Asymmetric Catalysis

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Squaramide-Catalyzed Enantioselective Michael Addition of Diphenyl Phosphite to Nitroalkenes**

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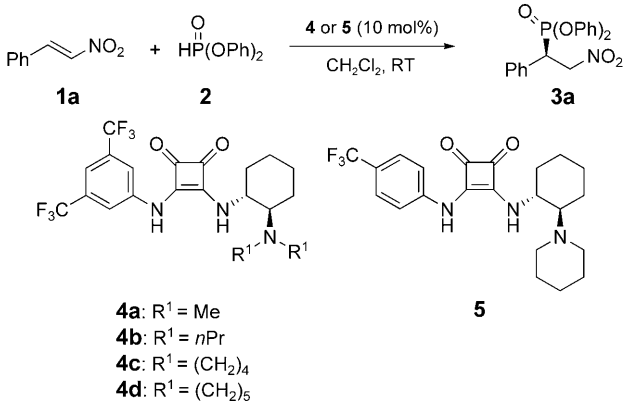
Horiguchi and Kandatsu's isolation of 2-amino ethyl phosphonic acid from the rumen protozoa in 1959 demonstrated for the first time the reported occurrence of a C–P bond in nature.[1] Such β-amino phosphonic acids, as phosphorus analogues of β-amino acids, have been the subject of intense interest owing to their diverse biological activities.[2] In contrast to the variety of methods for the asymmetric synthesis of α-amino phosphonic acid derivatives,[3,4] the enantioselective synthesis of β-amino phosphonic acids remains a considerable challenge.[5] One possible solution is the enantioselective Michael addition of diaryl or dialkyl phosphites to nitroalkenes to provide β-nitro phosphonates, wherein reduction of the nitro group would afford chiral β-amino phosphonates.[6–8] To date, there have been only two reports describing the use of metal-free catalysts for the conjugate addition reaction of phosphites.[9–11] Wang and co-workers showed that quinine successfully promotes this reaction to afford the phosphite addition products in modest to very good enantioselectivities.[9] Significantly higher *ee* values were obtained by Terada and co-workers, who used an intricate, axially chiral biaryl guanidine derivative to promote the conjugate addition.[10,12] In connection with our interest in enantioselective reactions promoted by hydrogen bond donors,[13,14] we have developed a new family of chiral catalysts based on a squaramide scaffold.[15] The modular nature of this scaffold allows quick access to a wide range of derivatives that can be tuned in regard to both their chiral environment and p*K*a of the donor hydrogen atoms. This new family of catalysts opens up opportunities for the exploration of new reactions and also the development of highly effective catalysts for known reactions. We report herein the use of a simple, easily prepared squaramide catalyst to promote the Michael addition reaction of diphenyl phosphite to a broad range of both aryl- and alkyl-substituted nitroalkenes, affording the products in high yields and uniformly excellent enantioselectivities.

Despite the plethora of successful reactions promoted by various thiourea-based catalysts,[16] the only reported use of a chiral thiourea to promote the addition of diphenyl phosphite to *trans*-β-nitrostyrene is that by Wang et al., who obtained the addition product in 21% yield and 8% *ee* after a reaction time of 24 h.[9] Given the structural differences between thioureas and squaramides, and particularly the spacing between the two donor hydrogen atoms,[15] we expected to see differences in their reactivity; indeed, addition of the dimethyl-substituted squaramide **4a**[17] to a solution of *trans*-β-nitrostyrene **1a** and diphenyl phosphite **2** at room temperature promoted a rapid reaction that went to 98% conversion after just 45 min, and afforded the addition product in 81% *ee* (Table 1, entry 1).

To optimize the catalyst, a brief study of the relationship between catalyst structure and reaction enantioselectivity was performed (Table 1). The effect of changing the substituents on the nitrogen atom of the catalyst was examined first (Table 1, entries 2–4). Catalyst **4b**, bearing bulkier *n*-propyl groups on the nitrogen, improved the enantioselectivity slightly, with an accompanying diminution in the reaction rate (Table 1, entry 2). Higher enantioselectivities were observed for the cyclic amine derivatives (Table 1, entries 3 and 4); thus, the pyrrolidine-substituted catalyst **4c** gave the product in 88% *ee*, and the corresponding piperidine-substituted catalyst **4d** gave the product in 95% *ee*. The improved enantioselectivities of the cyclic amine derivatives,

Table 1: Michael addition of diphenyl phosphite **2** to *trans*-β-nitrostyrene **1a**.[a]



4a: R^1 = Me
4b: R^1 = *n*Pr
4c: R^1 = $(CH_2)_4$
4d: R^1 = $(CH_2)_5$

Entry	Catalyst	*t*	Conversion [%][b]	*ee* [%]
1	**4a**	45 min	98	81
2	**4b**	1 h	96	84
3	**4c**	30 min	98	88
4	**4d**	30 min	97	95
5	**5**	15 min	99	96

[a] Reactions were carried out on 0.20 mmol of **1a**, with 1.25 equiv of **2** and 10 mol% **4** or **5** in 1.0 mL CH_2Cl_2 at room temperature. [b] Reaction conversions were determined by ^{1}H NMR spectroscopy.

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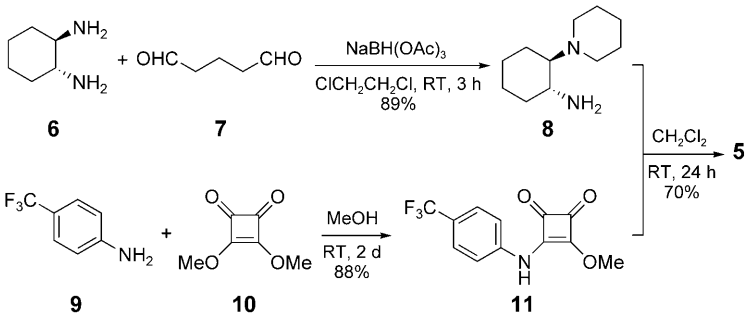
and particularly **4d**, are attributed to the relative conformational rigidity of these substituents, which allows a more organized transition state that better discriminates between the two sides of *trans*-β-nitrostyrene. After a brief investigation of different substituents on the aryl moiety, we chose catalyst **5** for further study owing to its ease of preparation and high enantioselectivity (Table 1, entry 5). Catalyst **5** can be prepared in three steps from commercial starting materials (Scheme 1).



Scheme 1. Synthesis of catalyst **5**.

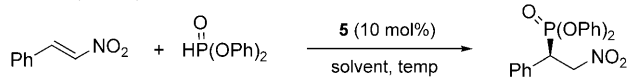
A survey of solvents showed that the phosphite conjugate addition reaction is relatively insensitive to the solvent used (Table 2). The enantioselectivity observed when the reaction was performed in toluene was essentially the same as that obtained in ether solvents, including tetrahydrofuran (Table 2, entries 1–4).[18] Even highly polar solvents, such as acetonitrile and acetone, afforded the addition product with *ee* values of at least 90% (Table 2, entries 5 and 6). The best solvent was found to be dichloromethane, in which, as noted earlier, reaction at room temperature gave the product in 96% *ee* (Table 2, entry 7). As expected, the enantioselectivity increased as the reaction temperature was lowered (Table 2, entries 8–10). Given the practical advantages of carrying out the reaction at 0°C, this temperature was used for evaluating the scope of the method.

A diverse range of aryl-substituted nitroalkene substrates were selected to evaluate the scope of the squaramide catalyzed conjugate addition reaction. As shown in Table 3, the enantioselective conjugate addition reaction is remarkably general: under the optimized conditions, the full spectrum of substrates underwent the reaction in 30 minutes or less and afforded the products in good yields with 96–99% *ee*, regardless of the electronic properties and locations of substituents. The parent reaction of the simple nitrostyrene can be scaled up without untoward effect on either the yield or enantioselectivity (Table 3, entry 1). It is worth noting that even substrates containing acidic protons, such as **1l** and **1q**, which are capable of forming competing hydrogen bonds, were tolerated by this procedure and afforded the expected products in 98% *ee* (Table 3, entries 12 and 17).

Among the most challenging substrates for the organocatalyzed phosphite conjugate addition reaction are alkyl-substituted nitroalkenes.[9,10] The highest enantioselectivity recorded in the literature for such substrates is 87% *ee*.[19] To evaluate the effectiveness of catalyst **5** in these reactions, several alkyl-substituted nitroalkenes were subjected to the optimized conditions. As summarized in Table 4, excellent enantioselectivities were obtained even for aliphatic nitroalkenes (95–97% *ee*). Compared to aryl-substituted substrates, the reactions of alkyl substrates were slower, presumably owing to steric and electronic factors. To circumvent the slow rate of reaction of substrates with secondary and tertiary alkyl groups, the catalyst loading was increased to 20 mol% (Table 4, entries 4-6). With this modification, even the highly hindered *tert*-butyl-containing substrate **3w** reacted to completion, giving the phosphite addition product in 83% yield and 96% *ee* (Table 4, entry 6).

The results above show squaramide **5** to be a remarkably effective catalyst for the enantioselective Michael addition reactions of diphenyl phosphite to nitroalkenes. The reaction provides a simple, highly enantioselective synthesis of chiral β-nitro phosphonates, which are precursors to biologically active β-amino phosphonic acids. The high yields and uniformly excellent enantioselectivities obtained for both aryl- and alkyl-substituted nitroalkenes, including those bearing acidic protons or sterically-demanding substituents, point to the unique capability of the squaramide scaffold. Given the simple, modular assembly of squaramides, and the ready availability of its precursors, this scaffold is expected to provide many further opportunities in asymmetric catalysis.

Table 2: Michael addition of diphenyl phosphite **2** to *trans*-β-nitrostyrene **1a**, catalyzed by **5**.[a]



Entry	Solvent	*T* [°C]	*t*	Conversion [%][b]	*ee* [%]
1	toluene	RT	1 h	90	94
2	Et_2O	RT	1 h	81	93
3	*t*BuOMe	RT	1 h	71	94
4	THF	RT	1 h	99	93
5	MeCN	RT	1 h	89	90
6	acetone	RT	1 h	64	93
7	CH_2Cl_2	RT	15 min	99	96
8	CH_2Cl_2	0	30 min	99 (95[c])	97
9	CH_2Cl_2	−10	1 h	99	98
10	CH_2Cl_2	−20	2 h	99	98.4

[a] Reactions were carried out on 0.20 mmol of **1a**, with 1.25 equiv of **2** and 10 mol% **5**, in 1.0 mL solvent. [b] Reaction conversions were determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product.

Experimental Section

Representative procedure (**3a**): Compound **1a** (30 mg, 0.20 mmol) and catalyst (*R*,*R*)-**5** (8.4 mg, 0.020 mmol) was added to dichloromethane (1.0 mL) at room temperature. The stirred mixture was cooled in an ice-water bath for 10 min before addition of **2** (48 μL, 0.25 mmol). After 30 min, the reaction mixture was loaded directly onto a flash chromatography column. Elution with hexanes/ethyl acetate (10:1 to 6:1 to 3:1) afforded the title compound as a white solid: 73 mg, 95% yield, 97% *ee*. On a 1 mmol scale, the product was obtained in 99% yield, 97% *ee*.

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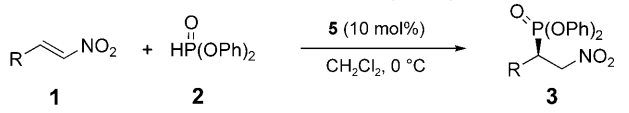
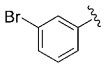
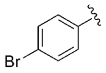
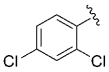
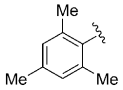
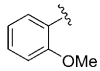
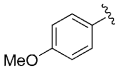
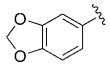
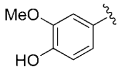
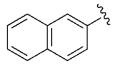
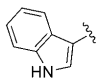
Table 3: Enantioselective Michael addition reaction of diphenyl phosphite **2** to aromatic *trans*-nitroalkenes **1** catalyzed by **5**.[a]

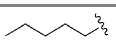
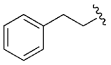


1 **2** **3**

Entry	Product	R	*t* [min]	Yield [%][b]	*ee* [%]
1[c]	**3a**		30	99	97
2	**3b**		15	92	97
3	**3c**		15	98	97
4	**3d**		15	94	97
5	**3e**		15	98	97
6	**3f**		30	96	97
7	**3g**		30	97	99
8	**3h**		30	98	96
9	**3i**		15	98	98
10	**3j**		30	98	99
11	**3k**		30	99	98
12	**3l**		30	79	98
13	**3m**		15	98	97
14	**3n**		15	99	99
15	**3o**		30	83	97
16[d]	**3p**		30	84	97
17	**3q**		15	99	98

[a] Unless otherwise noted, reactions were carried out on 0.20 mmol of **1**, with 1.25 equiv of **2** and 10 mol% **5** in 1.0 mL CH_2Cl_2 at 0°C. [b] Yield of isolated product. [c] 1.0 mmol scale reaction. [d] The absolute configuration of **3p** was assigned as *S* (see the Supporting Information).

Table 4: Enantioselective Michael addition reaction of diphenyl phosphite **2** to aliphatic *trans*-nitroalkenes **1** catalyzed by **5**.[a]

Entry	Product	R	*t* [h]	Yield [%][b]	*ee* [%]
1	**3r**		1.5	94	96
2	**3s**		1.5	95	95
3	**3t**		1.5	69	96
4[c]	**3u**		1.5	89	95
5[c]	**3v**		1.5	87	97
6[c]	**3w**		1.5	83	96

[a] Unless otherwise noted, reactions were carried out on 0.20 mmol of **1**, with 1.25 equiv of **2** and 10 mol% **5** in 1.0 mL CH_2Cl_2 at 0°C. [b] Yield of isolated product. [c] Reaction was carried out using 20 mol% **5**.

Keywords: asymmetric catalysis · Michael addition · nitroalkanes · organocatalysis · squaramides

[1] a) M. Horiguchi, M. Kandatsu, *Nature* **1959**, *184*, 901–902; b) L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley, New York, NY, **2000**, pp. 351–386.

[2] For reviews on β-amino phosphonic acids and its derivatives thereof, see: a) F. Palacios, C. Alonso, J. M. de Los Santos, *Chem. Rev.* **2005**, *105*, 899–931; b) F. Palacios, C. Alonso, J. M. de Los Santos in *Enantioselective Synthesis of β-Amino Acids*, 2nd ed. (Eds.: E. Juaristi, V. A. Soloshonok), Wiley, Hoboken, NJ, **2005**, pp. 277–318.

[3] For the biological activity of α-amino phosphonic acids, see: a) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity* (Eds.: V. P. Kukhar, H. R. Hudson), Wiley, New York, NY, **2000**; b) W. W. Metcalf, W. A. van der Donk, *Annu. Rev. Biochem.* **2009**, *78*, 65–94, and references therein.

[4] For reviews on stereoselective synthesis of α-amino phosphonic acids and their derivatives, see: a) J. A. Ma, *Chem. Soc. Rev.* **2006**, *35*, 630–636; b) M. Ordóñez, H. Rojas-Cabrera, C. Cativiela, *Tetrahedron* **2009**, *65*, 17–49.

[5] Examples of the catalytic asymmetric synthesis of β-amino phosphonates and related compounds include: β-amino-α-hydroxy phosphonates by aminohydroxylation: a) G. Cravotto, G. B. Giovenzana, R. Pagliarin, G. Palmisano, M. Sisti, *Tetrahedron: Asymmetry* **1998**, *9*, 745–748; b) A. A. Thomas, K. B. Sharpless, *J. Org. Chem.* **1999**, *64*, 8379–8385; α-hydroxy-β-nitro phosphonates using the nitroaldol reaction: c) T. Mandal, S. Samanta, C. Zhao, *Org. Lett.* **2007**, *9*, 943–945; d) X. Chen, J. Wang, Y. Zhu, D. Shang, B. Gao, X. Liu, X. Feng, Z. Su, C. Hu, *Chem. Eur. J.* **2008**, *14*, 10896–10899; α-acyl-β-amino phosphonates by using Mannich reactions: e) A. Kjærsgaard, K. A. Jorgensen, *Org. Biomol. Chem.* **2005**, *3*, 804–808; f) Z. Chen, K. Yakura, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 3239–3242; α-diazo-β-amino phosphonates using Mannich reactions: g) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054–10055; β-amino-α-nitro phosphonates using the Mannich reaction: h) J. C. Wilt, M. Pink, J. N. Johnston, *Chem. Commun.* **2008**, 4177–4179; β-substituted-β-amino phosphonates from hydrogenations: i) R. Kadyrov, J. Holz, B. Schaeffner, O. Zayas, J. Almena, A. Boerner, *Tetrahedron: Asymmetry* **2008**, *19*, 1189–1192; j) S. Doherty, J. G. Knight, A. L. Bell, S. El-Menabawey, C. M. Vogels, A. Decken, S. A. Westcott, *Tetrahedron: Asymmetry* **2009**, *20*, 1437–1444.

[6] For reviews on the phospha-Michael reaction, see: a) A. N. Pudovik, I. V. Konovalova, *Synthesis* **1979**, 81–96; b) D. Enders,

A. Saint-Dizier, M. I. Lannou, A. Lenzen, *Eur. J. Org. Chem.* **2006**, 29 – 49.

[7] Examples of diastereoselective Michael addition reactions of dialkyl phosphites to nitroalkenes include: chiral nitroalkenes: a) H. Paulsen, W. Greve, *Chem. Ber.* **1973**, *106*, 2114 – 2123; b) H. Yamamoto, T. Hanaya, H. Kawamoto, S. Inokawa, M. Yamashita, M. A. Armour, T. T. Nakashima, *J. Org. Chem.* **1985**, *50*, 3516 – 3521; c) K. Pachamuthu, I. Figueroa-Perez, I. A. I. Ali, R. R. Schmidt, *Eur. J. Org. Chem.* **2004**, 3959 – 3961; chiral dialkyl phosphites: d) D. Enders, L. Tedeschi, J. W. Bats, *Angew. Chem.* **2000**, *112*, 4774 – 4776; *Angew. Chem. Int. Ed.* **2000**, *39*, 4605 – 4607; e) D. Enders, L. Tedeschi, D. Foerster, *Synthesis* **2006**, 1447 – 1460.

[8] For the enantioselective Michael addition reaction of dialkyl phosphites to nitroalkenes catalyzed by aluminum lithium bis(binaphthoxide), see: V. Rai, I. N. N. Namboothiri, *Tetrahedron: Asymmetry* **2008**, *19*, 2335 – 2338.

[9] J. Wang, L. D. Heikkinen, H. Li, L. Zu, W. Jiang, H. Xie, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 1052 – 1056.

[10] M. Terada, T. Ikehara, H. Ube, *J. Am. Chem. Soc.* **2007**, *129*, 14112 – 14113.

[11] For reviews on organocatalytic enantioselective conjugate addition reactions, see: a) D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; c) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065 – 2092.

[12] Metal-free enantioselective Michael addition reactions of other phosphorous nucleophiles have been reported: diaryl phosphine/phosphine oxide addition to nitroalkenes: a) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri, P. Melchiorre, *Chem. Commun.* **2007**, 722 – 724; b) X. Fu, Z. Jiang, C. Tan, *Chem. Commun.* **2007**, 5058 – 5060; hydrophosphination/phosphonylation of α,β-unsaturated aldehydes: c) A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem.* **2007**, *119*, 4588 – 4590; *Angew. Chem. Int. Ed.* **2007**, *46*, 4504 – 4506; d) I. Ibrahem, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo, A. Cordova, *Angew. Chem.* **2007**, *119*, 4591 – 4594; *Angew. Chem. Int. Ed.* **2007**, *46*, 4507 – 4510; e) E. Maerten, S. Cabrera, A. Kjaersgaard, K. A. Jorgensen, *J. Org. Chem.* **2007**, *72*, 8893 – 8903.

[13] a) Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146; b) A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5846 – 5850; c) J. D. McGilvra, A. K. Unni, K. Modi, V. H. Rawal, *Angew. Chem.* **2006**, *118*, 6276 – 6279; *Angew. Chem. Int. Ed.* **2006**, *45*, 6130 – 6133; d) V. B. Gondi, K. Hagihara, V. H. Rawal, *Angew. Chem.* **2009**, *121*, 790 – 793; *Angew. Chem. Int. Ed.* **2009**, *48*, 776 – 779.

[14] For reviews on hydrogen bond donor catalysis, see: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713 – 5743; b) J. D. McGilvra, V. B. Gondi, V. H. Rawal in *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**, pp. 189 – 254; c) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797 – 5815; d) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516 – 532.

[15] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416 – 14417.

[16] For a review on thiourea-catalyzed asymmetric nucleophilic reactions, see: Y. Takemoto, H. Miyabe, *Chimia* **2007**, *61*, 269 – 275.

[17] Compound **4a** was first synthesized by Koji Hagihara in our laboratory.

[18] When the phosphite addition reaction was carried out in either diethyl ether or *tert*-butyl methyl ether, a noticeable amount of white precipitate formed, even at room temperature. The precipitate was separated by filtration and identified by NMR spectroscopy as the desired product (**3a**). The precipitate had a lower *ee* than the product that remained in solution. These observations indicate that the product enriched in the racemate precipitates from the solution, leaving behind product that is even more enriched in the major enantiomer.

[19] Wang et al. (see Ref. [9]) reported four alkyl-substituted substrates (45–63% *ee*) and Terada et al. (see Ref. [10]) reported three (80–87% *ee*).

