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Pd-Catalyzed Enantio- and Regioselective Formation of Allylic Aryl Ethers

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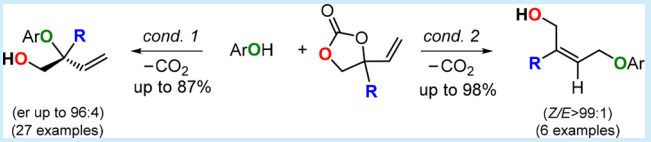
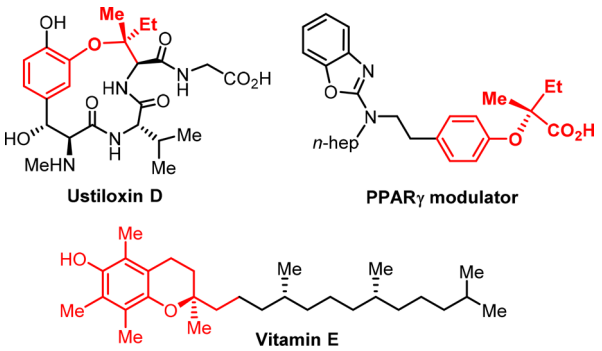
Supporting Information

ABSTRACT: A general methodology for the synthesis of enantioenriched tertiary allylic aryl ethers through Pd-catalyzed decarboxylative reactions of vinyl cyclic carbonates and phenols is presented. Switching of the regioselectivity toward the formation of linear products by a judicious choice of the ligand is also reported.



Chiral tertiary allylic aryl ethers are important building blocks in the synthesis of natural products and biologically active compounds such as Ustiloxin D, vitamin E, and products known as peroxisome proliferator-activated receptor γ (PPARγ) modulators (Scheme 1).[1−3] The asymmetric allylic substitution

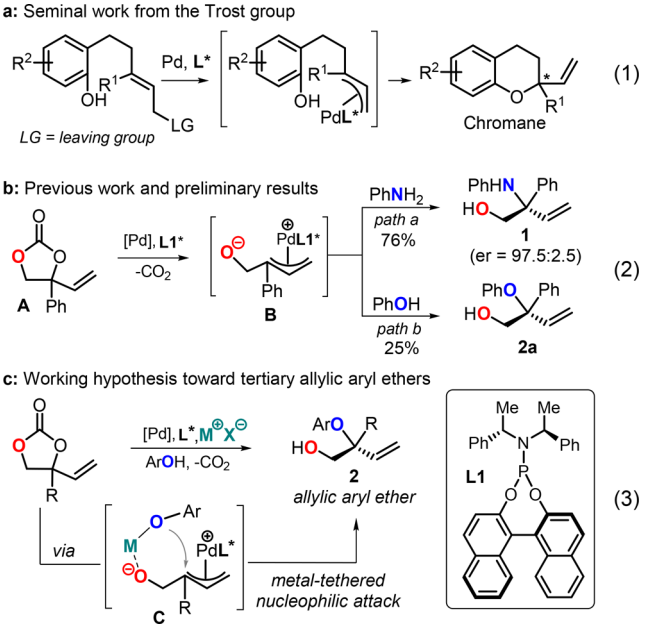
Scheme 1. Representatives of Natural Products or Pharmaceuticals Featuring Chiral Tertiary Aryl Ether Fragments



with phenols as nucleophiles represents the most versatile and straightforward method toward the synthesis of sterically hindered tertiary allylic aryl ethers. The synthesis of enantioenriched secondary allylic aryl ethers through phenol nucleophilic substitution has been well-established.[4] However, the regioselective synthesis of sterically congested tertiary allylic aryl ethers featuring a tertiary carbon stereocenter through allylic substitution is still a huge challenge.[5−7] Seminal work from Trost illustrated the use of an intramolecular strategy[2a−d] to give rise to the desired aryl ethers, avoiding the formation of regioisomers, though only focused on the preparation of chromanes and with limitations in substitution diversity (Scheme 2, eq 1).

Transition-metal-catalyzed decarboxylative transformation of vinyl cyclic carbonates has proven to be a versatile method toward the formation of various allylic scaffolds.[8,9] Our group

Scheme 2. Pd-Catalyzed Asymmetric Synthesis of Allylic Scaffolds Featuring Tertiary Carbon Stereocenters



recently reported the first regio- and enantioselective synthesis of α,α-disubstituted allylic *N*-arylamines based on a Pd-catalyzed conversion of cyclic carbonate **A** through a zwitterionic intermediate **B** in the presence of phosphoramidite ligand **L1** (Scheme 2, eq 2, path a, **L1** inset in Scheme 2).[10] We expected that the synthesis of enantioenriched tertiary aryl ether **2a** would be feasible by changing the nucleophile from aniline to phenol under the similar reaction conditions; thus, the reaction of carbonate **A** and phenol was performed, but unfortunately, only

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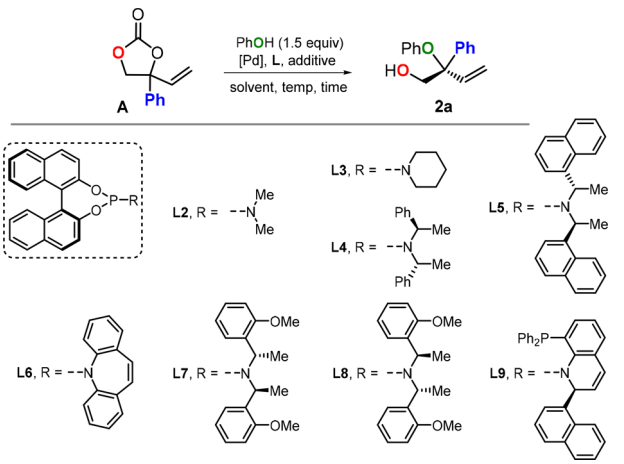
25% of the aryl ether **2a** was isolated. Notably, substantial amount of undesired linear product (Scheme 2, eq 2, path b) was formed. Considering the strong interaction between oxygen and metal cationic species,[11] we envisaged that, in the presence of a phosphoramidite ligand, the presence of suitable metal cations would help to direct the nucleophilic attack toward the internal carbon center of the Pd-allyl intermediate **C** rather than the less hindered terminal one (Scheme 2, eq 3).[12]

In order to check our working hypothesis, we chose the reaction of cyclic carbonate **A** and phenol as a model reaction (Table 1). Cs_2CO_3 was first examined as the metal cation source with the use of **L1** (inset in Scheme 2).[13] We were pleased to find that the addition of three equivalents of Cs_2CO_3 led to appreciable product formation (**2a**, 56% yield) with an *er* of 87:13 (Table 1, entries 1−3). The control reaction in the absence of Cs_2CO_3 only gave rise to 10% of product, suggesting the crucial role of the Cs salt (Table 1, entry 4). The reactions performed at lower concentration or the use of other solvents/potassium salts[13] did not improve the results significantly (Table 1, entries 5−9). No reaction was observed in the presence of DBU suggesting that basicity is probably not a key parameter (Table 1, entry 10). The use of CsF (Table 1, entry 11) showed a similar outcome (cf., entry 3) further confirming the key role of the Cs cation in this reaction.[13] Lowering the reaction temperature to 0 °C significantly improved the yield (76%) and enantioselectivity (Table 1, entries 12−13, *er* = 94.5:5.5) despite the requirement of longer reaction times. The attempt to improve the enantioselectivity with other phosphoramidite ligands **L2**−**L9** was not successful (Table 1, entries 14−21). A lower amount of phenol (Table 1, entry 22) or catalyst loading (Table 1, entry 23) gave slightly inferior results. Performing the reaction under diluted conditions gave **2a** in 85% yield with an *er* of 95:5 (Table 1, entry 24), and these optimized reaction conditions were then applied to investigate the scope of these allylic etherifications.

Various substituted phenols proved to be suitable reaction partners to produce a range of allylic tertiary aryl ethers **2** (Scheme 3) in good yields and appreciable enantioinduction (generally *er* > 90:10). Various *para*-substitutions on the phenol reagents including electron-withdrawing and -donating groups were endorsed, and *meta*- (**2i**−**2k**, **2m**, **2n**) and *ortho*-substituted

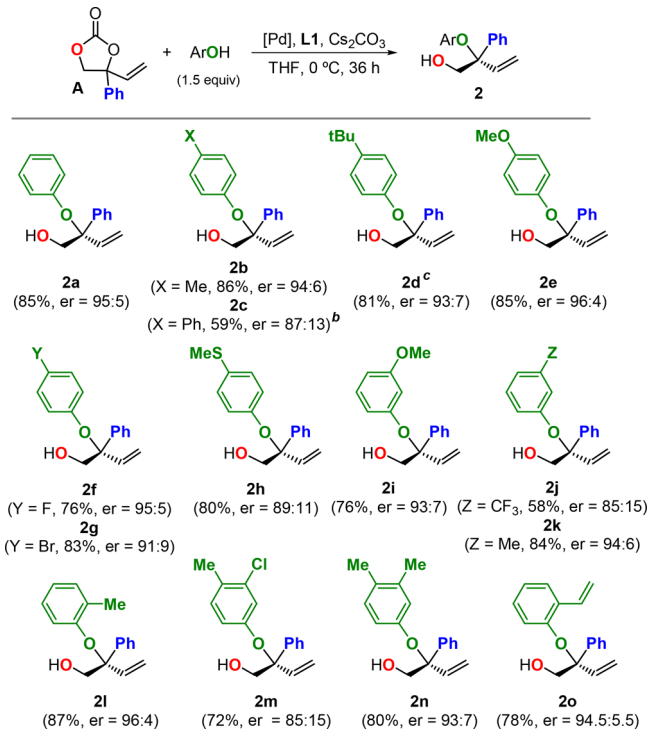
Table 1. Selected Data for the Optimization of the Reaction Conditions Towards the Enantioenriched Aryl Ether 2a[a]



entry	additive (equiv)	L, solv	temp (°C)	*t* (h)	**2a** (%)[b]	*er*[c]
1	Cs_2CO_3 (1)	**L1**, THF	25	12	19 (53)	67.5:32.5
2	Cs_2CO_3 (2)	**L1**, THF	25	12	44 (35)	76:24
3	Cs_2CO_3 (3)	**L1**, THF	25	12	56 (18)	87:13
4		**L1**, THF	25	12	10	
5[d]	Cs_2CO_3 (3)	**L1**, THF	25	12	53	88.5:11.5
6	Cs_2CO_3 (3)	**L1**, DCM	25	12	0	
7	Cs_2CO_3 (3)	**L1**, Tol	25	12	0	
8	K_3PO_4 (3)	**L1**, THF	25	12	0 (75)	
9	K_2CO_3 (3)	**L1**, THF	25	12	36 (59)	74:26
10	DBU (3)	**L1**, THF	25	12	0	
11	CsF (3)	**L1**, THF	25	12	50	74.5:25.5
12	Cs_2CO_3 (3)	**L1**, THF	10	12	73	91:9
13	Cs_2CO_3 (3)	**L1**, THF	0	36	76 (10)	94.5:5.5
14	Cs_2CO_3 (3)	**L2**, THF	0	36	0	
15	Cs_2CO_3 (3)	**L3**, THF	0	36	0	
16	Cs_2CO_3 (3)	**L4**, THF	0	36	65	86:14
17	Cs_2CO_3 (3)	**L5**, THF	0	36	81	78:22
18	Cs_2CO_3 (3)	**L6**, THF	0	36	0	
19	Cs_2CO_3 (3)	**L7**, THF	0	36	88	85:15
20	Cs_2CO_3 (3)	**L8**, THF	0	36	85	23:77
21	Cs_2CO_3 (3)	**L9**, THF	0	36	0	
22[e]	Cs_2CO_3 (3)	**L1**, THF	0	36	74	94:6
23[f]	Cs_2CO_3 (3)	**L1**, THF	0	36	68	93:7
24[d]	Cs_2CO_3 (3)	**L1**, THF	0	36	85	95:5

[a]Reaction conditions unless otherwise stated: carbonate **A** (0.20 mmol, 1 equiv), phenol (1.5 equiv), $Pd_2(dba)_3$·$CHCl_3$ (2 mol %), ligand **L** (8 mol %), THF (0.20 mL), open to air. [b]Isolated yield of **2a**; in brackets, the NMR yield of the linear product. [c]Determined by HPLC. [d]Using 0.30 mL of THF. [e]Phenol (1.2 equiv). [f]$Pd_2(dba)_3$·$CHCl_3$ (1.25 mol %), ligand **L1** (5 mol %).

Scheme 3. Scope in Phenols To Produce Aryl Ethers 2[a]



[a]Reaction conditions unless stated otherwise: carbonate **A** (0.20 mmol), phenol partner (1.5 equiv), THF (0.30 mL), $Pd_2(dba)_3$·$CHCl_3$ (2 mol %), **L1** (8 mol %), Cs_2CO_3 (3 equiv), 0 °C, 36 h. Isolated yields are reported. [b]60 h. [c]45 h.

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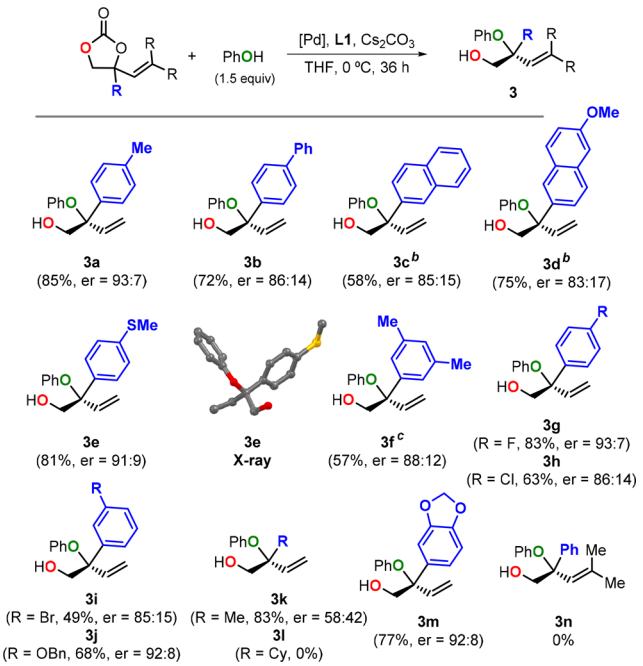
phenols (**2l**, **2o**) also showed good reactivity. It is worth noting that the introduction of two vinyl fragments in the aryl ether product is feasible as exemplified by the successful isolation of product **2o**; this kind of product has potential in the synthesis of highly functionalized enantioenriched chromanes through olefin metathesis reactions.[14]

In order to further amplify the scope of the reaction, we then systematically varied the cyclic carbonates (Scheme 4) producing

Scheme 4. Scope in Cyclic Carbonates To Produce Allylic Aryl Ethers 3[a]

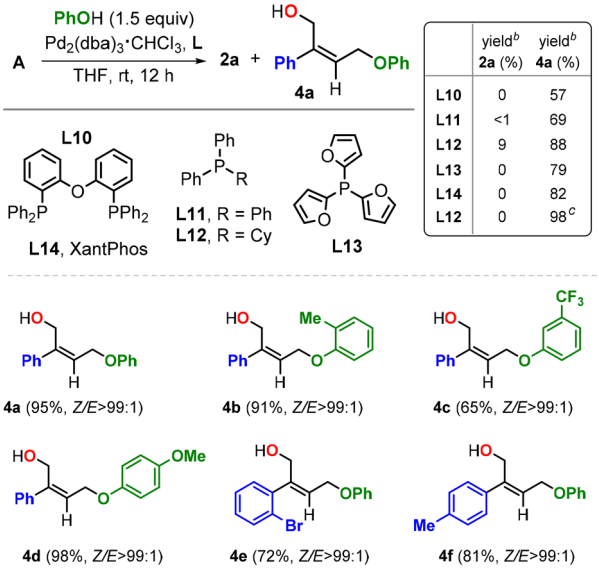


[a]Reaction conditions unless stated otherwise: carbonate (0.20 mmol), phenol (1.5 equiv), THF (0.30 mL), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol %), **L1** (8 mol %), Cs_2CO_3 (3 equiv), 0 °C, 36 h. Isolated yields are reported. [b]60 h. [c]Using 0.20 mL of THF.

allylic aryl ethers **3**. Various aromatic substituents in the vinyl cyclic carbonate, including those having *para*- or *meta*-substitutions, were tolerated. The sulfur-containing substrate allowed to produce compound **3e** without noticeable deactivation of the palladium catalyst (see also product **2h**).[15] The aryl ether with bulky naphthyl group (**3c**, **3d**) could be obtained through requiring longer reaction times. The methyl-substituted cyclic carbonate also proved to be reactive albeit with lower enantioselectivity (**3k**), while the bulky cyclohexyl-substituted carbonate showed no reactivity. The installation of a heterocycle in the aryl ether was feasible (**3m**),[16] whereas attempts to install substituents on the vinyl group failed (**3n**). The absolute configuration of these tertiary aryl ethers (*S*) was deduced by the X-ray diffraction of the product **3e** (Scheme 4).

Encouraged by our previous success in (*Z*)-stereoselective synthesis of linear allylic amines,[9a] we also probed the regio- and stereoselective synthesis of highly functionalized linear allylic aryl ethers through a six-membered palladacyclic intermediate[9a] in the presence of suitable ligand. We first chose the reaction of phenol and cyclic carbonate **A** in THF at rt as a model reaction (Scheme 5). The use of **L10** led to an appreciable yield of the linear product **4a** (57%), while the branched product **2a** was not observed (Table in Scheme 5). Further screening of ligands

Scheme 5. (*Z*)-Stereoselective Formation of the Linear Allylic Aryl Ethers 4[a]



	yield[b] 2a (%)	yield[b] 4a (%)
L10	0	57
L11	<1	69
L12	9	88
L13	0	79
L14	0	82
L12	0	98[c]

[a]Reaction conditions for the optimization toward linear aryl ether **4a**: carbonate **A** (0.20 mmol), phenol (1.5 equiv), THF (0.20 mL), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol %), **L** (4 mol % for **L10** and **L14**; 8 mol % for **L11**–**L13**), rt, 12 h. [b]Determined by ^{1}H NMR. [c]Cs_2CO_3 (3 equiv) was added. Reaction conditions for **4a**–**4f**: carbonate (0.20 mmol), phenol (1.5 equiv), THF (0.20 mL), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol %), **L12** (8 mol), Cs_2CO_3 (3 equiv), rt, 12 h. Isolated yields are reported.

(**L11**–**L14**) suggested that **L12** is the best ligand for the selective formation of linear allylic aryl ether **4a** (88% yield). In contrast, only a small amount of the branched product **2a** (<9%) was observed suggesting that a judicious choice of the ligand is crucial to control the regioselectivity. Interestingly, the formation of the branched product was further suppressed by the addition of Cs_2CO_3, and the yield of the linear product was improved to 98% indicating a subtle role of Cs_2CO_3 in this ligand-governed process.[17] It is worth noting that the use of ligands **L10**–**L14** gave rise to product **4a** with excellent stereoselectivity (*Z*/*E* > 99:1), while the stereoselectivity in linear allylic amine formation strongly depended on the ligand utilized indicating the different reactivity of anilines and phenols.[9a] With the conditions optimized, the formation of linear allylic aryl ethers **4b**–**f** was then investigated (Scheme 5) and showed in all cases good yields and excellent stereoselectivity. The (*Z*)-configuration of all the linear products was supported by ^{1}H-selective 1D NOESY NMR analysis (see SI for details).

In summary, we here present a general method for the synthesis of otherwise synthetically challenging enantioenriched tertiary allylic aryl ethers through Pd-catalyzed decarboxylative reaction of vinyl cyclic carbonate and phenol type nucleophiles. The addition of Cs_2CO_3 proved to be crucial toward the formation of sterically hindered branched products. A judicious choice of the ligand switches the regioselectivity toward the (*Z*)-stereoselective formation of highly functionalized linear products. This mild protocol is characterized by a fair scope in reaction partners, overall good yields and appreciable enantioinduction.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03247.

Experimental details and spectra for new products (PDF)

Accession Codes

CCDC 1585738 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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‡These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(5) To the best of our knowledge, there is only one known example of the asymmetric synthesis of tertiary allylic aryl ethers through phenol nucleophilic substitution. However, this protocol has quite limited scope, see ref 2a. Controlling the regioselectivity in allylic substitution with phenols is challenging, see: (a) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.

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(12) Hydrogen bond assistance should also be considered, please refer to ref 9a and ref 10.

(13) Alkali metal cations have strong affinity for oxygen donors, see for example ref 11.

(14) Enantioenriched chromanes are important fragments in many drugs and natural products such as vitamin E, Clusifoliol, Siccanin, and Calanolide A; see ref 2.

(15) The S-containing substrates have the potential to poison the Pd-catalyst and typically require higher reaction temperatures, see ref 9f.

(16) Enantioenriched compounds with 1,3-benzodioxole fragments are of interest in pharmaceutical development: Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem.* **1992**, *35*, 3081.

(17) In the presence of **L12**, the likely formation of the more nucleophilic CsOPh species further facilitates catalytic turnover.

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