Asymmetric [3 + 2] Cycloaddition of 2,3-Butadienoates with Electron-Deficient Olefins Catalyzed by Novel Chiral 2,5-Dialkyl-7-phenyl-7-phosphabicyclo[2.2.1]heptanes

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The efficient synthesis of highly functionalized cyclopentane rings remains an important challenge in organic chemistry.[1] Among the reported methods, [3 + 2] cycloaddition has the advantage of forming multiple bonds although issues of chemo-, regio-, diastereo-, and enantioselectivity must be resolved if the process is to achieve useful generality. Transition metal-catalyzed,[2] anionic,[3] cationic,[4] and free radical mediated[5] [3 + 2] cycloadditions have been investigated. Recently, an important finding by Lu's group shows that phosphines can catalyze a [3 + 2] annulation reaction.[6] This novel [3 + 2] approach involves cycloaddition of electron-deficient olefins with simple 2,3-butadienoates as the three-carbon source. Inspired by this elegant work, herein we report the first asymmetric version of this reaction with new chiral monophosphines, 2,5-dialkyl-7-phenyl-7-phosphabicyclo[2.2.1]heptanes, as catalysts.

Several chiral monophosphines have been reported in the literature.[7] Most applications of these phosphines were in formation of asymmetric catalysts with transition metals.[7] Some chiral phosphines have also been used directly as catalysts for asymmetric reactions.[8] Our new chiral phosphines contain a rigid phosphabicyclic structure (Figure 2). The rigid, fused bicyclic [2.2.1] structure eliminates the conformational flexibility associated with the five-membered rings in other chiral phosphines (e.g., Duphos and BPE ligands[9]) and represents a new motif for chiral ligand design.

The syntheses of chiral monophosphines **7** and **8** are shown in Figure 2. Halterman[10] and Vollhardt[11] have previously prepared chiral cyclopentadiene derivatives from the chiral diols. Halterman[10] has synthesized chiral diols **1** and **2** via Birch reduction[12] followed by asymmetric hydroboration.[13] Conversion of the optically pure diols to the corresponding mesylates proceeded cleanly. Nucleophilic addition of Li_2PPh to the chiral dimesylates **3** and **4** generated the corresponding bicyclic phosphines, which were trapped by BH_3·THF to form the air-stable boron-protected monophosphines **5** and **6**, respectively. Deprotection with a strong acid[14] produced the desired products (**7**, (1*R*,2*S*,4*R*,5*S*)-(+)-2,5-dimethyl-7-phenyl-7-phosphabicyclo-[2.2.1]heptane; **8**, (1*R*,2*R*,4*R*,5*R*)-(+)-2,5-diisopropyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane) in high yields.

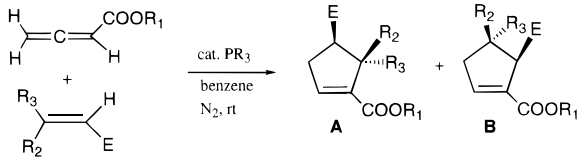

Figure 1.

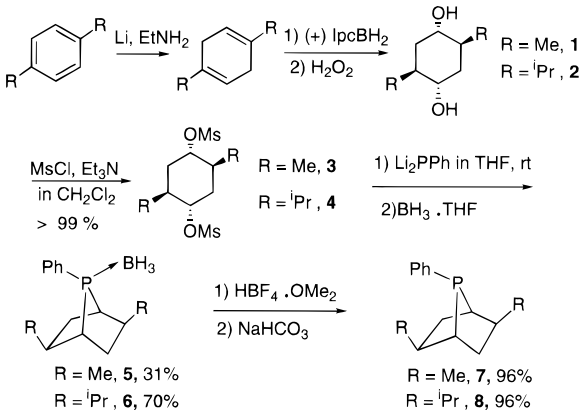

Figure 2. Synthesis of chiral monophosphines.

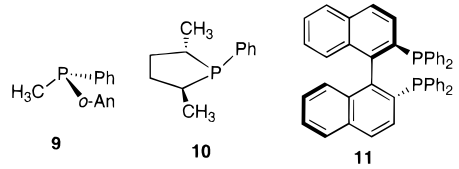

Figure 3.

We performed the asymmetric [3 + 2] annulation reaction[15] with several known chiral phosphines as catalysts in addition to **7** and **8** (Figure 3). Table 1 lists the results under different sets of conditions and with various substrates. Some general characteristics[6] of this reaction include the following: (1) two regioisomers **A** and **B** are formed, but isomer **A** generally is preferred (Figure 1); (2) the geometry of the starting electron-deficient olefins remains unchanged in the cycloaddition reaction.

We screened the asymmetric reaction with the chiral phosphines by mixing ethyl 2,3-butadienoate and ethyl acrylate in benzene with 10 mol % of phosphine at room temperature (entries 1−5). New phosphines **7**−**8** are more effective in terms of both regioselectivity (**A**:**B**) and enantioselectivity (% ee of **A**) than known phosphines **9**−**11**. The absolute configuration of product **A** (entries 1−5) was assigned by correlation with (1*R*,3*R*)-dihydroxymethyl-3-cyclopentane.[16] In particular, the enantioselectivity is much higher with **7** (81% ee, *R*, entry 1) than with **10** (6% ee, *S*, entry 4), which illustrates the consequences of using a rigid bicyclic [2.2.1] structure rather than the conformationally more flexible five-membered ring. Changing the size of the ester group in the electron-deficient olefin alters the enantioselectivity. With phosphine **7**, the enantioselectivity increases as the size of the ester increases (entry 1, Et, 81% ee; entry 6, ^{i}Bu, 86% ee; entry 7, ^{t}Bu, 89%

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(15) For an example of asymmetric [3 + 2] cycloaddition, see: Yamamoto, A.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 375.
(16) (a) Richter, W. J.; Richter, B. *Isr. J. Chem.* **1976**, *15*, 57. (b) Birch, S. F.; Dean, R. A. *J. Chem. Soc.* **1953**, 2477. The detailed procedure is reported in the Supporting Information.

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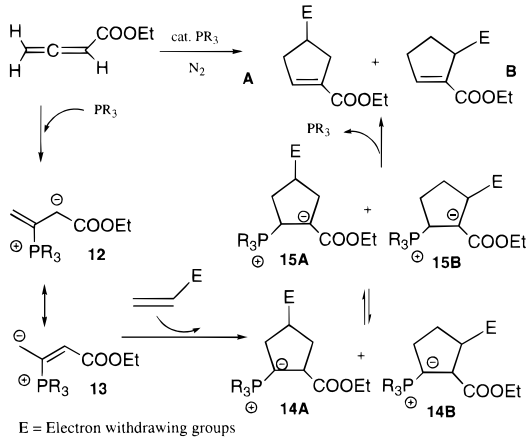
Table 1. Phosphine-Catalyzed Asymmetric [3 + 2] Cycloaddition[a]

entry	phosphine	E	R_1	R_2	R_3	solvent	T (°C)[e]	yield (%)	**A**:**B**[b]	% ee of **A**[b]	config[c]
1	**7**	COOEt	Et	H	H	benzene	rt	66	95:5	81	(−) *R*
2	**8**	COOEt	Et	H	H	benzene	rt	76	97:3	81	(−) *R*
3	**9**	COOEt	Et	H	H	benzene	rt	80	80:20	56	(+) *S*
4	**10**	COOEt	Et	H	H	benzene	rt	83	72:29	6	(+) *S*
5	**11**	COOEt	Et	H	H	benzene	rt	33	73:27	12	(−) *R*
6	**7**	COO^{i}Bu	Et	H	H	benzene	rt	46	100:0	86	(−) *R*
7	**7**	COO^{t}Bu	Et	H	H	benzene	rt	69	95:5	89	(−) *R*
8	**7**	COO^{t}Bu	Et	H	H	toluene	0	42	97:3	93	(−) *R*
9	**8**	COOMe	Et	H	H	benzene	rt	87	96:4	79	(−) *R*
10	**8**	COO^{i}Bu	Et	H	H	benzene	rt	92	100:0	88	(−) *R*
11	**8**	COO^{i}Bu	Et	H	H	toluene	0	**88**	**100**:0	**93**	(−) *R*
12	**8**	COO^{t}Bu	Et	H	H	benzene	rt	75	95:5	88	(−) *R*
13	**7**	COOEt	^{t}Bu	H	H	benzene	rt	13	97:3	89	(−) *R*
14	**8**	COOEt	^{t}Bu	H	H	benzene	rt	84	94:6	69	(−) *R*
15[d]	**8**	COOEt	Et	COOEt	H	toluene	0	49		79	(+)
16[d]	**8**	COOMe	Et	H	COOMe	benzene	rt	84		36	(−)

[a] The reaction was carried out under N_2 with a chiral phosphine (10 mol %), 2,3-butadienoate (100 mol %), and electron deficient olefins (1000 mol %). [b] **A**:**B** and % ee were measured by GC with β and γ-DEX columns. [c] The absolute configuration was determined by comparing the optical rotation with the literature value.[16] [d] Olefins (200 mol %) were used. [e] rt = room temperature.

Scheme 1



ee). A similar trend was observed with phosphine **8** (entries 2, 9−10, and 12). Upon cooling the reaction to 0 °C in toluene, up to 93% ee of **A** was obtained with phosphines **7** and **8** with excellent regioselectivity (entries 8 and 11). Increasing the size of the ester moiety in the 2,3-butadienoates, however, has different effects on the product ee with phosphine **7** (entry 1, Et, 81% ee; entry 13, ^{t}Bu, 89% ee) or **8** (entry 2, Et, 81% ee; entry 14, ^{t}Bu, 69% ee). A second major difference between catalysis by **7** or **8** is in the yield of products. The conversion to the desired products is generally higher with **8** than with **7** (e.g., entries 6−8 vs entries 9−12). With diethyl maleate (entry 15) and dimethyl fumarate (entry 16) as substrates, single *cis* and *trans* products were obtained with **8**, respectively. While the % ee of the *cis* product (entry 15, 79% ee) is slightly lower than the result with ethyl acrylate (entry 2, 81% ee), the *trans* product has much lower optical purity (entry 16, 36% ee). For two-atom species[17] other than acrylates, we have studied acrylonitrile and methyl vinyl ketone as substrates. With ethyl 2,3-butadienoate as the three-atom species and **7** as the catalyst, 48% ee of **A**, **A**/**B** (97/3) and 94% yield were obtained with acrylonitrile while 27% ee of **A**, **A**/**B** (81/19) and 33% yield were achieved with methyl vinyl ketone.

(17) Substrates such as β-substituted enones do not work because 2,3-butadienoates are better acceptors and dimerization of 2,3-butadienoates occurs (see ref 6).

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(19) A stepwise mechanism was suggested for a related [3 + 2] cyclization reaction: Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 1617.

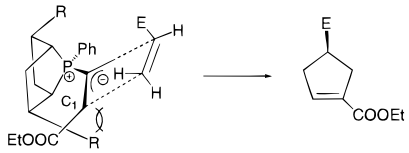

Figure 4.

A detailed mechanism of this reaction has not been rigorously proven. Scheme 1 shows Lu's proposed mechanism.[6] A catalytic amount of the phosphine acts as a nucleophilic trigger.[18] Formation of cyclic intermediates **14A** and **14B** is the key step for asymmetric induction. The stereochemistry of the starting *E* and *Z* olefins is preserved in the products, which provides suggestive evidence that this reaction proceeds through a concerted mechanism.[19] Based on this model, we offer a mechanistic rationale for the high asymmetric induction with **7** and **8** (Figure 4). The R groups from **7** and **8** can effectively block the "bottom" face of the allylic carbanion **12**/**13**, and this shielding forces the electron-deficient olefins to approach from the "top" face. The electron-withdrawing olefins approach with the *endo* orientation as shown in Figure 4. The *Z* olefins (e.g., diethyl maleate) show a similar degree of selectivity as do the acrylates, while *E* olefins (e.g., dimethyl fumarate) introduce large groups around the sterically crowded C_1 center. It is possible that the lower enantioselectivity obtained with *E* olefins is due to this disfavored interaction between COOEt and substituents of *E* olefins.

In conclusion, we have developed a new family of chiral phosphines with a unique fused bicyclic [2.2.1] ring structure. A [3 + 2] cycloaddition between 2,3-butadienoates and electron-deficient olefins catalyzed by these chiral monophosphines gives cyclopentene products with excellent regioselectivity and enantioselectivity. This method is a potentially powerful tool for the synthesis of chiral cyclopentanoids.

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Supporting Information Available: Spectroscopic data for compounds **5**−**8** and experimental details (7 pages). See any current masthead page for ordering and Internet access instructions.

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