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# Catalytic Asymmetric Synthesis of Allylic Aryl Ethers

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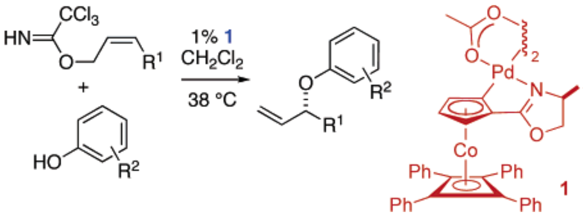
## ABSTRACT



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**The reaction of trichloroacetimidate derivatives of (*Z*)-2-alken-1-ols with phenol nucleophiles in the presence of the palladium(II) catalyst [COP-OAc]$_2$ provides 3-aryloxy-1-alkenes in high yields and high enantiomeric purity (typically 63–90% yield and 90–97% ee). The reaction is exemplified by 20 examples. The method employs 1 mol % of the commercially available catalysts (*S*)- or (*R*)-[COPOAc]$_2$, produces the branched isomer with unprecedented regioselectivity, and is compatible with the presence of base-labile functionality in either reactant.**

Enantioenriched chiral allylic aryl ethers are valuable building blocks for asymmetric synthesis. In recent years, useful catalytic asymmetric methods for their construction from phenols (or phenoxides) and prochiral allylic precursors have been described that employ Pd,[1] Ru,[2] or Ir[3] complexes.[4] Allylic substitutions of 2-alken-1-ol precursors brought about by Pd(0) or Ru(II) complexes afford branched 3-aryloxy-1-alkene products in generally high enantioselectivity, although yields can be diminished by competitive formation of achiral linear products.[1,2] The best combination of high enantioselectivity, yield, and branched/linear ratios is achieved in the Ir(I)-catalyzed reactions developed by Hartwig and coworkers.[3] The need to use phenoxides as nucleophiles, however, provides some limitation to the iridium-catalyzed method. In this communication, we report a broadly applicable enantioselective synthesis of chiral 3-aryloxy-1-alkenes that employs Pd(II) catalysts, proceeds with heretofore unprecedented branched/linear ratios, and tolerates base-labile functionality.

Recently, we disclosed that trichloroacetimidate derivatives of prochiral (*Z*)-allylic alcohols are transformed in high enantioselectivity to branched allylic esters when exposed to carboxylic acids in the presence of the palladium(II) catalyst [COP-OAc]$_2$ (**1**, Figure 1).[5,6] In this reaction, the catalyst is believed to activate the carbon−carbon $\pi$-bond

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(1) Reactions with phenols in the presence of Pd(0) complexes: (a) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161−166. (b) Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014−7024. (c) Trost, B. M.; Crawley, M. L. *Chem.−Eur. J.* **2004**, *10*, 2237−2252. (d) Trost, B. M.; Guzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396−10415. (e) Trost, B. M.; Tsui, H. C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534−3535. (f) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545−4554. (g) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815−816. (h) Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A: Chem.* **1997**, *122*, 91−93.

(2) Reactions with phenols in the presence of Ru(II) complexes and K$_2$CO$_3$: Mbaye, M. D.; Renaud, J.; Demerseman, B.; Bruneau, C. *Chem. Commun.* **2004**, 1870−1871.

(3) Reactions with phenoxides in the presence of Ir(I) complexes: (a) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770−11771. (b) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093−1096. (c) Kiener, C. A.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272−14273. (d) Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426−3427.

(4) A number of useful catalytic asymmetric methods for the synthesis of allylic alkyl ethers have been developed also; representative examples include: (a) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204−6207. (b) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794−4797. (c) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702−12703.

(5) Kirsch, S.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866−2867.

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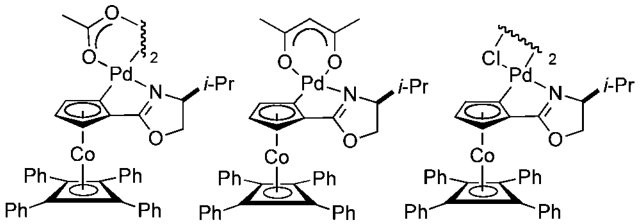


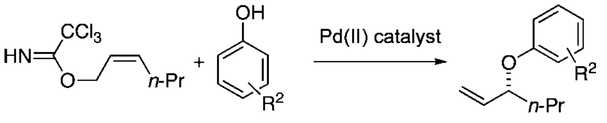
**1** [(*S*)-COP-OAc]$_2$ **2** (*S*)-COP-acac **3** [(*S*)-COP-Cl]$_2$

**Figure 1.** Palladium(II) catalysts examined in the allylic etherification.

for attack by the external oxygen nucleophile, with the trichloroacetimidate functional group both templating the catalyst to the double bond and serving as a leaving group. We report herein the [COP-OAc]$_2$-catalyzed reaction of phenols with (*Z*)-allylic trichloroacetimidates to provide branched allylic aryl ethers in high enantiopurity and yield under mild reaction conditions.

The reaction of (*Z*)-allylic trichloroacetimidate **4a**[7,8] with phenol to give enantioenriched allylic phenyl ether **5a** (R$^2$ = H, eq 1) was initially examined using several palladium(II) complexes (Scheme 1). Of the catalysts screened, [(*S*)-COP-OAc]$_2$ (**1**) and (*S*)-COP-acac (**2**) proved to be the most effective, giving (*R*)-**5a** in 92% ee and 86−90% yield; the chloride-bridged dimer [(*S*)-COP-Cl]$_2$ (**3**) showed comparable enantiomeric selectivity but an inferior catalytic rate.[6,9] Because both enantiomers of [COP-OAc]$_2$ are available commercially, this catalyst was chosen for additional studies.[10,11]

**Scheme 1**



**4a** **5a–j**

We next examined other reaction variables and the scope of the reaction of (*Z*)-allylic trichloroacetimidate **4a** with a range of phenols. The nature of the solvent had a considerable effect on the catalytic rate, with the yield of (*R*)-**5a** produced under otherwise identical conditions decreasing in the following order: $CH_2Cl_2$ (85%) > PhMe (38%) > THF (26%) > MeCN (5%) > DMSO (0%).[12] Selecting $CH_2Cl_2$ as the optimal solvent, we explored the scope of the reaction of various phenols with allylic imidate **4a** at 38 °C in the presence of 1 mol % of [(*S*)-COP-OAc]$_2$ (Table 1). Reactions with phenols containing electron-donating or mild electron-withdrawing groups provided the corresponding allylic aryl ethers **5a**−**e** in 90−92% ee and 63−96% yield (entries 1−5).[13] Successful reaction of trichloroacetimidate **4a** with 2-acetoxy-, 3-acetoxy-, and 4-acetoxyphenol to provide allylic ethers **5f**−**h** in 90−94% ee and 93−95% yield demonstrates the compatibility of this synthetic method with base-labile functionality (entries 6−8). The reaction of imidate **4a** with 3-hydroxybenzaldehyde to give allylic ether **5i** in 94% ee and 90% yield also highlights the mildness of this method (entry 9). Whereas 3-nitrophenol was a competent nucleophile, providing allylic ether **5j** in 90% yield, albeit with reduced enantioselectivity (65% ee, entry 10),[14] 2-nitrophenol, 4-nitrophenol, 2-cyanophenol, and 2-allylphenol failed to furnish the corresponding allylic ethers.[15] The *R* absolute configuration of allylic ethers **5a**−**h** was established by direct comparison with authentic samples.[16,17]

**Table 1.** [(*S*)-COP-OAc]$_2$-Catalyzed Asymmetric Synthesis of Allylic Aryl Ethers **5** from Allylic Trichloroacetimidate **4a**$^{a,b}$

| entry | R$^2$ | time [h] | 5 | yield [%]$^c$ | ee [%]$^d$ (abs configuration) |
|---|---|---|---|---|---|
| 1 | H | 36 | **5a** | 86 | 92 (*R*) |
| 2 | 4-Me | 96 | **5b** | 79 | 90 (*R*) |
| 3 | 4-OMe | 96 | **5c** | 63 | 90 (*R*) |
| 4 | 4-Cl | 36 | **5d** | 96 | 91 (*R*) |
| 5 | 2-Br | 24 | **5e** | 87 | 90 (*R*) |
| 6 | 4-OAc | 36 | **5f** | 93 | 94 (*R*) |
| 7 | 2-OAc | 36 | **5g** | 90 | 90 (*R*) |
| 8 | 3-OAc | 36 | **5h** | 91 | 92 (*R*) |
| 9$^e$ | 3-CHO | 72 | **5i** | 90 | 94 |
| 10$^e$ | 3-NO$_2$ | 72 | **5j** | 90 | 65 |

[a] Conditions: 0.41 mmol of **4a**, 1.0 mol % of [(*S*)-COP-OAc]$_2$, 1.23 mmol (3 equiv) of ArOH, $CH_2Cl_2$ (1.0 M), 38 °C. [b] % yields and % ee's are an average of reactions run in triplicate. [c] Yield of pure product after column chromatography. [d] Determined by SFC or HPLC analysis using a chiral stationary phase. [e] 2 equiv of ArOH.

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(6) (a) Anderson, C. E.; Kirsch, S. F.; Overman, L. E.; Richards, C. J.; Watson, M. P. *Org. Synth.* **2007**, *84*, 148−155. (b) Anderson, C. E.; Overman, L. E.; Richards, C. J.; Watson, M. P.; White, N. *Org. Synth.* **2007**, *84*, 139−147. (c) Stevens, A. M.; Richards, C. J. *Organometallics* **1999**, *18*, 1346−1348.

(7) Allylic trichloroacetimidates used in this study were prepared by the reaction of allylic alcohols with 1 equiv of trichloroacetonitrile (0.2 M in dichloromethane) in the presence of 0.06 equiv of DBU at room temperature.[8]

(8) (a) Numata, M.; Sugimoto, M.; Koike, K.; Ogawa, T. *Carbohydr. Res.* **1987**, *163*, 209−225. (b) Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Fukuda, Y.; Isobe, M. *Tetrahedron* **2001**, *57*, 3875−3883. For a discussion of various ways to prepare allylic trichloroacetimidates, see: Overman, L. E.; Carpenter, N. E. The Allylic Trichloroacetimidate Rearrangement. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: Hoboken, NJ, 2005; Vol. 66, pp 1−107.

(9) Using 1 mol % of the dimeric catalysts **1** or **3** (or 2 mol % of monomeric catalyst **2**) and identical reaction conditions (3 equiv of phenol, 38 °C, [**4a**] = 1 M in $CH_2Cl_2$, 36 h). Enantiomeric excess was determined by HPLC analysis; see Supporting Information for details.

(10) Both enantiomers of [COP-OAc]$_2$ are available from Aldrich Chemical Co. The planar chiral fragment of enantiomer **1** [(*S*)-COP-OAc]$_2$ has *Rp* absolute configuration;[10] thus, more precisely, **1** would be called [(*Rp*,*S*)-COP-OAc]$_2$. *ent*-**1**, which we have termed [(*R*)-COP-OAc]$_2$, has the *Sp*,*R* absolute configuration.

(11) The convention of Schlögl is used: Schlögl, K. *Top. Stereochem.* **1967**, *1*, 39−91.

(12) Reaction conditions: 3 equiv of phenol, 38 °C, [**4a**] = 1 M, 36 h; all reactions provided (*R*)-**5a** in high enantiopurity (92−94% ee).

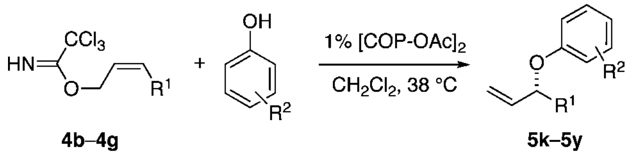
(13) Identical reaction of imidate **4a** with phenol in the presence of [(*R*)-COP-OAc]$_2$ provided *ent*-**5a** in 86% yield and 92% enantiopurity.

(14) The enantiopurity of **5j** decreased to 38% ee when 3 equiv of 3-nitrophenol was employed.

A salient feature of this catalytic asymmetric synthesis of 3-aryloxy-1-alkenes from 2-alken-1-ol precursors is the exceptionally high preference for forming the branched allylic ether product. For example, the corresponding (*Z*)- or (*E*)-1-phenoxy-2-alkenes were not seen by $^1$H NMR analysis of crude reaction products. Moreover, capillary GC analysis showed the branched/linear ratio in the formation of 3-phenoxy-1-hexene (**5a**) to be at least 800:1.[18,19]

The scope of the [COP-OAc]$_2$-catalyzed synthesis of allylic phenyl ethers was explored further by reactions of four diversely functionalized allylic trichloroacetimidates **4b**−**e** with various phenols (Table 2). These reactions gave the corresponding allylic ethers **5k**−**q** and **5s**−**v** in 90−97% ee and 70−97% yield (entries 1−7 and 9−12). 1-Naphthol was also a competent nucleophile, providing allylic ether **5r** in 98% ee and 61% yield (entry 8). Reactions of imidate **4f** ($R^1 = CH_2CH_2OAc$) with phenol and 4-acetoxyphenol gave the corresponding allylic ethers **5w** and **5x** in 92−96% ee and 91−93% yield, again highlighting the compatibility of this method with base-labile functionality (entries 13 and 14). This catalytic substitution reaction takes place at a practical rate only when the $\gamma$-substituent of the allylic imidate is unbranched; for example, allylic ether **5y** was obtained in 30% yield after 96 h (entry 15). Reactions of the *E* stereoisomer of trichloroacetimidate **4a** with phenol in the presence of 1 mol % of [(*S*)-COP-OAc]$_2$ under standard reaction conditions provided (*S*)-**5a** in 90% ee and 32% yield, the major side product being the branched allylic trichloroacetamide product.

**Table 2.** Scope of the [(*S*)-COP-OAc]$_2$-Catalyzed Asymmetric Synthesis of Allylic Aryl Ethers with Precursors Containing Additional Functionality[a,b]



| entry | R$^1$ | R$^2$ | time [h] | **5** | yield [%][c] | ee [%][d,e] |
|---|---|---|---|---|---|---|
| 1 | $CH_2OTBDPS$ (**4c**) | 4-OMe | 72 | **5k** | 82 | 97 (*S*)[f] |
| 2 | $CH_2OTBS$ (**4c**) | H | 72 | **5l** | 81 | 96 |
| 3 | **4c** | 4-Me | 96 | **5m** | 70 | 97 |
| 4 | **4c** | 4-Cl | 36 | **5n** | 90 | 96 |
| 5 | **4c** | 4-OAc | 36 | **5o** | 97 | 96 |
| 6 | **4c** | 2,6-F | 36 | **5p** | 97 | 90 |
| 7 | **4c** | 3-OMe | 96 | **5q** | 80 | 97 |
| 8 | **4c** | 1-naphtyl | 72 | **5r** | 61 | 98 |
| 9 | $CH_2CH_2OTBS$ (**4d**) | H | 24 | **5s** | 87 | 90 |
| 10 | **4d** | 4-OAc | 24 | **5t** | 97 | 92 |
| 11 | $CH_2CH_2Ph$ (**4e**) | H | 36 | **5u** | 91 | 95 |
| 12 | **4e** | 4-OAc | 36 | **5v** | 97 | 92 |
| 13 | $CH_2CH_2OAc$ (**4f**) | H | 72 | **5w** | 91 | 92 |
| 14 | **4f** | 4-OAc | 48 | **5x** | 93 | 96 |
| 15 | $C_6H_{11}$ (**4g**) | 4-OAc | 96 | **5y** | 30 | 90 |

[a] Conditions: 0.41 mmol of **4**, 1 mol % of [(*S*)-COP-OAc]$_2$, 1.23 mmol (3 equiv) of ArOH, $CH_2Cl_2$ (1.0 M), 38 °C. [b] % yields and % ee's are an average of reactions run in triplicate. [c] Yield of pure product after column chromatography. [d] Determined by SFC or HPLC analysis using a chiral stationary phase. [e] For entries 1−10, % ee was determined after cleavage of the silyl protecting group. [f] Absolute configuration was determined by optical rotation of the product formed after ceric ammonium nitrate deprotection.

In summary, a mild catalytic asymmetric etherification is described that uses a palladium(II) catalyst and phenol nucleophiles to construct 3-aryloxy-1-alkenes in high enantiopurity and high yield. Attractive features of the method include the following: only 1 mol % of the commercially available catalysts (*S*)- or (*R*)-[COP-OAc]$_2$ is used; products are produced in high yields and high % ees; the branched product is produced with unprecedented regioselectivity; and the method is compatible with the presence of base-labile functionality in either reactant.

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**Supporting Information Available:** Representative experimental procedures, copies of SFC and HPLC traces used to determine enantiopurity, $^1$H and $^{13}$C NMR spectra of new compounds, and details of experiments to establish absolute configuration of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) When trichloroacetimidate **4a** (1 M) was allowed to react with 3 equiv of phenol and 1 equiv of 2-nitrophenol (or 4-nitrophenol, 2-cyanophenol, or 2-allylphenol) in the presence of 1 mol % of [(*S*)-COP-OAc]$_2$ in $CH_2Cl_2$ at 38 °C for 72 h, the corresponding allylic ether **5a** was obtained in low yields. These experiments and NMR studies of catalyst compositions show that these 2-substituted phenols deactivate the catalyst.

(16) Prepared from (*S*)-1-hexyn-3-ol by Mitsunobu reaction with the phenol followed by Lindlar hydrogenation.[17]

(17) (a) Landor, S. R.; Miller, B. J.; Tatchell, A. R. *J. Chem. Soc. (C)* **1971**, 2339−2341. (b) Anand, R. V.; Baktharaman, S.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 3356−3359.

(18) The limits of detection of the branched products by this method were 0.01%.

(19) Studies to optimize this transformation are underway.