UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

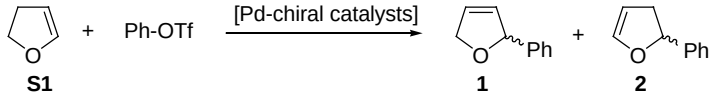
4.2. Screening of a modular sugar-based phosphite-oxazoline ligand library in asymmetric Pd-catalyzed Heck reactions

Abstract. We have also tested the previously described phosphite-oxazoline ligand library **L1-L4a-g** in the palladium-catalyzed Heck reactions. Excellent regio- (up to 99%) and enantioselectivities (ee's up to 99%) and improved activities have been achieved for several substrates in standard thermal conditions. The results indicate that the catalytic performance is highly affected by the oxazoline and biaryl-phosphite substituents and the axial chirality of the biaryl moiety of the ligand. The Heck reactions were also performed under microwave irradiation conditions, allowing a considerably shorter reaction time (full conversion in minutes) maintaining the excellent regio- and enantioselectivities.

4.2.1. Introduction

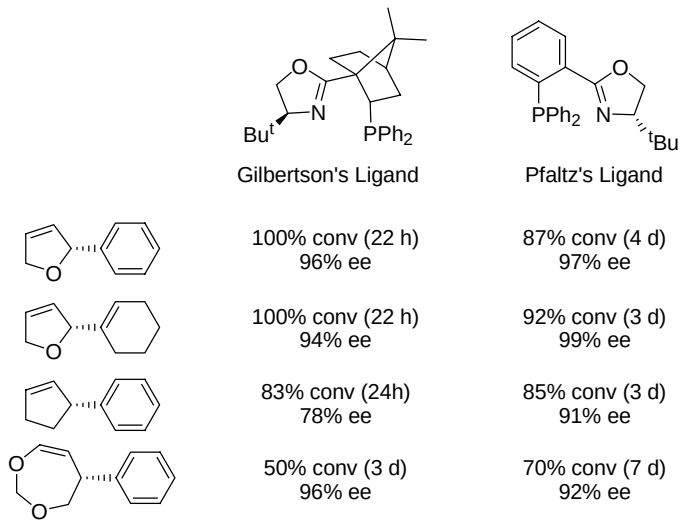
Catalytic asymmetric carbon-carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis. In this respect, the asymmetric Pd-catalyzed Heck reaction coupling of an aryl or alkenyl halide or triflate to an alkene is a powerful and highly versatile procedure because it tolerates several functional groups.[1] Chiral bidentate phosphine ligands have played a key role in the success of this process.[1] However, in the intermolecular Heck reaction, regioselectivity is often a problem. So, for example, in the Heck reaction of 2,3-dihydrofuran **S1** with phenyl triflate, a mixture of two products is obtained - the expected product 2-phenyl-2,5-dihydrofuran (**1**) and 2-phenyl-2,3-dihydrofuran (**2**; Scheme 1). The latter is formed due to an isomerization process.[1]

Org. Lett. **2005**, *7*, 5597 and *Chem. Eur. J.* **2007**, *13*, 3296



Scheme 1. Model Pd-catalyzed Heck reaction of 2,3-dihydrofurane **S1**.

In the last few years, a class of heterodonor ligands - the phosphine-oxazoline - have emerged as suitable ligands for the intermolecular Heck reaction.[2] Two of the most representative examples of this type of ligands are the PHOX ligands developed by Pfaltz[2a,b] and coworkers and the phosphine-oxazoline based on ketopinic acid developed by Gilberston and coworkers[2e]. Despite these successes, ligands that provide good regio- and enantioselectivities usually have two considerable drawbacks: (1) reaction times are usually long and (2) they are prepared from expensive chiral synthons or in tedious synthetic steps (Scheme 2). Therefore, it is very important to develop ligands that induce higher rates and selectivities (regio- and enantioselectivities) based on simple starting materials in this reaction. Carbohydrates are particularly advantageous for this purpose due to their low price and easy modular constructions.



Scheme 2. Summary of the best results using the most representative ligand families developed for the Pd-catalyzed Heck reactions (reactions usually carried out with 3-5 mol% of Pd).

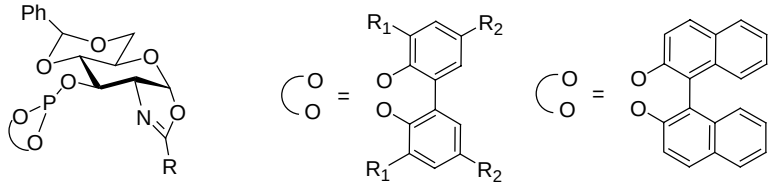
UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

In this context, to further expand the range of ligands and to improve the performance of these asymmetric Pd-catalyzed Heck reactions, we tested the library of chiral phosphite-oxazoline ligands **L1-L4a-g** (Figure 1), previously synthesized in section 3.2. As previously mentioned in Chapter 3, these ligands are derived from natural D-glucosamine and have the advantages of carbohydrate and phosphite ligands, such as availability at a low price from readily available alcohols and facile modular constructions.[3] Furthermore, they are less sensitive to air than typical phosphines, which are widely used as ligands in asymmetric catalysis. In addition, the introduction of a phosphite moiety in the ligand design is proved to be highly advantageous in terms of activity because of its greater π-acceptor ability.[4] All these favourable features enable a series of chiral ligands to be synthesized and screened in the search for high activity and selectivity. Although carbohydrate-based ligands have been successfully used in other enantioselective reactions,[3] there are only two reports on the highly enantioselective palladium-catalysed asymmetric Heck reaction using this type of ligand.[5]

Herein, we screen the potential use of the phosphite-oxazoline ligand library **L1-L4a-g** in the Pd-catalyzed asymmetric Heck reaction of several substrates and triflate sources. The screening of the library were performed using a series of parallel reactors each equipped with 12 different positions. With this library we fully investigated the effects of systematically varying the electronic and steric properties of the oxazoline substituents (**L1**-**L4**) and different substituents/configurations in the biaryl phosphite moiety (**a**-**g**). By carefully selecting these elements, we achieved high selectivities (regio- and enantioselectivities) and activities in different substrate types and aryl sources.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-690-[illegible]

Org. Lett. **2005**, *7*, 5597 and *Chem. Eur. J.* **2007**, *13*, 3296



L1 R= Ph
L2 R= ^{i}Pr
L3 R= ^{t}Bu
L4 R= Me

a $R_1 = R_2 = {}^{t}Bu$
b $R_1 = {}^{t}Bu$; R_2 = OMe
c $R_1 = SiMe_3$; R_2 = H
d $R_1 = R_2$ = Me
e $R_1 = R_2$ = H

f $(S)^{ax}$
g $(R)^{ax}$

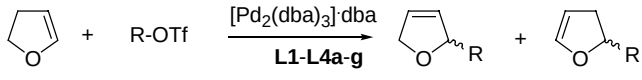
Figure 1. Carbohydrate-based phosphite-oxazoline ligands **L1-L4a-g**

4.2.2. Results and Discussion

4.2.2.1. Asymmetric Heck Reactions under thermal conditions

4.2.2.1.1. Heck reaction of 2,3-dihydrofuran S1 (equation 1)

In this section, we report the use of the chiral phosphite-oxazoline ligand library **L1-L4a-g** (Figure 1) in the Pd-catalyzed asymmetric Heck reaction of 2,3-dihydrofuran **S1** (equation 1) using several triflates with different electronic and steric properties: phenyl triflate, 1-naphthyl triflate, toluyl tryflate, *para*-nitrophenyltriflate and cyclohexenyl triflate. In all cases, the catalysts were generated *in situ* by mixing $[Pd_2(dba)_3]\cdot dba$ with the corresponding chiral ligand.



S1 **1** **2**

R= C_6H_5, 1-Naphthyl, *p*-CH_3-C_6H_4, *p*-NO_2-C_6H_4, C_6H_9

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

For an initial evaluation of this new type of ligand in the palladium-catalysed asymmetric Heck reaction, we chose the phenylation of **S1** (eq 1, R= C_6H_5). As this reaction has been carried out with a variety of ligands carrying different donor groups, it is possible to directly compare the efficacy of different ligand systems.

In a first set of experiments, we determined the optimal reaction conditions by conducting a series of experiments in which we varied the solvent, temperature and base. In all cases, the formation of the desired product 2-phenyl-2,5-dihydrofuran **1** was favored over the formation of 2-phenyl-2,3-dihydrofuran **2**.

We first studied the effect of the solvent. Four solvents (tetrahydrofurane (THF), benzene, toluene and dimethylformamide (DMF)) and four ligands (**L1a**, **L2a**, **L3a** and **L4a**) were tested. The results show that the efficiency of the process strongly depended on the nature of the solvent (Figure 1). The best activity and selectivity (regio- and enantioselectivity) was achieved with tetrahydrofurane as the solvent.

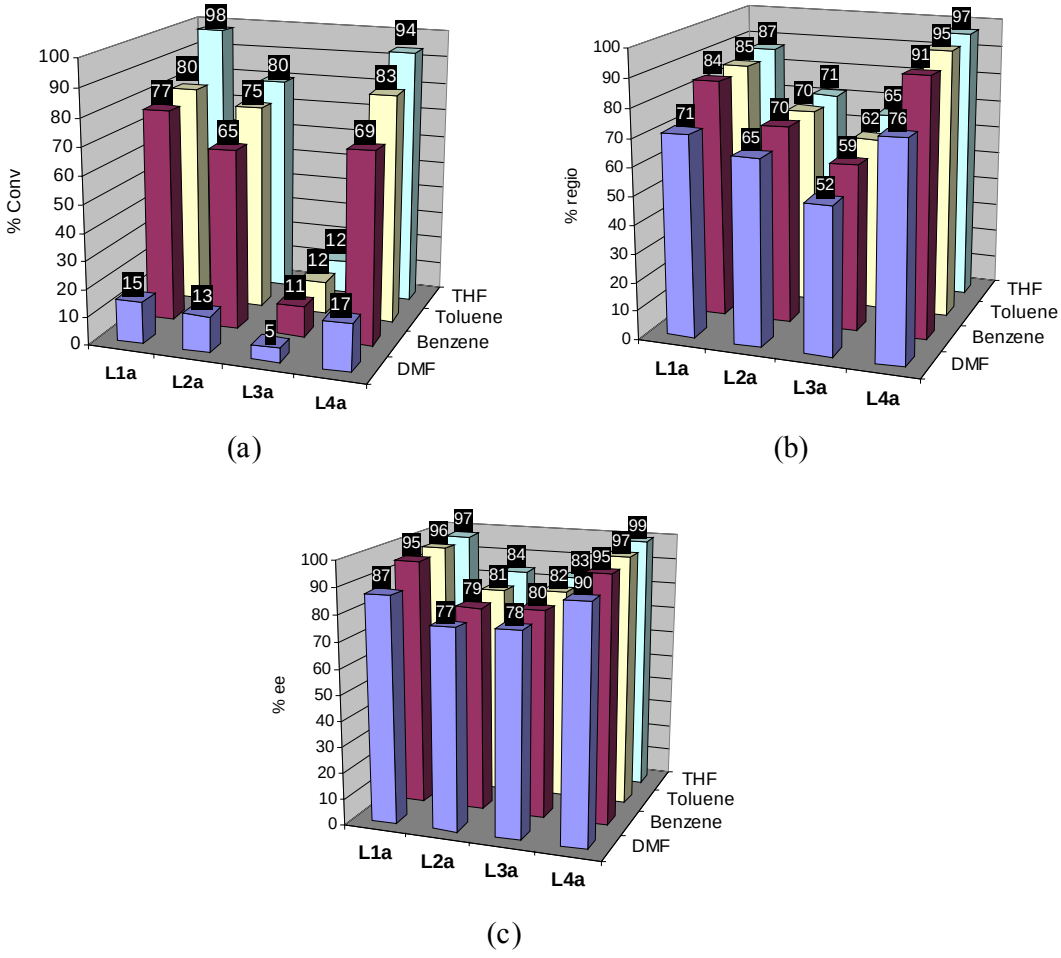


Figure 1. Catalytic results of the phenylation of **S1** using ligands **L1a**, **L2a**, **L3a** and **L4a** in four solvents at 50 ºC and using $^{i}Pr_2NEt$ as base. (a) Conversions after 24h. (b) Regioselectivities in product **1**. (c) Enantioselectivities of product **1**. Positive numbers refer to the formation of the *R*-isomer in excess.

We next studied the effect of varying the temperature. The conversion and selectivity when THF was used as a solvent and ligands **L1a** and **L4a** are shown in Table 1 (similar tendencies were observed with other solvents and ligands). We observed that this parameter affected both activity and selectivity. Increasing the temperature from 50 ºC to 75 ºC had a negative effect on regio- and enantioselectivity (Table 1, entries 1 and 4 vs 2 and 5). Lowering the temperature to 25 ºC hardly affected regio- and

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

enantioselectivity, but activities dropped considerably (Table 1, entry 1 and 3 vs 4 and 6). The best trade-off between activity and selectivity was therefore achieved at 50 ºC.

Table 1. Selected results for the Pd-catalysed enantioselective phenylation of **S1** using ligands **L1a** and **L4a**. Effect of temperature.[a]

Entry	Ligand	T (ºC)	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	50	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	75	100 (80:20)	93 (*R*)	87 (*R*)
3	**L1a**	25	28 (88:12)	98 (*R*)	88 (*R*)
4	**L4a**	50	94 (97:3)	99 (*R*)	nd[d]
5	**L4a**	75	100 (91:9)	94 (*R*)	91 (*R*)
6	**L4a**	25	29 (97:3)	99 (*R*)	nd[d]

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

We then studied the effect of several bases. The conversion and selectivity when THF was used as a solvent with ligands **L1a** and **L4a** are shown in Table 2 (similar trends were observed for the other solvents and ligands). Although the activities and regioselectivities obtained with proton sponge (PS) and diisopropylethylamine are comparable, the use of the latter base provides slightly better enantioselectivities (Table 2, entries 1 and 9 vs 2 and 10). On the other hand, sodium acetate yielded the highest regioselectivity, but its activities and enantioselectivities are lower than those of diisopropylethylamine (Table 2, entries 1 and 9 vs 3 and 11). The remainder of the bases tested provided lower activities and selectivities than those obtained with diisopropylamine (Table 2, entries 1 and 9 vs 4-8, 12 and 13). In conclusion we chose diisopropylethylamine as our base.

Table 2. Selected results for the Pd-catalysed enantioselective phenylation of 2,3-dihydrofuran **S1** using ligands **L1a** and **L4a**. Effect of the base.[a]

Entry	Ligand	Base	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	$^{i}Pr_2NEt$	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	PS	99 (87:13)	95 (*R*)	87 (*R*)
3	**L1a**	NaOAc	91 (91:9)	91 (*R*)	56 (*R*)
4	**L1a**	NEt_3	97 (82:18)	87 (*R*)	84 (*R*)
5	**L1a**	KOAc	53 (82:18)	43 (*R*)	47 (*R*)
6	**L1a**	K_2CO_3	89 (86:14)	88 (*R*)	27 (*R*)
7	**L1a**	Li_2CO_3	92 (68:32)	95 (*R*)	92 (*R*)
8	**L1a**	DBU	6 (72:28)	65 (*R*)	43 (*R*)
9	**L4a**	$^{i}Pr_2NEt$	94 (97:3)	99 (*R*)	nd[d]
10	**L4a**	PS	94 (96:4)	98 (*R*)	nd[d]
11	**L4a**	NaOAc	89 (98:2)	92 (*R*)	nd[d]
12	**L4a**	NEt_3	93 (88:12)	95 (*R*)	89 (*R*)
13	**L4a**	KOAc	62 (84:16)	57 (*R*)	38 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), base (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

In the end we found that, the optimum trade-off between selectivities and reaction rates was achieved with tetrahydrofurane, a temperature of 50 ºC and diisopropylethylamine as a base. These optimal conditions were then used to test the catalytic performance of the complete series of ligands. The results, which are summarized in Table 3, indicate that the catalytic performance (activity and selectivity) is highly affected by the substituents at both oxazoline and phosphite moiety and by the axial chirality of the biaryl phosphite moiety. In general, high activities, regio- (up to 98%) and enantioselectivities (ee's up to 99%) were obtained in the phenylation of **S1**.

The effect of the oxazoline substituent was studied with ligands **L1a, L2a, L3a, L4a** (Table 3, entries 1, 8-10). We found that these substituents affected both activities

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

and selectivities. Therefore, we observed that when the size of the group on the oxazoline decreased, the regio- and enantioselectivity of the catalyst increased (i.e. Me > Ph > ^{i}Pr > ^{t}Bu). This contrasts with the oxazoline-substituent effect observed for phosphine-oxazoline PHOX ligands, whose enantioselectivities are higher when bulky *tert*-butyl groups are present.[2a,b] In terms of activity, this is mainly affected by the bulkiness of the oxazoline group. Therefore, activity decreases when bulky substituents are present (Table 3, entries 1 and 9 vs 8 and 9). However, the electronic properties of the oxazoline substituent have a slight but important effect on activity. Activities are therefore highest when a phenyl oxazoline moiety is present (Table 3, entries 1 vs 10).

The effects of phosphite moieties were studied using ligands **L1a-g** (Table 3, entries 1-7, 10, 11). We found that this moiety affected both activity and selectivity. Bulky substituents in the *ortho* positions of the biphenyl moiety are needed for high activities, regio- and enantioselectivities. Thus, ligands **L1a**, **L1b** and **L1c** with bulky substituents at the *ortho* positions of the biphenyl moiety provided higher activities and selectivities than ligands **L1d** and **L1e** with small substituents in these positions (Table 3, entries 1, 2, 3 vs 4, 5). However, substituents in the *para* positions also play a small but crucial role. Therefore, the best activities and selectivities were obtained using ligands **L1c**, which contain bulky trimethylsilyl groups at the *ortho* positions and a small hydrogen at the *para* positions of the biphenyl moiety. To further investigate how enantioselectivity was influenced by the groups attached to the biaryl moiety, ligands **L1f** and **L1g** containing different enantiomerically pure binapthyl moieties were also tested (Table 3, entries 6 and 7). The results indicate that there is a cooperative effect between the configuration of the biaryl moiety and the configurations of the ligand backbone on enantioselectivity that results in a matched combination for ligand **L1g**, which contains an *R*-binaphtyl moiety.

To sum up, the best result was obtained with ligand **L4c**, which contains the optimal combination of substituents in the oxazoline and in the biaryl phosphite moieties (Table 3, entry 11). These results clearly show the efficiency of using highly modular scaffolds in the ligand design. In addition, the introduction of a phosphite moiety in the

ligand design have been very advantageous in terms of activity (total conversion in 15 hours). These results are among the best reported so far.[2a,b,e]

Table 3. Selected results for the Pd-catalysed enantioselective phenylation of 2,3-dihydrofuran **S1** using phosphite-oxazoline ligand library **L1-L4a-g**.[a]

Entry	Ligand	% Conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1b**	86 (85:15)	97 (*R*)	89 (*R*)
3[d]	**L1c**	100 (97:3)	99 (*R*)	nd[e]
4	**L1d**	42 (72:28)	25 (*R*)	16 (*R*)
5	**L1e**	45 (60:40)	80 (*R*)	69 (*R*)
6	**L1f**	32 (58:42)	6 (*R*)	19 (*R*)
7	**L1g**	28 (55:45)	73 (*R*)	48 (*R*)
8	**L2a**	80 (71:29)	84 (*R*)	90 (*R*)
9	**L3a**	12 (65:35)	83 (*R*)	23 (*R*)
10	**L4a**	94 (97:3)	99 (*R*)	nd[e]
11	**L4c**	100 (98:2)	99 (*R*)	nd[e]

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 50 ºC, t = 24 h. [d] t = 15 h. [e] not determined.

To further study the effects of electronic and steric properties of the aryl triflate source on the product outcome, we tested these new ligands in the Pd-catalyzed Heck reaction of **S1** with several aryl triflates, in which these properties were systematically varied (eq 1, R= 1-naphthyl, *p*-CH_3-C_6H_4, *p*-NO_2-C_6H_4). The most noteworthy results are shown in Table 4. They followed the same trend in terms of the effect of the oxazoline and phosphite moieties as the phenylation of **S1** (see section 4.2.7. Supporting information, Table 9). In general, high activities, regio- (up to 99%) and enantioselectivities (ee's up to 99%) were also obtained in the arylation of **S1**. The results indicates that both steric and electronic parameters on the triflate affected

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

catalytic performance. Thus, enantioselectivities are best for 1-naphthyl- and phenyltriflate (Table 4, entries 1, 2, 5, 6, 9 and 10). On the other hand regioselectivities are better when electron-withdrawing aryl triflates are used (Table 4, entries 4, 8, 12).

Table 4. Selected results for Pd-catalysed enantioselective arylation of 2,3-dihydrofuran **S1** using ligands **L1a**, **L1c** and **L4a**.[a]

Entry	Ligand	R	% Conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	C_6H_5	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	1-Naphthyl	88 (86:14)	97 (*R*)	89 (*R*)
3	**L1a**	*p*-CH_3-C_6H_4	99 (82:18)	94 (*R*)	91 (*R*)
4	**L1a**	*p*-NO_2-C_6H_4	94 (95:5)	88 (*R*)	nd[f]
5[e]	**L1c**	C_6H_5	100 (97:3)	99 (R)	nd[f]
6[e]	**L1c**	1-Naphthyl	89 (95:5)	99 (*R*)[d]	93 (*R*)
7[e]	**L1c**	*p*-CH_3-C_6H_4	94 (85:15)	96 (*R*)	93 (*R*)
8[e]	**L1c**	*p*-NO_2-C_6H_4	89 (>99:1)	90 (*R*)	nd[f]
9	**L4a**	C_6H_5	94 (97:3)	99 (*R*)	nd[f]
10	**L4a**	1-Naphthyl	85 (95:5)	99 (*R*)	nd[f]
11	**L4a**	*p*-CH_3-C_6H_4	95 (87:13)	96 (*R*)	89 (*R*)
12	**L4a**	*p*-NO_2-C_6H_4	87 (>99:1)	91 (*R*)	nd[f]

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), aryl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Enantiomeric excesses measured by HPLC. [e] t = 15 h. [f] not determined.

We also evaluated the ligand library in the Heck reaction of **S1** using cyclohexenyl triflate. The preliminary investigations performed into the solvent and base effect revealed a different trend regarding the base effect than those with the previously tested aryl triflates. Therefore, the best selectivities (regio- and enantioselectivities) and reaction rates were obtained when THF and proton sponge are used as a solvent and base, respectively (see section 4.2.7. Supporting information, Tables 10-12).

The results of using ligands **L1-L4a-g** under the optimised conditions are shown in Table 5. In general, high activities, regio- (up to 98%) and enantioselectivities (ee's up to

Org. Lett. **2005**, *7*, 5597 and *Chem. Eur. J.* **2007**, *13*, 3296

98%) were also obtained in this case. Again enantioselectivity was affected by the substituents at both oxazoline and phosphite moiety and the cooperative effect between stereocenters. However, the effect of these parameters was different from those observed in the arylation of **S1**. Thus, regio- and enantioselectivities were best with ligand **L1a** (regio's up to 98%, ee's up to 98%). These results clearly show the importance of using modular scaffolds in the ligand design.

Regarding the effect of the oxazoline substituents, again the presence of bulky substituents in this position considerably decreased activities and selectivities (Table 5, entries 1, 8-10). However, in contrast to the arylation of **S1**, the electronic effect was more important. Therefore, selectivities are higher when a phenyl substituent is present (Table 5, entry 1 vs 10).

Concerning the effect of the phosphite moiety on catalytic performance, again the presence of bulky substituents in the *ortho* positions of the biphenyl moiety were necessary for high selectivities. However, the effect of the type of substituents at the *para* positions in selectivity is more pronounced than for the arylation of **S1**. Thus, whereas good selectivities are obtained with ligands **L1a** and **L1c**, regioselectivity dropped considerably for ligand **L1b**, which contains methoxy groups at the *para* positions (Table 5, entries 1 and 3 vs 2).

Finally, the effect of the configuration of the biaryl phosphite moiety follows a similar trend as those with the previous arylation of **S1** (Table 5, entries 6 and 7).

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

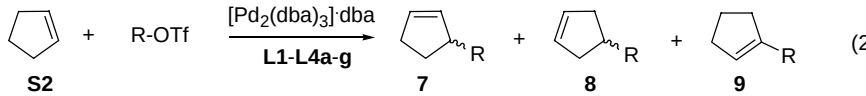
Table 5. Selected results for the Pd-catalysed enantioselective cyclohexenylation of 2,3-dihydrofuran **S1** using ligands **L1-L4a-g**.[a]

Entry	Ligand	% Conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	100 (98:2)	98 (*R*)	nd[d]
2	**L1b**	88 (80:20)	96 (*R*)	36 (*R*)
3	**L1c**	100 (92:8)	97 (*R*)	52 (*R*)
4	**L1d**	99 (74:26)	82 (*R*)	76 (*R*)
5	**L1e**	57 (58:42)	45 (*R*)	32 (*R*)
6	**L1f**	42 (55:45)	12 (*R*)	9 (*R*)
7	**L1g**	38 (53:47)	38 (*R*)	9 (*R*)
8	**L2a**	94 (84:16)	98 (*R*)	45 (*R*)
9	**L3a**	44 (51:49)	77 (*R*)	5 (*R*)
10	**L4a**	100 (88:12)	95 (*R*)	56 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), cyclohexyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), proton sponge (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not measured.

4.2.2.1.2. Heck reaction of cyclopentene S2 (equation 2)

We also screened the phosphite-oxazoline ligand library in the phenylation and alkenylation of cyclopentene **S2** (equation 2). Selectivity for **S2** is more difficult to control than for functionalized alkenes such as **S1** due to extensive double bond migration.[1] Moreover, in addition to the desired product **7**, regioisomer **8** and the achiral product **9** can also be obtained. Therefore, to date only high regio- (regio's up to 96% in product **7**) and enantioselectivities (ee's up to 91%) have been obtained with the phosphine-oxazoline PHOX ligands developed by Pfaltz and coworkers.[2a,b]



R= C_6H_5, C_6H_9

In this section, we report that the chiral phosphite-oxazoline ligands **L1**-**L4a-g** applied in the previous section to the Pd-catalyzed arylation and alkenylation of substrate **S1**, can also be used for unfunctionalised alkene substrate **S2**. In this case, two triflate sources were used (eq 2): phenyl triflate and cyclohexenyl triflate. In general, high activities and selectivities (regio's up to 94% and ee's up to 96%) were obtained in the phenylation and cyclohexenylation of **S2**. Interestingly, the formation of achiral product **9** did not take place. These results compete favourably with the best reported in the literature.[2a,b]

Preliminary investigations into the solvent and base effects revealed the same trends as those with the previously tested substrate **S1** with aryltriflate. The trade-off between selectivities and reaction rates was optimum with THF as solvent and diisopropylethylamine as base (see section 4.2.7. Supporting information, Tables 13-15).

The results of using the phosphite-oxazoline ligand library under the optimized conditions are shown in Table 6. In general, they follow the same trends as for the alkenylation of **S1**. Although, as expected, the activities were lower than in the alkenylation of **S1**, they were much higher than those obtained with the most successful ligand system.[2a,b] Again, the presence of a phosphite moiety in the ligand design has been highly advantageous in terms of activity and enantioselectivity.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Table 6. Selected results for Pd-catalyzed enantioselective phenylation and cycloalkenylation of cyclopentene **S2** using ligands **L1-L4a-g**.[a]

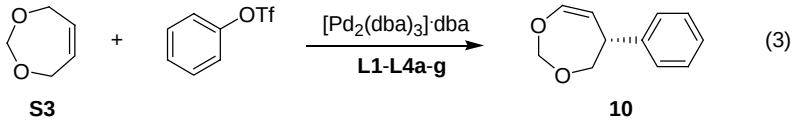
Entry	Ligand	R	% Conv (**7**:**8**)[b]	% ee **7**[c]	% ee **8**[c]
1	**L1a**	C_6H_5	100 (94:6)	95 (*R*)	nd[d]
2	**L1b**	C_6H_5	98 (85:15)	94 (*R*)	66 (*R*)
3	**L1c**	C_6H_5	100 (92:8)	95 (*R*)	82 (*R*)
4	**L1d**	C_6H_5	93 (79:21)	75 (*R*)	57 (*R*)
5	**L1e**	C_6H_5	47 (51:49)	44 (*R*)	34 (*R*)
6	**L1f**	C_6H_5	42 (45:55)	12 (*R*)	9 (*R*)
7	**L1g**	C_6H_5	44 (52:48)	45 (*R*)	42 (*R*)
8	**L2a**	C_6H_5	94 (86:14)	87 (*R*)	68 (*R*)
9	**L3a**	C_6H_5	34 (49:51)	59 (*R*)	11 (*R*)
10	**L4a**	C_6H_5	100 (93:7)	94 (*R*)	86 (*R*)
11	**L1a**	C_6H_9	100 (95:5)	96 (*R*)	nd[d]
12	**L1b**	C_6H_9	94 (83:17)	95 (*R*)	67 (*R*)
13	**L1c**	C_6H_9	100 (93:7)	96 (*R*)	78 (*R*)
14	**L1d**	C_6H_9	100 (78:22)	82 (*R*)	79 (*R*)
15	**L1e**	C_6H_9	45 (54:46)	51 (*R*)	60 (*R*)
16	**L1f**	C_6H_9	41 (52:48)	11 (*R*)	5 (*R*)
17	**L1g**	C_6H_9	47 (53:47)	49 (*R*)	16 (*R*)
18	**L2a**	C_6H_9	98 (85:15)	93 (*R*)	89 (*R*)
19	**L3a**	C_6H_9	56 (63:37)	61 (*R*)	18 (*R*)
20	**L4a**	C_6H_9	100 (92:8)	94 (*R*)	89 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S2** (2.0 mmol), triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol), T = 70 ºC, t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

4.2.2.1.3. Heck reaction of 4,7-dihydro-1,3-dioxepin S3 (equation 3)

Encouraged by the excellent results obtained for the arylation and alkenylation of 2,3-dihydrofuran **S1** and cyclopentene **S2**, we also examined the phenylation of 4,7-dihydro-1,3-dioxepin **S3** (eq. 3). This substrate is of great importance since the resulting

enolethers **10** are easily converted to chiral β-aryl-γ-butyrolactones, which are useful synthetic intermediates.[6] Despite this interesting characteristic, there are only few reports that study this substrate.[2a,b,e,h] An important drawback for this substrate is that the catalysts developed to date proceed at low reaction rates (i.e. the reaction takes typically 5 to 7 days for full conversion).[2a,b,e,h]



S3 **10** (3)

Interestingly, under non optimized conditions, our new ligands also proved to be highly efficient in terms of activity and enantioselectivity in the phenylation of **S3** (Table 7). The results indicated that enantioselectivities and activities are mainly affected by the steric properties of the oxazoline substituents. We found that when the size of the group on the oxazoline increased, activity and enantioselectivity of the catalyst decreased (entries 1 vs 4 and 5). The highest enantioselectivities (ee's up to 92%) and activities were obtained using ligands **L1a** and **L1c**. In addition, comparing these excellent results with the activities obtained with Pfaltz's and Gilbertson's ligand Pd-systems (Scheme 2) in the phenylation of **S3** we can conclude that the presence of a phosphite moiety has been highly advantageous. These results are among the best reported so far.[2a,b,e]

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Table 7. Selected results for the Pd-catalysed enantioselective phenylation of **S3** using ligands **L1-L4a-g**.[a]

Entry	Ligand	% Conv[b]	% ee **10**[c]
1	**L1a**	100	92 (*R*)
2	**L1b**	98	88 (*R*)
3[d]	**L1c**	100	92 (*R*)
4	**L2a**	95	75 (*R*)
5	**L3a**	54	61 (*R*)
6	**L4a**	100	90 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S3** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 70 ºC, t = 2.5 days. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC.[d] t = 2 days

4.2.2.2. Microwave-assisted asymmetric Heck Reactions

The benefits of microwave irradiation, including reduction of reaction rates and electricity costs, have already been reported in several C-C coupling reactions.[7] Therefore, we decided to use the advantages of microwave irradiation in the asymmetric Pd-catalyzed Heck reactions using the ligand library **L1-L4a-g**. To the best of our knowledge there is only one report on the use of microwave irradiation for the enantioselective Heck reactions using PHOX Pfaltz's and BINAP ligands. Under optimal reaction conditions they considerably shortened reaction times (from 4 days to 1 hour) but enantioselectivities were lower compared to those obtained under thermal conditions.[8]

As an initial evaluation we studied the Pd-catalyzed asymmetric Heck reaction of substrate **S1** using two different triflate sources (phenyl triflate and cyclohexenyl triflate) with ligands **L1a** and **L1c** (Table 8). After studying three different temperatures, we found that the optimal temperature was 70 ºC. At lower temperatures, activities and selectivities decreased (Table 8, entries 3 and 6 vs 1, 2, 4 and 5).

It is interesting to note that under microwave irradiation, reaction times have been dramatically improved (from 15 hours to 10 minutes) while maintaining the excellent regio- (up to 98%) and enantioselectivities (ee's up to 99%) obtained under thermal conditions.

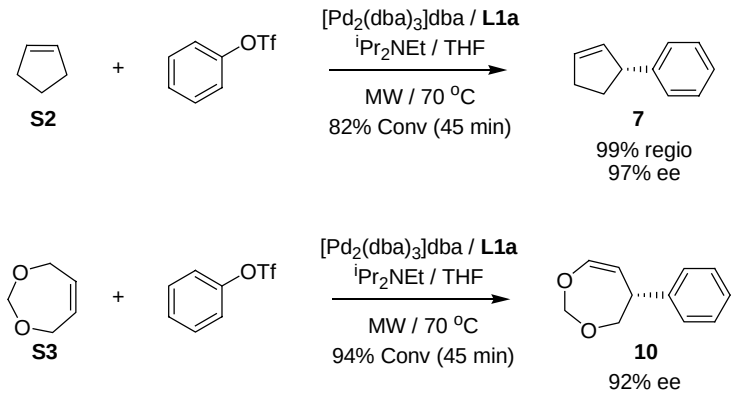
Table 8. Microwave-assisted Pd-catalysed enantioselective arylation and alkenylation of 2,3-dihydrofuran **S1** using ligands **L1a** and **L1c**.[a]

Entry	Ligand	R	T (ºC)	t (min)	% Conv (**1**:**2**)[b]	% ee **1**[c]
1	**L1a**	C_6H_5	50	15	81 (96:4)	93 (*R*)
2	**L1a**	C_6H_5	40	15	12 (94:6)	91 (*R*)
3	**L1a**	C_6H_5	70	10	99 (96:4)	96 (*R*)
4	**L1c**	C_6H_5	70	10	100 (98:2)	99 (*R*)
5	**L1a**	C_6H_9	50	15	82 (93:7)	89 (*R*)
6	**L1a**	C_6H_9	70	10	100 (95:5)	93 (*R*)
7	**L1c**	C_6H_9	70	10	100 (93:7)	97 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol). [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC.

Encouraged by these excellent results, we also studied the phenylation of cyclopentene **S2** and 4,7-dihydro-1,3-dioxepin **S3** which required longer reaction times under thermal conditions than substrate **S1** (Scheme 4). Again, the use of microwaves was highly advantageous, providing excellent regio- and enantioselectivities with much lower reaction times (from 2 days to 45 minutes). It should be noted that for substrate **S2**, the use of microwave irradiation also improved regio- and enantioselectivity. Therefore, the reaction of cyclopentene **S2** and phenyltriflate at 70 ºC gave the coupling product **7** with 97 % ee in 99% regioselectivity.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007



Scheme 4. Pd-catalyzed Heck reactions of **S2** and **S3** using ligand **L1a** under microwave irradiation.

4.2.3. Conclusions

A library of readily available phosphite-oxazoline ligands has been applied in Pd-catalyzed asymmetric Heck reactions of several substrates and triflates under thermal and microwave conditions. These ligands have the advantage that they are easily prepared in a few steps from commercial D-glucosamine as an inexpensive natural chiral source. In addition, they can be easily tuned in the oxazoline and biaryl phosphite moieties, so that their effect on catalytic performance can be explored. We found that the degree of isomerization and the effectiveness in transferring the chiral information in the product and the activity can be tuned by correctly choosing ligand components (phosphite and oxazoline substituents). Excellent activities (up to 100% conversion in 10 minutes), regio- (up to >99%) and enantioselectivities (ee's up to 99%) were obtained in a wide range of substrates and triflate sources. These results compete favourably with the most successful ligands developed for this reaction.[1]Note also that these ligands provided higher activities than those for other successful ligands. The use of microwave irradiation conditions allowed a considerably shorter reaction times (full conversion in few minutes) maintaining excellent regio- and enantioselectivities. These results open up a new class of ligands for the highly active and enantioselective Pd-catalysed Heck reaction, which will be of great practical interest.

ISBN:978-84-690-8326-3/DL:T.2159-2007

4.2.4. Experimental Section

4.2.4.1. General Considerations

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L1-L4a-f** have been previously described in Chapter 3.2. All other reagents were used as commercially available. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. The chemical shifts are referenced to tetramethylsilane (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. The ^{1}H and ^{13}C NMR spectral assignments were determined by ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectra. Microwave experiments were carried out using a CEM Explorer, in which the temperature is controlled by a non-contact infrared sensor that is located beneath the cavity floor and "looks" up at the bottom of the vessel.

4.2.4.2. General procedure for the Pd-catalyzed enantioselective Heck reactions

A mixture of $[Pd_2(dba)_3]$dba (12 mg, 1.25 x 10-2 mmol) and the corresponding chiral ligand (2.8 x 10-2 mmol) in dry degassed solvent (3.0 mL) was stirred under argon at room temperature for 15 min. The corresponding olefin (2.0 mmol), triflate (0.50 mmol) and base (1.0 mmol) were added to the catalyst solution. The solution was stirred at the desired temperature under argon. After the desired reaction time, the mixture was diluted with additional diethyl ether and washed with water, dried over $MgSO_4$ and evaporated. For compounds 2-(1-naphthyl)-2,5-dihydrofuran and 2-(4-nitrophenyl)-2,5-dihydrofuran conversion was measured by ^{1}H-NMR and selectivity was measured by HPLC.[2b] For the rest of compounds, conversion and selectivity were determined by GC.[2e]

4.2.5. Acknowledgements

We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2004-04412/BQU and Ramon y Cajal fellowship to O.P.) and the Generalitat de Catalunya (2005SGR007777 and Distinction to M.D.) for financial support. We thank ICIQ (Institut Català d'Investigació Química) for technical support on the microwave experiments.

4.2.6. References

[1] For recent reviews, see: a) Tietze, L. T.; Ila, H.; Bell, H. P. *Chem Rev.* **2004**, *104*, 3453. b) Dai, L.X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659. c) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem. Int. Ed.* **2001**, *44*, 3284. d) Shibasaki, M.; Vogl E. M. *in Comprehensive Asymmetric Catalysis* (Eds. Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H. Springer, Heidelberg, **1999**. e) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schemees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16. f) Beller, M.; Riermeier, T. H.; Stark G. *in Transition Metals for Organic Synthesis* (Eds. Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, **1998**.

[2] See for instance: a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 200. b) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338. c) Tu, T.; Hou, X.L.; Dai, L.X. *Org. Lett.* **2003**, *5*, 3651. d) Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240. e) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161. f) Tu, T.; Deng, W.P.; Hou, X.L.; Dai, L.X.; Dong, X.C. *Chem. Eur. J.* **2003**, *9*, 3073. g) Gilberston, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885. h) Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205. i) Hou, X. L.; Dong, D. X.; Yuan, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2189. j) Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460.

[3] See for instance: a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189. b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem.*

Rev. **2004**, *248*, 2165. c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957. d) Pàmies, O.; Diéguez, M.; Ruiz, A.; Claver, C. *Chemistry Today* **2004**, 12. e) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. in *Methodologies in Asymmetric Catalysis* (Ed. Malhotra, S. V.); American Chemical Society, Washington DC, **2004**. f) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113.

[4] a) van Strijdonck, G.P.F.; Boele, M.D.K.; Kamer, P.C.J.; de Vries, J.G.; van Leeuwen, P.W.N.M. *Eur. J. Inorg. Chem.* **1999**, 1073. b) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646.

[5] a) Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K. G.; Ohe, K.; Uemura, S. *J. Organomet. Chem*. **2000**, *603*, 40. b) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc*. **2002**, *124*, 184.

[6] Takano, S.; Dsmizu, K.; Ogasawara, K. *Synlett* **1993**, 393.

[7] See for instance: Microwave Assisted Organic Synthesis. Tierney, J. P.; Lidström, P., Eds. Blackwell Publishing Ltd. Oxford. 2005 and references therein.

[8] Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* **2002**, 1611.

4.2.7. Supporting information

1.- Table 9. Pd-catalyzed arylation of **S1**.

2.- Table 10. Pd-catalyzed cyclohexenylation of **S1**. Effect of the solvent.

3.- Table 11. Pd-catalyzed cyclohexenylation of **S1**. Effect of the temperature.

4.- Table 12. Pd-catalyzed cyclohexenylation of **S1**. Effect of the base.

5.- Table 13. Pd-catalyzed phenylation of **S2**. Effect of the solvent.

6.- Table 14. Pd-catalyzed phenylation of **S2**. Effect of the temperature.

7.- Table 15. Pd-catalyzed phenylation of **S2**. Effect of the base.

8.- Temperature, power and pressure vs time profiles for the microwaves experiments.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Table 9. Selected results for the Pd-catalysed enantioselective arylation of 2,3-dihydrofuran **S1**.[a]

Entry	Ligand	R	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1b**	C_6H_5	86 (85:15)	97 (*R*)	89 (*R*)
2	**L1b**	1-Naphthyl	81(86:14)	97 (*R*)[d]	90 (*R*)[d]
3	**L1b**	*p*-CH_3-C_6H_4	93 (81:19)	94 (*R*)	89 (*R*)
4	**L1b**	*p*-NO_2-C_6H_4	95 (92:8)	91 (*R*)[d]	nd[e]
5	**L1d**	C_6H_5	42 (72:28)	25 (*R*)	16 (*R*)
6	**L1d**	1-Naphthyl	42 (73:27)	26 (*R*)[d]	21 (*R*)[d]
7	**L1d**	*p*-CH_3-C_6H_4	43 (75:25)	27 (*R*)	22 (*R*)
8	**L1d**	*p*-NO_2-C_6H_4	40 (76:24)	27 (*R*)[d]	nd[e]
9	**L1e**	C_6H_5	45 (60:40)	80 (*R*)	69 (*R*)
10	**L1e**	1-Naphthyl	38 (63:37)	82 (*R*)[d]	76 (*R*)[d]
11	**L1e**	*p*-CH_3-C_6H_4	45 (65:35)	78 (*R*)	67 (*R*)
12	**L1e**	*p*-NO_2-C_6H_4	55 (70:30)	77 (*R*)[d]	nd[e]
13	**L1f**	C_6H_5	32 (58:42)	6 (*R*)	19 (*R*)
14	**L1f**	1-Naphthyl	22 (57:43)	9 (*R*)[d]	21 (*R*)[d]
15	**L1f**	*p*-CH_3-C_6H_4	34 (55:45)	11 (*R*)	19 (*R*)
16	**L1f**	*p*-NO_2-C_6H_4	44 (65:35)	7 (*R*)[d]	nd[e]
17	**L1g**	C_6H_5	28 (55:45)	73 (*R*)	48 (*R*)
18	**L1g**	1-Naphthyl	21 (52:48)	67 (*R*)[d]	43 (*R*)[d]
19	**L1g**	*p*-CH_3-C_6H_4	34 (53:47)	63 (*R*)	39 (*R*)
20	**L1g**	*p*-NO_2-C_6H_4	34 (56:44)	75 (*R*)[d]	nd[e]
21	**L2a**	C_6H_5	80 (71:29)	84 (*R*)	90 (*R*)
22	**L2a**	1-Naphthyl	75 (72:38)	84 (*R*)[d]	81 (*R*)[d]
23	**L2a**	*p*-CH_3-C_6H_4	82 (72:38)	85 (*R*)	86 (*R*)
24	**L2a**	*p*-NO_2-C_6H_4	89 (81:19)	81 (*R*)[d]	nd[e]
25	**L3a**	C_6H_5	12 (65:35)	83 (*R*)	23 (*R*)
26	**L3a**	1-Naphthyl	9 (63:37)	81 (*R*)[d]	45 (*R*)[d]
27	**L3a**	*p*-CH_3-C_6H_4	18 (65:35)	79 (*R*)	25 (*R*)
28	**L3a**	*p*-NO_2-C_6H_4	24 (71:29)	75 (*R*)	nd[e]

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), aryl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Enantiomeric excesses measured by HPLC. [e] not determined.

Table 10. Selected results for the Pd-catalysed enantioselective cyclohexenylation of **S1** using ligands **L1a - L4a**. Effect of the solvent.[a]

Entry	Ligand	Solvent	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	DMF	21 (71:29)	89 (*R*)	67 (*R*)
2	**L1a**	THF	100 (98:2)	98 (*R*)	nd[d]
3	**L1a**	Benzene	83 (96:4)	96 (*R*)	nd[d]
4	**L1a**	Toluene	85 (95:5)	96 (*R*)	nd[d]
5	**L2a**	DMF	24 (69:31)	91 (*R*)	75 (*R*)
6	**L2a**	THF	94 (84:16)	98 (*R*)	45 (*R*)
7	**L2a**	Benzene	92 (83:17)	97 (*R*)	56 (*R*)
8	**L2a**	Toluene	93 (81:19)	97 (*R*)	54 (*R*)
9	**L3a**	DMF	9 (52:48)	43 (*R*)	8 (*R*)
10	**L3a**	THF	44 (51:49)	77 (*R*)	5 (*R*)
11	**L3a**	Benzene	39 (52:48)	69 (*R*)	6 (*R*)
12	**L3a**	Toluene	38 (48:52)	73 (*R*)	9 (*R*)
13	**L4a**	DMF	38 (71:294)	83 (*R*)	42 (*R*)
14	**L4a**	THF	100 (88:12)	95 (*R*)	56 (*R*)
15	**L4a**	Benzene	92 (86:14)	94 (*R*)	63 (*R*)
16	**L4a**	Toluene	91 (85:15)	95 (*R*)	61 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S1** (2.0 mmol), cyclohexenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), solvent (3 mL), proton sponge (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Table 11. Selected results for the Pd-catalysed enantioselective cyclohexenylation of **S1** using ligands **L1a** - **L4a**. Effect of the temperature.[a]

Entry	Ligand	T (ºC)	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	50	100 (98:2)	98 (*R*)	nd[d]
2	**L1a**	75	100 (94:6)	94 (*R*)	nd[d]
3	**L1a**	25	21 (98:2)	98 (*R*)	nd[d]
4	**L2a**	50	94 (84:16)	91 (*R*)	75 (*R*)
5	**L2a**	75	100 (82:18)	88 (*R*)	69 (*R*)
6	**L2a**	25	19 (86:14)	92 (*R*)	81 (*R*)
4	**L3a**	50	44 (51:49)	77 (*R*)	5 (*R*)
5	**L3a**	75	69 (49:51)	72 (*R*)	4 (*R*)
6	**L3a**	25	8 (52:48)	79 (*R*)	7 (*R*)
4	**L4a**	50	100 (88:12)	95 (*R*)	56 (*R*)
5	**L4a**	75	100 (81:19)	92 (*R*)	51 (*R*)
6	**L4a**	25	28 (89:11)	96 (*R*)	64 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), cyclohexenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

Table 12. Selected results for the Pd-catalysed enantioselective cyclohexenylation of **S1** using ligands **L1a - L4a**. Effect of the base.[a]

Entry	Ligand	Base	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	$^{i}Pr_2NEt$	98 (97:3)	97 (*R*)	nd[d]
2	**L1a**	PS	100 (98:2)	98 (*R*)	nd[d]
3	**L1a**	NaOAc	97 (95:5)	96 (*R*)	nd[d]
4	**L1a**	NEt_3	95 (92:8)	93 (*R*)	89 (*R*)
5	**L1a**	KOAc	67 (90:10)	78 (*R*)	65 (*R*)
6	**L1a**	K_2CO_3	88 (96:4)	92 (*R*)	90 (*R*)
7	**L1a**	Li_2CO_3	91 (79:21)	93 (*R*)	90 (*R*)
8	**L2a**	$^{i}Pr_2NEt$	92 (85:15)	90 (*R*)	71 (*R*)
9	**L2a**	PS	94 (84:16)	91 (*R*)	75 (*R*)
10	**L2a**	NaOAc	93 (80:20)	88 (*R*)	65 (*R*)
11	**L3a**	$^{i}Pr_2NEt$	42 (51:49)	77 (*R*)	8 (*R*)
12	**L3a**	PS	44 (51:49)	77 (*R*)	5 (*R*)
13	**L3a**	NaOAc	39 (50:50)	75 (*R*)	9 (*R*)
14	**L4a**	$^{i}Pr_2NEt$	97 (87:13)	95 (*R*)	62 (*R*)
15	**L4a**	PS	100 (88:12)	95 (*R*)	56 (*R*)
16	**L4a**	NaOAc	93 (78:22)	93 (*R*)	78 (*R*)
17	**L4a**	NEt_3	92 (85:15)	92 (*R*)	81 (*R*)
18	**L4a**	KOAc	57 (76:24)	68 (*R*)	45 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), cyclohexenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), base (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Table 13. Selected results for the Pd-catalysed enantioselective phenylation of **S2** using ligands **L1a - L4a**. Effect of the solvent.[a]

Entry	Ligand	Solvent	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	DMF	31 (81:19)	89 (*R*)	61 (*R*)
2	**L1a**	THF	100 (94:6)	95 (*R*)	nd
3	**L1a**	Benzene	88 (92:8)	94 (*R*)	81 (*R*)
4	**L1a**	Toluene	92 (93:7)	94 (*R*)	89 (*R*)
5	**L2a**	DMF	24 (77:23)	78 (*R*)	44 (*R*)
6	**L2a**	THF	94 (86:14)	87 (*R*)	68 (*R*)
7	**L2a**	Benzene	89 (84:16)	85 (*R*)	71 (*R*)
8	**L2a**	Toluene	90 (83:17)	84 (*R*)	72 (*R*)
9	**L3a**	DMF	8 (44:1856)	39 (*R*)	8 (*R*)
10	**L3a**	THF	34 (49:51)	59 (*R*)	11 (*R*)
11	**L3a**	Benzene	29 (45:55)	53 (*R*)	13 (*R*)
12	**L3a**	Toluene	30 (48:52)	58 (*R*)	14 (*R*)
13	**L4a**	DMF	42 (85:15)	86 (*R*)	59 (*R*)
14	**L4a**	THF	100 (93:7)	94 (*R*)	86 (*R*)
15	**L4a**	Benzene	94 (95:5)	91 (*R*)	nd
16	**L4a**	Toluene	98 (94:6)	92 (*R*)	88 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S2** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), solvent (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 50 ºC, t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

Table 14. Selected results for the Pd-catalysed enantioselective phenylation of **S2** using ligands **L1a** - **L4a**. Effect of the temperature.[a]

Entry	Ligand	T (ºC)	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	50	100 (94:6)	95 (*R*)	nd[d]
2	**L1a**	70	100 (89:11)	92 (*R*)	87 (*R*)
3	**L1a**	25	21 (95:5)	96 (*R*)	nd[d]
4	**L2a**	50	94 (86:14)	87 (*R*)	68 (*R*)
5	**L2a**	70	100 (80:20)	72 (*R*)	59 (*R*)
6	**L2a**	25	19 (88:12)	88 (*R*)	66 (*R*)
4	**L3a**	50	34 (49:51)	59 (*R*)	11 (*R*)
5	**L3a**	70	62 (50:50)	56 (*R*)	3 (*R*)
6	**L3a**	25	12 (48:52)	60 (*R*)	13 (*R*)
4	**L4a**	50	100 (93:7)	94 (*R*)	86 (*R*)
5	**L4a**	70	100 (90:10)	88 (*R*)	71 (*R*)
6	**L4a**	25	21 (94:6)	95 (*R*)	nd[d]

[a] $[Pd_2(dba)_3]$·dba (1.25 x 10^{-2} mmol), **S2** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

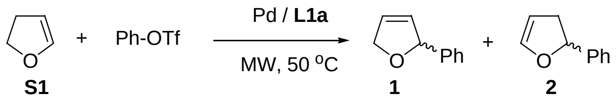
Table 15. Selected results for the Pd-catalysed enantioselective phenylation of **S2** using ligands **L1a - L4a**. Effect of the base.[a]

Entry	Ligand	Base	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	$^{i}Pr_2NEt$	100 (94:6)	95 (*R*)	nd
2	**L1a**	PS	100 (93:7)	95 (*R*)	92 (*R*)
3	**L1a**	NaOAc	98 (95:5)	92 (*R*)	nd
4	**L1a**	NEt_3	95 (89:11)	91 (*R*)	89 (*R*)
5	**L1a**	KOAc	78 (92:8)	81 (*R*)	79 (*R*)
6	**L1a**	K_2CO_3	89 (95:5)	90 (*R*)	79 (*R*)
7	**L1a**	Li_2CO_3	98 (86:14)	92 (*R*)	65 (*R*)
8	**L2a**	$^{i}Pr_2NEt$	94 (86:14)	87 (*R*)	68 (*R*)
9	**L2a**	PS	95 (85:15)	85 (*R*)	71 (*R*)
10	**L2a**	NaOAc	100 (80:20)	83 (*R*)	59 (*R*)
11	**L3a**	$^{i}Pr_2NEt$	34 (49:51)	59 (*R*)	11 (*R*)
12	**L3a**	PS	38 (50:50)	57 (*R*)	8 (*R*)
13	**L3a**	NaOAc	35 (48:52)	51 (*R*)	6 (*R*)
14	**L4a**	$^{i}Pr_2NEt$	100 (93:7)	94 (*R*)	86 (*R*)
15	**L4a**	PS	100 (91:9)	92 (*R*)	83 (*R*)
16	**L4a**	NaOAc	99 (89:11)	93 (*R*)	81 (*R*)
17	**L4a**	NEt_3	95 (90:10)	92 (*R*)	84 (*R*)
18	**L4a**	KOAc	73 (89:11)	65 (*R*)	78 (*R*)

[a] $[Pd_2(dba)_3]$·dba (1.25×10^{-2} mmol), **S2** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), base (1 mmol), T = 50 ºC, t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

8. Temperature, power and pressure vs time profiles for the microwaves experiments

Table 8, entry 1.



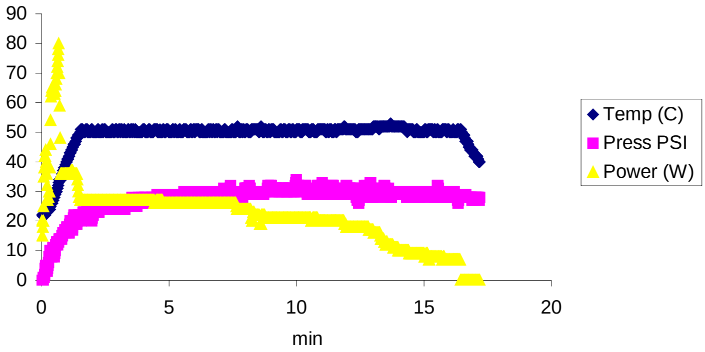
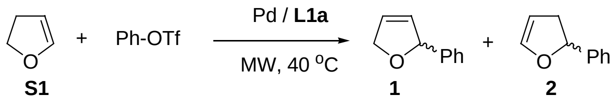
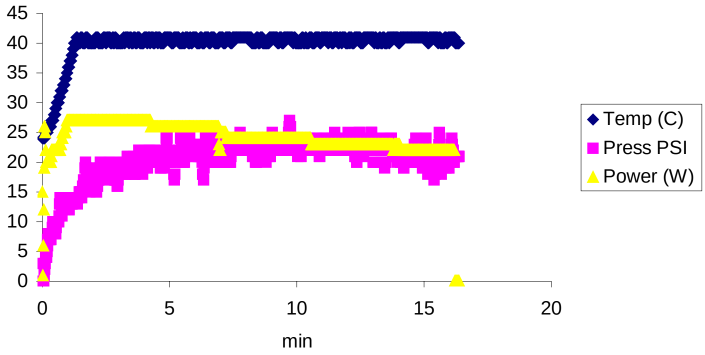


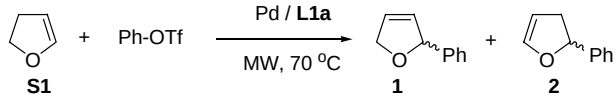
Table 8, entry 2.





UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

Table 8, entry 3.



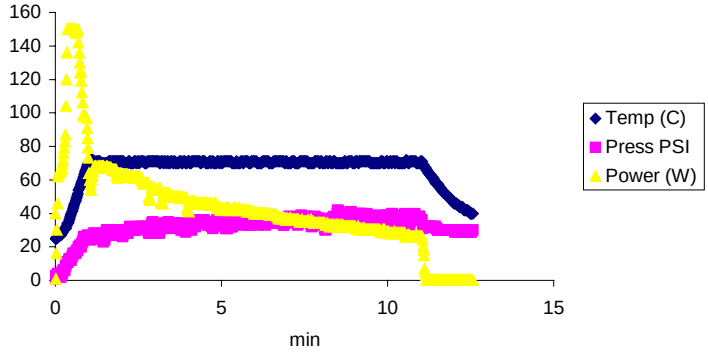
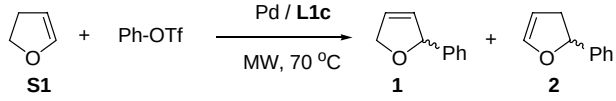


Table 8, entry 4.



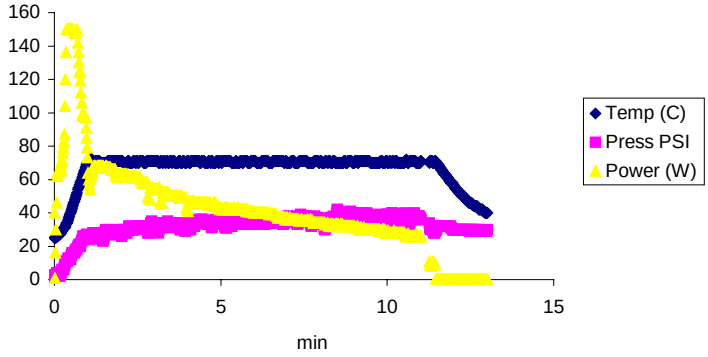


Table 8, entry 5.

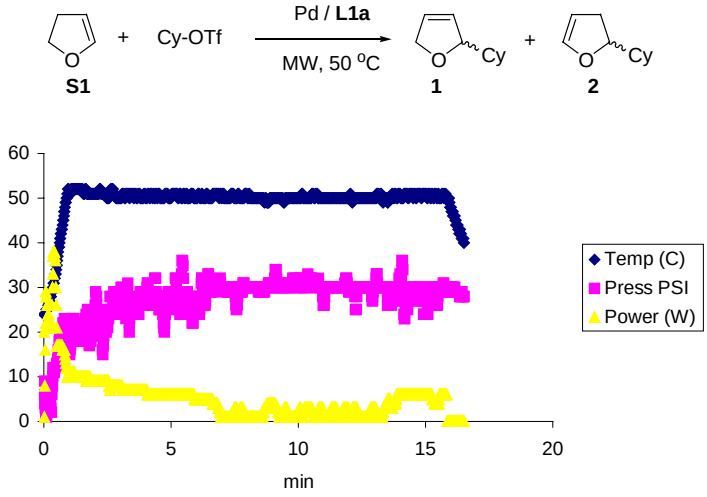
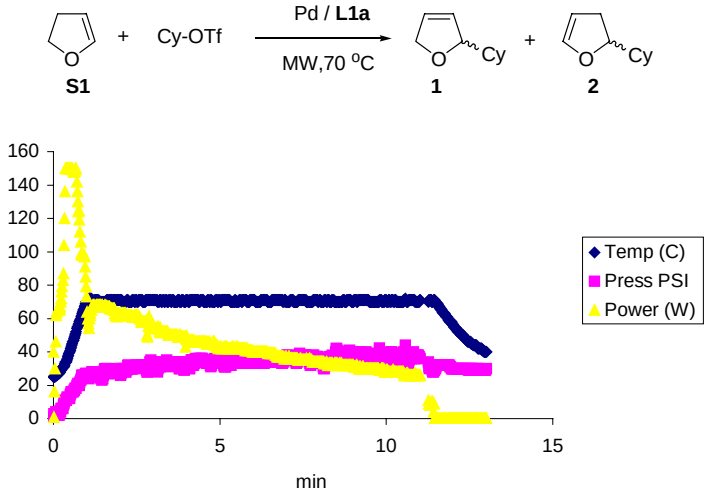
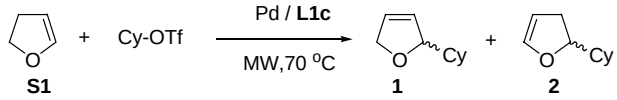


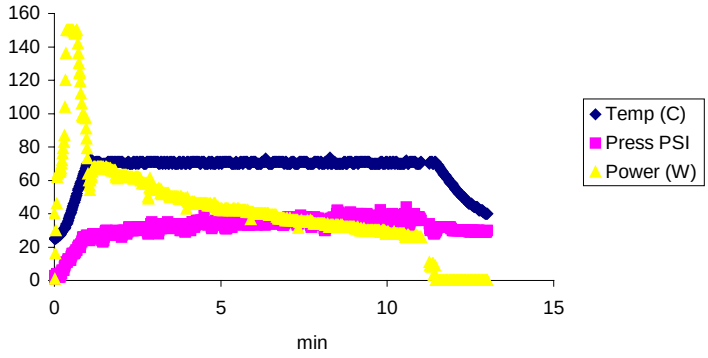
Table 8, entry 6.



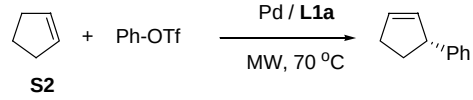
UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

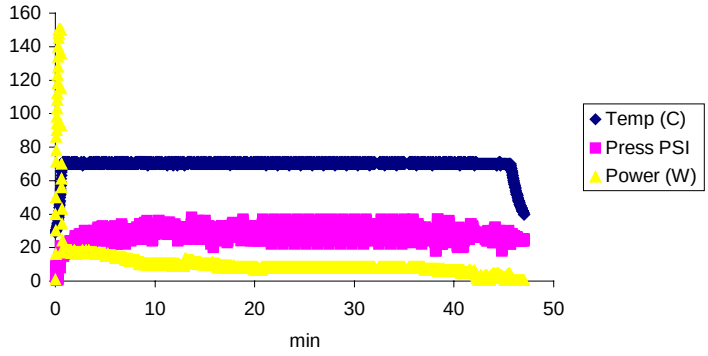
Table 8, entry 7.



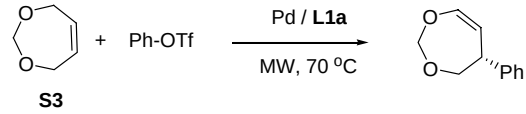


Scheme 4.





Org. Lett. **2005**, *7*, 5597 and *Chem. Eur. J.* **2007**, *13*, 3296



S3