

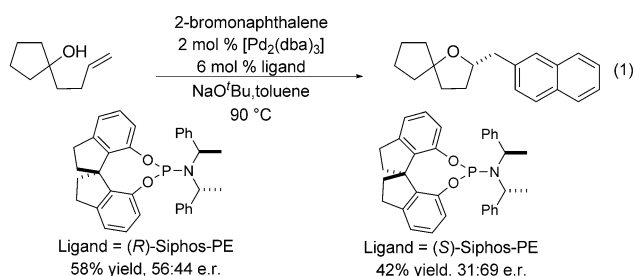
Development of Enantioselective Palladium-Catalyzed Alkene Carboalkoxylation Reactions for the Synthesis of Tetrahydrofurans

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Abstract: The Pd-catalyzed coupling of γ -hydroxyalkenes with aryl bromides affords enantiomerically enriched 2-(arylmethyl)tetrahydrofuran derivatives in good yield and up to 96:4 e.r. This transformation was achieved through the development of a new TADDOL/2-arylcyclohexanol-derived chiral phosphite ligand. The transformations are effective with an array of different aryl bromides, and can be used for the preparation of products bearing quaternary stereocenters.

Tetrahydrofurans bearing substituents at the C2 position are prominent moieties displayed in many biologically active compounds.^[1] As such, the asymmetric construction of tetrahydrofurans is an important challenge in organic synthesis that has attracted considerable attention over the years.^[2]

Our group has previously reported the development of Pd-catalyzed alkene carboalkoxylation reactions between γ -hydroxyalkenes and aryl or alkenyl halides for the construction of substituted tetrahydrofurans with high diastereoselectivity.^[3–5] These reactions effect formation of the heterocyclic ring along with a C–O bond, a C–C bond, and one or two stereocenters with high diastereoselectivity. However, the successful development of an enantioselective variant of these reactions has remained elusive.^[6–9] For example, although we have illustrated the chiral phosphoramidite ligands (*R*)- or (*S*)-Siphos-PE provided satisfactory results in related asymmetric alkene carboamination reactions of alkenes bearing pendant nitrogen nucleophiles,^[10] use of these ligands for the coupling of alcohol **1a** with 2-bromonaphthalene led to very low levels of asymmetric induction [Eq. (1)]. Similarly poor results were also obtained with a variety of other chiral phosphine and phosphoramidite ligands.



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Table 1: Initial TADDOL ligand screen.^[a]

Ligand	Yield	e.r.
L1	72% yield	81:19 e.r.
L2	75% yield	21:79 e.r.
L3	45% yield	75:25 e.r.
L4	40% yield	27:73 e.r.
L5	63% yield	85:15 e.r.
L6	80% yield	16:84 e.r.
L7	62% yield	88:12 e.r.
L8	61% yield	13:87 e.r.

[a] Conditions: 1.0 equiv **1a**, 1.8 equiv 2-bromonaphthalene, 1.8 equiv NaO^tBu , 2 mol % $[\text{Pd}_2(\text{dba})_3]$, 6 mol % chiral ligand, toluene (0.2 M), 90 °C, 12–14 h. Reactions were conducted on a 0.10 mmol scale. In all cases regioisomer **3** was formed in ca. 10% yield.

During the course of a rather extensive screen of chiral ligands, we encountered a promising lead result. As shown in Table 1, a chiral phosphite ligand **L1** derived from (*S,S*)-TADDOL and (–)-menthol, afforded the desired product **2a** in 72% yield with 81:19 e.r. We sought to further optimize this result through modification of this ligand, which can easily be prepared from a TADDOL and a chiral alcohol.^[11] We initially investigated changes to the TADDOL backbone, but replacement of the phenyl group or the *gem*-dimethyl groups with other substituents failed to provide improved results. As such, we turned our attention to the chiral alcohol component. Ligands **L2–L6** were synthesized from PCl_3 and either (*S,S*)- or (*R,R*)-TADDOL along with (–)-menthol, (+)-isopinocampheol, or (+)-2-phenylcyclohexanol. As shown in Table 1, similar enantiomeric ratios were obtained with each pair of ligand diastereomers (e.g., **L1** vs **L2**), although the absolute stereochemistry of the product was reversed. However, improved results were obtained with the 2-phenylcyclohexanol derivatives **L5** and **L6**. All transformations provided small amounts (ca. 5–10%) of side product **3a**, which likely derives from competing β -hydride elimination of an intermediate $[\text{L}_n\text{Pd}(\text{Ar})(\text{alkyl})]$ complex in the catalytic cycle.^[4b]

Since **L5** afforded the best enantioselectivity for this reaction, we decided to synthesize a variety of chiral 2-aryl-

substituted cyclohexanols to test the effect of the aryl group on asymmetric induction.^[12] After some experimentation we discovered that ligand **L7** provided slightly improved results (88:12 e.r.), and that use of 1,4-dioxane as solvent in place of toluene resulted in a further increase to 89:11 e.r. (Table 2, entry 2). Further modification of reaction conditions by changing solvent, base, or temperature did not lead to further improvement of selectivity. Similar results were obtained with the use of 2-iodonaphthalene in place of 2-bromonaphthalene.^[13]

Table 2: Enantioselective carboalkoxylation reactions.^[a]

Entry	R	R ¹ -X	Product	Yield [%] ^[b]	e.r.
1 ^[c]	(CH ₂) ₄ (1a)		2a	62	88:12
2	1a	4a	2a	58	89:11
3 ^[c]	1a		2a	59	87:13
4	1a		2b	54	82:18
5	H (1b)	4c	2c	23	58:42
6 ^[e]	Ph (1c)		2d	67	95:5
7 ^[c,d,e]	1c	4a	2d	60	96:4
8	1c		2e	64	92:8
9 ^{c,d}	1c	4c	2e	61	95:5
10	1c		2f	66	95:5
11	1c		2g	63	94:6
12 ^[c,d]	1c	4e	2g	54	95:5
13	1c		2h	71	93:7
14	1c		2i	18	79:21

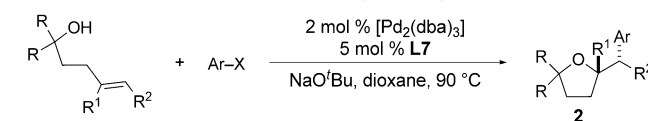
[a] Conditions: 1.0 equiv substrate, 1.8 equiv R¹-X, 1.8 equiv NaO^tBu, 2 mol% [Pd₂(dba)₃], 5 mol% **L7**, dioxane (0.2 M), 90 °C, 12–14 h. Reactions were conducted on a 0.20 mmol scale. Small amounts (ca. 10–15%) of regioisomeric products analogous to **3a** were also obtained in reactions of substrates **1a** and **1b**. Product **2a** could be easily separated from the regioisomer, whereas the regioisomer could not be separated from **2b** and the yield is for the mixture of products. [b] Isolated yield (average of two or more runs). [c] The reaction was conducted in toluene solvent. [d] 2 equiv of H₂O were added to the reaction mixture. [e] The reaction was conducted using 1.4 equiv Ar-X.

Having developed a suitable catalyst system and adequate reaction conditions we proceeded to explore the scope of this transformation. As shown in table 2, use of 4-penten-1-ol **1b** as a substrate resulted in poor yield and low selectivity (entry 5). However, the transformation of substrate **1c**, which contains a *gem*-diphenyl group at C1, proceeded with higher selectivity (entry 6, 95:5 e.r.) than that of **1a**. The reactions of **1c** were effective with several different aryl bromides, including electron-rich, electron-poor, and heteroaryl electrophiles. However, use of alkenyl bromide **4g** led to low yield and poor enantioselectivity.

Our prior studies on asymmetric Pd-catalyzed alkene carboamination reactions of *N*-allylureas revealed a surprising positive influence of the addition of water on selectivity.^[10b] Thus, we examined the addition of 2 equiv of water to reactions of **1c** with different electrophiles (Table 2, entries 7, 9, and 12). In all cases this led to a slight improvement in asymmetric induction. However, these improvements were less significant than those observed in the urea carboamination reactions.

To further explore the scope and potential utility of this method, we elected to examine reactions of substituted alkenes (Table 3). The coupling of substrate **1d** with 4-bromobenzophenone proceeded in good yield, but with poor enantioselectivity (entry 1). However, we were gratified to find that related substrate **1e**, which contains a *gem*-diphenyl group rather than a *gem*-dimethyl group at C1, was transformed in good yield and 95:5 e.r. (Table 3, entry 2). The

Table 3: Enantioselective formation of quaternary centers.^[a]



1d: R, R¹ = Me, R² = H; **1e:** R = Ph, R¹ = Me, R² = H;

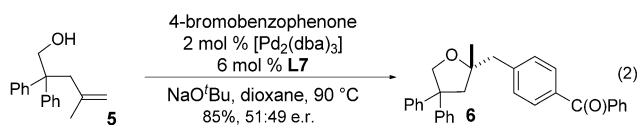
1f: R = Ph, R¹ = H, R² = Me; **1g:** R = Ph, R¹, R² = (CH₂)₄

Entry	Substrate	Ar-X	Product	Yield [%] ^[b]	e.r.
1	1d		2j	85	68:32
2	1e	4c	2k	85	95:5
3	1e		2l	94	96:4
4	1e		2m	85	93:7
5 ^[c]	1e		2n	39	87:13
6	1f	4c	–	no rxn	N/A
7	1g	4c	–	no rxn	N/A

[a] Conditions: 1.0 equiv substrate, 1.8 equiv Ar-X, 1.8 equiv NaO^tBu, 2 mol% [Pd₂(dba)₃], 5 mol% **L7**, dioxane (0.2 M), 90 °C, 12–14 h. Reactions were conducted on a 0.20 mmol scale. [b] Isolated yield (average of two or more runs). [c] The reaction proceeded to ca. 75% conversion.

reactions were effective with the 5-bromoindole derivative **4f** and 4-bromophenyl morpholine **4h**. However, use of 4-bromobenzonitrile as the electrophile led to the formation of product **2m** in a modest 39% yield and 87:13 e.r. Furthermore, substrates bearing internal alkenes such as **1f** and **1g** were unreactive under these conditions.

Finally, we briefly explored the reactivity of substrate **5**, which contains disubstitution at C2 rather than C1. As shown in [Eq. (2)], the coupling of **5** with 4-bromobenzophenone proceeded in good yield, but afforded product **6** in essentially racemic form. This further illustrates the importance of *gem*-disubstitution at the C1 position of the substrate.



In conclusion, we have developed a new enantioselective synthesis of tetrahydrofurans via asymmetric Pd-catalyzed carboalkoxylation reactions of γ -hydroxyalkenes with aryl bromides. The development and optimization of ligand **L7** was key to obtaining high levels of asymmetric induction. Our preliminary studies on the influence of TADDOL-based phosphite ligand structure on enantioselectivity indicate the structure of the phosphite alkoxy group (derived from a chiral alcohol) has the greatest influence on relative levels of asymmetric induction obtained with a structurally related series of ligands. Moreover (and perhaps not surprisingly), large changes in the alkoxy group have a larger impact on selectivity than fine-tuning of closely related structures. These results should help to guide future development of other chiral catalysts for heterocycle-forming alkene difunctionalization reactions.

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