

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 mediated⁵ [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 ligands⁹) and represents a new motif for chiral ligand design.

The syntheses of chiral monophosphines **7** and **8** are shown in Figure 2. Halterman¹⁰ and Vollhardt¹¹ have previously prepared chiral cyclopentadiene derivatives from the chiral diols. Halterman¹⁰ has synthesized chiral diols **1** and **2** via Birch reduction¹² followed by asymmetric hydroboration.¹³ Conversion of the optically pure diols to the corresponding mesylates proceeded cleanly. Nucleophilic addition of Li₂PPh to the chiral dimesylates **3** and **4** generated the corresponding bicyclic phosphines, which were trapped by BH₃·THF to form the air-

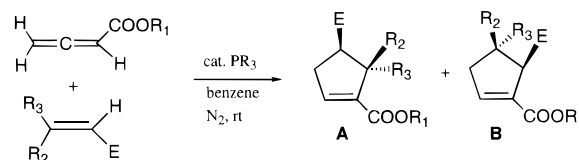


Figure 1.

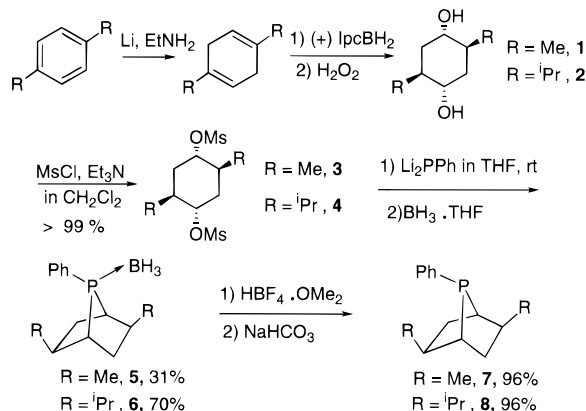


Figure 2. Synthesis of chiral monophosphines.

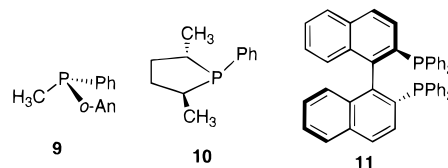


Figure 3.

stable boron-protected monophosphines **5** and **6**, respectively. Deprotection with a strong acid¹⁴ 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.

We performed the asymmetric [3 + 2] annulation reaction¹⁵ 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 characteristics⁶ 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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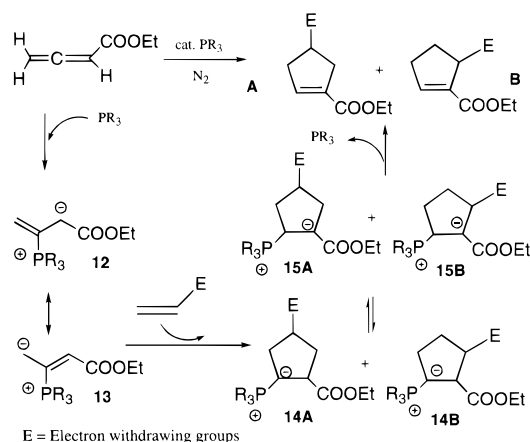
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Table 1. Phosphine-Catalyzed Asymmetric [3 + 2] Cycloaddition^a

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 ^t 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 ^t Bu	Et	H	H	benzene	rt	92	100:0	88	(-) R
11	8	COO ^t 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 N₂ 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.

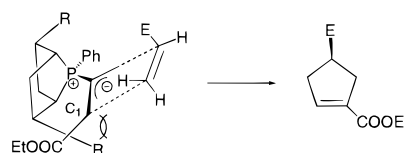
Scheme 1

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, ^tBu, 89% ee) or **8** (entry 2, Et, 81% ee; entry 14, ^tBu, 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 species¹⁷ 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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**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 C₁ 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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