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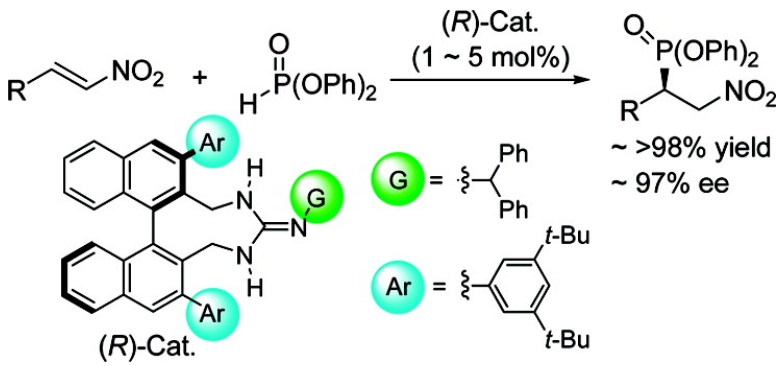

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Enantioselective 1,4-Addition Reactions of Diphenyl Phosphite to Nitroalkenes Catalyzed by an Axially Chiral Guanidine

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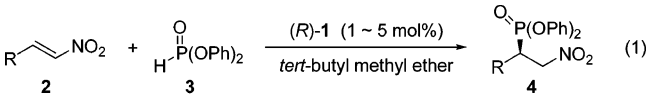
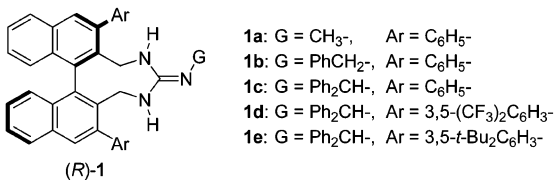
Optically active α- and *β*-amino phosphonic acids and their phosphonate esters are an attractive class of compounds owing to their potent biological activities as non-proteinogenic analogues of α- and *β*-amino acids.[1,2] Although several excellent methods for enantioselective synthesis of α-amino phosphonate esters have been established,[3] using either metal-based catalysts or organocatalysts,[4] asymmetric synthesis of *β*-amino phosphonate derivatives has been largely unexplored, despite the intriguing therapeutic action of these compounds.[2] In this context, it is considered that asymmetric 1,4-addition reaction of dialkyl phosphites to nitroalkenes[5,6] provides a practical route to the *β*-amino phosphonates, which can be transformed from the corresponding 1,4-addition products,[7] *β*-nitro phosphonates, through simple reduction of the nitro group. The development of catalytic enantioselective 1,4-addition reaction of nitroalkenes with disubstituted phosphites is hence a substantial step toward the synthesis of enantioenriched *β*-amino phosphonates.[8] Recently, we successfully developed novel axially chiral guanidines (**1**)[9] as highly efficient Brønsted base catalysts for promotion of enantioselective transformations[10] via deprotonation of 1,3-dicarbonyl compounds. Herein, we report the first highly enantioselective 1,4-addition reaction of nitroalkenes (**2**) with diphenyl phosphite (**3**) catalyzed by axially chiral guanidines (**1**) (eq 1). The guanidine catalyst (**1**) successfully activated the phosphorus nucleophile and enabled high enantioselectivity and catalytic efficiency for a broad range of nitroalkenes bearing aromatic or aliphatic substituents.





During the course of our studies, enantioselective catalysis of the 1,4-addition reactions of **2** with **3** were reported by Wang and co-workers.[11] In their report, moderate to high enantioselectivities were attained through extensive screening of cinchona alkaloid derivatives,[12] which have been widely utilized as efficient organocatalysts. In our approach, we explored suitable substituents on the axially chiral guanidine catalyst (**1**) by changing the alkyl moiety G and the Ar group. An initial screening was performed in the reaction of *β*-nitrostyrene (**2a**: R = Ph) with diphenyl phosphite (**3**) using 5 mol % of **1** in diethyl ether at 0 °C in the presence of molecular sieves (MS) 4A.[13] As shown in Table 1, it is noteworthy that G and Ar substituents exhibited a strong impact not only on the enantioselectivity but also on the catalytic efficiency (entries 1−5). The enantioselectivity increased step by step with an increase in the steric size of the alkyl moiety G (entries 1−3). The introduction of 3,5-substituents to the phenyl ring of the Ar substituents was the most effective in enhancing both the enantioselectivity and catalytic efficiency (entries 4 and 5); the reaction was completed within 10 min with a marked increase in enantioselectivity relative to the catalyst (**1c**) having the unsubstituted Ar group, regardless of the electronic properties of the Ar substituents. As expected, lowering the temperature to −40 °C resulted in an enhanced enantioselectivity (entry 6). Further screening of ethereal solvents using (*R*)-**1d** revealed that *tert*-butyl methyl ether was the best solvent among those examined (entries 6−9). Thus catalysis by (*R*)-**1e** was reinvestigated in *tert*-butyl methyl ether. As a result, it was found that **2a** was consumed completely within 10 min even at −40 °C, while the enantioselectivity was as high as that observed in catalysis by (*R*)-**1d** (entry 10 vs 9). The catalytic activity of (*R*)-**1e** is prominent; the catalyst loading can be reduced from 5 to 1 mol % without any loss in enantioselectivity (entry 10 vs 11).

Table 1. Enantioselective 1,4-Addition Reaction of Nitroalkene (**2a**: R = Ph) with Diphenyl Phosphite (**3**) Catalyzed by (*R*)-**1**[a]

entry	**1** (mol %)	solvent	temp	time	yield (%)	ee (%)[b]
1	**1a** (5)	Et_2O	0 °C	4 h	66	6
2	**1b** (5)	Et_2O	0 °C	20 min	70	16
3	**1c** (5)	Et_2O	0 °C	20 min	58	43
4	**1d** (5)	Et_2O	0 °C	10 min	98	83
5	**1e** (5)	Et_2O	0 °C	10 min	>98	79
6	**1d** (5)	Et_2O	−40 °C	30 min	91	87
7	**1d** (5)	*i*-Pr_2O	−40 °C	2 h	92	86
8	**1d** (5)	CPME[c]	−40 °C	4 h	81	86
9	**1d** (5)	*t*-BuOMe	−40 °C	1 h	>98	92
10	**1e** (5)	*t*-BuOMe	−40 °C	10 min	>98	92
11[d]	**1e** (1)	*t*-BuOMe	−40 °C	2 h	94	92

[a] Unless otherwise noted, all reactions were carried out using 0.0025 mmol of (*R*)-**1** (5 mol %), 0.05 mmol of **2a**, and 0.075 mmol of **3** (1.5 equiv) in 0.25 mL of indicated solvent in the presence of MS 4A (20 mg). [b] Enantiomeric excess was determined by chiral HPLC analysis (see Supporting Information for details). [c] Cyclopentyl methyl ether. [d] The reaction was carried out using 0.002 mmol of (*R*)-**1e** (1 mol %), 0.2 mmol of **2a**, and 0.22 mmol of **3** (1.1 equiv) in 1.0 mL of *tert*-butyl methyl ether in the presence of MS 4A (80 mg).

With the optimized reaction conditions in hand, we then investigated the scope of the enantioselective 1,4-addition reaction using (*R*)-**1e** as a promising catalyst. As shown in Table 2, a broad range of nitroalkenes (**2**) is applicable to the present transformation. A series of nitroalkenes (**2b**−**g**) bearing aromatic substituents with various electronic properties all proved to be excellent substrates with respect to enantioselectivity and chemical yield (entries 1−6). The reaction proceeded smoothly in the presence of 1 mol % catalyst, giving the corresponding product (**4b**−**g**) in nearly quantitative yield with high enantioselectivity. In contrast, heteroaromatic-substituted nitroalkenes (**2h** and **i**) gave the products (**4h** and **i**) in modest yield (around 50%) under the optimized

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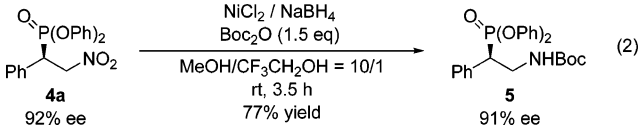
Table 2. Enantioselective 1,4-addition of Various Nitroalkenes (**2**) with **3** Catalyzed by (*R*)-**1e** (1 mol %)[a]

entry	2	4	time (h)	yield (%)[b]	ee (%)[c]
1	**2b**: 4-$MeOC_6H_4$−	**4b**	4.5	91	91
2	**2c**: 4-BrC_6H_4−	**4c**	1	97	91
3	**2d**: 2-$MeOC_6H_4$−	**4d**	3	>98	88
4	**2e**: 2-BrC_6H_4−	**4e**	0.5	98	94
5	**2f**: 2-$NO_2C_6H_4$−	**4f**	0.5	96	97
6	**2g**: α-naphthyl	**4g**	0.5	>98	94
7[d]	**2h**: 2-furyl	**4h**	7	79	89
8[d]	**2i**: thiophen-2-yl	**4i**	4.5	86	91
9[e]	**2j**: $(CH_3)_2CHCH_2$−	**4j**	0.5	84	80
10[e]	**2k**: *c*-C_6H_{11}−	**4k**	1	87	85
11	**2l**: $CH_3(CH_2)_4$−	**4l**	6	>98	87

[a] Unless otherwise noted, all reactions were carried out using 0.002 mmol of (*R*)-**1e** (1 mol %), 0.2 mmol of **2**, and 0.22 mmol of **3** (1.1 equiv) in the presence of MS 4A (80 mg) in 1.0 mL of *tert*-butyl methyl ether at −40 °C. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis. Absolute configuration was determined to be *S* for **4i** (see Supporting Information for details). [d] The reaction was carried out using 0.01 mmol of (*R*)-**1e** (5 mol %) at −60 °C. [e] The reaction was carried out using 0.01 mmol of (*R*)-**1e** (5 mol %).

reaction conditions (1 mol % of (*R*)-**1e**, at −40 °C). This problem could be circumvented by lowering the reaction temperature to −60 °C and increasing the catalyst loading to 5 mol % (entries 7 and 8). Although aliphatic-substituted nitroalkenes (**2j**−**l**) exhibited slightly lower enantioselectivities than those of their aromatic counterparts (entries 9−11), their performance in the present enantioselective reaction with diphenyl phosphite (**3**) is still good taking into account their typically low reactivity in 1,4-addition reactions; the corresponding products (**4j**−**l**) were obtained in high chemical yield.

Finally, the reduction of the nitro group in **4a** was examined under modified nickel boride conditions (eq 2). The reduction was readily accomplished in the presence of Boc_2O to yield *N*-Boc β-amino phosphonate (**5**) without compromising the integrity of the stereogenic center.[14]



(2)

In conclusion, we have demonstrated the highly enantioselective 1,4-addition reaction of nitroalkenes with diphenyl phosphite catalyzed by a newly developed axially chiral guainidine. A broad range of nitroalkenes, bearing not only aromatic but also aliphatic substituents, is applicable to the present enantioselective reaction. The method facilitates the highly enantioenriched synthesis of β-amino phosphonate derivatives of biological and pharmaceutical importance. Further studies utilizing the activation of phosphorus nucleophiles by axially chiral guanidines are underway in our laboratory.

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Supporting Information Available: Representative experimental procedure, spectroscopic data for axially chiral guanidine catalysts (**1**), and 1,4-addition products (**4**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **5** was hydrolyzed to *N*-Boc protected phosphonic acid without considerable loss of stereochemical integrity under hydrogenation conditions (see Supporting Information for details); also see ref 11.

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