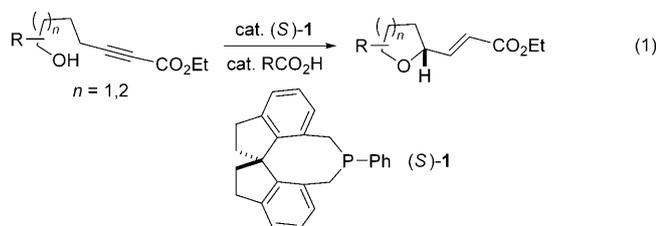


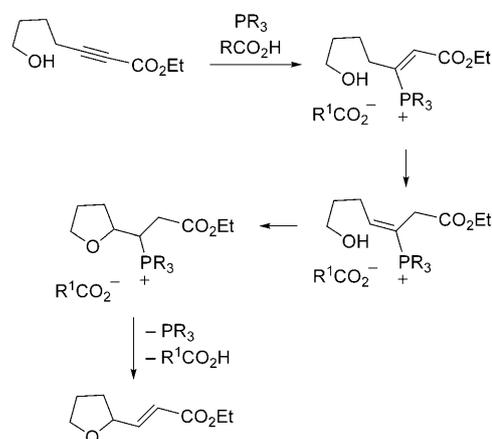
## Phosphine-Catalyzed Enantioselective Synthesis of Oxygen Heterocycles\*\*

Ying Kit Chung and Gregory C. Fu\*

Although phosphines serve as nucleophilic catalysts for an array of useful transformations, comparatively few highly enantioselective variants in the presence of chiral phosphines have been described.<sup>[1,2]</sup> In 1994, Trost discovered a novel dppp-catalyzed (dppp = 1,3-bis(diphenylphosphino)propane) cyclization of hydroxy-2-alkynoates that generates saturated oxygen heterocycles.<sup>[3]</sup> Despite the importance of such structures, owing to their presence in a wide range of bioactive molecules,<sup>[4]</sup> there has been no progress toward the development of an asymmetric version of the Trost cyclization. Herein, we establish that chiral spiro phosphepine **1** can achieve this objective with a variety of hydroxy-2-alkynoates with good enantiomeric excess [Eq. (1)].



A plausible pathway for the phosphine-catalyzed cyclization of hydroxy-2-alkynoates has been suggested by Trost and Li (Scheme 1).<sup>[3]</sup> On the basis of this mechanism, it seemed reasonable to anticipate that the catalytic asymmetric synthesis of oxygen heterocycles might be achieved through the use of an appropriate chiral phosphine. In our initial studies, we investigated the cyclization of hydroxy-2-alkynoate **2** to form tetrahydrofuran **3** in the presence of an array of chiral bisphosphines (Table 1, entries 1–4), since Trost had reported that dppp is significantly more effective than PPh<sub>3</sub> for non-symmetric processes.<sup>[3]</sup> Because the results were not especially promising, we turned our attention to monophosphines (Table 1, entries 5–9). Phosphepines emerged as the most



**Scheme 1.** Outline of a possible pathway for the phosphine-catalyzed synthesis of oxygen heterocycles from hydroxy-2-alkynoates. For the sake of simplicity, all elementary steps are drawn as irreversible and all olefins are depicted as single isomers.

promising catalysts,<sup>[5,6]</sup> with the spiro phosphepine **1**<sup>[7]</sup> accomplishing the desired cyclization with particularly good *ee* value and yield (Table 1, entry 9).<sup>[8]</sup>

The conditions that we developed for the cyclization of hydroxy-2-alkynoate **2** can be applied to a variety of substrates (Table 2), providing not only tetrahydrofurans (Table 2, entries 1–3), but also tetrahydropyrans (Table 2, entries 4–8), with high *ee* values and generally good yields. Substituents could be tolerated  $\alpha$ ,  $\beta$ , or  $\gamma$  to the hydroxy group.

To date, phenols have not been utilized as nucleophiles in phosphine-catalyzed syntheses of oxygen heterocycles from 2-alkynoates. We have determined that, under similar conditions as for aliphatic alcohols,<sup>[9]</sup> spiro phosphepine **1** catalyzes the cyclization of 2-alkynoates that bear pendant phenols, thereby providing access to enantioenriched dihydrobenzopyrans<sup>[10]</sup> (Table 3). Phenols with *ortho* substituents or those fused to nitrogen heterocycles are suitable substrates.

We have not yet pursued extensive mechanistic studies of this phosphine-catalyzed method for the enantioselective synthesis of oxygen heterocycles. According to <sup>31</sup>P NMR spectroscopy, when benzoic acid is added to a solution of spiro phosphepine **1** in THF, proton transfer to form an ion pair does not occur. Furthermore, the resting state of the phosphepine during the catalytic cycle is free phosphepine **1** (rather than, for example, a phosphonium salt, as illustrated in Scheme 1). Spiro phosphepine **1** is reasonably air-stable. After exposure of the solid to air for three days at room temperature, no phosphine oxide was detected by <sup>1</sup>H NMR

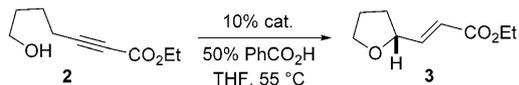
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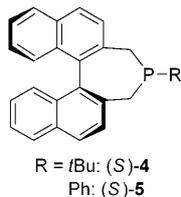
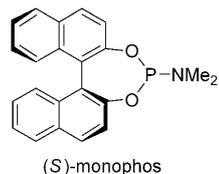
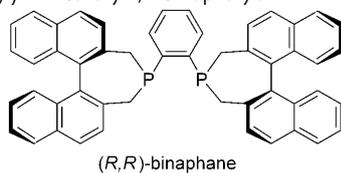
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200805377>.

**Table 1:** Catalytic enantioselective synthesis of oxygen heterocycles by chiral bidentate and monodentate phosphines.



Entry	Catalyst	ee [%] <sup>[a]</sup>	Yield [%] <sup>[b]</sup>
1	( <i>S,S</i> )-chiraphos	–	< 2
2	( <i>R,R</i> )-dipamp	22	70
3	( <i>R,R</i> )-Me-duphos	–	< 2
4	( <i>R,R</i> )-binaphane	17	9
5	( <i>R</i> )-mop	–	< 2
6	( <i>S</i> )-monophos	–	< 2
7	( <i>S</i> )-4	–66	72
8	( <i>S</i> )-5	–45	65
9	( <i>S</i> )-1	87	80

All data are the average of two experiments. [a] A negative value for the ee signifies that the enantiomer of **3** is formed preferentially. [b] The yield was determined by GC analysis with the aid of a calibrated internal standard. Chiraphos = 2,3-bis(diphenylphosphano)butane; dipamp = 1,2-ethanediylbis[(2-methoxyphenyl)phenylphosphane]; Me-duphos = 1,2-bis(2,5-dimethylphospholanyl)benzene; mop = 2-(diphenylphosphanyl)-2'-methoxy-1,1'-binaphthyl.

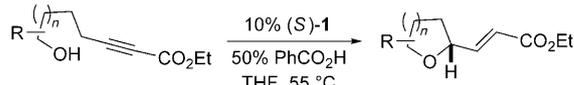


spectroscopy. In addition, the phosphine oxide does not serve as a catalyst for the cyclization.

Prior to this study, three types of phosphine-catalyzed processes had been described that furnish very good enantioselectivity with some generality: acylations of alcohols, Morita–Baylis–Hillman reactions, and couplings of allenes with an unsaturated partner, such as an alkene or imine.<sup>[2]</sup> The current process, adding to some promising earlier results with carbon nucleophiles,<sup>[11]</sup> represents a fourth class of asymmetric transformations that can be effectively catalyzed by chiral phosphines,  $\gamma$  additions of nucleophiles to unsaturated carbonyl compounds.

In summary, we have established that a chiral phosphine can catalyze the transformation of an array of hydroxy-2-alkynoates into saturated oxygen heterocycles with good enantioselectivity. In particular, we have demonstrated that spiro phosphine **1**, which had previously proved effective as a chiral ligand in transition-metal chemistry, catalyzes the synthesis of tetrahydrofurans, tetrahydropyrans, and dihydrobenzopyrans with high efficiency. Additional studies are

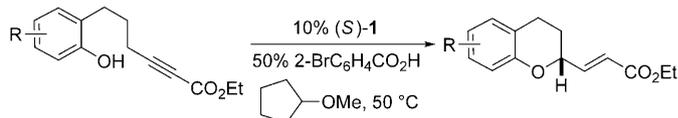
**Table 2:** Catalytic enantioselective synthesis of tetrahydrofurans and tetrahydropyrans.



Entry	Substrate	ee [%]	Yield [%] <sup>[a]</sup>
1		87	78
2		94	90
3		87	63
4		92	90
5		94	85
6		92	72
7		94	82
8		91	80

All data are the average of two experiments. [a] Yield of purified product.

**Table 3:** Catalytic enantioselective synthesis of dihydrobenzopyrans.



Entry	Substrate	ee [%]	Yield [%] <sup>[a]</sup>
1		88	86
2		63	82
3		84	89
4		84	79

All data are the average of two experiments. [a] Yield of purified product.

underway that exploit the rich potential of chiral phosphines as asymmetric nucleophilic catalysts.

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- [6] For our efforts to employ phosphepine **4** as a chiral nucleophilic catalyst, see Reference [2c].
- [7] a) S.-F. Zhu, Y. Yang, L.-X. Wang, B. Liu, Q.-L. Zhou, *Org. Lett.* **2005**, *7*, 2333–2335; b) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581–593. To our knowledge, until now, spiro phosphepine **1** had been used exclusively as a ligand for transition-metal catalyzed asymmetric processes, not as an enantioselective nucleophilic catalyst.
- [8] Notes: a) In the absence of benzoic acid, under otherwise identical conditions, spiro phosphepine **1** generates the tetrahydrofuran with 80% *ee* and 13% yield. An array of other acids, including chiral acids, furnish lower *ee* values and/or yields; b) With catalyst **1** (5 mol%) and benzoic acid (25 mol%), the reaction proceeded more slowly (e.g., for the substrate illustrated in entry 1 of Table 2, the product was generated in 86% *ee* and 58% yield after four days).
- [9] For the substrate illustrated in entry 1 of Table 3, we obtained 65% *ee* and 86% yield under the conditions employed in Table 2.
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