Bicyclic guanidine-catalyzed enantioselective phospha-Michael reaction: synthesis of chiral β-aminophosphine oxides and β-aminophosphines†

Xiao Fu, Zhiyong Jiang and Choon-Hong Tan*

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Chiral bicyclic guanidine has been found to catalyze the phospha-Michael reactions of diaryl phosphine oxide to nitroalkenes with high enantioselectivities, offering a direct methodology to prepare chiral β-aminophosphine oxides and β-aminophosphines.

Chiral compounds containing P–C bonds have found important synthetic roles in metal-catalyzed[1] and organocatalytic reactions.[2] Such compounds are typically prepared using enantiopure starting materials, chiral auxiliaries or by resolution of the racemic phosphines.[3] Successful catalytic methods include the synthesis of chiral α-amino phosphonic acids *via* the hydrophosphonylation of imines with dialkyl phosphites [$(RO)_2P(O)H$].[4] Catalysts such as lanthanoid–potassium–BINOL complexes,[5] quinine,[6] thiourea,[7] and chiral phosphoric acid[8] were employed. It is also possible to conduct catalytic asymmetric hydrophosphination of alkenes with secondary phosphines (R_2PH) using organonickel complexes[9] or bifunctional *Cinchona* alkaloid.[10] Recently, hydrophosphination of α,β-unsaturated aldehydes with secondary phosphines were achieved with an iminium-ion strategy using chiral protected diarylprolinols.[11]

The direct addition of P(O)–H bonds (dialkyl phosphites or dialkyl phosphine oxides [$R_2P(O)H$]) across activated alkenes is one of the most convenient routes to generate P–C bonds.[12] Synthetically useful examples have utilized chiral phosphite,[13] *P*-chiral phosphine oxides[14] or chiral α,β-unsaturated amides[15] as acceptors. Strong inorganic bases such as LDA, *n*BuLi or NaH were generally used and these are sometimes described as phospha-Michael reactions. A quinine-catalyzed version were recently attempted with diphenyl phosphite and nitroalkenes.[16]

Phospha-Michael reactions can be effectively catalyzed by a strong organic Brønsted base such as guanidine.[17] The donors, dialkyl phosphites or dialkyl phosphine oxides, are in equilibrium with their σ^3,λ^3-tautomers,[6b,8,18] $(RO)_2P(OH)$ and $R_2P(OH)$. In the presence of guanidine, the equilibrium is likely to favor the active intermediate, the σ^3,λ^3-tautomers. Chiral guanidines and guanidinium salts are excellent enantioselective catalysts for a variety of reactions[19] including Strecker, Diels–Alder and Michael reactions.[20] Thus, we envisioned an enantioselective phospha-Michael reaction using chiral guanidines.

Department of Chemistry, 3 Science Drive 3, National University of Singapore, Singapore, 117543. E-mail: chmtanch@nus.edu.sg
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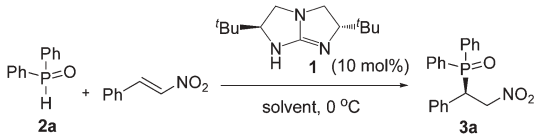
We found that with 10 mol% of chiral bicyclic guanidine **1**, the addition of diphenyl phosphine oxide **2a** to β-nitrostyrene proceeded smoothly in various solvents (Table 1, entries 1–3).‡ Moderate enantioselectivities were obtained which improved when ether type solvents were used (entries 4–6). Diethyl ether gave the best results, providing the adduct **3a** in 60% ee (entry 7). Subsequently, a series of diaryl phosphine oxides **2a–f**, with a variety of substituents were tested (Table 2, entries 2–4); the enantioselectivities obtained were similar to diphenyl phosphine oxide **2a**. Di(1-naphthyl)- and di(2-naphthyl)phosphine oxides, **2e** and **2f** (entries 5 and 6) were also evaluated; enantioselectivities of 65 and 82% were obtained respectively. Most adducts except **3d** are crystalline and we were able to improve the optical purity of all adducts to >90% ee after a single recrystallization from MeOH or *t*BuOMe–CH_2Cl_2.

The reaction between di(1-naphthyl) phosphine oxide **2f** and β-nitrostyrene can be further optimized to 91% ee by decreasing the reaction temperature to −40 °C (Table 3, entry 1). Using the optimized conditions, the addition of **2f** to various aryl nitroalkenes were investigated (entries 2–9). Adducts **4a–c** were obtained using *o*-, *m*- and *p*-chloro substituted aryl nitroalkenes (entries 2–4). High yields and high ees were obtained; showing that substitution pattern on the aryl ring would not affect the enantioselectivity. Other substrates containing bromo, nitro and methyl substituents (entries 5–8) also gave good results. Most substrates required only 12 h or less of reaction time, but the bulky (*E*)-2-(2-nitrovinyl)naphthalene (entry 9) required >36 h for the reaction to be complete. The optical purity of most adducts **3f** and

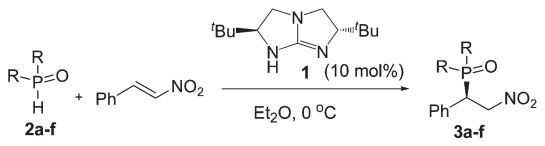
Table 1 Chiral bicyclic guanidine-catalyzed phospha-Michael reactions of β-nitrostyrene



Entry	Solvent	*t*/h	Yield[a] (%)	ee[b] (%)
1	CH_3CN	1	91	12
2	CH_2Cl_2	4	54	30
3	Toluene	0.5	82	40
4	*t*-BuOMe	15	79	30
5[c]	*p*-Dioxane	27	60	40
6	THF	1	85	45
7	Et_2O	13	64	60

[a] Isolated yield. [b] Determined by HPLC. [c] Reaction performed at rt.

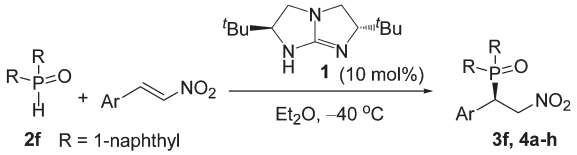
Table 2 Chiral bicyclic guanidine-catalyzed phospha-Michael reactions with various diaryl phosphine oxides



Entry	**2** [R]	Adduct	*t*/h	Yield[a] (%)	ee[b] (%)
1	**2a** [Ph]	**3a**	13	64	60 (96)
2	**2b** [4-FC_6H_4]	**3b**	14	92	60 (>99)
3	**2c** [4-PhC_6H_4]	**3c**	40	85	50 (91)
4[c]	**2d** [2-EtC_6H_4]	**3d**	40	77	75[d]
5	**2e** [2-naphthyl]	**3e**	6	92	65 (99)
6	**2f** [1-naphthyl]	**3f**	8	95	82

[a] Isolated yield. [b] Chiral HPLC; ee in parentheses was obtained after single recrystallization. [c] Reaction performed at −40 °C. [d] Adduct is a liquid.

Table 3 Chiral bicyclic guanidine-catalyzed phospha-Michael reactions of aryl nitroalkenes



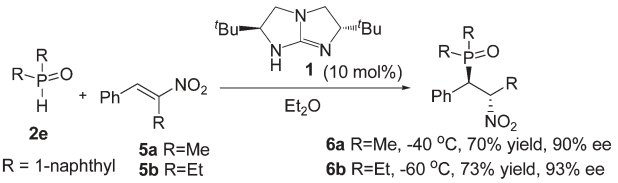
2f R = 1-naphthyl — **3f, 4a-h**

Entry	Ar	Adduct	*t*/h	Yield[a] (%)	ee[b] (%)
1	Ph	**3f**	36	94	91 (95)
2	4-ClC_6H_4	**4a**	12	94	96 (>99)
3	3-ClC_6H_4	**4b**	12	96	90 (95)
4	2-ClC_6H_4	**4c**[c]	12	98	93 (99)
5	4-BrC_6H_4	**4d**	12	99	93 (>99)
6	3-$NO_2C_6H_4$	**4e**	12	95	96 (96)
7	2-$NO_2C_6H_4$	**4f**	12	99	96[d]
8	4-MeC_6H_4	**4g**	16	90	90 (96)
9	2-naphthyl	**4h**	36	75	92 (92)

[a] Isolated yield. [b] Chiral HPLC; ee in parentheses was obtained after single recrystallization from hexane and CH_2Cl_2. [c] The absolute configuration was determined through X-ray crystallographic analysis of **4c**. [d] Recrystallization did not work.

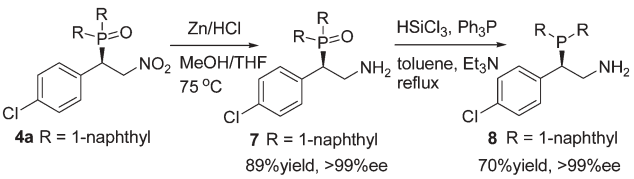
4a–h can be further enhanced with a single crystallization. Excellent optical purity (>99% ee) can be obtained for several samples. For highly crystalline adducts (**4a**, **4c** and **4d**), a more convenient and practical protocol was developed for their synthesis. At 0 °C, the reactions of these substrates were completed within 3 h. The reaction mixture was left standing in the −80 °C freezer overnight. Adducts with excellent ee (>99%) and yield of 70–90% can be obtained by simple filtration and no further purification was needed.

The diastereoselectivity of this reaction were investigated using two tri-substituted nitroalkenes, (*E*)-β-methyl-β-nitrostyrene **5a** and (*E*)-β-ethyl-β-nitrostyrene **5b**, which was prepared from nitroethane and nitropropane respectively (Scheme 1). Using di(1-naphthyl) phosphine oxide **2f** as the donor, good diastereometric ratios (dr) of 95 : 5 were observed (see ESI† for relative stereochemistry determination). Good enantioselectivities of 90 and 93% ee were obtained for adducts **6a** and **6b** respectively.



Scheme 1 Phospha-Michael reaction between phosphine oxide and trisubstituted nitroalkenes.

This reaction is an attractive strategy for the synthesis of optically active α-substituted β-aminophosphine oxides. These chiral phosphine oxides can be investigated as catalysts for allylation and ring opening reactions of *meso*-epoxides[21] or as ligands in metal-catalyzed reactions.[22] However, it is the potential to prepare novel α-substituted β-aminophosphines as P,N-ligands[23] for metal-catalyzed reactions that is particularly exciting. These ligands will be complementary to the α-aminophosphines, which are readily prepared from amino acids.[24] The β-aminophosphine oxide **7** can be obtained by the selective reduction of the nitro group using zinc in acidic conditions (Scheme 2). The optical activity was found to remain at >99% ee. β-Aminophosphines oxide **7** can be further reduced to β-aminophosphines **8** using trichlorosilane with no loss in optical activity (determined by converting **8** back to **7** using H_2O_2).



Scheme 2 Synthesis of chiral β-aminophosphine oxides and β-aminophosphines.

In summary, we have disclosed the first catalytic asymmetric phospha-Michael reaction between diaryl phosphine oxide and nitroalkenes. This is a direct and atom economical method to synthesize chiral α-substituted β-phosphine oxides and β-aminophosphines. These novel aminophosphines are potentially useful as organocatalysts and ligands in metal-catalyzed reactions.

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Notes and references

‡ Standard bicyclic guanidine catalyzed reactions between diaryl phosphine oxide and nitroalkenes: To a 50 ml RBF containing catalyst **1** (1.8 mg, 0.008 mmol, 10 mol%) and a stirring bar, di(1-naphthyl) phosphine oxide **2f** (24.2 mg, 0.08 mmol) and anhydrous diethyl ether (25 ml), were added in this sequence and stirred at −40 °C for 1 h. 4-Chloro-β-nitrostyrene (73.4 mg, 0.4 mmol, 5 eq.) was added to the reaction mixture and stirred at −40 °C for 12 h. Solvent was removed from the reaction mixture and loaded onto a short silica gel column. This was followed by flash chromatography (gradient elution with hexane–EA mixtures; 10 : 1 to 2 : 1). Adduct **4a** (36.5 mg) was obtained as a white solid in 94% yield and 96% ee.

Crystal data for **4c**: CCDC 659170. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b713151h

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