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Highly Stereoselective Synthesis of Cyclopropylphosphonates Catalyzed by Chiral Ru(II)-Pheox Complex

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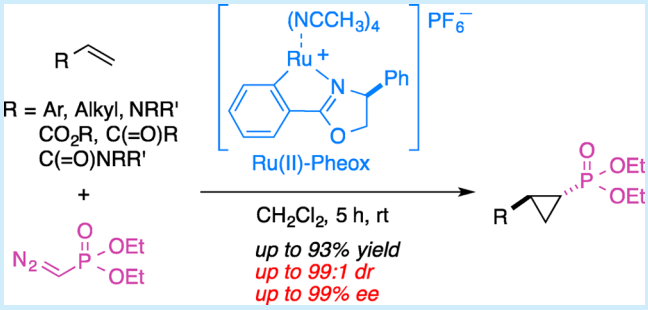
Supporting Information

ABSTRACT: Ru(II)-Pheox-catalyzed asymmetric cyclopropanation of diethyl diazomethylphosphonate with alkenes, including α,β-unsaturated carbonyl compounds, afforded the corresponding optically active cyclopropylphosphonates in high yields and with excellent diastereoselectivity (up to 99:1) and enantioselectivity (up to 99% ee).



Optically active cyclopropylphosphonate derivatives are important units and found in useful biologically active natural products or pharmacologically interesting compounds such as an analogue of nucleotide **1**,[1] an intermediate for HCV NS3 protease inhibitor **2**,[2] an analogue of L-Glu **3**,[3] and an analogue of fosmidomycin **4**[4] (Figure 1). Moreover, cyclopropylphosphonates are also convenient intermediates for the synthesis of alkylidenecyclopropane derivatives by the Wadsworth−Emmons reaction.[5]

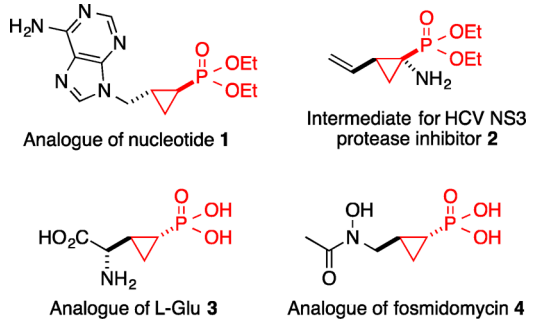


Figure 1. Examples of biologically relevant cyclopropylphosphonate derivatives.

Among the few methods developed for the synthesis of optically active cyclopropylphosphonate derivatives,[1−4,6] the catalytic asymmetric cyclopropanation of alkenes with diazomethylphosphonates is the most efficient method from a stereoselective synthesis perspective. Over the past decade, efficient catalytic systems have been developed using chiral Cu(I),[7] Rh(II),[8] and Ru(II)[9] catalysts to afford the corresponding cyclopropylphosphonates in good yields and with high diastereo- and enantioselectivity. However, the bulkiness of the diazomethylphosphonate moiety was found to be an important factor in providing high diastereocontrol, and the cyclopropanation of diazomethylphosphonate with electron-deficient alkenes such as α,β-unsaturated carbonyl compounds has not been reported yet. Herein, we report a highly stereoselective synthesis of cyclopropylphosphonates by the catalytic asymmetric cyclopropanation of simple diethyl diazomethylphosphonate with various alkenes, including α,β-unsaturated carbonyl compounds, catalyzed by a Ru(II)-Pheox complex.

Recently, we reported that the complex, Ru(II)-Pheox, is extremely efficient in carbene transfer reactions, particularly cyclopropanation and N−H insertion reactions.[10] Therefore, we attempted the cyclopropanation of styrene **5a** with diethyl diazomethylphosphonate **6** in the presence of the Ru(II)-Pheox catalyst and first optimized the reaction conditions (Table 1).

The cyclopropanation reaction of the simple diethyl diazomethylphosphonate **6** proceeded smoothly at room temperature in various solvents to afford the corresponding cyclopropylphosphonate **7** in an excellent *trans*/*cis* ratio (99:1 in most cases) and with high enantioselectivity (94−98% ee) (Table 1, entries 1−6). The cyclopropanation in toluene and CH_3OH afforded low yields of the desired product due to the formation of the dimer from the diazo compound and an O−H insertion compound as the byproducts, respectively (Table 1, entries 2 and 5). Conducting the reaction at a lower temperature afforded lower yields and diastereoselectivity (Table 1, entries 6−8). The catalyst loading could be decreased to 1 mol %; however, the yield of **7** slightly decreased (Table 1, entry 9).

With the optimal reaction conditions in hand, we further studied the generality of the asymmetric cyclopropanation of

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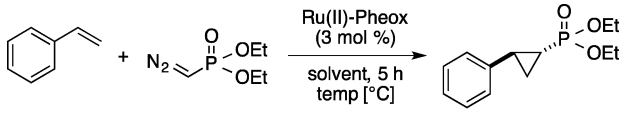
Table 1. Optimization of Reaction Conditions[a]



5a (5 equiv) **6** **7**

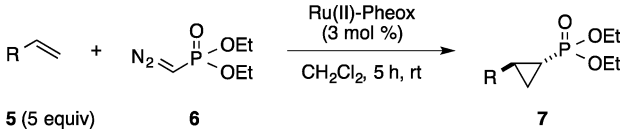
entry	solvent	temp [°C]	yield[b] [%]	*trans*/*cis*[c]	ee[d] [%] *trans*
1	THF	rt	81	96:4	97
2	toluene	rt	43	99:1	94
3	acetone	rt	79	99:1	98
4	dioxane	rt	81	99:1	97
5	CH_3OH	rt	36	99:1	97
6	**CH_2Cl_2**	**rt**	**93**	**99:1**	**97**
7	CH_2Cl_2	0	93	98:2	97
8	CH_2Cl_2	−10	78	98:2	97
9[e]	CH_2Cl_2	rt	67	99:1	97

[a]Reaction conditions: styrene (1 mmol) and diethyl diazomethylphosphonate (0.2 mmol) in the presence of Ru(II)-Pheox (3 mol %) under Ar. [b]Isolated yield. [c]Determined by NMR. [d]Determined by chiral HPLC analysis. [e]With 1 mol % of catalyst.

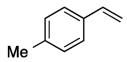
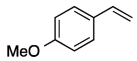
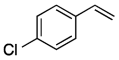
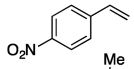
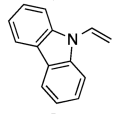
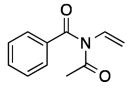
various styrene derivatives in the presence of the chiral Ru(II)-Pheox catalyst. As summarized in Table 2, styrene derivatives bearing an electron-donating group such as methyl or methoxy could also be easily cyclopropanated to afford the desired cyclopropane products in high yields and with high diastereo- and enantioselectivity (Table 2, entries 2−4). Moreover, the cyclopropanation of styrene derivatives bearing an electron-withdrawing group such as chloro and nitro was also investigated (Table 2, entries 5 and 6). Interestingly, the enantioselectivity could be increased to 99% ee, while the diastereoselectivity decreased slightly to 98:2 dr. The cyclopropanation of α-methylstyrene smoothly afforded the corresponding cyclopropylphosphonate in a high yield and with high enantioselectivity (Table 2, entry 7). However, the diastereoselectivity was lower compared to that of the styrene without a substituent at the α-position. Vinylamine derivatives could also be cyclopropanated under the same reaction conditions to afford the corresponding 2-amino cyclopropylphosphonates in high yields and with high diastereo- and enantioselectivity (Table 2, entries 8 and 9).[10b,e] We also examined the cyclopropanation of inner alkenes such as *trans*-2-hexene and *cis*-2-hexene; however, no cyclopropane products were observed due to the formation of a dimer from the diazo compound.

Encouraged by the results obtained with the styrene and vinylamine derivatives, we next turned our attention to the cyclopropanation of diethyl diazomethylphosphonate with electron-deficient alkenes such as α,β-unsaturated esters, ketones, and amides (Table 3). Surprisingly, the reaction with phenyl acrylate afforded cyclopropane product **7j** in 65% yield and with an excellent *trans*/*cis* ratio (99/1) and enantioselectivity (98% ee). Moreover, 1-phenylprop-2-en-1-one and *N*-phenylacrylamide could also be cyclopropanated to afford the corresponding products, **7k** and **7l**, in high yields and with high diastereo- and enantioselectivity (Table 3, entries 2 and 3). Although the reaction was sensitive to the *N*-substituents of acrylamides in terms of the yield (Table 3, entries 4 and 5), to

Table 2. Ru(II)-Pheox Catalyzed Asymmetric Cyclopropanation of Various Alkenes with Diethyl Diazomethylphosphonate[a]

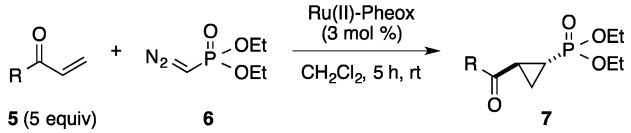


5 (5 equiv) **6** **7**

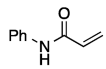
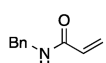
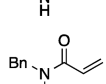
entry	R	7 yield[b] [%]	*trans*/*cis*[c]	ee[d] [%] *trans*
1		93 **7a**	99:1	97
2		87 **7b**	99:1	98
3		92 **7c**	98:2	97
4		87 **7d**	99:1	96
5		84 **7e**	98:2	98
6		92 **7f**	98:2	99
7		72 **7g**	62:38	99
8		84 **7h**	93:7	98
9		79 **7i**	99:1	94

[a]Reaction conditions: alkenes **5** (1 mmol) and diethyl diazomethylphosphonate **6** (0.2 mmol) in the presence of catalyst (3 mol %) under Ar. [b]Isolated yield. [c]Determined by NMR. [d]Determined by chiral HPLC analysis.

Table 3. Ru(II)-Pheox Catalyzed Asymmetric Cyclopropanation of Various α,β-Unsaturated Carbonyl Compounds with Diethyl Diazomethylphosphonate[a]



5 (5 equiv) **6** **7**

entry	**5**	7 yield[b] [%]	*trans*/*cis*[c]	*trans* ee[d] [%]
1		65 **7j**	99:1	98
2		87 **7k**	98:2	98
3		71 **7l**	99:1	98
4		33 **7m**	98:2	78
5		40 **7n**	98:2	87

[a]Reaction conditions: alkenes **5** (1 mmol) and diethyl diazomethylphosphonate **6** (0.2 mmol) in the presence of catalyst (3 mol %) under Ar. [b]Isolated yield. [c]Determined by NMR. [d]Determined by chiral HPLC analysis. Bn = benzyl.

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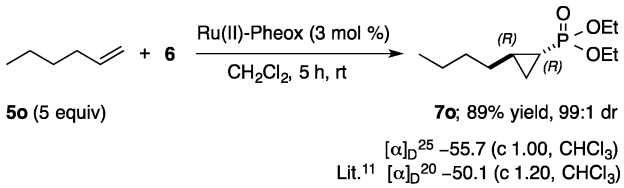
the best of our knowledge, this is the first example of the catalytic asymmetric cyclopropanation of diazomethylphosphonate with electron-deficient alkenes.

To determine the absolute configuration of cyclopropylphosphonates obtained using this catalytic system, we decided to synthesize a known compound, diethyl-2-(butyl)cyclopropylphosphonate **7o**, by carrying out the Ru(II)-Pheox-catalyzed cyclopropanation of diethyl diazomethylphosphonate with hex-1-ene **5o** (Scheme 1). The (1*R*,2*R*) configuration was

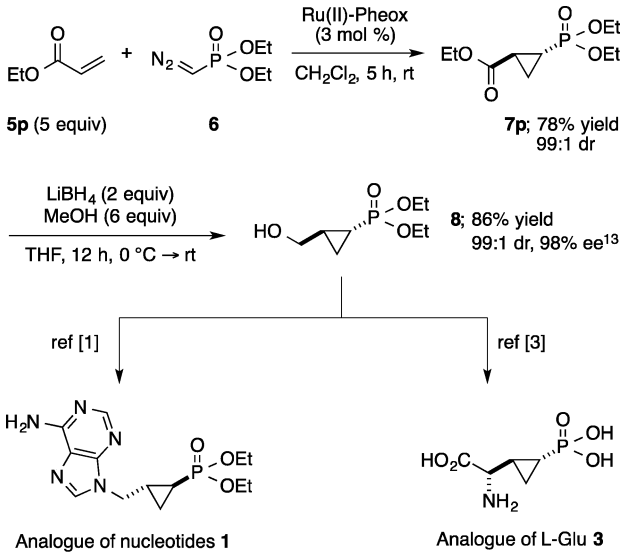
Scheme 1. Determination of Absolute Configuration of Diethyl-2-(butyl)cyclopropylphosphonate 7o



confirmed by a comparison of the optical rotation value reported in the literature.[11] Interestingly, although a normal alkene **5o** was used as the substrate, highly stereoselective cyclopropanation could also be achieved (*trans*/*cis* = 99:1).

Finally, to demonstrate the utility of our highly stereoselective cyclopropylphosphonate synthesis, we prepared a key intermediate in the reported synthesis of the analogue of nucleotide **1** and L-Glu **3** (Scheme 2). The optically active

Scheme 2. Preparation of (−)-Diethyl-2-(hydroxymethyl)cyclopropylphosphonate 8, a Key Intermediate in the Synthesis of Analogue of Nucleotide 1 and L-Glu 3



cyclopropylphosphonate **7p** was readily synthesized by the cyclopropanation of diethyl diazomethylphosphonate with ethyl acrylate **5p** in 78% yield and with high diastereoselectivity (99:1 dr). The reaction of **7p** with 2 equiv of $LiBH_4$ and 6 equiv of MeOH in THF afforded the desired product, (−)-diethyl-2-(hydroxymethyl)cyclopropylphosphonate **8**, in 86% yield and with excellent diastereoselectivity (99:1 dr) and enantioselectivity (98% ee).[12] This novel synthetic route represents a significant improvement in terms of fewer steps and the diastereo- and enantioselectivity efficiency reported until now.[1,3,14]

In conclusion, we developed the highly stereoselective cyclopropanation of alkenes with diethyl diazomethylphosphonate by using the Ru(II)-Pheox complex as the catalyst. Moreover, the cyclopropanation of electron-deficient alkenes such as α,β-unsaturated ester, ketone, and amides could be carried out smoothly under mild reaction conditions to afford the corresponding cyclopropylphosphonate products in high yields and with excellent diastereo- and enantioselectivity. Furthermore, this method confirms the synthetic value of (−)-diethyl-2-(hydroxymethyl) cyclopropylphosphonate **8**, a key intermediate in the synthesis of the analogue of nucleotide **1** and L-Glu **3**. This efficient procedure can contribute to the progress of synthetic organic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Absolute configuration of **7o** was determined to be (1*R*,2*R*) by comparing the reported specific optical rotation: $[\alpha]_D^{25}$ −55.7 (*c* 1.00, $CHCl_3$), Lit. $[\alpha]_D^{20}$ −50.1 (*c* 1.20, $CHCl_3$) for 1*R*,2*R*-isomer, see: Krawczyk, H.; Wasek, K.; Kedzia, J. *Synthesis* **2009**, *9*, 1473−1476.
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