* = 1721; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{18}NaO_4$) 185.1097 $(M+Na)^+$: found: 185.1100.



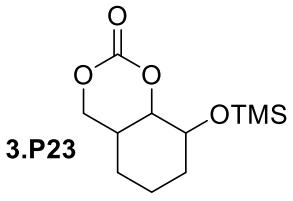
3.P20

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 62%, 13.0 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.61 (t, *J* = 3.8 Hz, 1H), 4.21 (t, *J* = 3.5 Hz, 1H), 2.74 (s, 1H), 2.20 (ddd, *J* = 12.3, 4.7, 3.1 Hz, 1H), 2.13 – 2.06 (m, 1H), 1.95 (d, *J* = 3.7 Hz, 1H), 1.81 (s, 3H), 1.79 – 1.65 (m, 4H), 1.52 – 1.42 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.66, 80.96, 80.11, 77.01, 75.61, 66.60, 36.21, 28.27, 27.33, 22.31, 17.95; **IR** (neat, C=O, cm^{-1}): *v* = 1726; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{14}NaO_4$) 233.0784 $(M+Na)^+$: found: 233.0783.



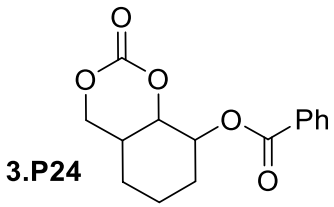
3.P22

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 75%, 25.5 mg, exo/endo 65:35 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.95 (dt, *J* = 5.3, 1.2 Hz, 1H), 4.76 (dd, *J* = 11.9, 1.2 Hz, 1.85H), 4.44 (dd, *J* = 10.6, 5.1 Hz, 2H), 4.36 (ddd, *J* = 11.3, 5.0, 1.5 Hz, 1.13H), 4.30 – 4.15 (m, 3H), 2.87 (dp, *J* = 9.8, 5.1 Hz, 1H), 2.67 – 2.39 (m, 6.11H), 2.37 – 2.15 (m, 3.99H), 2.09 – 1.75 (m, 8.18H), 1.58 (tdd, *J* = 13.3, 12.0, 3.9 Hz, 2.32H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.47, 199.92, 147.24, 146.72, 82.10, 81.90, 71.71, 69.08, 39.55, 38.94, 38.31, 34.70, 25.49, 24.83, 23.67, 23.46; **IR** (neat, C=O, cm^{-1}): *v* = 1741; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_8H_{10}O_4$) 193.0471 $(M+H)^+$: found: 193.0466.



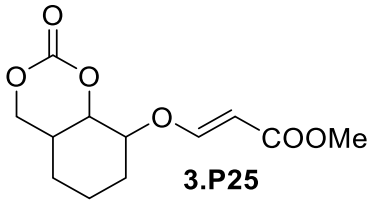
3.P23

The product was isolated as a white solid, eluent: 10% EA in hexane. Yield: 91%, 44.5 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 11.0, 3.7 Hz, 1H), 4.32 (t, *J* = 3.5 Hz, 1H), 4.18 (dd, *J* = 11.0, 1.8 Hz, 1H), 4.00 (q, *J* = 3.1 Hz, 1H), 2.30 – 2.23 (m, 1H), 1.78 – 1.64 (m, 2H), 1.58 – 1.50 (m, 4H), 0.12 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.35, 79.21, 77.42, 77.16, 76.91, 73.04, 67.12, 27.81, 27.45, 22.80, 17.92, 0.08; **IR** (neat, C=O, cm^{-1}): *v* = 1757; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{20}NaO_4Si$) 267.1023 $(M+Na)^+$: found: 267.1029.



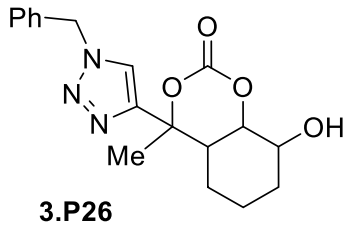
3.P24

The product was isolated as a white solid, eluent: 50% EA in hexane. Yield: 74%, 41.0 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.62 – 7.55 (m, 1H), 7.49 – 7.42 (m, 2H), 5.35 (q, *J* = 3.5 Hz, 1H), 4.69 (t, *J* = 3.6 Hz, 1H), 4.49 (dd, *J* = 11.1, 3.7 Hz, 1H), 4.25 (dd, *J* = 11.1, 2.3 Hz, 1H), 2.30 (tdd, *J* = 7.0, 5.4, 3.3 Hz, 1H), 1.91 (dt, *J* = 7.3, 3.6 Hz, 2H), 1.82 – 1.65 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.19, 147.68, 133.59, 129.75, 128.65, 76.05, 72.27, 69.05, 28.82, 24.71, 22.53, 18.86; **IR** (neat, C=O, cm^{-1}): *v* = 1749, 1717; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{16}NaO_5$) 299.0890 $(M+Na)^+$: found: 299.0892.



3.P25

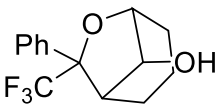
The product was isolated as a colorless oil, eluent: 50% EA in hexane. Yield: 76%, 38.9 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 12.5, 0.9 Hz, 1H), 5.33 (dd, *J* = 12.5, 1.0 Hz, 1H), 4.60 (dt, *J* = 3.8, 2.0 Hz, 1H), 4.53 – 4.45 (m, 1H), 4.28 (d, *J* = 3.2 Hz, 1H), 4.22 (dd, *J* = 11.2, 1.7 Hz, 1H), 3.70 (s, 3H), 2.28 – 2.16 (m, 1H), 1.94 – 1.86 (m, 1H), 1.82 – 1.72 (m, 1H), 1.70 – 1.59 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.82, 160.27, 147.46, 99.09, 76.45, 75.83, 72.53, 51.42, 28.18, 24.25, 22.26, 18.02; **IR** (neat, C=O, cm^{-1}): *v* = 1748, 1703, 1640, 1625; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{16}NaO_6$) 279.0839 $(M+Na)^+$: found: 279.0841.



3.P26

The product was isolated as a white solid, eluent: 70% EA in hexane. Yield: 85%, 58.4 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.40 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.31 – 7.27 (m, 2H), 5.53 (d, *J* = 14.7 Hz, 1H), 5.45 (d, *J* = 14.7 Hz, 1H), 4.20 (t, *J* = 3.2 Hz, 1H), 4.02 (s, 1H), 2.91 (ddd, *J* = 13.1, 4.8, 2.7 Hz, 1H), 1.93 (dd, *J* = 13.4, 4.0 Hz, 2H), 1.82 – 1.65 (m, 4H), 1.63 (s, 3H), 1.40 (qd, *J* = 12.8, 4.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.82, 148.40, 133.97, 129.48, 129.27, 128.48, 121.20, 84.00, 76.58, 66.34, 54.67, 34.35, 26.69, 26.30, 19.93, 17.73; **IR** (neat, C=O, cm^{-1}): *v* = 1734; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{18}H_{21}N_3NaO_4$) 366.1424 $(M+Na)^+$: found: 366.1424.

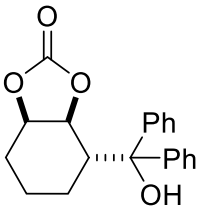
Intramolecular isomerization product



3.P21

The product was isolated as a colorless oil, eluent: 30% EA in hexane. Yield: 56%, 15.3 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 5H), 4.89 (dd, *J* = 8.2, 5.0 Hz, 1H), 4.06 (dt, *J* = 10.0, 5.2 Hz, 1H), 3.56 (q, *J* = 7.8 Hz, 1H), 1.98 (s, 1H), 1.84 – 1.72 (m, 1H), 1.54 – 1.35 (m, 3H), 1.31 – 1.18 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.41, 129.70, 128.70, 128.28, 126.87, 126.31, 124.04, 121.21, 86.78 (q, *J* = 30.2 Hz), 82.93, 71.35, 37.34, 26.70, 20.81, 17.75; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -81.50; **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_{14}H_{15}F_3NaO_2$) 295.0916 $(M+Na)^+$: found: 295.0925.

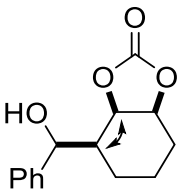
5-Membered cyclic carbonate product



3.P15^{b}

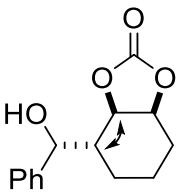
The product was isolated as white solid, eluent: 20% EA in hexane. Yield: 18%, 5.8 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (ddd, *J* = 8.2, 2.7, 1.2 Hz, 4H), 7.34 (ddd, *J* = 13.0, 8.6, 7.0 Hz, 4H), 7.27 – 7.21 (m, 3H), 4.82 (t, *J* = 6.6 Hz, 1H), 4.74 (dt, *J* = 6.5, 4.2 Hz, 1H), 2.97 (ddd, *J* = 10.4, 6.6, 5.0 Hz, 1H), 2.54 (s, 1H), 2.13 – 2.03 (m, 1H), 1.84 – 1.77 (m, 1H), 1.75 – 1.60 (m, 3H), 1.11 (dtd, *J* = 14.3, 10.6, 3.9 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.88, 145.03, 144.92, 128.65, 128.54, 127.46, 127.41, 126.12, 125.96, 80.17, 76.84, 76.71, 46.26, 27.16, 23.99, 18.55; **IR (neat, C=O, cm^{-1}):** *v* = 1783; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{20}H_{20}NaO_4$) 347.1254 $(M+Na)^+$: found: 347.1256.

Products derived from the from *syn* isomer of substrate 3.1a



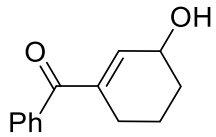
3.P1^{a} *syn*

The product was isolated as a colorless oil, eluent: 15% EA in hexane. Yield: 29%, 36.0 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H), 4.71 (d, *J* = 8.8 Hz, 1H), 4.57 (dt, *J* = 8.0, 6.3 Hz, 1H), 4.17 (ddd, *J* = 6.6, 2.9, 1.0 Hz, 1H), 2.23 – 2.12 (m, 1H), 2.08 – 1.99 (m, 1H), 1.95 – 1.79 (m, 2H), 1.65 – 1.45 (m, 3H), 1.41 – 1.30 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.08, 142.00, 128.89, 128.49, 126.74, 76.80, 76.03, 75.62, 44.81, 26.94, 20.62, 18.70; **IR** (neat, C=O, cm^{-1}): *v* = 1787; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{16}NaO_4$) 271.0941 $(M+Na)^+$: found: 271.0940.



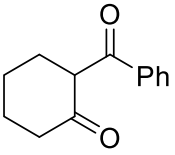
3.P1^{b} *anti*

The product was isolated as a white solid, eluent: 20% EA in hexane. Yield: 37%, 45.9 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 5.08 (d, *J* = 2.5 Hz, 1H), 4.89 (dd, *J* = 9.3, 6.2 Hz, 1H), 4.82 (ddd, *J* = 6.4, 4.0, 2.8 Hz, 1H), 2.28 – 2.20 (m, 1H), 2.14 (s, 1H), 1.81 – 1.74 (m, 1H), 1.71 – 1.54 (m, 3H), 1.44 (dqd, *J* = 13.4, 3.7, 1.9 Hz, 1H), 1.37 – 1.28 (m, 1H), 1.20 (dtd, *J* = 13.7, 12.5, 3.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.54, 142.19, 128.52, 127.67, 125.77, 77.23, 77.14, 72.09, 47.21, 26.55, 19.39, 18.97; **IR** (neat, C=O, cm^{-1}): *v* = 1786; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{16}NaO_4$) 271.0941 $(M+Na)^+$: found: 271.0937.



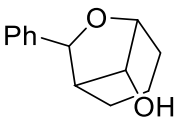
3.ByP1

The product was isolated as white solid, eluent: 15% EA in hexane. Yield: 7%, 7.1 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 2H), 7.56 – 7.49 (m, 1H), 7.46 – 7.39 (m, 2H), 6.43 (qd, *J* = 1.9, 0.9 Hz, 1H), 4.45 (s, 1H), 2.49 – 2.35 (m, 2H), 2.02 (dddd, *J* = 12.5, 8.2, 5.1, 2.2 Hz, 1H), 1.91 (dddd, *J* = 13.3, 10.7, 5.4, 3.1 Hz, 1H), 1.77 – 1.62 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.23, 142.45, 140.20, 137.88, 132.07, 129.47, 128.35, 66.48, 31.61, 24.40, 19.27; **IR** (neat, C=O, cm^{-1}): *v* = 1637; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{14}NaO_2$) 225.0886 $(M+Na)^+$: found: 225.0882.



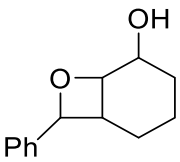
3.ByP2

The product was isolated as yellow oil, eluent: 20% EA in hexane. Yield: 7%, 7.2 mg **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 – 7.92 (m, 2H), 7.61 – 7.57 (m, 1H), 7.49 (ddt, *J* = 7.9, 6.7, 1.2 Hz, 2H), 3.82 (tt, *J* = 10.6, 4.2 Hz, 1H), 2.72 (ddd, *J* = 14.5, 10.8, 1.1 Hz, 1H), 2.53 – 2.39 (m, 3H), 2.12 (dddd, *J* = 11.2, 6.9, 5.7, 3.1 Hz, 2H), 1.90 – 1.80 (m, 2H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.42, 200.56, 135.49, 133.65, 129.02, 128.54, 45.33, 43.31, 41.15, 28.55, 24.98; **IR** (neat, C=O, cm^{-1}): *v* = 1709, 1676; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{14}NaO_2$) 225.0886 $(M+Na)^+$: found: 225.0886.



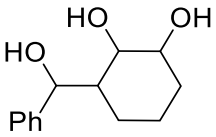
3.ByP3

The product was isolated as white solid, eluent: 30% EA in hexane. Yield: 46%, 47.0 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (dq, *J* = 7.4, 1.2 Hz, 2H), 7.35 (dd, *J* = 8.6, 6.9 Hz, 2H), 7.26 – 7.22 (m, 1H), 5.28 (d, *J* = 4.1 Hz, 1H), 4.55 (q, *J* = 4.9 Hz, 1H), 4.31 (t, *J* = 5.3 Hz, 1H), 2.55 (p, *J* = 3.8 Hz, 1H), 1.95 (d, *J* = 4.6 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.70 – 1.64 (m, 1H), 1.50 – 1.38 (m, 1H), 1.25 – 1.14 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.43, 128.19, 126.48, 125.34, 80.01, 76.52, 72.26, 42.30, 24.84, 18.95, 16.58; **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_{13}H_{15}O$) 187.1121 $(M-OH)^+$: found: 187.1117.



3.ByP4

The product was isolated as white solid, eluent: 15% EA in hexane. Yield: 16%, 16.3 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (dq, *J* = 7.5, 1.2 Hz, 2H), 7.37 – 7.34 (m, 2H), 7.23 (dddd, *J* = 7.7, 6.7, 2.3, 1.1 Hz, 1H), 5.49 (d, *J* = 4.4 Hz, 1H), 4.36 (d, *J* = 5.2 Hz, 1H), 4.07 (d, *J* = 3.5 Hz, 1H), 2.61 (s, 1H), 1.97 – 1.88 (m, 2H), 1.52 – 1.46 (m, 2H), 1.40 – 1.33 (m, 2H), 1.14 – 1.06 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.20, 128.17, 126.37, 125.59, 82.06, 80.83, 80.68, 45.96, 31.11, 25.82, 16.46; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{16}NaO_2$) 227.1043 $(M+Na)^+$: found: 227.1040.



3.ByP5

The product was isolated as white solid, eluent: 50% EA in hexane. Yield: 72%, 80 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 4H), 7.28 – 7.26 (m, 1H), 5.02 (d, *J* = 3.2 Hz, 1H), 3.98 (t, *J* = 3.0 Hz, 1H), 3.88 (q, *J* = 3.3 Hz, 1H), 2.02 (dtd, *J* = 12.5, 3.6, 2.5 Hz, 1H), 1.93 – 1.81 (m, 1H), 1.64 (qd, *J* = 12.8, 4.0 Hz, 1H), 1.56 – 1.39 (m, 3H), 1.30 – 1.25 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.13, 128.35, 127.39, 125.92, 78.08, 74.77, 70.32, 42.43, 27.68, 19.44, 18.07; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{18}NaO_3$) 245.1148 $(M+Na)^+$: found: 245.1150.

Chapter 3

Chapter 4.

Domino Synthesis of Bicyclic 3,5-Anhydro Furanose Mimics using a Binary Al(III) Complex/Halide Catalyst

The results described in this chapter have been published in:

C. Qiao, A. Villar-Yanez, D. Garay-Ruiz, J. B. Buchholz, C. Bo A. W. Kleij, *ACS Catal*. **2022**, *12*, 5464–5469.

Chapter 4

4.1 Introduction

Catalytic cascade or domino approaches are intrinsically attractive for synthetic method development as these minimize the amount of necessary purification steps and increase the overall process selectivity and efficiency.[1] Epoxide-opening cascade reactions have often been utilized in preparative chemistry to rapidly construct (ladder-type) polycyclic ethers through biomimetic approaches.[2] Such polycyclic ethers are structurally reminiscent to various natural products, and preparative methods that allow for the formation of such compounds may help to unravel the intricacies involved in the biogenesis of biologically active, natural polyethers such as Brevetoxin B and Teurilene (Scheme 4.1a).

Smaller cyclic ether derivatives, such as 3,5-anhydro-furanose scaffolds, have recently emerged as potent bicyclic monomers in polymer science creating new impetus for the design of biobased polyether and polyester macromolecules with tunable properties.[3] For instance, Buchard and coworkers used a protected bicyclic and chiral 3,5-anhydro furanose monomer **A** (Scheme 4.1b) to prepare carbohydrate based polyethers with delicate control over their crystallinity resulting in enhanced thermal resistance and thus new potential in biomedical applications.[3a]

4.2 Aims and objectives

While these furanose derivatives are derived from natural sources, they offer little structural diversity towards more elaborate frameworks. With this limitation in mind we

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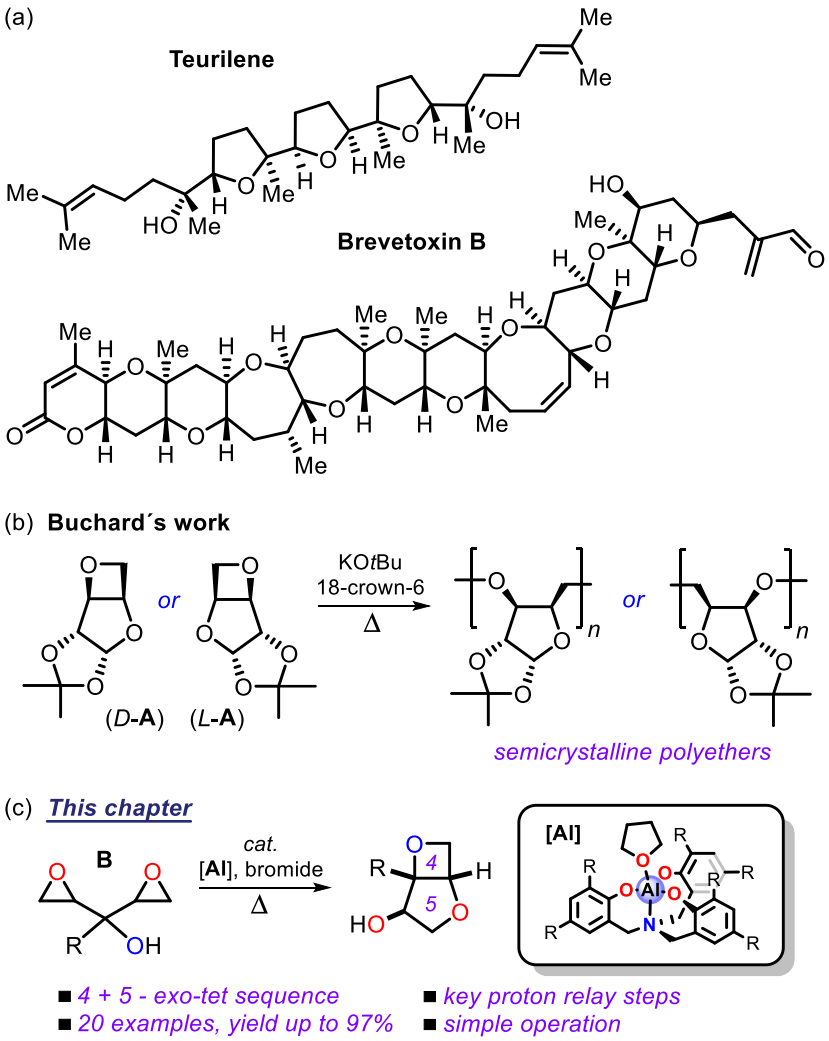
[1] a) Y. Zhu, L. Sun, P. Lu, Y. Wang, *ACS Catal*. **2014**, *4*, 1911–1925; b) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas, *ACS Catal*. **2014**, *4*, 743–762; c) H.-M. Huang, M. H. Garduño-Castro, C. Morrilla, D. Procter, J. *Chem. Soc. Rev*. **2019**, *48*, 4626–4638; d) A. M. Walji, D. W. C. MacMillan, *Synlett*. **2007**, 1477–1489; e) H. Pellissier, *Adv. Synth. Catal*. **2019**, *361*, 1733–1755.

[2] a) I. Vilotijevic, T. F. Jamison, *Mar. Drugs* **2010**, *8*, 763–809; b) R. Ardkhean, D. F. J. Caputo, S. M. Morrow, H. Shi, Y. Xiong, E. A. Anderson, *Chem. Soc. Rev*. **2016**, *45*, 1557–1569; c) G. L. Simpson, T. P. Heffron, E. Merino, T. F. Jamison, *J. Am. Chem. Soc*. **2006**, *128*, 1056–1057; d) K. Nishikawa, K. Morita, S. Hashimoto, A. Hoshino, T. Ikeuchi, M. Kumagai, Y. Morimoto, *Angew. Chem. Int. Ed*. **2019**, *58*, 10168–10172; e) J. Rodríguez-López, F. Pinacho Crisóstomo, N. Ortega, M. López-Rodríguez, V. S. Martín, T. Martín, *Angew. Chem. Int. Ed*. **2013**, *52*, 3659–3662; f) I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189–1192.

[3] a) T. M. McGuire, J. Bowles, E. Deane, E. H. E. Farrar, M. N. Grayson, A. Buchard, *Angew. Chem. Int. Ed*. **2021**, *60*, 4524–4528; b) T. M. McGuire, E. F. Clark, A. Buchard, *Macromolecules* **2021**, *54*, 5094–5105; c) T. M. McGuire, A. Buchard, *Polym. Chem*. **2021**, *12*, 4253–4261; d) M. Piccini, J. Lightfoot, B. Castro Dominguez, A. Buchard, *ACS Appl. Polym. Mater.* **2021**, *3*, 5870−5881; e) D. K. Tran, A. Z. Rashad, D. J. Darensbourg, K. L. Wooley, *Polym. Chem*. **2021**, *12*, 5271–5278.

hypothesized that a suitable bis-epoxy precursor (**B**, Scheme 4.1c) could overcome this synthetic void using an epoxy ring-opening cascade. Inspired by the seminal examples of water-promoted cascade processes reported by Nishikawa and Morimoto[2d] and Jamison,[2f] we envisioned a strategy that would contemplate on the potential of Al(III) aminotriphenolate complexes that was previously demonstrated in the activation and conversion of epoxy alcohols.[4]



Scheme 4.1 Examples of natural polyethers, a 3,5-anhydro furanose-based monomer for carbohydrate polyether formation, and current approach towards anhydro furanose diversity.

[4] a) J. Rintjema, R. Epping, G. Fiorani, E. Martín, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed*. **2016**, *55*, 3972–3976; b) S. Sopeña, M. Cozzolino, C. Maquilón, E. C. Escudero-Adán, M. Martínez Belmonte, A. W. Kleij, *Angew. Chem. Int. Ed*. **2018**, *57*, 11203–11207; c) R. Huang, J. Rintjema, J. González-Fabra, E. Martín, E. C. Escudero-Adán, C. Bo, A. Urakawa, A. W. Kleij, *Nat. Catal.* **2019**, *2*, 62–70; d) C. Qiao, A. Villar-Yanez, J. Sprachmann, B. Limburg, C. Bo, A. W. Kleij, *Angew. Chem. Int. Ed.* **2020**, *59*, 18446–18451.

In the manifolds mentioned above, the Al(III) complex has a dual function acting both as a Lewis acid for epoxide activation and a proton-relay catalyst facilitated through one of the phenolates of the ligand backbone. Thus, the utilization of this versatile catalyst under conditions that provoke an epoxide ring opening cascade[5] can offer a useful strategy that expands the portfolio of 3,5-anhydro furanose structures. Here we show that such manifolds are feasible under mild operating conditions providing access to a variety of bicyclic ether synthons. Various control experiments combined with detailed computation (DFT) rationalizes the preference of the bis-epoxy alcohol precursor to first undergo a 4-*exo-tet* cyclization thereby first forming an oxetane ring, followed by a second 5-*exo-tet* cyclization producing the final bicyclic target. The functional diversity of these bicyclic ethers is demonstrated by several post-synthetic transformations.

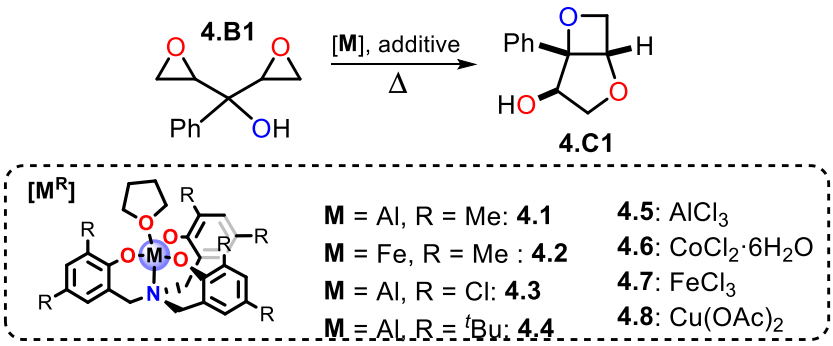
4.3 Results and discussion

We started our screening phase with bis-epoxy substrates **4.B1** and 2 mol% of Al(III) aminotriphenolate complex **4.1**. At 75 ºC (Table 4.1, entry 1), virtually no conversion of **4.B1** was observed. The presence of a halide source such as tetrabutylammonium bromide (TBAB, [Br]; entry 2 with additional screening data in Table 4.2) was also not productive, but when both components were combined (entry 3), full substrate conversion was achieved while the desired product **4.C1** was isolated in good yield (86%). The use of binary catalysts comprising either Fe(III) complex **4.2** or the Cl-substituted Al(III) complex **4.3** were also nearly as productive as the combination of **4.1** and TBAB (entries 4 and 5), though the presence of Al-complex **4.4** (entry 6) did not provoke conversion of **4.B1**. The latter result seems predictable on the basis of the higher steric demand when using this Lewis acid activator. Other, more simple metal salts were also tested (entries 7-10) but these did not give rise to formation of **4.C1**, showing the privileged nature of the aminotriphenolate complexes.

Variation of the reaction temperature (Table 4.1, entries 11-13, also see Table 4.3) demonstrated that moderately high temperatures (65-75 ºC) are a requisite for efficient substrate conversion, while the presence of other **4.1**/TBAB ratios were less effective (entries 14-16). Interestingly, the type of solvent had a pronounced effect on the substrate conversion and product formation

[5] Designer ring-opening cascade transformations are of our current interest, see ref. 4c and: J. Xie, X. Li, A. W. Kleij, *Chem. Sci*. **2020**, *11*, 8839–8845.

Table 4.1 Catalytic Conversion of bis-epoxy Substrate **4.B1** into 3,5-anhydro furanose derivative **4.C1** in the presence of various metal complexes or precursors [M] and additives[a]



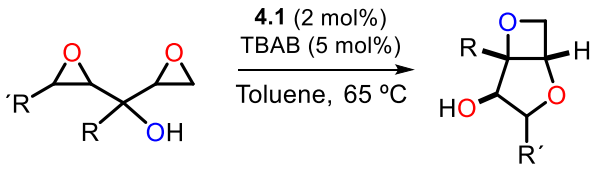
Entry	[**M**] (%)	Add. (%)	T (ºC)	Solv.	Conv. (%)[b]	Y. **4.C1** (%)
1	**4.1**, 2	–	75	MEK	<1	–
2	–	[Br], 5	75	MEK	<1	–
3	**4.1**, 2	[Br], 5	75	MEK	>99	86[c]
4	**4.2**, 2	[Br], 5	75	MEK	>99	84[c]
5	**4.3**, 2	[Br], 5	75	MEK	>99	82[c]
6	**4.4**, 2	[Br], 5	75	MEK	trace	–
7[e]	**4.5**, 20	[Br], 5	75	MEK	>99	<1
8[e]	**4.6**, 20	[Br], 5	75	MEK	>99	<1
9[e]	**4.7**, 20	[Br], 5	75	MEK	>99	<1
10	**4.8**, 4	[Br], 5	75	MEK	10	<1
11	**4.1**, 2	[Br], 5	25	MEK	<1	<1
12	**4.1**, 2	[Br], 5	50	MEK	46	13
13	**4.1**, 2	[Br], 5	65	MEK	61	55
14	**4.1**, 1	[Br], 5	65	MEK	13	14
15	**4.1**, 3	[Br], 5	65	MEK	56	56
16	**4.1**, 2	[Br], 2	65	MEK	30	24
17	**4.1**, 2	[Br], 5	65	THF	5	trace
18	**4.1**, 2	[Br], 5	65	ACN	71	40
19	**4.1**, 2	[Br], 5	65	DMF	>99	<1
20	**4.1**, 2	[Br], 5	65	EtOH	24	<1
21	**4.1, 2**	**[Br], 5**	**65**	**Tol**	**>99**	**90**[c,d]

[a] Substrate **4.B1** (0.20 mmol), [**M**] in mol%, additive in mol%, solvent noted (1.0 mL), 20 h, in air. [b] All reported yields and conversions are based on NMR measurements using mesitylene as an internal standard unless noted otherwise. [c] Yield of isolated product. [d] Duplicate experiment. Abbreviations: MEK = methyl ethyl ketone, Tol = toluene, Y = yield, [Br] = tetrabutylammonium bromide. [e] The majority of the substrate decomposed with mostly unidentified byproducts.

(entries 17-21). Polar solvents like ACN and DMF provided good conversion of **4.B1** albeit with moderate/low amounts of product **4.C1** being formed, whereas the presence of a protic solvent (EtOH) gave poor results. The use of toluene, however, was highly beneficial and resulted in the isolation of **4.C1** in 90% yield.

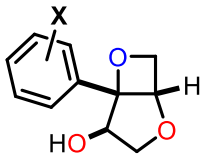
With these latter optimized conditions we investigated the scope of this cascade transformation using various bis-epoxy substrates (**4.B1**-**4.B19**; conditions (a), Scheme 4.2). The aryl substituent R in the precursor **4.B** could be varied to accommodate the formation of furanose like derivatives **4.C1**-**4.C14** in typically good to excellent isolated yields (73-97%). For the preparation of **4.C8** (38%), more forcing conditions (Scheme 4.2, footnote b) were required and provided **4.C8** in 61% yield. This *ortho* effect on the catalytic efficiency was also noted with substrate **4.C5** (having an *o*-Me-substituted aryl, see Table 4.4 for more details), and in this latter case an increased temperature and binary catalyst loading also gave the target product in moderately high yield (61%). The X-ray analysis for **4.C1** confirmed both the proposed connectivity as well as the relative configuration of the OH and aryl groups. Apart from aryl-based precursors, alkyl-substituted substrates **4.B15**-**4.B18** were also productive giving access to bicyclic compounds **4.C15**-**4.C18** in good yields (77-86%). The preparation of **4.C19** was more challenging attested by the relatively low yield (26%). The epoxy precursor **4.B19** carries an additional phenyl substituent (R′) which presumably complicates the double cyclization through an increased steric demand.

Scheme 4.2 Scope of 3,5-anhydro furanose type bicycles produced from their bis-epoxy precursors mediated by **4.1**/TBAB[a]



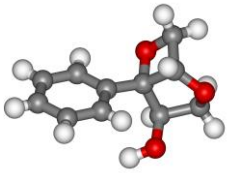
4.B1-4.B19 → **4.C1-4.C19**

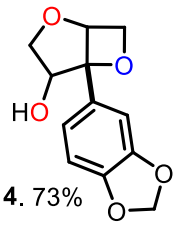
*(for **4.C1-4.C18**: R´ = H)*



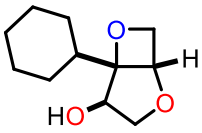
4.C1. X = H, 90%
4.C2. X = *p*-OCH_3, 89%
4.C3. X = *p*-CH_3, 91%
4.C4. X = *m*-CH_3, 91%
4.C5. X = *o*-CH_3, 22% (61%)[b]
4.C6. X = *p*-F, 87%
4.C7. X = *o*-F, 90%
4.C8. X = *o,o*-difluoro, 38% (61%)[b]
4.C9. X = *p*-Cl, 83%
4.C10. X = *p*-Br, 97%
4.C11. X = *p*-Ph, 97%
4.C12. X = *p*-ethynyl, 94%
4.C13. X = *p*-OAc, 84%

*X-ray of 4.**C1***
CCDC-2152782

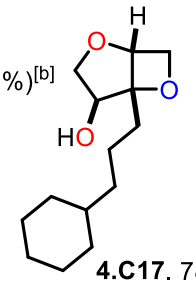




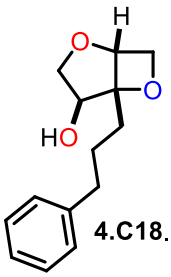
4.C14. 73%



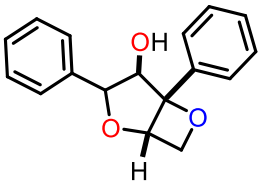
4.C15. 77%



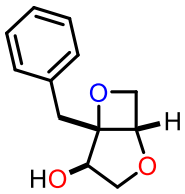
4.C17. 78%



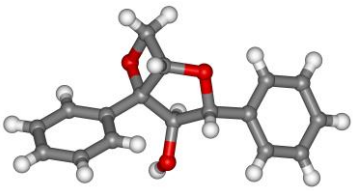
4.C18. 83%



4.C19. 26%[b]



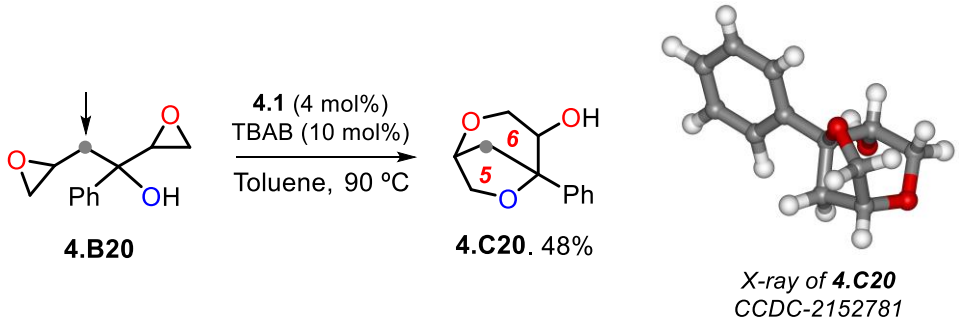
4.C16. 86%



*X-ray of 4.**C19***
CCDC-2152780

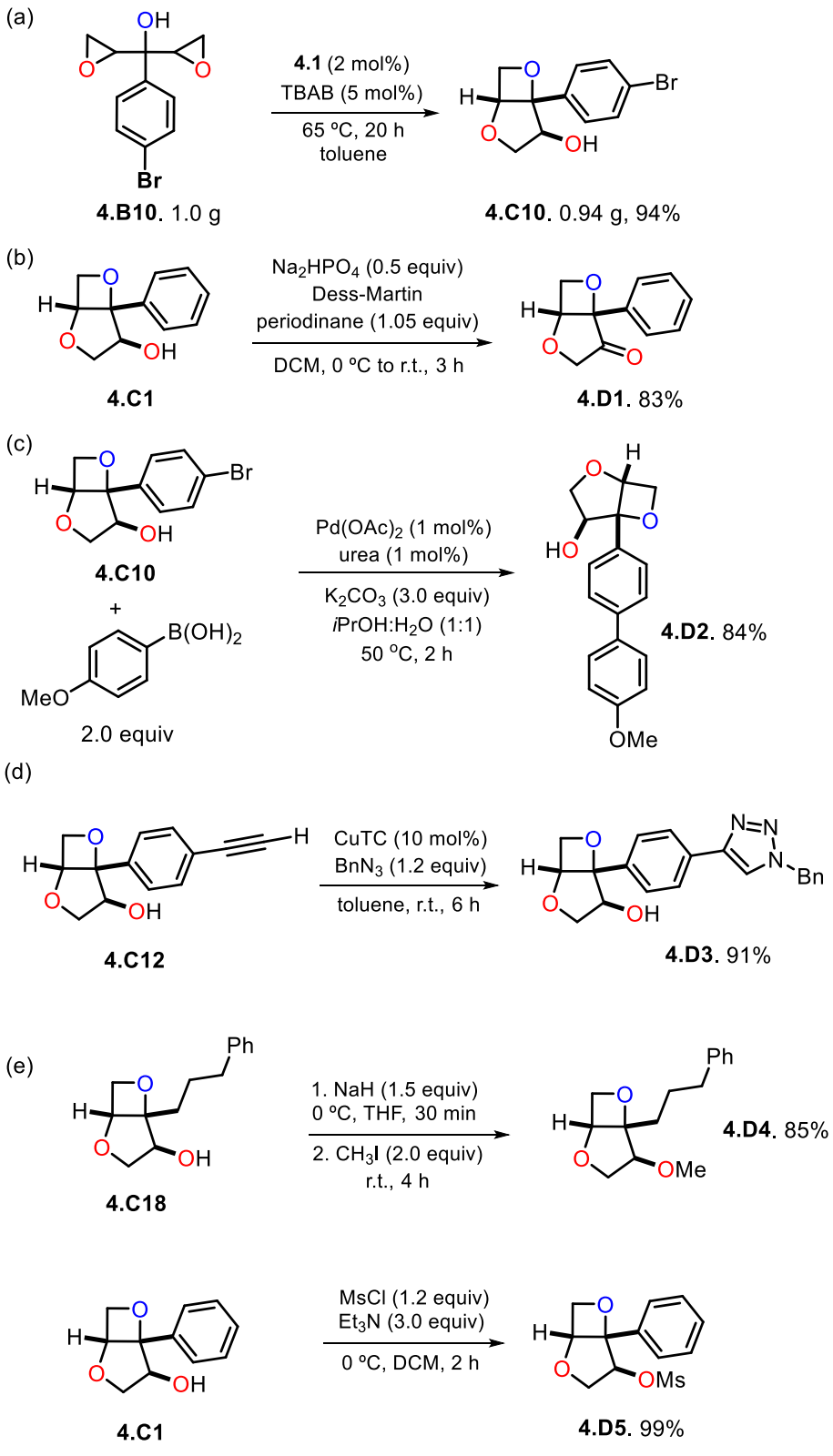
[a] Substrate **4.B** (0.20 mmol), **4.1** (2 mol%), TBAB (5 mol%), 65 ºC, 20 h. [b] Substrate **4.B** (0.10 mmol), **4.1** (4 mol%), TBAB (10 mol%), 90 ºC, 20 h.

When the bis-epoxy substrate was equipped with one additional methylene fragment between the tertiary carbon center and one of the oxirane groups (**4.B20**, Scheme 4.3), access to a different bicycle (**4.C20**, 48%; a 3,6-anhydro pyranose mimic) was feasible combining a fused five– and six-membered cyclic ether. The synthesis of **4.C20** provides evidence that the current protocol may also serve to design other types of cyclic polyethers.



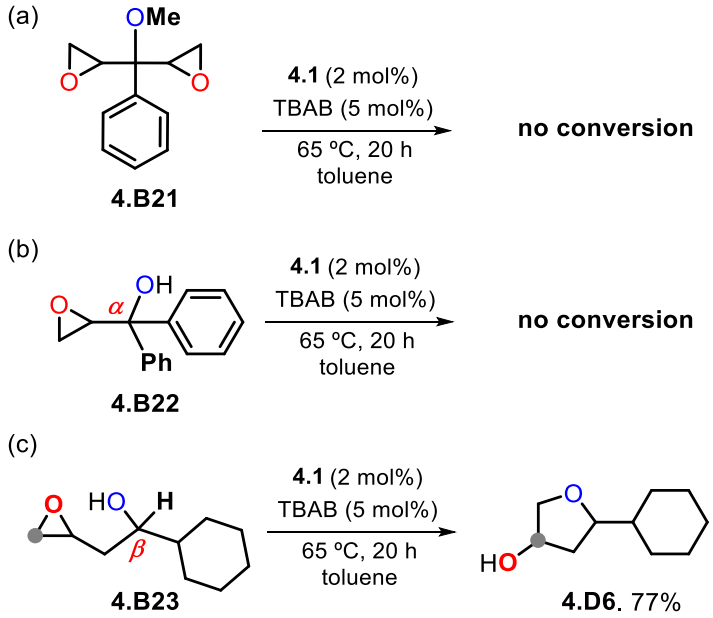
Scheme 4.3 Synthesis of [5+6] bicycle **4.C20** from precursor **4.B20**.

To examine the stability and synthetic utility of these bicyclic ether compounds, several transformations were carried out (Scheme 4.4). First, the synthesis of **4.C10** was scaled up to around a gram (Scheme 4.4a). Then, **4.C1** was subjected to Dess Martin oxidation conditions (Scheme 4.4b) providing the ketone **4.D1** in 83% yield. The aryl-bromide **4.C10** was cross-coupled with *p*-methoxy-phenyl boronic acid furnishing the biphenyl product **4.D2** (84%) in good yield (Scheme 4.4c). Terminal alkyne **4.C12** served as a suitable starting point for a Cu-promoted azide/alkyne "click" reaction producing 1,2,3-triazole **4.D3** (91%, Scheme 4.4d). Finally, *O*-protection of **4.C1** with either MeI or MsCl gave as expected clean formation of *O*-protected compounds **4.D4** and **4.D5** in 85% and 99% yield, respectively (Scheme 4.4e).



Scheme 4.4 Product diversification studies.

In order to shed light on the operative mechanism, first some control experiments (Scheme 4.5) were performed. When substrate **4.B1** was protected (i.e., **4.B21** in Scheme 4.5a), no conversion took place under the optimized conditions of Table 4.1 (entry 21). This strongly suggests that the cascade process involves the free alcohol that requires a suitable catalyst to initiate the multi-step manifold. Substrate **4.B22** (Scheme 4.5b) was designed to scrutinize the formation of the envisioned oxetane product under the optimized reaction conditions, but no conversion could be observed. We found that oxetane formation from **B22** is kinetically disfavored with a barrier of 29.2 kcal/mol as determined by DFT analysis. Precursor **4.B23** was subsequently subjected to the same conditions as **4.B21** and **4.B22** (Scheme 4.5c) and the substituted tetrahydrofuran **4.D6** was isolated in 77% yield. Taken together, the latter results indeed indicate that the second annulation step thermodynamically favors the domino process towards the 3,5-anhydro furanose like product.



Scheme 4.5 Mechanistic control experiments.

4.4 DFT studies

Intrigued by this hypothesis, we further investigated the cascade process by computational methods. We first assessed the potential of TBAB as a single component catalyst for the transformation of substrate **4.B1** into product **4.C1**.[6] The energetic span of this process is 31.4 kcal·mol^{-1}, in line with the absence of any substrate conversion as experimentally noted in Table 4.1 (entry 2). Then two cascade pathways were computed, one that describes first the formation of the four-membered oxetane ring followed by a second annulation step producing the substituted tetrahydrofuran ring (**pathway 1**, Figure 4.1), and a second one which is the reversed manifold (**pathway 2**, Figure 4.2). The difference in activation energy between these two pathways ($\Delta\Delta G^{\ddagger}$) is huge (16.8 kcal·mol^{-1}) and in favor of **pathway 1**. This pathway will be discussed in detail below (Figure 4.3 with **4.1**/TBAB as binary catalyst).

[6] Substrate **4.B1** has a clear plane of symmetry, see Experimental section **4.6.10** for details. We used this configuration as a starting point for the DFT analysis.

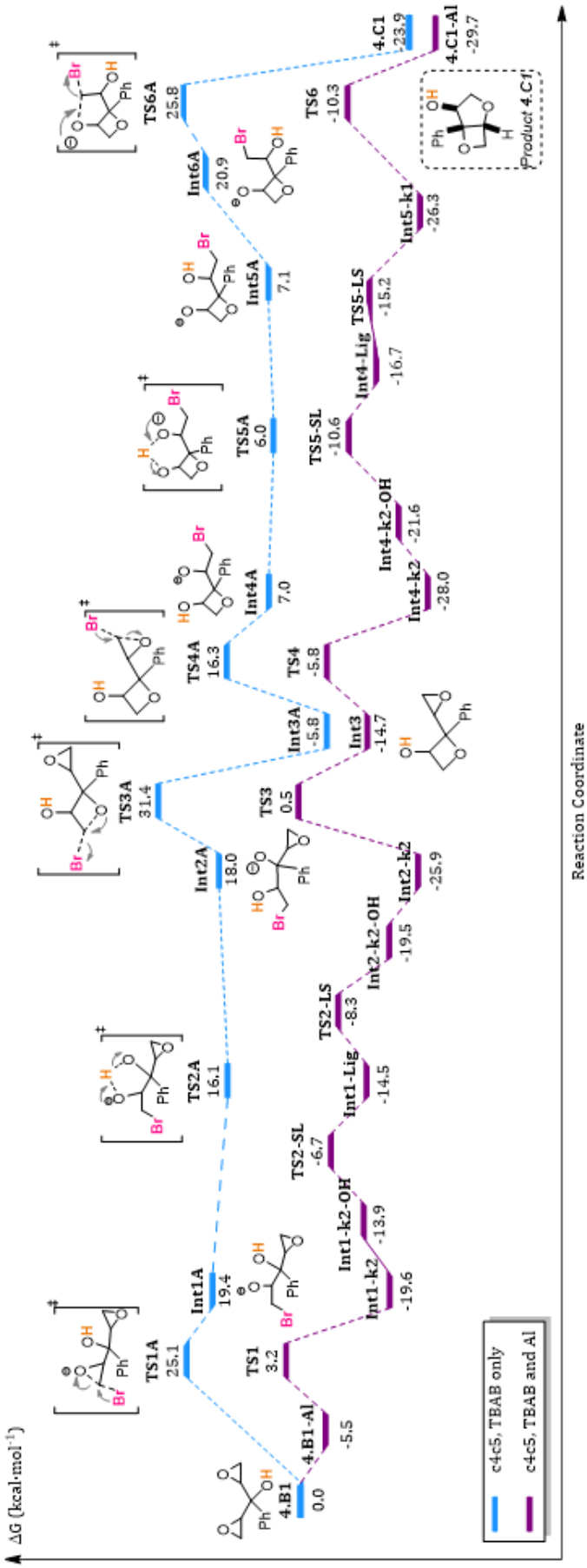


Figure 4.1 DFT computed *c4c5* pathway (4-membered oxetane ring forms first, then the 5-membered tetrahydrofuran) towards 3,5-anhydro-furanose like bicycle **4.C1** from precursor **4.B1**. In purple, the computed route in the presence of Al-complex **4.1**/TBAB, and in light blue, the calculated pathway in the presence of TBAB only. All energy values are Gibbs free energies in kcal·mol^{-1}.

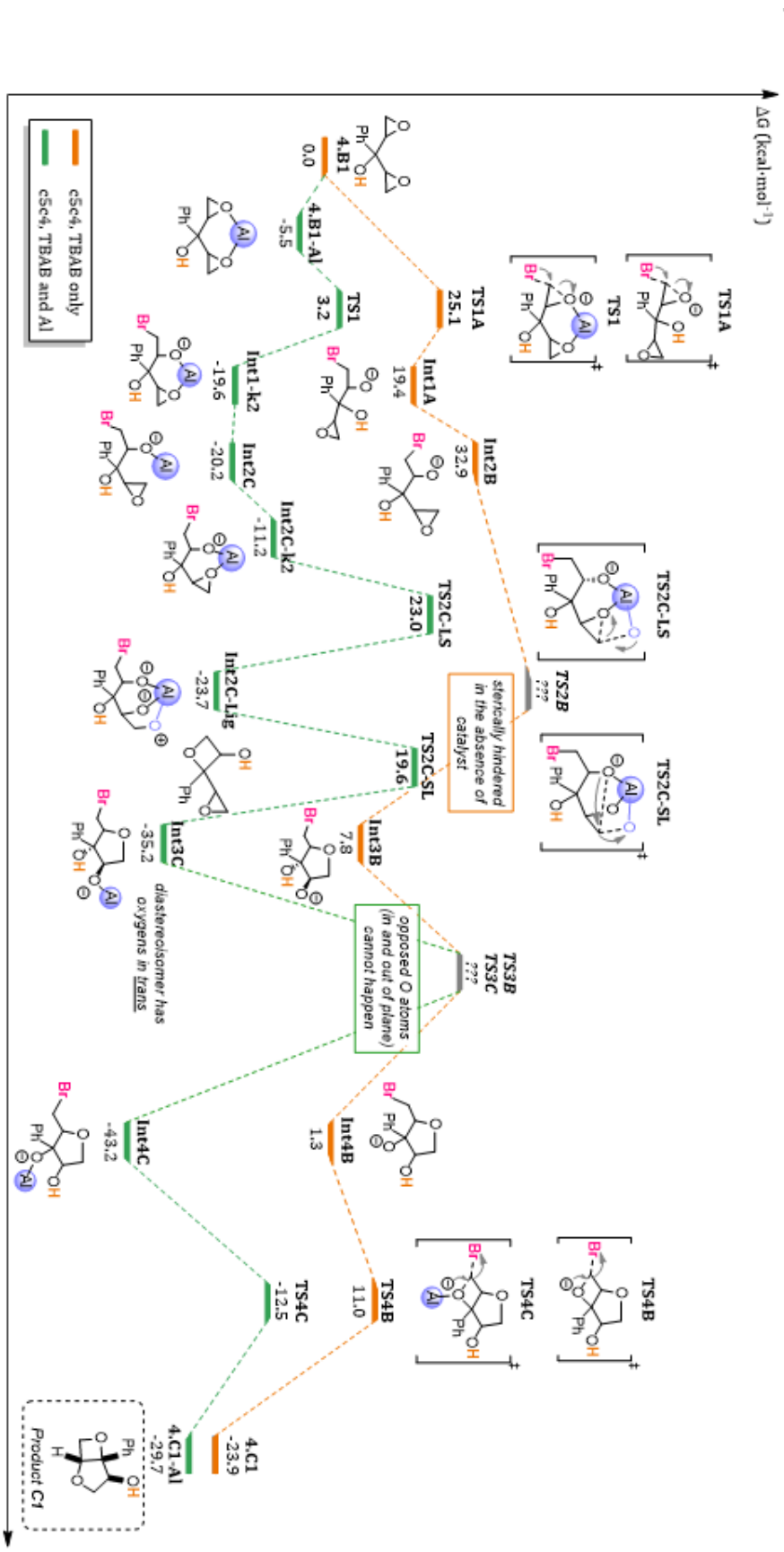


Figure 4.2 DFT computed *c5c4* pathways (5-membered tetrahydrofuran ring forms first, then the 4-membered oxetane) towards 3,5-anhydro-furanose like bicycle **4.C1** from precursor **4.B1**. In orange, the route in the presence of Al-complex **4.1**/TBAB, and in green the pathway in the presence of TBAB only. All energy values are Gibbs free energies in kcal·mol^{-1}.

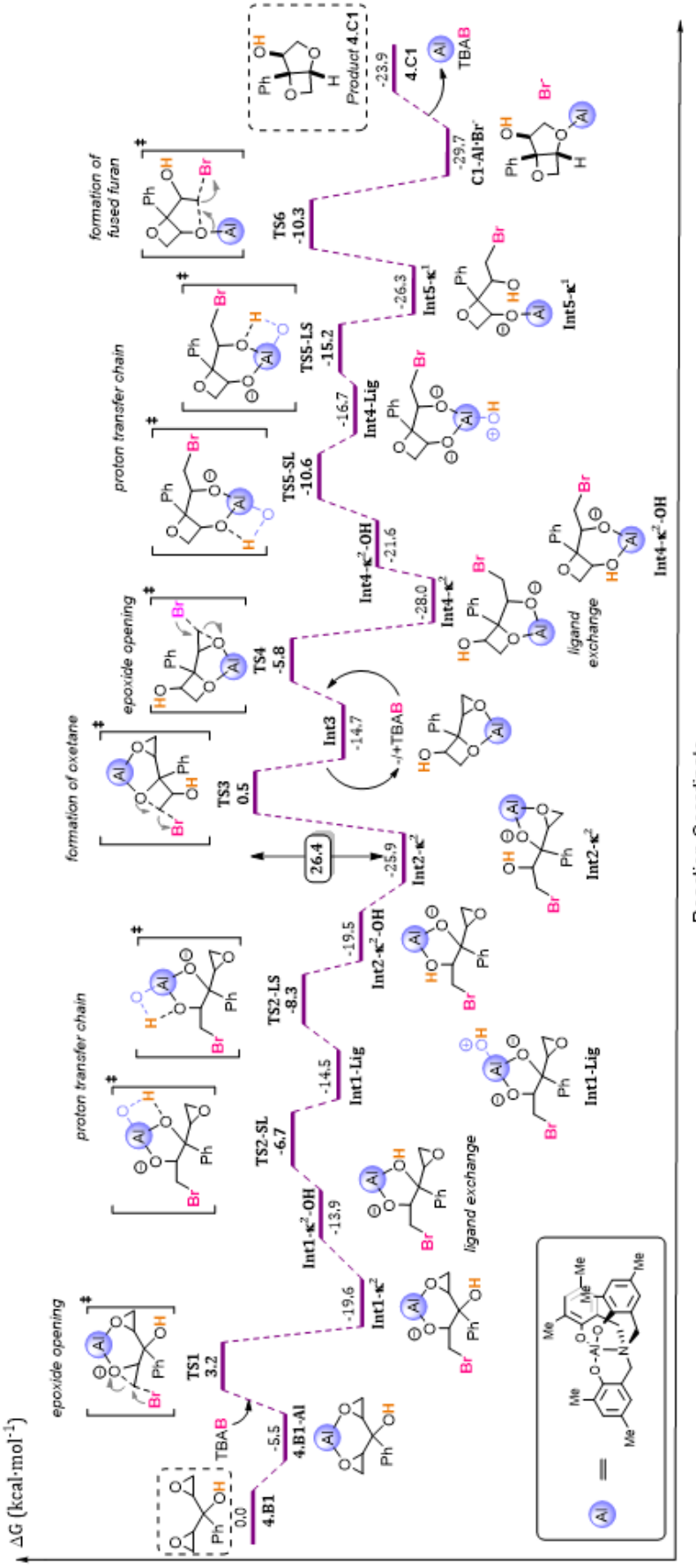


Figure 4.3 DFT computed pathway towards 3,5-anhydro furanose like bicycle **4.C1** from precursor **4.B1** in the presence of **4.1**/TBAB as a binary catalyst. All energy values are Gibbs free energies in kcal·mol^{-1}. Atoms in light blue correspond to atoms in the aminotriphenolate ligand which participate in some steps of the reaction.

The preferred order of steps starts off with by formation of an initial coordination complex (**4.B1-Al**) between Al-complex **4.1** (represented by "Al") and substrate **4.B1** (being a single isomer as further supported by X-ray analysis, see Figure 4.9). Through a first low-lying transition state **TS1**, TBAB facilitates ring-opening of one of the (activated) epoxy groups providing intermediate **Int1-κ²** (at -19.6 kcal·mol^{-1}). Alcohol-for-epoxide ligand exchange (as previously noted)[4d,e] furnishes intermediate **Int1-κ²-OH**. From here the reaction advances through a proton-relay mechanism mediated by the aminotriphenolate ligand in the Al-complex. A first proton transfer from the substrate to the ligand occurs through **TS2-SL** (at -6.7 kcal·mol^{-1}, with **S** referring to the substrate and **L** to the ligand) giving intermediate **Int1-Lig** (-14.5 kcal·mol^{-1}), in which one of the basic phenolate donor atoms (black-colored O) has captured a proton from the substrate. From there, the proton in the phenol group is transferred back from the ligand to the substrate via **TS2-LS** (-8.3 kcal·mol^{-1}: **L** for ligand and **S** for substrate), to the other alkoxide in the molecule, affording **Int2-κ²-OH** (–19.5 kcal·mol^{-1}). This Scheme 4.3 supposes, in the end, the formal proton transfer from the O-atom attached to a tertiary carbon to the one connected to a secondary carbon. Intramolecular ligand exchange on the Al center in the latter intermediate produces the more stable intermediate **Int2-κ²** (-25.6 kcal·mol^{-1}), in which the first nucleophilic O-for-Br displacement can take place through transition state **TS3** (at 0.5 kcal·mol^{-1}). This step represents the rate-determining step of the process, with an energetic span of 26.4 kcal·mol^{-1}, which is in reasonable agreement with the experimental notion of a kinetically slow process at 65 ºC (Table 4.1). The resultant intermediate **Int3** (-14.7 kcal·mol^{-1}) features a four-membered cyclic ether (oxetane) acting, together with the unaltered epoxide ring, as a bidentate ligand for the Al-complex.

From **Int3**, essentially, a similar sequence of steps enables propagation to the final product **4.C1**. First, ring-opening of **Int3** occurs in the presence of TBAB going through **TS4** (-5.8 kcal·mol^{-1}) delivering intermediate **Int4-κ²** located at -28.0 kcal·mol^{-1}. Intramolecular alcohol-for-oxetane ligand exchange on the Al-complex creates intermediate **Int4-κ²-OH** (-21.6 kcal·mol^{-1}). Then a second Al-complex assisted proton relay step occurs from **Int4-κ²-OH** through transition state **TS5-SL** (-10.6 kcal·mol^{-1}) and affords intermediate **Int4-Lig** at -16.7 kcal·mol^{-1}. Within this transient species, another back-proton transfer from the Al-complex to the O-atom attached to the secondary carbon takes place via **TS5-LS** (-15.2 kcal·mol^{-1}). Now, the intermediate

system (**Int5-κ^1**, -26.3 kcal·mol^{-1}) is prepared for **TS6**, -10.3 kcal·mol^{-1}) and yielding the bicyclic product **4.C1-Al·Br**$^-$ (-29.7 kcal·mol^{-1}), which after release of the aluminum complex and TBAB leads to the anhydro furanose **4.C1** (-23.9 kcal·mol^{-1}). The sequence of all steps involved demonstrates the intrinsic role of both catalyst components and how they operate in concert to advance the cascade process. Furthermore, from the computed manifold that only involves TBAB as catalyst (Figure 4.1), an estimation of the difference in free energy between the intermediate epoxy-oxetane (-5.8 kcal·mol^{-1}) versus the bicyclic end-product **4.C1** (–23.8 kcal·mol^{-1}) can be estimated. In line with the experimental observations in Scheme 5b and 5c, the formation of the second, substituted furan ring is thermodynamically favored, contributing to the driving force of the entire process. This was further substantiated by a microkinetic modelling study showing a clear consistency between the computed mechanism and the experimental observations.

4.5 Conclusions

In this chapter, a cascade process is presented that allows to prepare a wider series of 3,5-anhydro furanose type bicycles. Key to the selectivity of the process is the use of a binary couple of an Al(III) centered aminotriphenolate complex and a halide that cooperatively promote the conversion of bis-epoxy substrates. Through control experiments and DFT calculations the operating manifold was rationalized, and the process is a sequence of a 4-*exo*-*tet* (forming the oxetane ring) followed by a 5-*exo*-*tet* cyclization (forming the fused substituted furan ring). A preliminary exploration has shown the suitability of these bicyclic diethers to serve as synthons in preparative chemistry. Further investigations are underway to extent this cascade synthesis to larger, multicyclic products with potential synthetic value in fine-chemical and/or polymer synthesis.

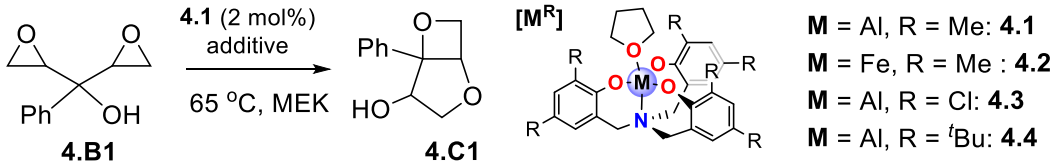
4.6 Experimental section

4.6.1 General comments

All reagents were used as received from commercial suppliers (Aldrich, Acros or TCI) unless stated otherwise. Carbon dioxide was purchased from PRAXAIR and used without further purification. NMR spectra were recorded on Bruker AV-400 or AV-500 spectrometers. The residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm, CD_3CN: δ_H = 1.94 ppm, δ_C = 1.32 ppm). ^{19}F NMR spectra were not calibrated by an internal reference. FT-IR measurements were carried out on a Bruker Optics FTIR-ATR TR0 spectrometer. Exact mass analyses and X-ray diffraction studies were performed by the Research Support Area (RSA) at ICIQ. Solvents were dried using an Innovative Technology PURE SOLV solvent purification system.

4.6.2 Additional screening data

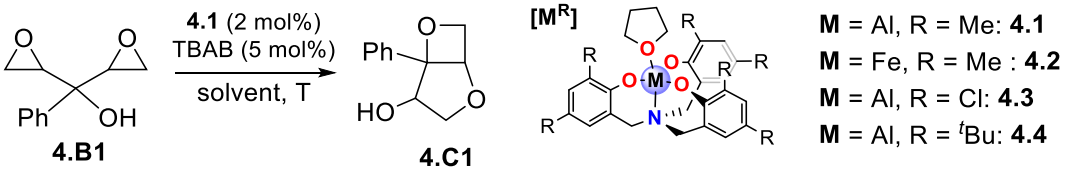
Table 4.2 Screening of other additives[a]



Entry	[M]	Additive (mol%)	T (°C)	Solvent	Conv. (%)[b]	Yield (%)[b]
1	**4.1**	TBAB, 5	65	MEK	61	55%
2	**4.1**	TBAF, 5	65	MEK	<1	–
3	**4.1**	TBACl, 5	65	MEK	39	31%
4	**4.1**	TBAI, 5	65	MEK	28	20%
5	**4.1**	DIPEA, 10	65	MEK	<1	–
6	**4.1**	DBU, 10	65	MEK	<1	–

[a] Substrate (0.2 mmol), Al-complex **4.1** (2 mol%), additive (5-10 mol%), MEK (1 mL), 20 h, under air. [b] reported yields and conversions are based on ^{1}H NMR ($CDCl_3$) measurements using mesitylene as an internal standard.

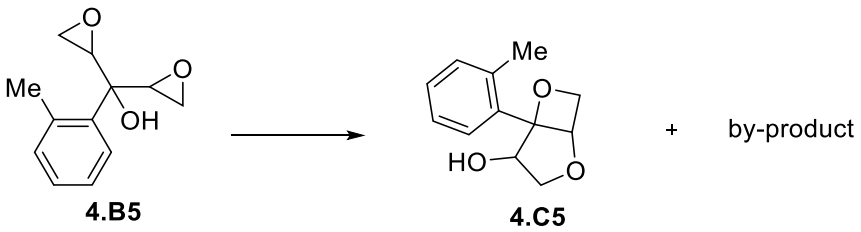
Table 4.3 Screening of other solvents and temperatures[a]



Entry	[M]	Additive (mol%)	T (°C)	Solvent	Conv. (%)[b]	Yield (%)[b]
1	**4.1**	TBAB, 5	35	Et_2O	>99	93[c]
2	**4.1**	TBAB, 5	30	Et_2O	21	5
3	**4.1**	TBAB, 5	40	DCM	>99	80[c]
4	**4.1**	TBAB, 5	30	Toluene	31	23
5	**4.1**	TBAB, 5	50	Toluene	>99	88 (84) [c]

[a] Substrate 0.2 mmol, Al-complex **4.1** (2 mol%), additive (5-10 mol%), solvent (1 mL), 20 h, air condition. [b] All reported yields and conversions are based on ^{1}H NMR ($CDCl_3$) measurements using mesitylene as an internal standard. [c] Yield of the isolated product.

Table 4.4 Further screening studies with substrate **4.B5**[a]

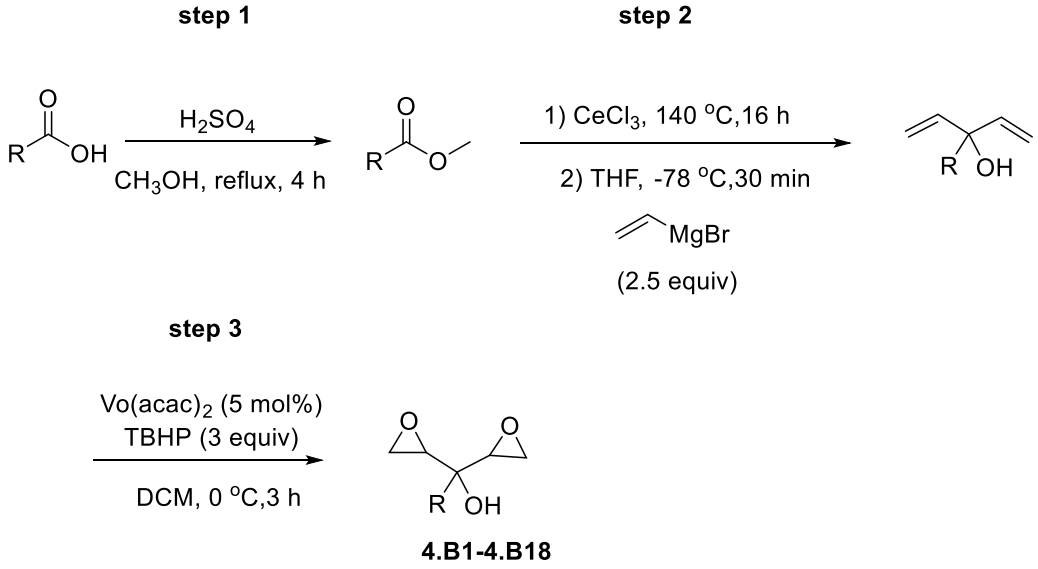


Entry	Substrate (mmol)	T (°C)	t (h)	Conv. (%)	Yield of **4.C5** (%)[b]	Yield of **byP** (%)[b]	Ratio **4.C5**:**byP**
1	0.2	65	20	40	22	16	1.4:1
2	0.1	90	20	>95	69	24	2.9:1
3	0.1	90	6	>95	68	24	2.9:1
4	0.2	110	2	>99	71	25	2.8:1

[a] Conditions mentioned in the Table 4.4 per entry. [b] All reported yields and conversions are based on ^{1}H NMR ($CDCl_3$) measurements using mesitylene as an internal standard.

4.6.3 Experimental procedures for the synthesis of 4.B1-4.B20

Bis-epoxy alcohols 4.B1-4.B18



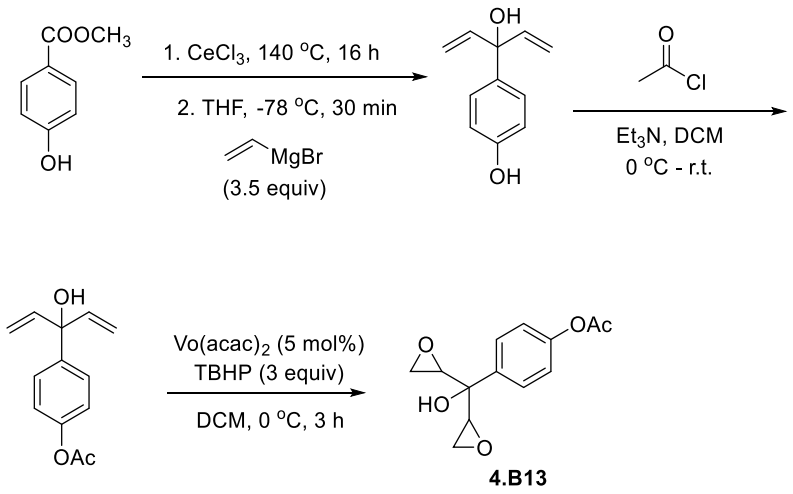
Step 1: ***Note*** – the methyl esters which were not commercially available were synthesized as follows: the respective carboxylic acid (20 mmol, 1.0 equiv) was added to a 100 mL two-necked flask, then 50 mL MeOH was added. H_2SO_4 (30 mmol, 1.6 mL, 1.5 equiv) was added via a syringe. The reaction mixture was stirred at reflux temperature for 4 h. After the system had cooled down to room temperature, the methanol was removed under vacuum. Then 30 mL water was added, and the organics extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 30 mL), saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and then concentrated to obtain the corresponding methyl ester. All methyl esters prepared using **step 1** were used directly for the next step without further purification.

Step 2:[7] $CeCl_3 \cdot 7H_2O$ (30 mmol, 11.0 g, 3.0 equiv) were added to a 150 mL oven-dried Schlenk flask. The content was stirred at 140 ºC for 16 h under vacuum to achieve a white powder. After the system had cooled down to room temperature, 80 mL dry THF was added via a syringe together with 10 mmol of the respective methyl ester dissolved in THF. The reaction mixture was stirred at room temperature for 2 hours before it was cooled down to −78 ºC. Then, 25 mL of vinylmagnesium bromide (1.0 M THF solution, 2.5 equiv) was added dropwise at −78 ºC. After 30 min, the mixture was quenched with 50 mL of a 2% aqueous acetic acid solution and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 30 mL), saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and then concentrated to obtain the corresponding bis-vinyl alcohol. All the bis-vinyl alcohols synthesized using **step 2** were used directly for the next step without further purification.

Step 3:[8] The respective bis-vinyl alcohol (5 mmol, 1.0 equiv) and $VO(acac)_2$ (5 mol%, 32 mg) were dissolved in DCM (50 mL) at 0 °C. Then, TBHP (*tert*-butyl hydroperoxide solution, 3 mL of a 5.0-6.0 M solution in decane) was added. The mixture was stirred at 0 °C for 3 h. Hereafter, the solvent was removed under vacuum and the crude product was purified by flash chromatography employing 5% - 10% EA in hexane as eluent.

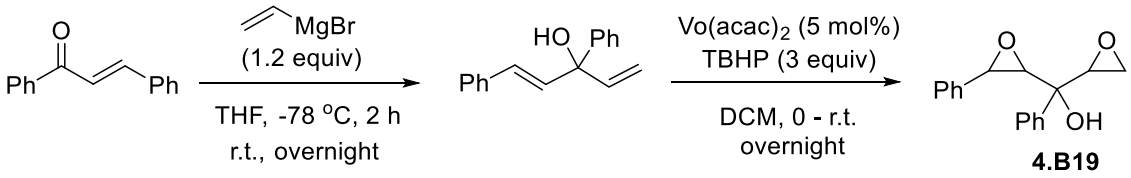
[7] J. M. Ndungu, K. K. Larson, R. Sarpong, *Org. Lett.* **2005**, *7*, 5845−5848.
[8] T. Itoh, K. Jitsukawa, K. Kaneda, S. Teranishi, *J. Am. Chem. Soc*. **1979**, *101*, 159–169.

Bis-epoxy alcohol 4.B13



The corresponding bis-vinyl alcohol was synthesized from commercially available methyl-4-hydroxybenzoate using the method mentioned above under **Step 2**. The bis-vinyl alcohol (5 mmol, 1.0 equiv) was dissolved in 20 mL of dry DCM at 0 °C. Then Et_3N (15 mmol, 2.1 mL, 3.0 equiv) and acetyl chloride (6 mmol, 0.72 mL, 1.2 equiv) were added via a syringe. The reaction mixture was stirred at room temperature for 2 h. Then it was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 30 mL), dried over Na_2SO_4, filtered, and then concentrated to obtain the desired product. This product was directly used for the subsequent epoxidation step without further purification. The desired bis-epoxy alcohol **4.B13** was obtained in 14% yield over 3 steps.

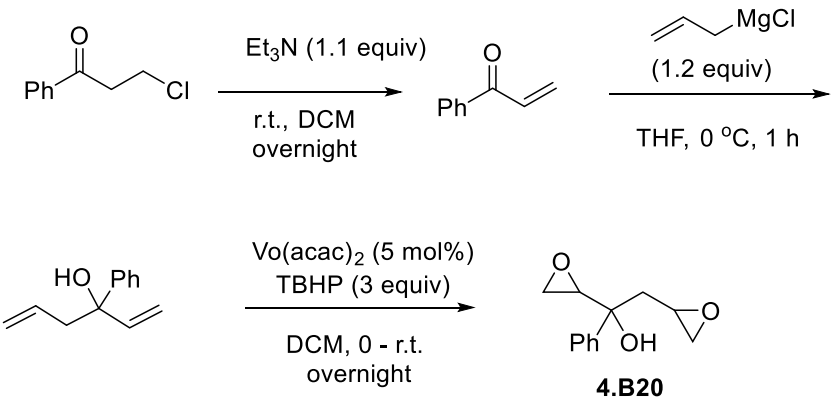
Bis-epoxy alcohol 4.B19



4.B19

1,3-Diphenyl-2-propenone (10 mmol, 2.08 g, 1.0 equiv) was added to a 50 mL oven-dried Schlenk flask under nitrogen, and then 10 mL of dry THF was added via a syringe. Vinyl magnesium bromide (12 mL, 1.0 M THF solution, 1.2 equiv) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and then warmed to room temperature while further stirred for 16 h. Then it was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated to obtain a mixture of a 1,2-addition and 1,4-addition product. The desired 1,2-addition product was isolated by flash column chromatography using 5% EA in hexane as eluent (30% yield). The next epoxidation step is similar to the procedure mentioned above under **Step 3**.

Bis-epoxy alcohol 4.B20



4.B20

3-Chloro-1-phenylpropan-1-one (20 mmol, 3.38 g, 1.0 equiv) was added to a 100 mL flask, then 50 mL of DCM was added followed by Et_3N (3.1 mL, 22 mmol, 1.0 equiv) via a syringe. The reaction mixture was stirred at room temperature for 16 h and quenched with 1% aqueous HCl and extracted with DCM (3 × 30 mL). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and then concentrated to obtain 1-phenyl-2-propen-1-one. This product was directly used for the next step without further purification.

1-Phenyl-2-propen-1-one (10 mmol, 1.32 g, 1.0 equiv) was added to a 50 mL oven-dried Schlenk flask under nitrogen, and then 10 mL of dry THF was added via a syringe. Allylmagnesium chloride (6 mL, 2.0 M THF solution, 1.2 equiv) was added dropwise at 0 °C using an ice-cooled water bath. The reaction was stirred at 0 °C for an hour, quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated to obtain 3-phenylhexa-1,5-dien-3-ol. This product was directly used for the next step without further purification. The epoxidation step is similar to the procedure mentioned above under **Step 3**.

4.6.4 Experimental procedures for the synthesis of bicycles 4.C1-4.C20

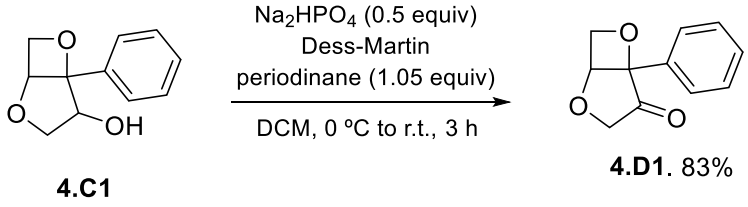
The non-commercial Fe(III) and Al(III) aminotriphenolate complexes **4.1-4.4** were prepared according to previously reported procedures.[9]

The respective bis-epoxy alcohol (0.20 mmol, 1.0 equiv), **4.1** (2 mol%, 0.004 mmol, 2.0 mg) and TBAB (5 mol%, 0.01 mmol, 3.2 mg) were added to a 10 mL oven-dried glass vial, and then 1.0 mL of toluene was added via a syringe. The reaction mixture was stirred at 65 °C. After 20 h, the mixture was purified by flash column chromatography using 25% - 50 % EA in hexane as eluent.

[9] C. J. Whiteoak, N. Kielland, V. Laserna, F. Castro-Gómez, E. Martin, E. C. Escudero-Adán, C. Bo, A. W. Kleij, *Chem. Eur. J.* **2014**, *20*, 2264−2275.

4.6.5 Experimental procedures for the product diversification studies

Synthesis of 4.D1[10]



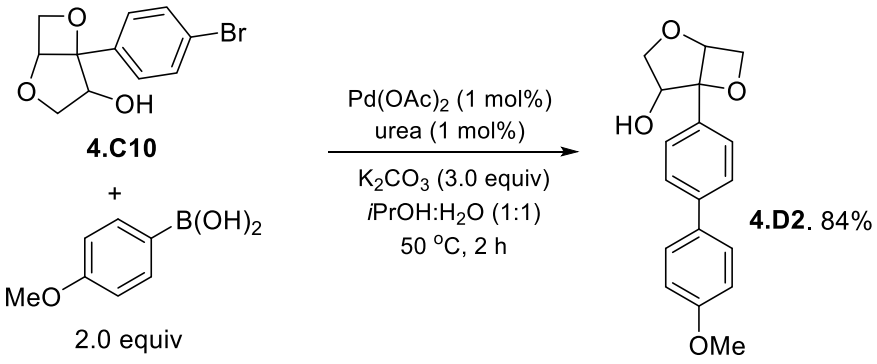
4.C1

4.D1. 83%

In a 10 mL oven-dried glassware glass vial, **4.C1** (0.20 mmol, 38.4 mg, 1.0 equiv) was dissolved in 1 mL of dry DCM under argon. The solution was cooled to 0 ^{o}C, and anhydrous Na_2HPO_4 (15.7 mg, 0.1 mmol, 0.5 equiv) was added. Dess-Martin periodinane (90 mg, 0.21 mmol, 1.05 equiv) was added at once at 0 ^{o}C, and the resulting suspension was warmed to room temperature and stirred for an additional 3 h. The reaction mixture was then quenched by successive addition of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 solutions (both 1.5 mL). The organics were extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford the desired ketone **4.D1** (33.1 mg, 84%) as a white solid.

[10] A. K. Ghosh, B. D. Chapsal, A. Baldridge, M. P. Steffey, D. E. Walters, Y. Koh, M. Amano, H. Mitsuya, *J. Med. Chem.* **2011**, *54*, 622−634.

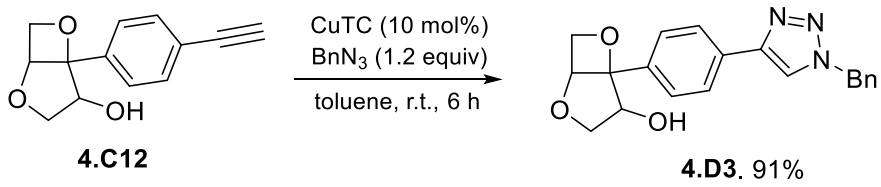
Synthesis of 4.D2[11]



In a 10 mL oven-dried glassware glass vial, a mixture of the aryl halide **4.C10** (0.20 mmol, 54.2 mg, 1.0 equiv), 4-methoxy-phenyl boronic acid (0.40 mmol, 60.8 mg, 2.0 equiv), $Pd(OAc)_2$ (1 mol%, 1 mg/mL in *i*PrOH/H_2O, 1:1 v/v, 0.45 mL), urea (1 mg/mL in *i*PrOH/H_2O, 1:1 v/v, 0.12 mL) and K_2CO_3 (0.6 mmol, 82.9 mg, 3.0 equiv) in 1 mL *i*PrOH/H_2O (1:1, v/v) was introduced. The reaction mixture was stirred at 50 °C for 2 h (monitored by TLC). After completion of the reaction, the organics were extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc from 3:1 to 1:1) to afford the desired compound **4.D2** (50.1 mg, 84%) as a white solid.

[11] B. Saikia, P.R. Boruah, A.A. Ali, D. Sarma, *Tetrahedron. Lett.*, **2015**, *56*, 633−635.

Synthesis of 4.D3[12]

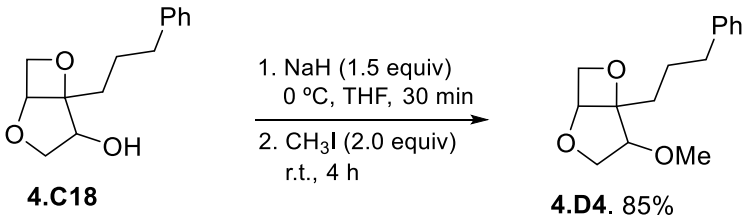


4.C12 **4.D3**. 91%

In a 10 mL oven-dried glass vial, a mixture of **4.C12** (43.2 mg, 0.20 mmol, 1.0 equiv) and copper(I) thiophene-2-carboxylate (CuTC, 3.8 mg, 0.02 mmol, 0.1 equiv) in anhydrous toluene (1 mL) was cooled using an ice-water bath. Subsequently, benzyl azide (30.0 μL, 0.24 mmol, 1.2 equiv) was added slowly, and the reaction mixture was allowed to warm to room temperature and stirred for 6 h while monitored by TLC. The mixture was then quenched by a saturated aqueous NH_4Cl solution, extracted with DCM (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford the desired triazole product **4.D3** (63.5 mg, 91%) as a white solid.

[12] J. E. Gómez, A. Cristofol, A. W. Kleij, *Angew. Chem., Int. Ed.* **2019**, *58*, 3903−3907.

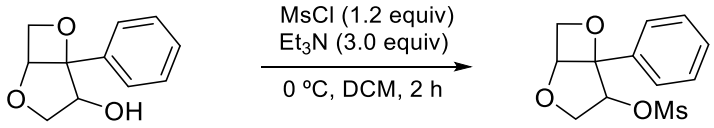
Synthesis of 4.D4



4.C18 **4.D4**. 85%

In a 25 mL oven-dried glass vial, a mixture of **4.C18** (5.0 mmol, 1.17 g, 1.0 equiv) and NaH (7.5 mmol, 180 mg, 1.5 equiv) was combined with 10 mL of dry THF under nitrogen at 0 °C. The solution was stirred at 0 °C for 30 min before methyl iodide (10 mmol, 0.62 mL, 2.0 equiv) was added, and the reaction mixture was allowed to warm to room temperature and stirred for an additional 4 h while monitored by TLC. The mixture was quenched by cold water, extracted with Et_2O (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford the desired compound **4.D4** (992 mg, 85%) as a colorless oil.

Synthesis of 4.D5



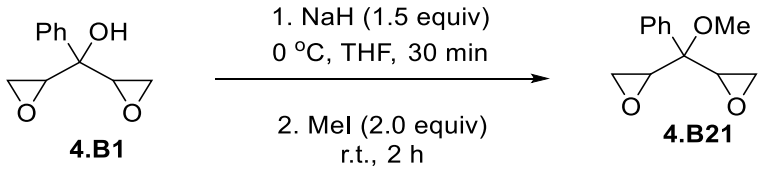
4.C1 **4.D5**. 99%

In a 10 mL flask, a mixture of **4.C1** (0.40 mmol, 76.8 mg, 1.0 equiv) and Et_3N (1.2 mmol, 1.7 mL, 3.0 equiv) were dissolved in 5 mL of dry DCM at 0 ^oC. MsCl (0.48 mmol, 55 mg, 1.2 equiv) was added dropwise, and the reaction mixture was stirred for 2 h at 0 ^oC. The solvent was then removed *in vacuo* and the residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford the desired compound **4.D5** (108 mg, 99%) as a colorless oil.

4.6.6 Experimental procedures for the substrates of the control experiments

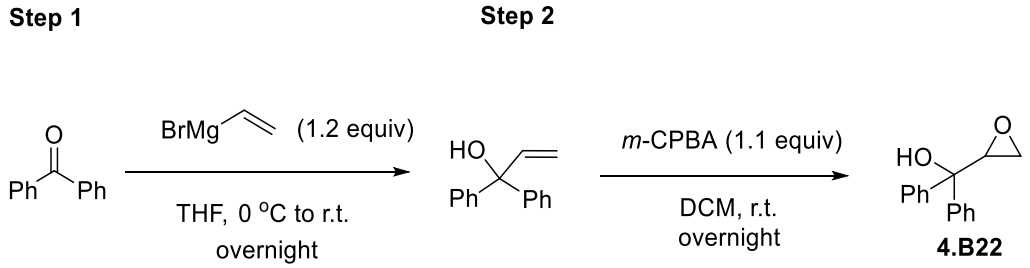
The non-commercial available epoxy alcohols were prepared according to previously reported literature procedures.[4e]

Experimental procedure for the synthesis of epoxy alcohol 4.B21



In a 25 mL oven-dried glass vial, a mixture of **4.B1** (1 mmol, 192 mg, 1.0 equiv) and NaH (1.5 mmol, 36 mg, 1.5 equiv) was combined with 5 mL of dry THF under nitrogen at 0 °C. The mixture was stirred at 0 °C for 30 min before methyl iodide (2 mmol, 125 μL, 2.0 equiv) was added, and the reaction mixture was allowed to warm to room temperature and stirred for another 2 h while being monitored by TLC. The mixture was then quenched by cold water, extracted with Et_2O (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 15:1) to afford the desired compound **4.B21** (63.4 mg, 31%) as a white solid.

Experimental procedures for the synthesis of epoxy alcohol 4.B22



Step 1: Benzophenone (10 mmol, 1.82 g, 1.0 equiv) was added to a 50 mL oven-dried Schlenk flask under nitrogen, and then 10 mL of dry THF was added via a syringe. Vinyl magnesium bromide (12 mL, 1.0 M THF solution, 1.2 equiv) was added dropwise at 0 °C using an ice-water bath. The reaction mixture was stirred at room temperature for 16 h, quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated to obtain the corresponding homoallylic alcohol.

Step 2: The homoallylic alcohol of the previous step was used without further purification. The homoallylic alcohol was dissolved in DCM (50 mL) at 0 °C and *m*-CPBA (11 mmol, 2.3 g, 1.1 equiv) was added. The mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was then washed with $NaHCO_3$ (4 × 30 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography employing 5% - 10% EA in hexane as eluent. The desired epoxy alcohol **4.B22** was obtained as a white solid (1.77 g, 78%).

4.6.7 Computational details

DFT calculations were performed using the ωB97XD[13] functional and the 6–311G**[14] basis set, through the Gaussian09[15] package and employing the SMD[16] solvent model parameters for toluene. All structures were characterized through unconstrained geometry optimizations. The nature of all minima and saddle points in the potential energy surface was confirmed through harmonic vibrational analysis. A data set collection of computational results is available on the ioChem-BD[17] repository and can be freely accessed at https://doi.org/10.19061/iochem-bd-1-232.

[13] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
[14] a) R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650–654; b) A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639–5648.
[15]) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian09 Revision D.01, Gaussian Inc. Wallingford CT.
[16] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
[17] M. Álvarez-Moreno, C. De-Graaf, N. López, F. Maseras, Poblet, M. J. C. Bo, *J. Chem. Inf. Model.* **2015**, *55*, 95–103.

Further comments regarding the computational details

Figures 4.1 and 4.2 show alternative routes for the formation of the bicyclic product **4.C1** from bis-epoxy alcohol **4.B1**. Both the initial formation of the oxetane ring (*c4c5*, Figure 4.3 and Figure 4.1) and the tetrahydrofuran ring (*c5c4*, Figure 4.2) were computed and examined, and both routes computed with either the halide salt (TBAB) or with the binary catalytic system **4.1**/TBAB.

The *c4c5* TBAB-only route (Figure 4.1, light blue) has the oxetane ring formation (**TS3A**) as its rate-determining step similar to the pathway that includes Al-complex **4.1** (**TS3**, Figure 4.3 and Figure 4.1, purple trace), but it has a larger energy barrier of 31.4 kcal·mol^{-1}, which is around 5 kcal·mol^{-1} higher than the binary catalyzed process. Proton transfers in this pathway (**TS2A** and **TS5A**) are remarkably easy due to strong hydrogen bonding between the alkoxy and alcohol groups: the corresponding saddle points are only slightly above the corresponding intermediates in potential energy and *below* them in free energy.

As for the *c5c4* route, some of the envisioned transformations cannot take place due to steric complications. In the TBAB-only pathway (Figure 4.2, orange trace), the high-energy intermediate **Int2B** (32.9 kcal·mol^{-1}) cannot directly undergo cyclization towards **Int3B**. However, when the Al-complex **1** is present (Figure 4.2, green trace), one of the phenolate groups in the ligand can assist in the advancement of the reaction, allowing the attack on the epoxide ring through **TS2C-LS** (23.0 kcal·mol^{-1}) to form **Int2C-Lig**, with an energetic span of 43.2 kcal·mol^{-1}. From there, another nucleophilic attack allows the alkoxy group to displace the phenolate via **TS2C-SL** (19.6 kcal·mol^{-1}) to eventually form the tetrahydrofuran ring in **Int3C**. However, neither **Int3B** nor **Int3C** can proceed with the proton transfer step required to form the oxetane, as the alkoxy and the hydroxy groups are *trans* to each other. No attempts to characterize alternative proton transfer manifolds were made, considering that the barrier for tetrahydrofuran formation was already much higher than in the computed *c4c5* pathway.

4.6.8 Comparison of the formation of different oxetane

A preliminary characterization of the kinetic barrier for oxetane formation starting from the epoxy alcohol substrate **4.B22** was also carried out (Figure 4.4) to ascertain the reasons behind its lack of reactivity in the control experiments reported in Scheme 4.5b. The change of substrate produces relevant changes on kinetics, with the overall barrier leading to oxetane formation increasing from 26.4 to 29.2 kcal·mol^{-1}, therefore satisfactorily explaining the lack of conversion observed from **4.B22**.

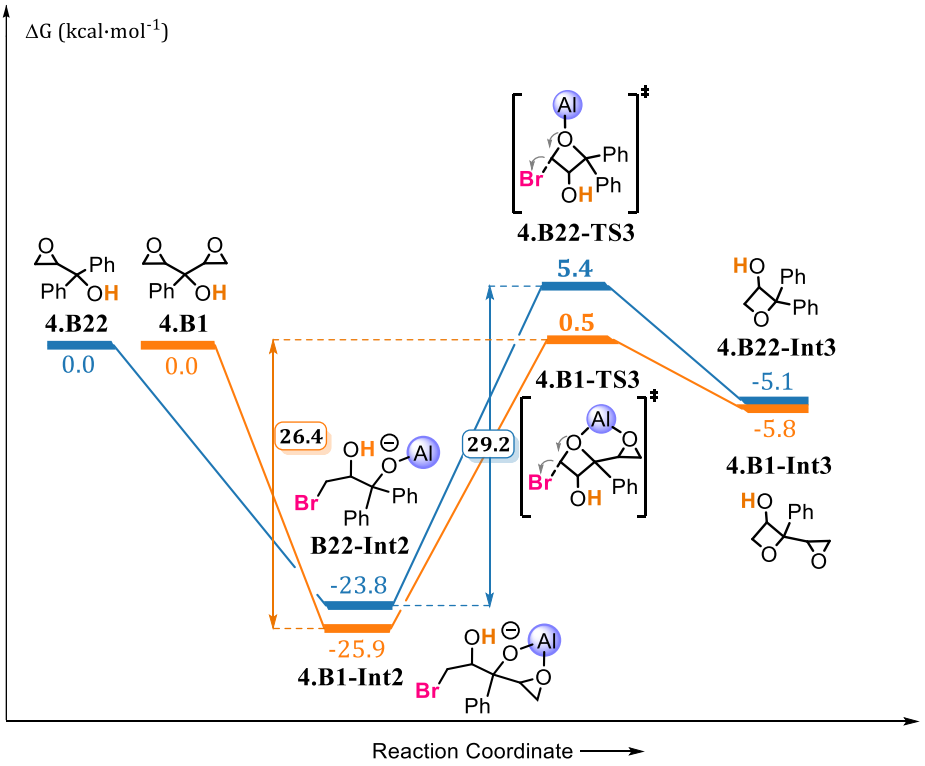


Figure 4.4 Comparison of the DFT computed pathways towards the formation of the epoxy oxetane from precursors **4.B1** and **4.B22** in the presence of **4.1**/TBAB as a binary catalyst. All energy values are Gibbs free energies in kcal·mol^{-1}.

4.6.9 Microkinetic modelling

As an additional demonstration of how our mechanistic proposal effectively predicts the formation of **4.C1** under reaction conditions, we carried out a microkinetic simulation.[18] Simulation conditions were:

T = 65 ºC **[4.B1]** = 0.2 M **[Al]** = 0.004 M (2 mol%)
[TBAB] = 0.010 M (5 mol%) Std. state: (1.0 M)

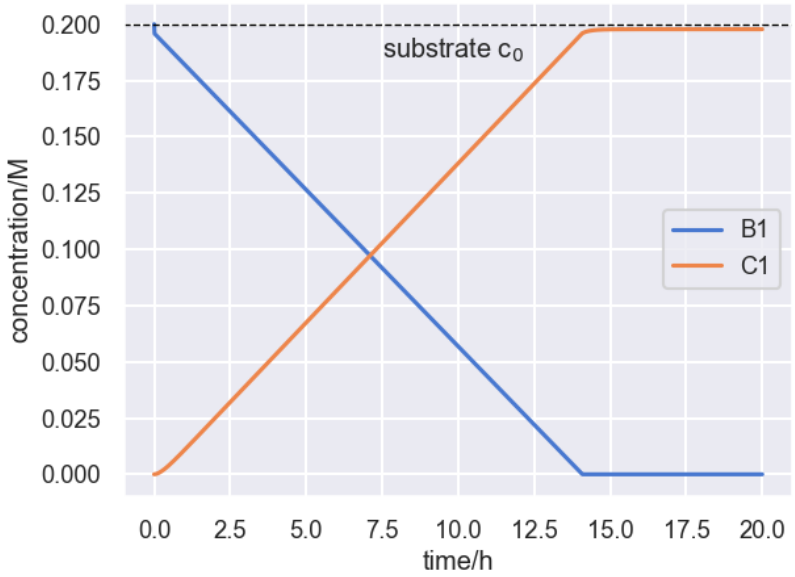


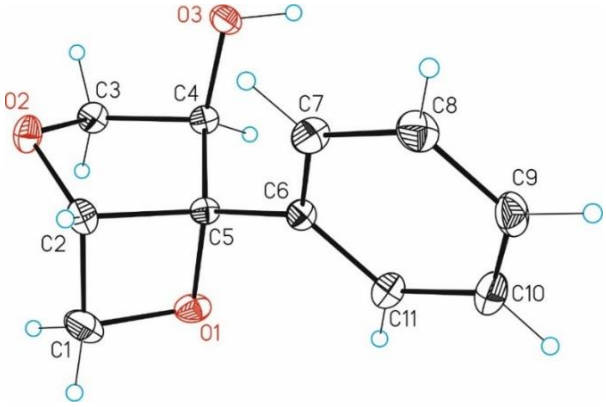
Figure 4.5 Microkinetic model for the mechanisms in Figure 4.1, showing the time evolution of the concentrations (in mol·L^{-1}) of the epoxy alcohol substrate **4.B1** and the anhydro furanose product **4.C1**.

The concentration/time plot shows how the reaction goes on to produce the anhydro furanose **4.C1**, with steady consumption of the initial bis-epoxy alcohol. The concentration of the epoxy oxetane **Int3A** remains low across the whole simulation, with a maximum value of $3.0 \cdot 10^{-3}$ M at t = 1 h and a negligible value at t = 20 h. All in all, the microkinetic simulation highlights the consistency between the computed mechanism and the experimental observations, such as the predicted 98.9% conversion after 20 h, matching the >99% value obtained in the laboratory.

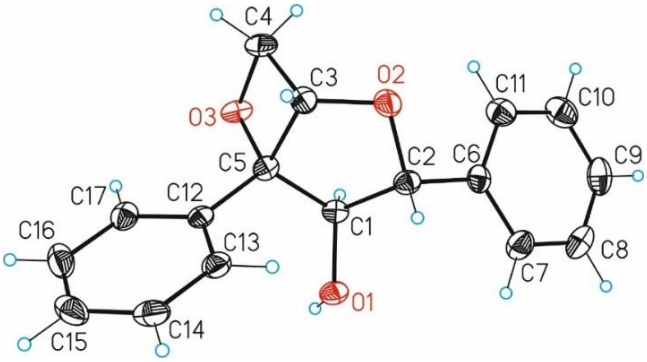
[18] With the COPASI (Ref: Hoops, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U., COPASI - A COmplex PAthway SImulator, *Bioinf.* **2006**, *22*, 3067–3074.) program, including the metal-catalyzed and the metal-free pathways in Figure 4.1.

4.6.10 X-ray molecular structures

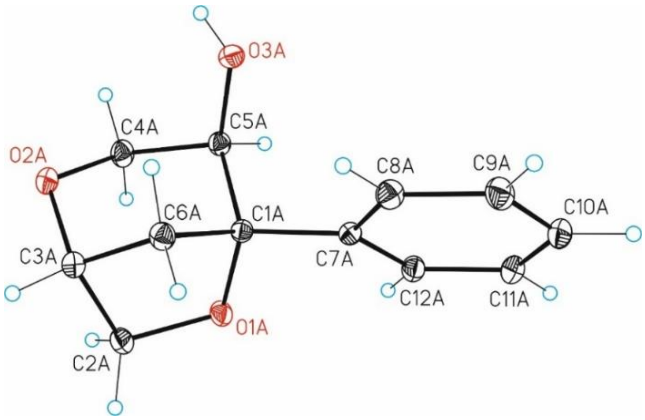
Note: the crystals were measured according to the general procedure reported in chapter 2.



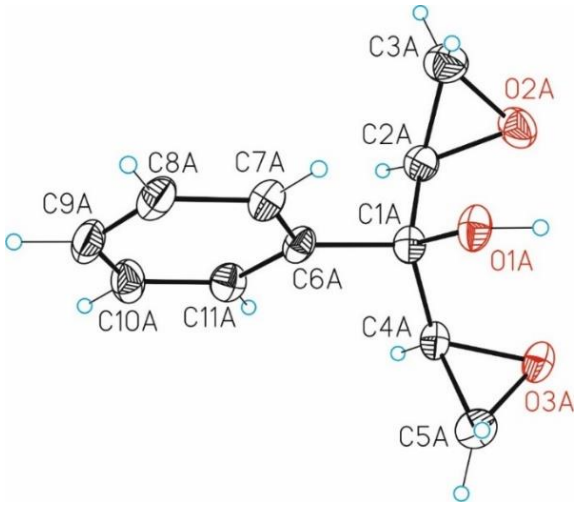
Crystallographic details for 4.C1: $C_{14.67}H_{16}O_4$, M_r = 256.27, T = 100(2) K, orthorhombic, *P*bca, a = 5.7145(3) Å, b = 16.4368(8) Å, c = 20.2457(10) Å, $\alpha = \beta = \gamma$ = 90°, V = 1901.64(17) Å^3, Z = 6, λ = 0.71073 Å, ρ = 1.343 Mg/m^3, μ = 0.097 mm^{-1}, F(000) = 816, crystal size = 0.200 × 0.050 × 0.050 mm^3, θ(min) = 2.012° θ(max) = 31.587°, 31851 reflections collected, 3175 reflections unique (R_{int} = 0.0286), GoF = 1.243, R_1 = 0.0389, wR_2 = 0.1421 [I>2σ(I)], R_1 = 0.0452, wR_2 = 0.1506 (all indices), max/min residual density = 0.505/-0.191 [e·Å^{-3}]. Completeness to θ(31.587°) = 99.5%. CCDC-2152782.



Crystallographic details for 4.C19: $C_{17}H_{16}O_3$, M_r = 268.30, T = 100(2) K, triclinic, *P*-1, a = 9.2782(4) Å, b = 9.3790(4) Å, c = 9.7193(4) Å, α = 116.988(5)°, β = 113.235(4)°, γ = 93.920(4)°, V = 982.85(15) Å^3, Z = 2, λ = 0.71073 Å, ρ = 1.350 Mg/m^3, μ = 0.092 mm^{-1}, F(000) = 284, crystal size = 0.200 × 0.200 × 0.100 mm^3, θ(min) = 2.556° θ(max) =28.658°, 11068 reflections collected, 2970 reflections unique (R_{int} = 0.0483), GoF = 1.019, R_1 = 0.0452, wR_2 = 0.0833 [I>2σ(I)], R_1 = 0.0997, wR_2 = 0.976 (all indices), max/min residual density = 0.231/-0.259 [e·Å^{-3}]. Completeness to θ(280658°) = 87.0%. CCDC-2152780.



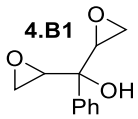
Crystallographic details for 4.C20: $C_{24}H_{28}O_6$, M_r = 412.46, T = 100(2) K, triclinic, P-1, a = 9.8649(9) Å, b = 9.9150(9) Å, c = 11.1058(10) Å, α = 68.9880(10)°, β = 79.951(2)°, γ = 77.022(2)°, V = 982.85(15) Å^3, Z = 2, λ = 0.71073 Å, ρ = 1.394 Mg/m^3, μ = 0.099 mm^{-1}, F(000) = 440, crystal size = 0.300 × 0.300 × 0.030 mm^3, θ(min) = 1.975° θ(max) =32.591°, 34069 reflections collected, 6937 reflections unique (R_{int} = 0.0217), GoF = 1.022, R_1 = 0.0408, wR_2 = 0.1118 [I>2σ(I)], R_1 = 0.0453, wR_2 = 0.1153 (all indices), max/min residual density = 0.556/–0.215 [e·Å^{-3}]. Completeness to θ(32.591°) = 96.9%. CCDC-2152781.



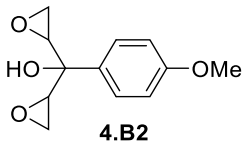
Crystallographic details for 4.B1: $C_{44}H_{48}O_{12}$, M_r = 768.82, T = 100(2)K, monoclinic, $P2_1/n$, a = 27.704(2) Å, b = 5.7172(4) Å, c = 27.7404(19) Å, α = γ = 90°, β = 119.487(2)°, V = 3824.6(5) Å^3, Z = 4, λ = 0.71073 Å, ρ = 1.335 Mg/m^3, μ = 0.097 mm^{-1}, F(000) = 1632, crystal size = 0.10 × 0.10 × 0.01 mm^3, θ(min) = 0.843° θ(max) =26.384°, 425309 reflections collected, 7514 reflections unique (R_{int} = 0.0286), GoF = 1.787, R_1 = 0.0572, wR_2 = 0.1465 [I>2σ(I)], R_1 = 0.0846, wR_2 = 0.1654 (all indices), max/min residual density = 0.296/-0.296 [e·Å^{-3}]. Completeness to θ(26.384°) = 96.1%. CCDC-2153758.

4.6.11 Characterization data for all new and relevant compounds

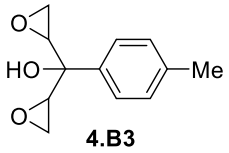
Bis-epoxy alcohols



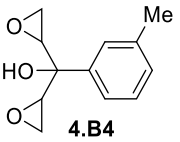
The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 38%, 365 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.44 – 7.37 (m, 2H), 7.37 – 7.32 (m, 1H), 3.41 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.87 (dd, *J* = 5.0, 2.8 Hz, 2H), 2.71 (dd, *J* = 5.0, 4.1 Hz, 2H), 2.44 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.54, 128.74, 128.21, 125.07, 70.52, 55.55, 42.88. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{12}NaO_3$) 215.0679, $(M+Na)^+$; found: 215.0677.



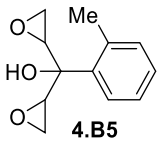
The product was isolated as a white solid, eluent: hexane: EA 10:1 to 5:1, yield: 32%, 354 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 6.96 – 6.90 (m, 2H), 3.82 (s, 3H), 3.37 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.86 (dd, *J* = 5.0, 2.8 Hz, 2H), 2.71 (dd, *J* = 5.0, 4.1 Hz, 2H), 2.40 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.55, 132.60, 126.39, 114.13, 70.29, 55.60, 55.44, 42.93. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_4$) 245.0784, $(M+Na)^+$; found: 245.0780.



The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 32%, 330 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.24 – 7.19 (m, 2H), 3.39 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.86 (dd, *J* = 5.0, 2.8 Hz, 2H), 2.70 (dd, *J* = 5.0, 4.1 Hz, 2H), 2.44 (s, 1H), 2.37 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.97, 137.53, 129.41, 124.99, 70.38, 55.63, 42.86, 21.23. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0844.

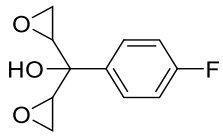


The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 40%, 413 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.29 (td, *J* = 7.5, 0.8 Hz, 1H), 7.18 – 7.13 (m, 1H), 3.40 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.86 (dd, *J* = 5.0, 2.7 Hz, 2H), 2.71 (dd, *J* = 5.0, 4.1 Hz, 2H), 2.41 (s, 1H), 2.39 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.45, 138.48, 128.98, 128.65, 125.67, 122.10, 70.46, 55.63, 42.89, 21.75. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0845.



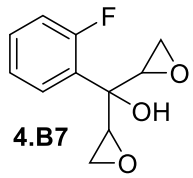
4.B5

The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 40%, 410 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 1H), 7.24 – 7.16 (m, 3H), 3.57 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.85 (dd, *J* = 5.0, 2.8 Hz, 2H), 2.77 (dd, *J* = 5.0, 4.1 Hz, 2H), 2.66 (s, 1H), 2.59 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.40, 136.04, 132.61, 128.09, 126.32, 126.02, 72.08, 55.47, 43.56, 22.27. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0839.



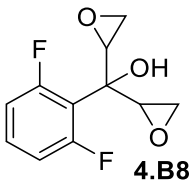
4.B6

The product was isolated as a white solid, eluent: hexane: EA 20:1, yield: 34%, 359 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.48 (m, 2H), 7.15 – 7.01 (m, 2H), 3.35 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.85 (dd, *J* = 4.9, 2.8 Hz, 2H), 2.72 (dd, *J* = 4.9, 4.1 Hz, 2H), 2.45 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.67 (d, *J* = 246.8 Hz), 136.42 (d, *J* = 3.1 Hz), 126.92 (d, *J* = 8.1 Hz), 115.63 (d, *J* = 21.5 Hz), 70.44, 55.31, 42.92. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.95. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{11}FNaO_3$) 233.0584 $(M+Na)^+$; found: 233.0593.



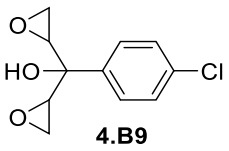
4.B7

The product was isolated as a white solid, hexane: EA 20:1, yield: 42%, 440 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (td, *J* = 7.7, 1.8 Hz, 1H), 7.33 (dddd, *J* = 8.2, 7.1, 5.2, 1.8 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.10 (ddd, *J* = 11.7, 8.2, 1.2 Hz, 1H), 3.78 (td, *J* = 3.9, 2.7 Hz, 2H), 2.74 (dd, *J* = 5.2, 2.7 Hz, 2H), 2.68 – 2.63 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.52 (d, *J* = 244.9 Hz), 129.85 (d, *J* = 8.4 Hz), 127.44 (d, *J* = 5.1 Hz), 126.63 (d, *J* = 14.4 Hz), 124.68 (d, *J* = 3.0 Hz), 115.89 (d, *J* = 22.8 Hz), 69.38 (d, *J* = 5.2 Hz), 54.94 (d, *J* = 6.6 Hz), 42.53. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.50. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{11}FNaO_3$) 233.0584 $(M+Na)^+$; found: 233.0589.



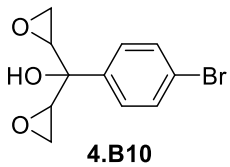
4.B8

The product was isolated as a light yellow oil, eluent: hexane: EA 15:1 to 10:1, yield: 30%, 341 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1H), 6.96 – 6.87 (m, 2H), 3.65 (dq, *J* = 4.1, 2.5 Hz, 2H), 2.95 (dd, *J* = 5.0, 2.7 Hz, 2H), 2.88 (s, 1H), 2.82 (dd, *J* = 5.0, 4.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.16 (dd, *J* = 251.8, 8.6 Hz), 130.35 (t, *J* = 11.3 Hz), 115.20 (t, *J* = 15.8 Hz), 112.93 – 112.54 (m), 71.15 (t, *J* = 3.8 Hz), 54.99 (t, *J* = 5.3 Hz), 43.48 (t, *J* = 2.2 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -106.34. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{10}F_2NaO_3$) 259.0490; $(M+Na)^+$ found: 259.0484.



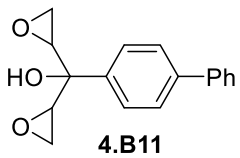
4.B9

The product was isolated as a white solid, eluent: hexane: EA 10:1 to 8:1, yield: 35%, 392 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.39 – 7.35 (m, 2H), 3.34 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.84 (dd, *J* = 4.9, 2.8 Hz, 2H), 2.71 (dd, *J* = 4.9, 4.1 Hz, 2H), 2.48 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.17, 134.19, 128.91, 126.55, 70.48, 55.16, 42.86. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{11}ClNaO_3$) 249.0289, $(M+Na)^+$; found: 249.0289.



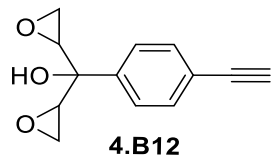
4.B10

The product was isolated as a white solid, eluent: hexane: EA 10:1 to 8:1, yield: 31%, 423 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.47 – 7.43 (m, 2H), 3.34 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.84 (dd, *J* = 4.9, 2.8 Hz, 2H), 2.71 (dd, *J* = 4.9, 4.1 Hz, 2H), 2.44 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.71, 131.89, 126.88, 122.38, 70.54, 55.11, 42.88. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{11}BrNaO_3$) 292.9784, $(M+Na)^+$; found: 292.9770.



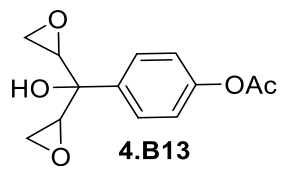
4.B11

The product was isolated as a white solid, eluent: hexane: EA 10:1 to 5:1, yield: 22%, 295 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (s, 4H), 7.62 – 7.57 (m, 2H), 7.49 – 7.42 (m, 2H), 7.40 – 7.33 (m, 1H), 3.44 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.91 (dd, *J* = 4.9, 2.8 Hz, 2H), 2.74 (dd, *J* = 5.0, 4.1 Hz, 2H), 2.49 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.17, 140.72, 139.51, 128.96, 127.61, 127.47, 127.26, 125.54, 70.53, 55.52, 42.94. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{16}NaO_3$) 291.0992, $(M+Na)^+$; found: 291.0993.



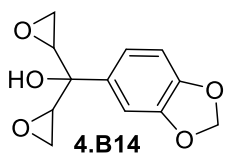
4.B12

The product was isolated as a light yellow solid, eluent: hexane: EA 10:1, yield: 28%, 303 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (s, 4H), 3.36 (dd, *J* = 4.1, 2.8 Hz, 2H), 3.09 (s, 1H), 2.84 (dd, *J* = 4.9, 2.8 Hz, 2H), 2.71 (dd, *J* = 4.9, 4.1 Hz, 2H), 2.44 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.25, 132.50, 125.09, 122.10, 83.32, 77.80, 70.61, 55.20, 42.86. **IR** (neat): *ν* (≡CH) = 3285 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{12}NaO_3$) 239.0679, $(M+Na)^+$; found: 239.0684.

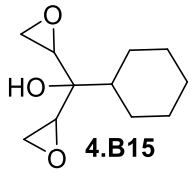


4.B13

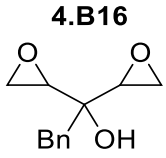
The product was isolated as a colorless oil, eluent: hexane: EA 10:1 to 6:1, yield: 14%, 175 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 3.39 – 3.32 (m, 2H), 2.88 – 2.81 (m, 2H), 2.70 (ddd, *J* = 5.0, 4.1, 1.0 Hz, 2H), 2.48 (s, 1H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.57, 150.53, 138.13, 126.30, 121.82, 70.45, 55.35, 42.91, 21.26. **IR** (neat): *ν* (C=O) 1753 cm^{-1}; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{14}NaO_5$) 273.0733, $(M+Na)^+$; found: 273.0735.



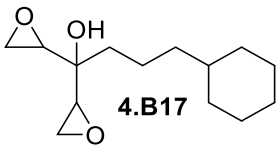
The product was isolated as a beige solid, eluent: hexane:EA 10:1 to 5:1, yield: 37%, 440 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 1.8, 0.4 Hz, 1H), 7.03 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.83 (dd, *J* = 8.1, 0.5 Hz, 1H), 5.97 (s, 2H), 3.33 (dd, *J* = 4.1, 2.8 Hz, 2H), 2.85 (dd, *J* = 4.9, 2.8 Hz, 2H), 2.71 (dd, *J* = 4.9, 4.1 Hz, 2H), 2.42 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.07, 147.47, 134.52, 118.47, 108.45, 106.06, 101.29, 70.49, 55.48, 42.91. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{12}NaO_5$) 259.0577, $(M+Na)^+$; found: 259.0578.



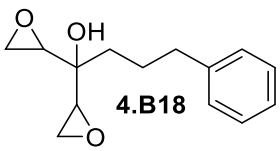
The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 35%, 347 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.14 (dd, *J* = 4.0, 2.8 Hz, 2H), 2.82 (dd, *J* = 5.1, 2.8 Hz, 2H), 2.74 (dd, *J* = 5.1, 4.0 Hz, 2H), 2.00 – 1.87 (m, 3H), 1.86 – 1.79 (m, 2H), 1.75 – 1.63 (m, 2H), 1.28 – 1.13 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 70.25, 54.38, 44.60, 42.98, 27.14, 26.63, 26.50. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{18}NaO_3$) 221.1148, $(M+Na)^+$; found: 221.1149.



The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 37%, 384 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 3.07 (t, *J* = 3.4 Hz, 2H), 2.99 (s, 2H), 2.66 – 2.61 (m, 4H), 1.98 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.31, 130.65, 128.22, 126.93, 69.32, 54.58, 43.25, 41.79. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0841.

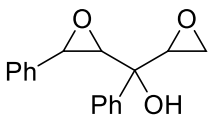


The product was isolated as a white solid, eluent: hexane: Et_2O 10:1, yield: 30%, 354 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.04 (dd, *J* = 4.0, 2.8 Hz, 2H), 2.80 (dd, *J* = 5.1, 2.8 Hz, 2H), 2.71 (dd, *J* = 5.1, 4.0 Hz, 2H), 1.93 (d, *J* = 1.0 Hz, 1H), 1.72 – 1.61 (m, 7H), 1.49 – 1.39 (m, 2H), 1.23 – 1.09 (m, 6H), 0.86 (qd, *J* = 10.7, 10.0, 4.5 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 68.95, 55.07, 43.00, 38.11, 37.68, 35.98, 33.51, 26.81, 26.52, 20.24. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{24}NaO_3$) 263.1618, $(M+Na)^+$; found: 263.1616.



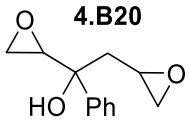
The product was isolated as a white solid, eluent: hexane: Et_2O 6:1, yield: 42%, 489 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (tt, *J* = 6.5, 1.2 Hz, 2H), 7.21 – 7.16 (m, 3H), 3.03 (dd, *J* = 4.0, 2.8 Hz, 2H), 2.79 (dd, *J* = 5.0, 2.8 Hz, 2H), 2.70 (dd, *J* = 5.1, 4.0 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 1.94 (s, 1H), 1.84 – 1.68 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.00, 128.54, 128.54, 126.06, 68.89, 55.00, 43.00, 36.42, 35.19, 24.89. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{18}NaO_3$) 257.1148, $(M+Na)^+$; found: 257.1144.

4.B19



The product was isolated as a white solid, eluent: hexane: EA 20:1, yield: 9%, 121 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 – 7.55 (m, 2H), 7.42 – 7.37 (m, 2H), 7.36 – 7.29 (m, 4H), 7.26 – 7.23 (m, 2H), 4.02 (d, J = 2.2 Hz, 1H), 3.50 – 3.46 (m, 2H), 2.93 (dd, J = 5.0, 2.8 Hz, 1H), 2.76 (dd, J = 4.9, 4.0 Hz, 1H), 2.64 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.22, 136.41, 128.82, 128.65, 128.52, 128.32, 125.95, 125.16, 70.89, 65.48, 55.66, 54.37, 43.02. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{16}NaO_3$) 291.0992, $(M+Na)^+$; found: 291.0992.

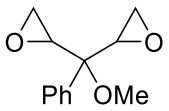
4.B20



The product was isolated as a colorless oil, eluent: hexane: EA 5:1, yield: 19%, 196 mg, *dr* = 7:3. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2.01H), 7.42 – 7.36 (m, 2.10H), 7.33 – 7.28 (m, 1.04H), 3.40 (dd, *J* = 4.1, 2.8 Hz, 0.71H), 3.33 (dd, *J* = 4.1, 2.8 Hz, 0.3H), 3.07 (dddd, *J* = 6.7, 4.9, 3.1, 2.0 Hz, 0.71H), 2.98 (dtd, *J* = 7.1, 4.3, 2.7 Hz, 0.29H), 2.86 – 2.83 (m, 1H), 2.76 (dd, *J* = 5.0, 4.0 Hz, 0.97H), 2.70 – 2.65 (m, 1.32H), 2.64 (t, *J* = 1.3 Hz, 0.65H), 2.51 (dd, *J* = 4.9, 2.7 Hz, 0.73H), 2.41 (dd, *J* = 4.9, 2.7 Hz, 0.29H), 2.34 (dd, *J* = 14.5, 4.5 Hz, 0.33H), 2.27 (dd, *J* = 14.5, 4.9 Hz, 0.79H), 2.23 – 2.17 (m, 0.78H), 2.10 (dd, *J* = 14.5, 7.1 Hz, 0.29H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.37, 142.11, 128.66, 128.64, 127.73, 127.65, 125.14, 125.05 72.81, 72.43, 57.95, 57.72, 48.93, 48.71, 47.18, 46.82, 44.40, 43.95, 43.70. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835; $(M+Na)^+$ found: 229.0833.

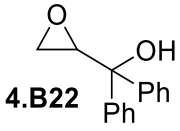
The product was isolated as a white solid, eluent: hexane:EA 15:1, yield: 31%, 63.4 mg. **^{1}H NMR**

4.B21



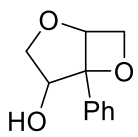
(500 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 3.40 (s, 3H), 3.30 (dd, *J* = 4.1, 2.8 Hz, 2H), 3.08 (dd, *J* = 5.3, 2.8 Hz, 2H), 2.75 (dd, *J* = 5.3, 4.2 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.87, 128.70, 128.40, 126.77, 77.12, 53.96, 52.48, 43.04. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0835.

4.B22



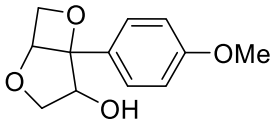
The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 78%, 1.77 g. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.2, 1.9 Hz, 2H), 7.43 – 7.27 (m, 8H), 3.81 (dd, *J* = 4.1, 2.7 Hz, 1H), 3.00 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.83 – 2.78 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.38, 143.33, 128.56, 128.34, 127.93, 127.64, 127.30, 126.38, 75.22, 57.32, 44.13. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{14}NaO_3$) 249.0886, $(M+Na)^+$;found: 249.0885.

3,5-Anhydro furanose type products 4.C1-4.C19 and 3,6-anhydro pyranose-like 4.C20



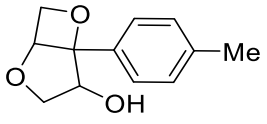
4.C1

The product was isolated as a white solid, eluent: hexane: EA 3:1, yield: 90%, 34.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.30 (m, 5H), 4.95 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.70 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.59 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.41 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.33 (d, *J* = 10.3 Hz, 1H), 4.07 (d, *J* = 3.3 Hz, 1H), 1.61 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.52, 128.48, 128.34, 125.97, 98.92, 81.26, 76.95, 74.83, 74.40. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{12}NaO_3$) 215.0679, $(M+Na)^+$; found: 215.0679.



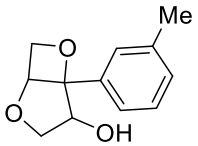
4.C2

The product was isolated as a light yellow solid, eluent: hexane: EA 2:1 to 1:1, yield: 89%, 39.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 6.99 – 6.93 (m, 2H), 4.98 – 4.91 (m, 1H), 4.71 (dd, *J* = 6.1, 3.9 Hz, 1H), 4.60 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.42 (dd, *J* = 9.4, 2.2 Hz, 1H), 4.34 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.75, 128.26, 127.35, 114.08, 98.93, 80.91, 76.86, 74.78, 74.36, 55.48. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_4$) 245.0784, $(M+Na)^+$; found: 245.0776.



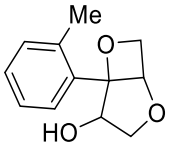
4.C3

The product was isolated as a light yellow solid, eluent: hexane: EA 2:1 to 1:1, yield: 91%, 37.5 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.22 (m, 2H), 4.97 (dd, *J* = 4.7, 2.2 Hz, 1H), 4.72 (ddd, *J* = 8.1, 4.7, 1.1 Hz, 1H), 4.61 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.43 (dt, *J* = 8.1, 1.7 Hz, 1H), 4.35 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.10 (t, *J* = 2.8 Hz, 1H), 2.38 (s, 3H), 1.37 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.35, 133.32, 129.32, 125.92, 99.01, 81.10, 76.95, 74.79, 74.41, 21.32. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0839.



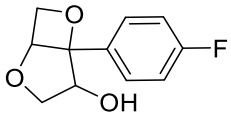
4.C4

The product was isolated as a light yellow solid, eluent: hexane: EA 2:1 to 1:1, yield: 91%, 37.3 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.6 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.20 – 7.16 (m, 1H), 5.00 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.72 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.61 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.44 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.36 (d, *J* = 10.3 Hz, 1H), 4.11 (d, *J* = 3.2 Hz, 1H), 2.39 (s, 3H), 1.36 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.46, 136.29, 129.27, 128.55, 126.55, 123.00, 99.05, 81.18, 77.03, 74.75, 74.43, 21.60. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0845.



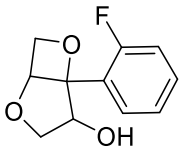
4.C5

The product was isolated as a white solid, eluent: hexane: Et_2O 3:1 to 1:1, yield: 61%, 12.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.25 – 7.20 (m, 2H), 5.25 (dd, *J* = 5.0, 2.6 Hz, 1H), 4.69 (dd, *J* = 8.2, 5.0 Hz, 1H), 4.61 (dd, *J* = 10.5, 3.4 Hz, 1H), 4.45 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.40 – 4.35 (m, 2H), 2.41 (s, 3H), 1.13 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.06, 133.65, 131.98, 128.89, 127.08, 125.70, 101.10, 80.57, 76.29, 74.50, 73.72, 20.42. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0841.



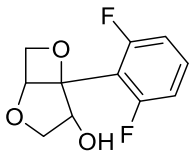
4.C6

The product was isolated as a colorless oil, eluent: hexane: EA 3:1, yield: 87%, 36.5 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.12 (t, *J* = 8.7 Hz, 2H), 4.93 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.72 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.62 (dd, *J* = 10.4, 3.3 Hz, 1H), 4.43 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.35 (d, *J* = 10.3 Hz, 1H), 4.09 (d, *J* = 3.1 Hz, 1H), 1.42 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.73 (d, *J* = 247.5 Hz), 132.41 (d, *J* = 3.2 Hz), 127.88 (d, *J* = 8.2 Hz), 115.49 (d, *J* = 21.6 Hz), 98.52, 81.30, 76.93, 74.96, 74.41. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.38. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{11}FNaO_3$) 233.0584; $(M+Na)^+$ found: 233.0583.



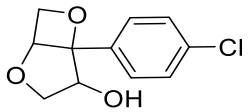
4.C7

The product was isolated as a colorless oil, eluent: hexane: EA 3:1, yield: 90%, 37.7 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (td, *J* = 7.6, 1.8 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.22 (td, *J* = 7.5, 1.2 Hz, 1H), 7.10 (ddd, *J* = 10.9, 8.2, 1.2 Hz, 1H), 5.23 (dt, *J* = 4.6, 2.2 Hz, 1H), 4.74 (dd, *J* = 8.2, 4.8 Hz, 1H), 4.65 – 4.59 (m, 1H), 4.45 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.33 (d, *J* = 10.5 Hz, 1H), 4.24 (dd, *J* = 3.4, 1.2 Hz, 1H), 1.76 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.22 (d, *J* = 246.0 Hz), 130.32 (d, *J* = 8.4 Hz), 128.31 (d, *J* = 4.2 Hz), 124.40 (d, *J* = 3.3 Hz), 124.29 (d, *J* = 13.6 Hz), 115.92 (d, *J* = 21.9 Hz), 97.33 (d, *J* = 2.2 Hz), 79.61 (d, *J* = 3.7 Hz), 77.58, 74.63, 74.60. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.65. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{11}FNaO_3$) 233.0584, $(M+Na)^+$; found: 233.0589.



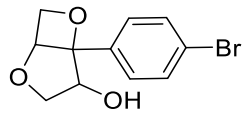
4.C8

The product was isolated as a colorless oil, eluent: hexane: EA 3:1, yield: 61%, 13.9 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (tt, *J* = 8.4, 6.3 Hz, 1H), 6.98 – 6.90 (m, 2H), 5.55 (td, *J* = 2.7, 1.1 Hz, 1H), 4.82 (dd, *J* = 8.2, 5.0 Hz, 1H), 4.58 (dd, *J* = 10.6, 3.1 Hz, 1H), 4.47 (s, 1H), 4.41 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.30 (d, *J* = 10.5 Hz, 1H), 1.85 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.08 (dd, *J* = 249.9, 8.4 Hz), 130.47 (t, *J* = 10.8 Hz), 113.52 (t, *J* = 17.1 Hz), 112.17 (d, *J* = 23.6 Hz), 96.48 – 96.34 (m), 79.33 (t, *J* = 5.9 Hz), 76.10, 74.89, 73.54. **^{19}F NMR** (376 MHz, MeOD) δ -110.64, –113.74. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{10}F_2NaO_3$) 251.0490, $(M+Na)^+$; found: 251.0484.



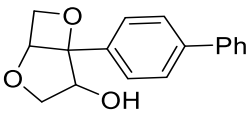
4.C9

The product was isolated as a light yellow solid, eluent: hexane: EA 3:1, yield: 83%, 37.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 4H), 4.92 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.71 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.62 (dd, *J* = 10.4, 3.3 Hz, 1H), 4.43 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.35 (d, *J* = 10.4 Hz, 1H), 4.10 (d, *J* = 3.2 Hz, 1H), 1.43 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.22, 134.36, 128.66, 127.49, 98.42, 81.45, 76.99, 75.03, 74.48. **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_{11}H_{10}ClO_2$) 209.0364, $(M\text{-}OH)^+$; found: 209.0360.



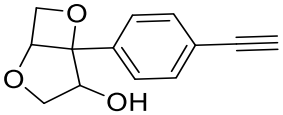
4.C10

The product was isolated as a white solid, eluent: hexane: EA 3:1, yield: 97%, 52.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.34 – 7.29 (m, 2H), 4.92 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.71 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.62 (dd, *J* = 10.4, 3.3 Hz, 1H), 4.43 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.35 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.09 (d, *J* = 3.2 Hz, 1H), 1.31(s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.76, 131.59, 127.80, 122.49, 98.44, 81.46, 76.96, 75.04, 74.49. **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_{11}H_{10}BrO_2$) 252.9859, $(M\text{-}OH)^+$; found: 252.9857.



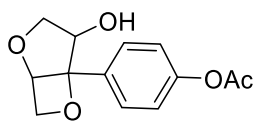
4.C11

The product was isolated as a light yellow solid, eluent: hexane: EA 2:1, yield: 97%, 51.6 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 2H), 7.63 – 7.58 (m, 2H), 7.54 – 7.50 (m, 2H), 7.49 – 7.42 (m, 2H), 7.40 – 7.35 (m, 1H), 5.03 (dt, *J* = 4.3, 1.8 Hz, 1H), 4.77 (ddd, *J* = 8.2, 4.7, 1.0 Hz, 1H), 4.66 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.47 (ddd, *J* = 8.1, 2.4, 1.1 Hz, 1H), 4.40 (dd, *J* = 10.3, 1.2 Hz, 1H), 4.17 (s, 1H), 1.45 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.44, 140.64, 135.46, 129.01, 127.73, 127.32, 127.28, 126.48, 98.90, 81.37, 77.11, 74.93, 74.53. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{16}NaO_3$) 291.0992, $(M+Na)^+$; found: 291.0996.



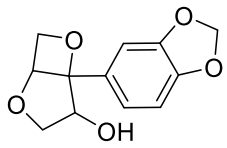
4.C12

The product was isolated as a yellow solid, eluent: hexane: EA 3:1, yield: 94%, 40.8 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.43 – 7.38 (m, 2H), 4.95 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.72 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.62 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.44 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.36 (d, *J* = 10.3 Hz, 1H), 4.11 (d, *J* = 3.3 Hz, 1H), 3.11 (s, 1H), 1.40 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.38, 132.17, 126.04, 122.24, 98.63, 83.27, 81.51, 77.96, 77.10, 75.00, 74.50. **IR** (neat): *v* 3295 cm^{-1} (≡CH); **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{12}NaO_3$) 239.0679, $(M+Na)^+$; found: 239.0676.



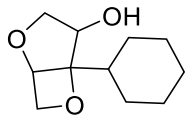
4.C13

The product was isolated as a colerless oil, eluent: hexane: EA 5:1 to 2:1, yield: 84%, 42.0 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.16 – 7.12 (m, 2H), 4.94 (dd, *J* = 4.6, 2.3 Hz, 1H), 4.72 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.62 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.44 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.37 (d, *J* = 10.3 Hz, 1H), 4.09 (t, *J* = 3.0 Hz, 1H), 2.32 (s, 3H), 1.51 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.72, 150.60, 134.28, 127.27, 121.68, 98.56, 81.54, 76.99, 74.93, 74.50, 21.25. **IR** (neat): *v* 1753 cm^{-1} (C=O); **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{13}H_{14}NaO_5$) 273.0733, $(M+Na)^+$; found: 273.0742.



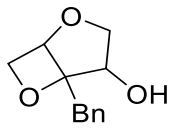
4.C14

The product was isolated as a white solid, eluent: hexane: EA 5:1 to 2:1, yield: 73%, 34.4 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 1.6, 0.6 Hz, 1H), 6.90 – 6.84 (m, 2H), 5.99 (q, *J* = 1.4 Hz, 2H), 4.92 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.71 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.59 (ddd, *J* = 10.3, 3.3, 1.5 Hz, 1H), 4.42 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.34 (d, *J* = 10.3 Hz, 1H), 4.07 (t, *J* = 3.1 Hz, 1H), 1.39 – 1.38 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.13, 147.81, 130.13, 119.48, 108.34, 106.73, 101.44, 99.02, 80.98, 76.88, 74.80, 74.35. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{12}NaO_5$) 259.0577, $(M+Na)^+$; found: 259.0581.



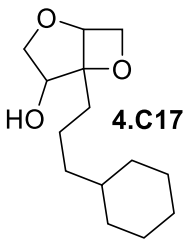
4.C15

The product was isolated as a light yellow solid, eluent: hexane: EA 5:1 to 2:1, yield: 77%, 30.3 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.72 (dd, *J* = 4.6, 2.3 Hz, 1H), 4.54 (dd, *J* = 8.3, 4.6 Hz, 1H), 4.43 (dd, *J* = 10.5, 3.1 Hz, 1H), 4.25 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.12 (d, *J* = 10.5 Hz, 1H), 4.06 (d, *J* = 3.0 Hz, 1H), 1.93 – 1.76 (m, 5H), 1.73 – 1.66 (m, 3H), 1.64 – 1.60 (m, 1H), 1.38 – 1.23 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 102.00, 77.62, 74.82, 74.27, 74.11, 37.61, 27.74, 26.40, 26.30, 26.27, 26.23. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{11}H_{18}NaO_3$) 221.1148, $(M+Na)^+$; found: 221.1146.



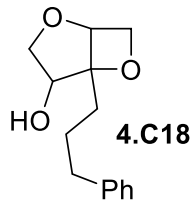
4.C16

The product was isolated as a light yellow solid, eluent: hexane: EA 3:1, yield: 86%, 35.5 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.26 (m, 1H), 4.54 (dd, *J* = 4.6, 2.4 Hz, 1H), 4.47 (dd, *J* = 10.5, 3.1 Hz, 1H), 4.23 – 4.11 (m, 3H), 3.99 (d, *J* = 3.0 Hz, 1H), 3.30 (d, *J* = 14.5 Hz, 1H), 3.12 (d, *J* = 14.4 Hz, 1H), 1.80 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.18, 130.15, 128.50, 126.85, 99.14, 75.44, 75.09, 73.49, 36.67. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0841.



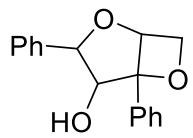
4.C17

The product was isolated as a white solid, eluent: hexane: Et_2O 1:1, yield: 78%, 37.5 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.63 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.59 (dd, *J* = 4.7, 2.1 Hz, 1H), 4.45 (dd, *J* = 10.5, 3.2 Hz, 1H), 4.27 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.11 (d, *J* = 10.5 Hz, 1H), 4.01 (d, *J* = 3.1 Hz, 1H), 1.94 (ddd, *J* = 14.2, 11.5, 4.9 Hz, 1H), 1.80 (ddd, *J* = 14.2, 11.7, 4.9 Hz, 1H), 1.73 – 1.61 (m, 6H), 1.61 – 1.47 (m, 2H), 1.28 – 1.08 (m, 6H), 0.89 (dtd, *J* = 17.3, 9.4, 8.8, 4.5 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 99.39, 79.07, 75.40, 74.86, 73.72, 37.97, 37.73, 33.56, 33.47, 31.06, 26.84, 26.55, 21.34. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{24}NaO_3$) 263.1618, $(M+Na)^+$; found: 263.1612.



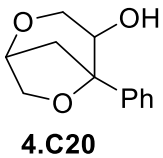
4.C18

The product was isolated as a white solid, eluent: hexane: Et_2O 1:1, yield: 83%, 38.8 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 4.62 (dd, *J* = 8.2, 4.6 Hz, 1H), 4.58 (dt, *J* = 4.3, 1.7 Hz, 1H), 4.44 (dd, *J* = 10.6, 3.2 Hz, 1H), 4.27 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.10 (dt, *J* = 10.5, 1.0 Hz, 1H), 4.00 (d, *J* = 3.1 Hz, 1H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.06 – 1.82 (m, 4H), 1.74 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.14, 128.57, 128.51, 126.01, 99.23, 78.99, 75.28, 74.84, 73.71, 36.26, 30.37, 25.88. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{14}H_{18}NaO_3$) 257.1148, $(M+Na)^+$; found: 257.1142.



4.C19

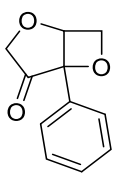
The product was isolated as a white solid, eluent: hexane: EA 3:1, yield: 26%, 7.0 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 4H), 7.33 – 7.26 (m, 5H), 7.25 (t, *J* = 1.7 Hz, 1H), 4.89 (ddd, *J* = 12.6, 7.1, 5.9 Hz, 1H), 4.76 (t, *J* = 7.0 Hz, 1H), 4.51 (dd, *J* = 6.8, 5.9 Hz, 1H), 4.26 (d, *J* = 2.1 Hz, 1H), 3.51 (d, *J* = 2.2 Hz, 1H), 3.32 (d, *J* = 12.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.36, 136.35, 128.79, 128.65, 128.54, 128.04, 126.06, 124.09, 91.39, 78.28, 75.87, 64.88, 53.65. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{17}H_{16}NaO_3$) 291.0992, $(M+Na)^+$; found: 291.1001.



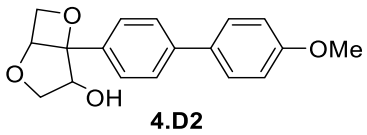
4.C20

The product was isolated as a white solid, eluent: hexane: EA 3:1, yield: 48%, 9.8 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.41 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 4.62 (td, *J* = 3.0, 1.3 Hz, 1H), 4.33 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.20 (dd, *J* = 12.7, 3.0 Hz, 1H), 4.01 (dd, *J* = 10.0, 3.0 Hz, 1H), 3.82 (d, *J* = 12.7 Hz, 1H), 3.66 (s, 1H), 2.91 (dt, *J* = 11.8, 1.4 Hz, 1H), 1.79 (ddt, *J* = 11.8, 2.7, 1.2 Hz, 1H), 1.71 (d, *J* = 3.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.72, 128.68, 128.13, 126.34, 85.55, 76.53, 73.45, 71.24, 67.14, 35.75. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_3$) 229.0835, $(M+Na)^+$; found: 229.0838.

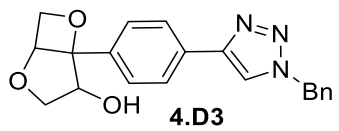
Derivatized products 4.D1-4.D6


4.D1

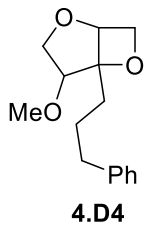
The product was isolated as a white solid, eluent: hexane: EA 10:1, yield: 83%, 33.1 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.38 (tt, *J* = 7.9, 1.4 Hz, 3H), 5.14 (dd, *J* = 5.3, 3.2 Hz, 1H), 4.99 (dd, *J* = 8.5, 5.3 Hz, 1H), 4.82 – 4.77 (m, 2H), 4.45 (d, *J* = 17.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.70, 134.05, 128.86, 128.79, 125.21, 88.13, 81.27, 75.38, 69.96. **IR** (neat): *ν* 1764 cm^{-1} (C=O); **HRMS** (APCI+; MeOH): *m/z* calcd. ($C_{11}H_{11}O_3$) 191.0703, $(M+H)^+$; found: 191.0712.


4.D2

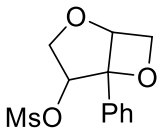
The product was isolated as a white solid, eluent: hexane: EA 3:1, yield: 84%, 50.1 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.56 – 7.52 (m, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 5.03 (dd, *J* = 4.7, 2.3 Hz, 1H), 4.76 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.65 (ddd, *J* = 10.4, 3.4, 1.2 Hz, 1H), 4.47 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.40 (d, *J* = 10.3 Hz, 1H), 4.16 (t, *J* = 3.1 Hz, 1H), 3.86 (s, 3H), 1.41 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.54, 141.07, 134.71, 133.11, 128.30, 126.88, 126.44, 114.47, 98.94, 81.30, 77.09, 74.89, 74.52, 55.51. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{18}H_{18}NaO_4$) 321.1097, $(M+Na)^+$; found: 321.1096.


4.D3

The product was isolated as a white solid, eluent: hexane: EA 1:1, yield: 91%, 63.5 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.66 (s, 1H), 7.47 – 7.43 (m, 2H), 7.42 – 7.36 (m, 3H), 7.33 – 7.28 (m, 2H), 5.57 (s, 2H), 4.98 (dd, *J* = 4.6, 2.3 Hz, 1H), 4.73 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.63 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.44 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.38 (d, *J* = 10.3 Hz, 1H), 4.15 (d, *J* = 3.2 Hz, 1H), 1.72 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.74, 136.51, 134.71, 130.56, 129.33, 128.99, 128.23, 126.49, 125.72, 119.77, 98.87, 81.37, 77.07, 74.98, 74.50, 54.42. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{20}H_{20}N_3O_3$) 350.1499, $(M+H)^+$; found: 350.1492.

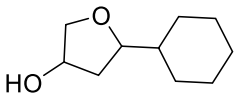

4.D4

The product was isolated as a colorless oil, eluent: hexane: EA 10:1, yield: 85%, 992mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 4.62 (dd, *J* = 8.1, 4.6 Hz, 1H), 4.56 (dd, *J* = 4.6, 2.2 Hz, 1H), 4.35 – 4.23 (m, 3H), 3.57 (d, *J* = 2.7 Hz, 1H), 3.34 (s, 3H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.07 – 1.97 (m, 1H), 1.94 – 1.81 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.34, 128.54, 128.45, 125.92, 99.34, 84.10, 79.04, 74.08, 70.14, 57.65, 36.34, 30.63, 25.94; **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{15}H_{20}NaO_3$) 271.1305, $(M+Na)^+$; found: 271.1306.



4.D5

The product was isolated as a colorless oil, eluent: hexane: EA 5:1, yield: 99%, 108 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 4H), 7.40 – 7.34 (m, 1H), 5.07 – 5.02 (m, 1H), 4.97 (d, *J* = 3.0 Hz, 1H), 4.79 – 4.71 (m, 2H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.49 (dd, *J* = 8.3, 2.3 Hz, 1H), 2.24 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.82, 128.67, 128.37, 126.15, 97.47, 83.50, 81.30, 74.76, 73.87, 37.61. **HRMS** (ESI+; MeOH): *m/z* calcd. ($C_{12}H_{14}NaO_5S$) 293.0454, $(M+Na)^+$; found: 293.0456.



4.D6

Note: this is a known derivative.[4e] The product was isolated as a yellow oil, eluent: hexane: EA 4:1, yield: 77%, 26.2 mg *dr* = 63:37. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.50 – 4.45 (m, 0.63H), 4.44 – 4.39 (m, 0.37H), 3.95 (dd, J = 9.8, 4.3 Hz, 0.66H), 3.88 – 3.77 (m, 1.03H), 3.69 (ddd, J = 9.8, 1.9, 1.1 Hz, 0.65H), 3.63 (dd, J = 9.8, 4.4 Hz, 0.39H), 3.48 (q, J = 7.7 Hz, 0.39H), 2.26 (dt, J = 13.6, 7.2 Hz, 0.4H), 2.01 – 1.87 (m, 1.78H), 1.81 – 1.53 (m, 7.30H), 1.52 – 1.31 (m, 1.33H), 1.27 – 1.10 (m, 3.57H), 1.07 – 0.90 (m, 2.18H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 83.75, 82.66, 75.50, 75.37, 72.77, 72.47, 43.20, 43.04, 39.41, 29.96, 29.85, 29.26, 29.02, 26.62, 26.15, 26.10, 25.98, 2

Chapter 5.

Summary and General Conclusions

UNIVERSITAT ROVIRA I VIRGILI
CATALYTIC FORMATION OF HETEROCYCLES FROM - AND -EPOXY ALCOHOLS
Chang Qiao

Chapter 5

Our main objective in this doctoral thesis was the development of the novel catalytic approaches using epoxy alcohols as substrates, which have unique reactivity in their coupling with carbon dioxide and comprise of both a nucleophilic and electrophilic site. This specific reactivity allows for to construct useful heterocyclic structures via unconventional manifolds while expanding the portfolio of functional intermediates and monomers derived from this renewable carbon feedstock. Al(III) aminotriphenolate complexes play a crucial role in the coupling of epoxy alcohols and CO_2, and compared to the state of the art at the beginning of this doctoral thesis, we have successfully introduced conceptually new processes by transforming epoxy alcohols into useful larger-ring cyclic carbonates and bicyclic [4+5] and [5+6] ether compounds.

Chapter 2 discloses a conceptually novel approach for the synthesis of six-membered cyclic carbonates derived from carbon dioxide. The approach utilizes homoallylic precursors that are converted into five-membered cyclic carbonates having a β-positioned alcohol group with respect to the carbonate ring. The activation of the pendent alcohol group through an *N*-heterocyclic base allows for equilibration towards a thermodynamically disfavored six-membered carbonate analogue that, however, can be conveniently trapped by an acylation agent. Various control experiments and computational analysis (DFT) of this manifold are in line with a process that is primarily dictated by a kinetically controlled acylation step. This cascade process delivers a wide diversity of novel six-membered cyclic carbonates in excellent yields and chemo-selectivities under remarkably mild reaction conditions. This newly developed protocol helps to expand the repertoire of CO_2-based heterocycles that are otherwise difficult to generate by conventional approaches. One problem associated with these six-membered cyclic carbonate scaffolds is their lack of stability under standard ring-opening polymerization (ROP) conditions (TBD as catalyst, BnOH as initiator and moderate reaction temperatures) causing *O*-deprotection, and virtually quantitative back-equilibration to a five-membered cyclic carbonate. Therefore, other approaches to polymerizable monomers had to be developed (cf., chapter 3).

In **Chapter 3**, a new and direct catalytic route is reported for the coupling of epoxy alcohols and carbon dioxide affording polymerizable six-membered bicyclic carbonates. Relatively rigid cyclic epoxides equipped with a β-positioned alcohol group can be conveniently transformed into structurally diverse bicyclic cyclic carbonates in good yields and with high selectivity. Key to the chemo-selectivity is the difference between

the reactivity of *syn*- and *anti*-configured epoxy alcohol precursors, with the latter leading to the formation of six-membered ring carbonates in the presence of a binary catalyst comprising of an Al(III) aminotriphenolate complex and DIPEA. X-ray crystallographic studies support the view that the conversion of the *syn*-configured epoxide likely evolves via a standard double inversion pathway providing a five-membered carbonate product, whereas the *anti*-isomer allows for activation of the oxirane unit (by the Al-complex) of the substrate opposite to the pendent alcohol, which activates the CO_2 in the presence of base. Thus, both functional groups are activated in concert and help to establish the efficient and direct formation of six-membered bicyclic carbonates from the trans precursors. The potential use of these bicyclic carbonates was shown in ROP offering access to new, rigid polycarbonates with markedly improved thermal resistance with the T_g up by almost 80 ºC compared to a non-substituted polycarbonate reference.

In **Chapter 4**, the preparation of structurally diverse heterobicyclic diethers in good yields is discussed through a catalytic domino process that is controlled by a versatile binary catalyst comprising of an Al(III) aminotriphenolate complex and a bromide salt. These bicycles, representing non-natural 3,5-anhydro furanose mimics, are derived from bis-epoxy α-alcohol substrates through a double cyclization pathway that is initiated by the activation of the free alcohol in the precursor compounds. Various mechanistic control experiments, X-ray analyses and computational investigations allowed to rationalize the intricacies of this multi-step process and the role of each catalyst component. Combined, these examinations revealed a clear preference for a sequence that starts with oxetane ring formation followed by an annulation step forming a fused and substituted tetrahydrofuran. The results hold promise for the catalytic and controlled build-up of even more complex polycyclic ether architectures.

Generally concluding, the results presented in this thesis show that epoxy alcohols are versatile synthons in the preparation of a wide variety of new and functional heterocyclic products, which significantly expand the repertoire of such scaffolds compared with the state of the art. Moreover, the catalytic strategies delineated in this thesis provide a means to access polymerizable CO_2-based monomers from relatively simple precursors, and to explore new reactivity patterns and properties in ROP. The diverse substrate scopes reported in chapters 2-4 exemplify the generality of the methods developed and provide important incentives to carbon recycling into polycarbonates with the ultimate aim to design circular processes and products.

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