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 Li2PPh3 to the chiral dimesylates 3 and 4 generated the corresponding bicyclic phosphines, which were trapped by BHF2·THF to form the air-stable boron-protected monophosphines 5 and 6, respectively. Deprotection with a strong acid14 produced the desired products 7. (1R,2S,5S)-(+) -2,5-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane; 8. (1R,2R,5R)-(++) -2,5-disopropyl-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 characteristics16 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 olefin 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 phosphate 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 (1R,3R)-dihydroxymethyl-3-cyclopentene.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, Bu, 86% ee; entry 7, Bu, 89% ee).


Figure 1.

Figure 2. Synthesis of chiral monophosphines.

Figure 3.
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 species, other than acrylates, we have studied 2,3-butadienoates as the three-atom species and diethyl maleate as the two-atom species other than acrylates. For the synthesis of chiral cyclopentanoids.

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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