Asymmetric Synthesis

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Synthesis of Functionalized Cyclopentenes through Catalytic Asymmetric [3+2] Cycloadditions of Allenes with Enones**

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Five-membered carbocycles are a common substructure in a wide array of natural and nonnatural products.[1] Among this family of compounds, cyclopentenes are particularly important targets, in part because derivatization of the olefin often occurs with good diastereoselectivity, thereby providing access to highly functionalized, stereochemically complex cyclopentanes. Although considerable progress has been described in developing methods for the asymmetric synthesis of cyclopentenes, the number of effective *catalytic* enantioselective processes is comparatively small.[2]

Recently, nucleophilic catalysis by phosphines has emerged as a powerful tool in synthetic organic chemistry.[3] For example, tertiary phosphines catalyze a variety of annulation reactions, including Lu's [3+2] cycloaddition of allenes with olefins to generate cyclopentenes.[4] In 1997, Zhang et al. reported a pioneering study in which he established that a chiral phosphine can furnish good enantioselectivity in this process; with respect to scope, only unsubstituted acrylate esters and diethyl maleate react with the allene to form the target cyclopentenes in high enantiomeric excess (*ee*) [Eq. (1) and (2)].[5]

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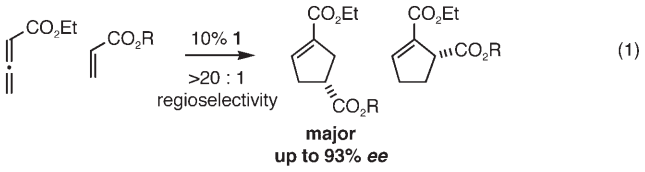
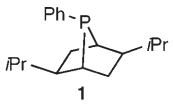


(1)



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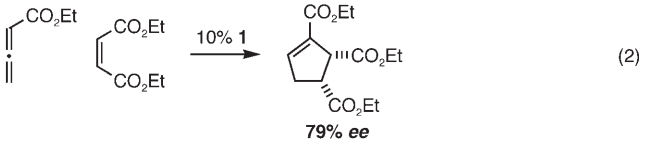
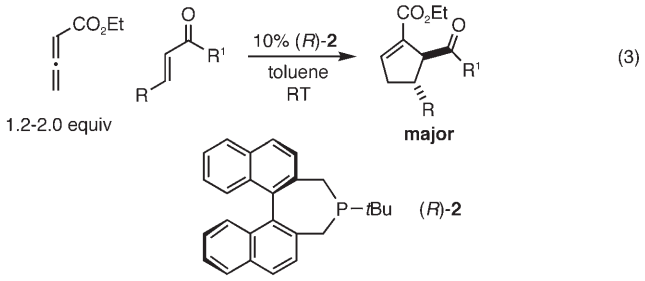


(2)

In general, there has been only very limited progress to date in the development of effective phosphine-based methods for asymmetric nucleophilic catalysis.[6] We recently reported that phosphepine **2**, which was originally designed as a ligand for metal-catalyzed processes,[7] catalyzes [4+2] annulations of allenes with imines to generate piperidine derivatives with good enantioselectivity.[6c,8] Since that initial study, we have been exploring the utilization of this phosphepine for a wide array of nucleophile-catalyzed reactions. Herein, we establish that **2** catalyzes enantioselective [3+2] cycloadditions of allenes with a variety of β-substituted α,β-unsaturated enones to produce highly functionalized cyclopentenes that contain two contiguous stereocenters [Eq. (3)].



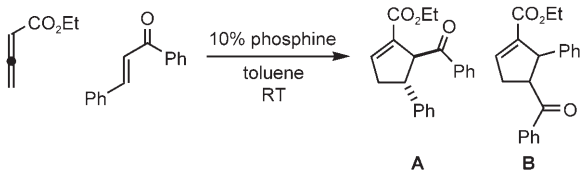
(3)

In a preliminary investigation, we surveyed the use of phosphepine **2** and a variety of commercially available mono- and bisphosphines as catalysts for the asymmetric cycloaddition of ethyl-2,3-butadienoate and chalcone (Table 1). Whereas **2** furnishes the target cyclopentene in good yield, *ee*, and regioselectivity (Table 1, entry 1), the other phosphines are either ineffective as catalysts (Table 1, entries 2–4) or provide relatively poor enantiomeric excess (Table 1, entries 5–7).

Phosphepine **2** catalyzes the asymmetric [3+2] cycloaddition of allenes with a wide array of enones (Table 2).[9] It is worth noting that these are the first such processes that employ β-substituted α,β-unsaturated carbonyl compounds (other than diethyl maleate)[10] and that the opposite regioisomer is produced preferentially as compared with substrates that lack a β substituent [cf. Eq. (1)].[4,5]

The desired cyclopentene is generated in good enantiomeric excess for both electron-rich and electron-poor chalcone derivatives (Table 2, entries 2–6), although cycloadditions of electron-rich substrates proceed somewhat less efficiently and therefore require additional allene (2.0 equivalents, rather than 1.2; Table 2, entries 4 and 6). The method tolerates heterocyclic substituents in either the β position (Table 2, entries 7 and 8) or attached to the carbonyl group (Table 2, entries 9 and 10) of the enone.

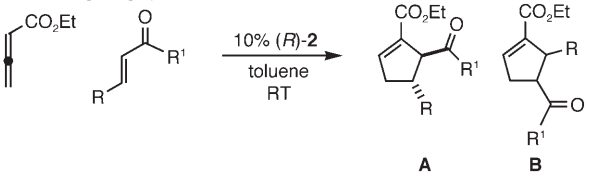
Table 1: Survey of chiral phosphine catalysts for the [3+2] cycloaddition of allenes with enones.[a]



Entry	Phosphine[b]	Yield [%][c]	*ee* [%][d]	**A**:**B**
1	(*R*)-**2**	64	88	13:1
2	(*S*)-binapine	0	–	–
3	(*R*)-binap	2	50	>20:1
4	(*R*)-nmdpp	4	−4	11:1
5	(*R*,*R*)-Me-bpe	61	−4	6:1
6	(*R*,*R*)-ferrotane	64	11	7:1
7	(*R*,*R*)-Et-DuPhos	61	58	7:1

[a] All data are the average of two experiments. [b] binap = 2,2'-Bis(diphenylphosphanyl)-1,1′-binaphthyl, nmdpp = neomenthyldiphenylphosphine. Molecular structures of (*S*)-binapine, (*R*,*R*)-Me-bpe, (*R*,*R*)-ferrotane, and (*R*,*R*)-Et-DuPhos are shown in Ref. [17]. [c] Yield of isolated **A** and **B**. [d] Enantiomeric excess of **A**. A negative value for *ee* signifies that the shown enantiomer of cyclopentene **A** is the minor product, rather than the major.

Table 2: Synthesis of functionalized cyclopentenes through catalytic asymmetric [3+2] cycloadditions.[a]

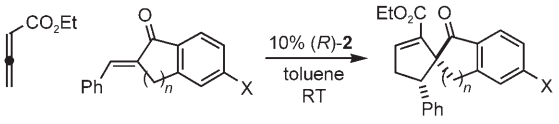


Entry	R	R^1	Yield [%][b]	*ee* [%][c]	**A**:**B**
1	Ph	Ph	64	88	13:1
2	Ph	4-chlorophenyl	76	82	7:1
3	Ph	4-methylphenyl	61	87	20:1
4	Ph	4-methoxyphenyl	54	88	>20:1
5	4-chlorophenyl	Ph	74	87	9:1
6	4-methoxyphenyl	Ph	67	87	10:1
7	2-furyl	Ph	69	88	3:1
8[d]	2-quinolyl	Ph	52	88	20:1
9[d]	4-chlorophenyl	2-(5-methylfuryl)	54	89	>20:1
10	Ph	2-thienyl	74	90	6:1
11	$C{\equiv}CC_5H_{11}$	Ph	65	85	6:1
12	C≡CTES	Ph	70	87	>20:1
13	C_5H_{11}	Ph	39[e]	75	>20:1

[a] All data are the average of two experiments. All cycloadditions employed 1.2 equiv of allene, except for entries 4, 6, 7, and 13, for which 2.0 equiv was used. [b] Yield of isolated **A** and **B**. [c] Enantiomeric excess of **A**. [d] Because of the low solubility of the enone in toluene, CH_2Cl_2 was employed as a co-solvent. [e] The enone can be recovered in 56% yield.

This process is not limited to β-(hetero)aryl enones. For example, phosphepine **2** catalyzes cycloadditions of enones that bear a β-alkynyl group with good enantiomeric excess (Table 2, entries 11 and 12). Under our standard conditions, if an alkyl substituent occupies the β position, formation of the cyclopentene proceeds sluggishly, but with fairly good selectivity (Table 2, entry 13).

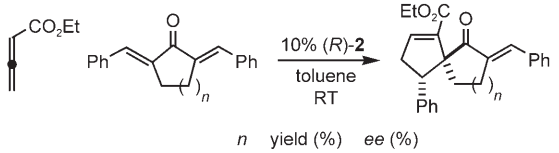
Catalyst **2** can achieve the enantioselective synthesis of spirocyclic compounds through reactions of trisubstituted enones, thereby generating adjacent quaternary[11] and tertiary stereocenters [Eq. (4); a single regioisomer is produced].[12–14] This method is not entirely general—the cycloaddition of an indanone proceeds in excellent yield, however, the reaction of a closely related tetralone is considerably less efficient [but highly enantioselective; Eq. (4)].[15]



(4)

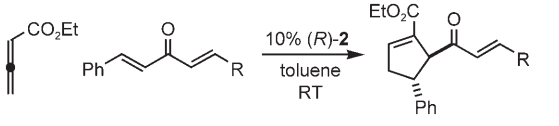
n	X	yield (%)	*ee* (%)
1	Br	97	89
2	H	32	95

Dienones are also suitable substrates, undergoing a single phosphine-catalyzed [3+2] cycloaddition [Eq. (5) and (6); only one regioisomer is observed]). Although for symmetrical dienones there is no issue of site selectivity, this complication does arise for unsymmetrical compounds. Interestingly, phosphepine **2** can achieve enantioselective cycloadditions with complete site selectivity [Eq. (6)].



(5)

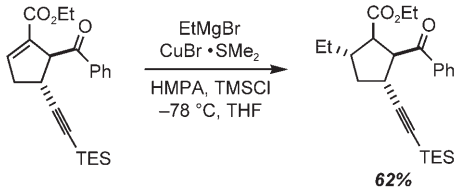
n	yield (%)	*ee* (%)
1	81	89
2	57	93



(6)

R	yield (%)	*ee* (%)
Ph	75	89
2,6-dichlorophenyl	68	73

We had anticipated that the enantiomerically enriched cyclopentenes generated in these asymmetric [3+2] cycloadditions should be attractive substrates for further functionalization. An example of such a process, which produces a diastereomerically pure cyclopentane that bears four contiguous stereocenters, is illustrated in Equation (7).[16]



(7)

In summary, we have described the first nucleophile-catalyzed asymmetric [3+2] cycloadditions of allenes with enones. We have determined that β-substituted enones undergo reaction with a different regiochemical preference compared with previously described cycloadditions of β-unsubstituted α,β-unsaturated carbonyl compounds. We have applied our method to reactions of trisubstituted olefins, thereby generating adjacent quaternary and tertiary stereocenters. Finally, we have established that the product cyclopentenes can be stereoselectively derivatized to provide cyclopentanes that bear four contiguous stereocenters. Ongoing efforts are directed at further expanding the currently limited range of enantioselective processes catalyzed by chiral phosphine nucleophiles.

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[1] For leading references and examples, see: a) R. C. Hartley, S. T. Caldwell, *J. Chem. Soc. Perkin Trans. 1* **2000**, 477–501, and previous reviews in this series; b) Prostaglandins: *Prostaglandins, Leukotrienes and Essential Fatty Acids* (Eds.: D. F. Horrobin, M. S. Manku, P. Sirois, P. Borgeat), Churchill Livingston, Edinburgh, **2002**; c) Carbasugars: G. Rassu, L. Auzzas, L. Pinna, L. Battistini, C. Curti, *Stud. Nat. Prod. Chem.* **2003**, *29*, 449–520; d) Polymers: I. Kuntz, *Encycl. Polym. Sci. Eng.* **1985**, *4*, 537–542.

[2] For recent examples of processes in which the asymmetry is introduced during the ring-forming reaction, see: a) H. M. L. Davies, B. Xiang, N. Kong, D. G. Stafford, *J. Am. Chem. Soc.* **2001**, *123*, 7461–7462; b) S. E. Gibson, A. Stevenazzi, *Angew. Chem.* **2003**, *115*, 1844–1855; *Angew. Chem. Int. Ed.* **2003**, *42*, 1800–1810.

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[4] a) C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906–2908; b) Z. Xu, X. Lu, *Tetrahedron Lett.* **1999**, *40*, 549–552; c) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535–544; d) Y. Du, X. Lu, Y. Yu, *J. Org. Chem.* **2002**, *67*, 8901–8905; e) Y. Du, X. Lu, *J. Org. Chem.* **2003**, *68*, 6463–6465.

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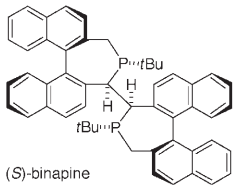
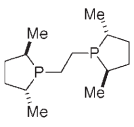
5176 – 5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066 – 5069, and references therein.
[8] For the initial report of this annulation method, see: X.-F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716 – 4717.
[9] Notes: a) Under these conditions, α,β-unsaturated ketones in which R^1 = alkyl or alkynyl or R = alkenyl (Table 2), α,β-unsaturated esters that bear a β substituent, *p*-benzoquinone, and *N*-phenylmaleimide are not suitable coupling partners. Benzyl and allyl-2,3-butadienoate are less reactive than ethyl-2,3-butadienoate. b) If access to racemic cyclopentenes is desired, PPh_3 or PBu_3 can be employed as the catalyst. c) Use of THF or CH_2Cl_2 as the solvent leads to poorer yield and regioselectivity. d) At lower temperature, the rate of cycloaddition decreases significantly, with only a small gain in *ee*. e) According to ^{31}P NMR spectroscopy, phosphepine **2** is the predominant phosphorus-containing species that is present during the [3+2] cycloaddition process. f) To the best of our knowledge, the stereochemistry of the enone is preserved in the cyclopentene.
[10] For non-asymmetric reactions, only maleates and fumarates have been shown to be suitable substrates. Lu et al. (e.g., ref. [4a]) and Zhang et al. (ref. [5]) were unable to achieve cycloadditions of other β-substituted α,β-unsaturated carbonyl compounds.
[11] For a recent discussion of the challenge of developing catalytic asymmetric methods for the synthesis of quaternary all-carbon centers, see: C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 – 5367.
[12] Lu et al. have described phosphine-catalyzed [3+2] cycloadditions that generate spirocycles from enones that lack a β substituent (refs. [4d] and [4e]). They observe predominant formation of a different regioisomer (the two carbonyl groups are in a 1,3 relationship on the cyclopentene ring) from that depicted in Equation (4).
[13] For leading references to an example of a naturally occurring spiroindanone that bears an all-carbon quaternary stereocenter (fredericamycin A), see: Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, K. Ueda, S. Akai, H. Fujioka, *J. Am. Chem. Soc.* **2001**, *123*, 3214 – 3222.
[14] For another recent example of a catalytic asymmetric method for the synthesis of spirocyclic compounds wherein an all-carbon quaternary stereocenter is established in the cyclization process, see: M. Hatano, K. Mikami, *J. Am. Chem. Soc.* **2003**, *125*, 4704 – 4705.
[15] For the tetralone, a considerable quantity of unreacted starting material was observed. Increasing the amount of allene did not improve the yield.
[16] These conditions were developed by Nakamura and Kuwajima: S. Matsuzawa, Y. Horiguchi, E. Nakamura, I. Kuwajima, *Tetrahedron* **1989**, *45*, 349 – 362.
[17] Molecular structures of phosphine catalysts given in Table 1:



(*S*)-binapine



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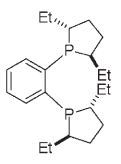
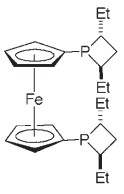


(*R*,*R*)-Et-DuPhos



(*R*,*R*)-ferrotane

