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# Catalytic Enantioselective Carbon–Oxygen Bond Formation: Phosphine-Catalyzed Synthesis of Benzylic Ethers via the Oxidation of Benzylic C–H Bonds

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Supporting Information

**ABSTRACT:** Benzylic alcohols and ethers are common subunits in bioactive molecules, as well as useful intermediates in organic chemistry. In this Communication, we describe a new approach to the enantioselective synthesis of benzylic ethers through the chiral phosphine-catalyzed coupling of two readily available partners, γ-aryl-substituted alkynoates and alcohols, under mild conditions. In this process, the alkynoate partner undergoes an internal redox reaction. Specifically, the benzylic position is oxidized with good enantioselectivity, and the alkyne is reduced to the alkene.

Enantioenriched benzylic ethers are valuable targets in chemistry, both as endpoints[1] and as intermediates in the synthesis of other useful families of molecules through simple deprotection,[2] coupling reactions,[3] and the like. A variety of strategies for the generation of chiral benzylic ethers have been described, including catalytic enantioselective processes. In the latter cases, the benzylic ether is typically produced from an enantioenriched benzylic alcohol, which is most often synthesized from a carbonyl compound via asymmetric hydrogenation or nucleophilic addition (Figure 1).[4] The enantioselective oxidation of C–H bonds provides an alternative approach to chiral benzylic alcohols.[5]

In this Communication, we describe a distinct, direct method for the catalytic asymmetric synthesis of benzylic ethers. Specifically, we demonstrate that, with the aid of a chiral phosphine catalyst, γ-aryl alkynoates can be coupled with alcohols to

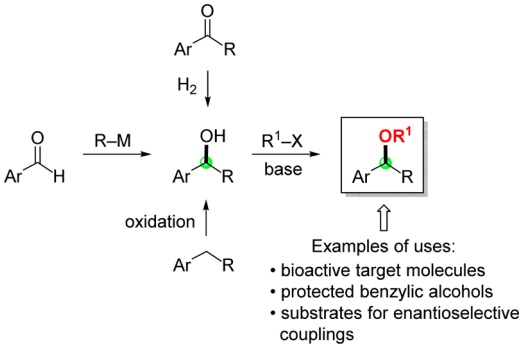
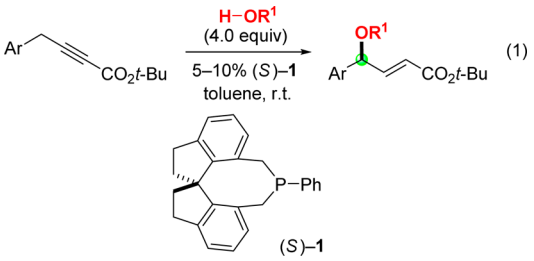
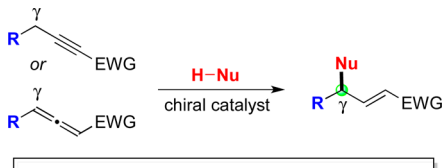



**Figure 1.** Enantioenriched benzylic ethers: common catalytic asymmetric methods for their synthesis via benzylic alcohols and examples of their significance.




generate benzylic ethers in good enantiomeric excess under notably simple and mild conditions (eq 1). If desired, the resulting ethers can be transformed into other useful compounds through functionalization of the olefin or conversion to a benzylic alcohol.

We recently reported that chiral phosphines can catalyze the enantioselective intermolecular coupling of an array of carbon, nitrogen, and sulfur nucleophiles with the γ position of allenoates and related compounds (Figure 2);[6–8] furthermore,




| R | Nu |
|---|---|
| alkyl | carbon, nitrogen, and sulfur nucleophiles (intermolecular couplings)<br>nitrogen and oxygen nucleophiles (intramolecular couplings) |
| aryl | no reports |

**Figure 2.** Reports to date of phosphine-catalyzed enantioselective γ additions (R ≠ H).

corresponding *intra*molecular reactions of nitrogen and oxygen nucleophiles can furnish enantioenriched heterocycles.[6e,9] More recently, through the use of a bifunctional phosphine catalyst, Jacobsen also achieved asymmetric intermolecular couplings of nitrogen nucleophiles.[10] With respect to even a racemic variant of the coupling illustrated in Figure 2, to the best of our knowledge, there are no reports of phosphine-catalyzed γ additions of any nucleophiles to alkynoates/allenoates that bear an aryl group in the γ position,[11] and there is only a single

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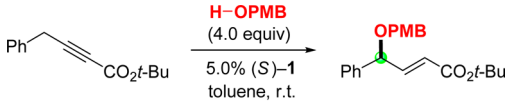
example of an intermolecular coupling of an oxygen nucleophile with any γ-substituted alkynoate/allenoate.[12]

We were therefore pleasantly surprised to determine that, under the simple conditions presented in Table 1, commercially

**Table 1. Phosphine-Catalyzed Asymmetric Synthesis of Benzylic Ethers: Effect of Reaction Parameters**[a]

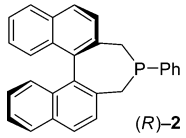



PMB = *para*-methoxybenzyl

"standard conditions"

| entry | change from the "standard conditions" | ee (%) | yield (%)[b] |
|---|---|---|---|
| 1 | **none** | **97** | **94** |
| 2 | allenoate (*tert*-butyl 4-phenylbuta-2,3-dienoate), instead of alkynoate | 96 | 88[c] |
| 3 | (*R*)–**2**, instead of (*S*)–**1** | 62 | 74 |
| 4 | 2.0% (*S*)–**1** | 97 | 89 |
| 5 | 2.0 equiv of H–OPMB | 97 | 88 |
| 6 | 1.2 equiv of H–OPMB | 97 | 80 |
| 7 | 2.0 equiv of added water | 97 | 84 |

[a]All data are the average of two experiments. [b]The yield was determined via $^1$H NMR spectroscopy, using diphenylmethane as an internal standard. [c]Yield of purified product.



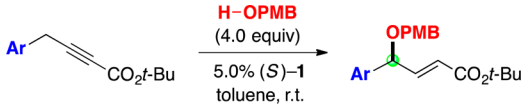

(*R*)–**2**

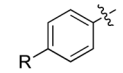
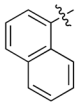
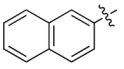
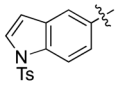
available spirophosphine **1**[6e,9,13] catalyzes the coupling of an alcohol with an alkynoate that is substituted with a phenyl group in the γ position, furnishing the desired benzylic ether with very good enantioselectivity and in high yield (97% ee, 94% yield; entry 1). This internal redox process oxidizes the benzylic carbon while reducing the alkyne. Use of the corresponding allenoate leads to essentially the same ee, although the yield is slightly lower (88%; entry 2). Phosphepine **2**, which has served as an effective catalyst for other couplings,[6b,f] provides the desired benzylic ether with diminished efficiency (62% ee, 74% yield; entry 3). Use of a lower catalyst loading or less of the alcohol has no impact on enantioselectivity, but results in a minor erosion in yield (80–89%; entries 4–6). Similarly, the ee of the coupling is unaffected by the presence of a small amount of water, although the yield is modestly lower (84%; entry 7).

We next examined the scope of this new transformation with regard to the aryl substituent of the alkynoate; these substrates are readily accessible via the coupling of benzylic chlorides with *tert*-butyl propiolate.[14] We have established that this phosphine-catalyzed asymmetric synthesis of benzylic ethers proceeds with good enantioselectivity with a wide array of aryl groups, furnishing the desired products under straightforward and mild conditions (Table 2). For example, the aromatic substituent can be electron-rich or electron-poor (entries 2 and 3), and it can be ortho-substituted, although in such cases a higher catalyst loading is required in order to obtain good yields (10% catalyst; entries 4 and 5). Furthermore, the aryl group can be an extended π-system (entries 6 and 7), and it can be a sulfur or a nitrogen heterocycle (entries 8–10). On a gram scale (1.40 g of product), the coupling depicted in entry 2 proceeds in 94% ee and 91% yield.[15]

The scope with respect to the electrophile is not limited to aryl- and ester-substituted compounds of the type depicted

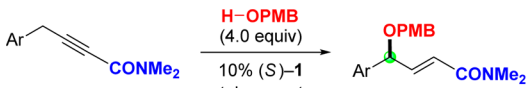
**Table 2. Phosphine-Catalyzed Asymmetric Synthesis of Benzylic Ethers: Scope with Respect to the Aryl Group**[a]



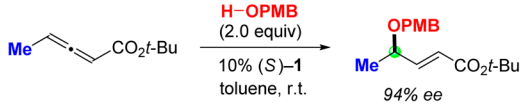

| entry | Ar | | ee (%) | yield (%)[b] |
|---|---|---|---|---|
| 1 |  | R = H | 96 | 94 |
| 2 | | OMe | 95 | 90 |
| 3 | | Cl | 96 | 84 |
| 4[c] |  | R = OMe | 88 | 76 |
| 5[c] | | Me | 86 | 86 |
| 6[c,d] |  | | 88 | 64 |
| 7 |  | | 94 | 97 |
| 8 |  | | 92 | 93 |
| 9 |  | | 92 | 96 |
| 10 |  | | 92 | 89 |

[a]All data are the average of two experiments. [b]Yield of purified, isolated product. [c]Catalyst loading: 10% (*S*)-**1**. [d]Amount of nucleophile: 2.0 equiv.

in Table 2. For example, substrates that bear an amide rather than an ester group (eq 2), as well as a methyl rather than an aryl substituent (eq 3), can be employed.[16] In both cases, the desired coupling product is generated with high enantioselectivity and in very good yield.




(2)




(3)

A variety of primary alcohols can be employed as the nucleophilic coupling partner (Table 3). For example, benzyl alcohol as well as an electron-poor benzylic alcohol are suitable substrates, furnishing ee's and yields that are similar to those observed for *p*-methoxybenzyl alcohol (entries 1–3). Other functionalized, as well as unfunctionalized, alcohols also afford the desired benzylic ether with very good enantioselectivity (entries 4–10). The efficiency of C–O bond formation is sensitive to the steric demand of the nucleophile: although coupling proceeds in fairly good yield with a β-branched primary alcohol (entry 10), cyclohexanol is not a useful partner under our standard conditions (<20% yield). An initial attempt to employ water as the nucleophile was not successful.

Although saturated secondary alcohols such as cyclohexanol are not effective coupling partners under our standard conditions,



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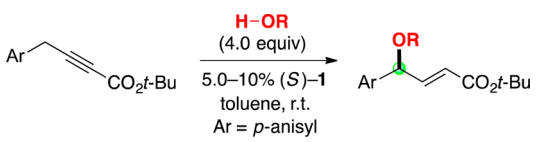
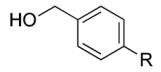
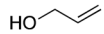
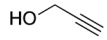
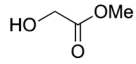
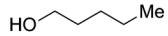
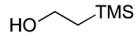
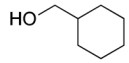
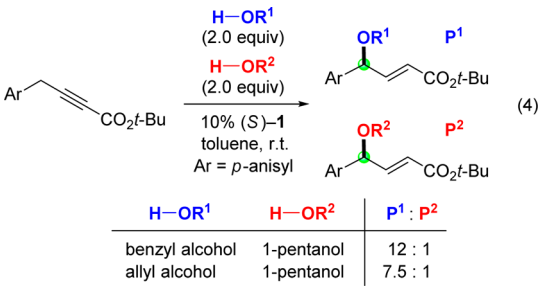
**Table 3. Phosphine-Catalyzed Asymmetric Synthesis of Benzylic Ethers: Scope with Respect to the Alcohol**[a]




| entry | H–OR | | ee (%) | yield (%)[b] |
|---|---|---|---|---|
| 1 |  | R = OMe | 95 | 90 |
| 2 | | H | 94 | 88 |
| 3[c] | | $CF_3$ | 91 | 86 |
| 4 |  | | 94 | 88 |
| 5 |  | | 91 | 86 |
| 6[c] |  | | 93 | 74 |
| 7[d] | HOMe | | 92 | 88 |
| 8 |  | | 96 | 82 |
| 9 |  | | 96 (95[e]) | 64 (79[e]) |
| 10 |  | | 96 | 75 |

[a]All data are the average of two experiments. [b]Yield of purified, isolated product. [c]Amount of nucleophile: 2.0 equiv. [d]The methyl rather than the *tert*-butyl ester of the alkynoate was used. [e]Catalyst loading: 20% (*S*)-**1**.

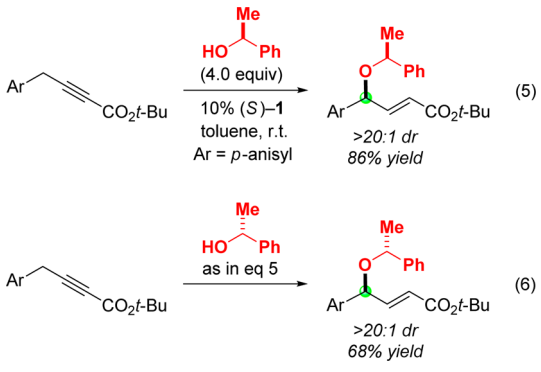
during our study of the use of primary alcohols as nucleophiles (Table 3), we observed that unsaturated alcohols such as benzyl alcohol and allyl alcohol are significantly more reactive than saturated alcohols (eq 4). This enhanced reactivity enables




(4)

| $H–OR^1$ | $H–OR^2$ | $P^1 : P^2$ |
|---|---|---|
| benzyl alcohol | 1-pentanol | 12 : 1 |
| allyl alcohol | 1-pentanol | 7.5 : 1 |

the application of our phosphine-catalyzed asymmetric coupling to a benzylic secondary alcohol, 1-phenylethanol (eqs 5 and 6). By examining the stereochemical outcome for the reaction of each enantiomer of this chiral alcohol, catalyzed by (*S*)-**1**, we can determine whether the stereochemistry of the new benzylic stereocenter is primarily controlled by the stereochemistry of the

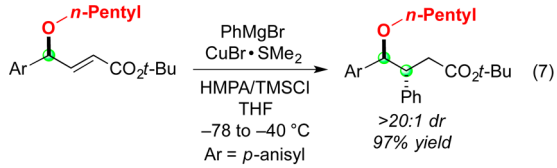



(5)

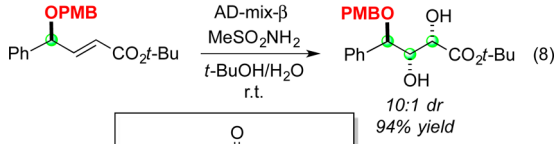
(6)

alcohol or that of the phosphine catalyst. Because different diastereomers of the benzylic ether are favored in these two couplings (both reactions proceed with >20:1 dr), we conclude that the stereochemical course is catalyst-controlled.[17]

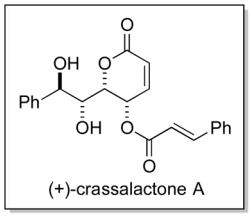
The enantioenriched benzylic ethers that are produced in these phosphine-catalyzed asymmetric couplings bear an olefin that can be further functionalized. For example, conjugate addition and dihydroxylation proceed with good diastereoselectivity and in good yield (eqs 7 and 8); the diol generated via dihydroxylation is related to an intermediate employed in the total synthesis of (+)-crassalactone A.[18] If the enantioenriched benzylic alcohol, rather than the ether, is the target, then deprotection can be achieved in good yield (eq 9).

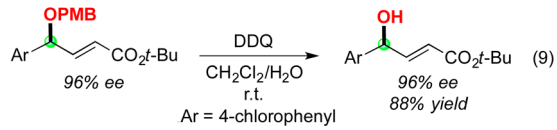



(7)




(8)




(9)

A possible mechanism for this method for the catalytic asymmetric synthesis of benzylic ethers is outlined in Figure 3.[7] Nucleophilic addition of the phosphine to the β position of the alkynoate generates a zwitterion (**A**) that tautomerizes to form

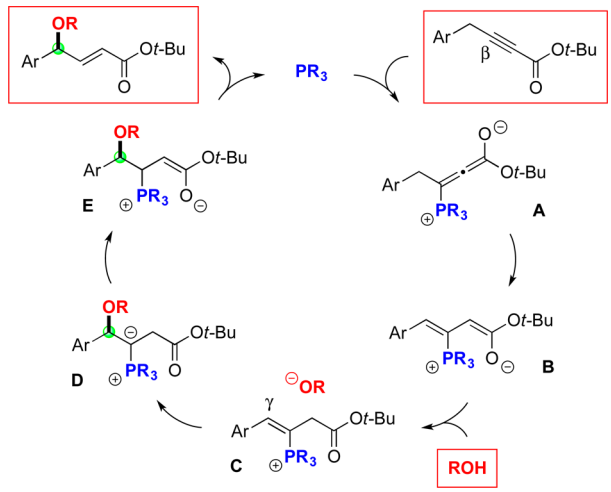



**Figure 3.** Outline of a possible pathway for the phosphine-catalyzed asymmetric synthesis of benzylic ethers. For the sake of simplicity, all steps are drawn as irreversible, and all alkenes are illustrated as single isomers.



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new zwitterion **B**. Intermediate **B** deprotonates the alcohol (ROH) to afford an ion pair (**C**). The alkoxide then adds to the electrophilic $\gamma$ carbon, producing ylide **D**. Tautomerization furnishes zwitterion **E**, which eliminates the phosphine to regenerate the catalyst and yield the product.

For the enantioselective coupling illustrated in entry 2 of Table 2, we have determined through $^{31}$P NMR spectroscopy that the free phosphine (**1**) is the resting state of the catalyst during the reaction. In addition, through $^{1}$H NMR spectroscopy, we have discovered that the alkynoate isomerizes to the allenoate to a significant extent during the coupling, presumably via elimination of the phosphine from intermediate **A** (Figure 3).

In summary, commercially available chiral phosphine **1** serves as an effective catalyst for the enantioselective coupling of alcohols with $\gamma$-aryl alkynoates, thereby directly generating benzylic ethers in good ee from readily available starting materials under simple and mild conditions. Although related asymmetric phosphine-catalyzed intermolecular couplings have been reported, no success has been described with an electrophile that bears an aryl substituent in the $\gamma$ position or with an oxygen nucleophile. A wide range of aromatic groups (including heterocycles) and a broad array of primary alcohols are compatible with this new process. The resulting enantioenriched benzylic ethers can be useful both as endpoints and as intermediates in organic chemistry. Further investigations of the use of phosphines as chiral nucleophilic catalysts are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08486.

Procedures and characterization data PDF)
X-ray data for P16308 CIF)
X-ray data for p16227ja (CIF)
X-ray data for jap16228 (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES


(1) For a recent example, see: Takano, R.; Yoshida, M.; Inoue, M.; Honda, T.; Nakashima, R.; Matsumoto, K.; Yano, T.; Ogata, T.; Watanabe, N.; Hirouchi, M.; Kimura, T.; Toda, N. *Bioorg. Med. Chem.* **2015**, *23*, 5546−5565. Other examples are omarigliptin and Strattera (Eli Lilly and Co.).

(2) Many benzylic alcohols are bioactive, including epinephrine and Zetia (Merck & Co., Inc.).

(3) For representative examples and leading references, see: (a) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344−2353. (b) Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825−7828.

(4) (a) For some leading references on the catalytic asymmetric hydrogenation of ketones, see: *Asymmetric Catalysis on Industrial Scale*; Blaser, H.-U., Federsel, H.-J., Eds.; Wiley-VCH: Weinheim, 2010. (b) For a discussion of the catalytic enantioselective alkylation of aldehydes, see: Santanilla, A. B.; Leighton, J. L. In *Science of Synthesis, Stereoselective Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme Verlag: Stuttgart, 2011; Vol. 2, pp 401−447.

(5) For a discussion and leading references, see: Andrus, M. B. In *Science of Synthesis, Stereoselective Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Georg Thieme Verlag: Stuttgart, 2011; Vol. 3, pp 469−482.

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(11) For examples of failed attempts, see the following: (a) Footnote 12 in ref 6f. (b) Entry 5 of Table 3 in Zhou, Q.-F.; Zhang, K.; Kwon, O. *Tetrahedron Lett.* **2015**, *56*, 3273−3276.

(12) See eq 2 in Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819−10820.

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(15) Phosphine catalyst **1** was recovered in 87% yield as the corresponding phosphine oxide after deliberate oxidation with *t*-BuOOH.

(16) Under our standard conditions, if the alkyl substituent in the $\gamma$ position is larger than a methyl group, good ee but modest yield is observed.

(17) When *racemic* 1-phenylethanol is employed as the nucleophile, a very modest kinetic resolution is observed (s = 2.2).

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