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Asymmetric organocatalytic Michael-type reaction of phosphorus ylides to nitroolefins: synthesis of γ-nitro-β-aryl-α-methylene carboxylic esters

Suresh Allu [a], Sermadurai Selvakumar [a], Vinod K. Singh [a,b,*]

[a] Department of Chemistry, Indian Institute of Technology, Kanpur, UP 208 016, India
[b] Indian Institute of Science Education and Research Bhopal, ITI (Gas Rahat) Building Govindpura, Bhopal, MP 460 023, India

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ABSTRACT

We report, for the first time, asymmetric organocatalytic Michael-type addition of stabilized phosphorus ylides to nitroolefins mediated by bisthiourea catalyst. Its subsequent reaction with formaldehyde provides γ-nitro-α-methylene carboxylic esters in moderate to good yields and enantioselectivities (up to 63% ee).

Enantioselective reactions catalyzed by small organic molecules (asymmetric organocatalysis) that mimic enzymes and utilize hydrogen bonds for activating the electrophiles have attracted attention from a large number of organic chemists working in the area of asymmetric synthesis.[1–4] Among them, organocatalytic Michael reaction of various nucleophiles with nitroalkenes represents a direct and the most appealing approach to access nitroalkanes that are versatile intermediates in organic synthesis.[5] Our recent success with nitroolefins as Michael acceptors[6] in enantioselective conjugate addition of carbonyl compounds prompted us to evaluate them for other useful transformations.

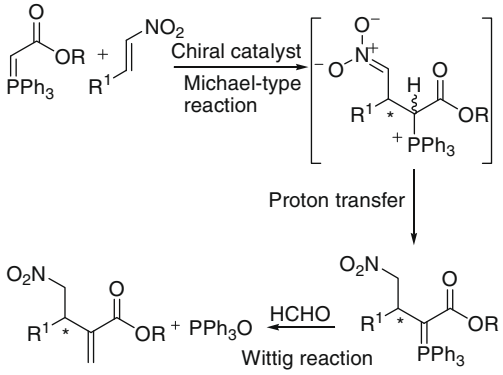
Stabilized phosphorus ylides (P-ylides), apart from the traditional Wittig reaction, have also been widely used in alkylation reactions.[7] Unlike sulfur ylides,[8] thier application in asymmetric synthesis has not been much explored. Inspired by the proven ability of stabilized phosphorous ylides to serve as good nucleophiles for the enantioselective addition to activated electrophiles,[9] we envisioned that P-ylides could serve as nucleophilic species to attack appropriately activated nitroolefins, followed by proton transfer to give chiral functionalized P-ylides (Scheme 1). This could be followed by the reaction with formaldehyde to provide the desired γ-nitro-β-aryl-α-methylene carbonyl compounds.

In recent years, chiral Brønsted acids have appeared to be effective organocatalysts for conjugate additions to nitroolefins. In particular, chiral thioureas have received much attention and have frequently been used as catalysts for transformations related to enantioselective activation of nitroolefins.[10] We envisioned that chiral thiourea would effectively catalyze this reaction by forming hydrogen bonding with nitroolefins to give optically pure γ-nitro-β-aryl-α-methylene carbonyl compound via enantioenriched phosphorane intermediate (Scheme 1).

As anticipated, the reaction occurred smoothly and we describe our results in this Letter.

Furthermore, the reaction provides highly functionalized γ-nitro carbonyl compounds, which cannot be accessed via conventional Morita–Baylis–Hillman (MBH) reaction of nitroolefins and acrylates (Scheme 2).[11]

At the outset, a series of reactions were carried out between P-ylide **2a** and nitroolefin **3a** in toluene with 10 mol % of chiral Brønsted acid catalyst **1a** (Fig. 1). The reaction was complete in 24 h at room temperature and the expected P-ylide was isolated as a stable compound. This was followed by its reaction with formalin to give γ-nitro-β-aryl-α-methylenic ester **4a** in 59% yield and 10% ee (Table 1, entry 1). However, on decreasing the reaction temperature from rt to 0 °C and −20 °C, enantioselectivity increased gradually with a decrease in the rate of the reaction (Table 1, entries 2 and 3). When the catalyst loading was increased from 10 to 30 mol %, a major enhancement in chemical yield of the reaction was observed, with no appreciable change in enantioselectiv-



Scheme 1. A novel route to chiral γ-nitro carbonyl compounds.

* Corresponding author. Tel.: +91 512 2597291; fax: +91 512 2597436.
E-mail address: vinodks@iitk.ac.in (V.K. Singh).

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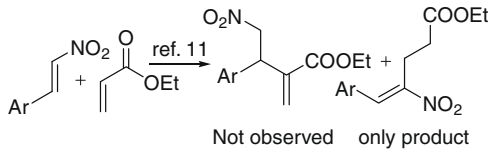


Scheme 2. Alternate approach to γ-nitro carbonyl compounds.

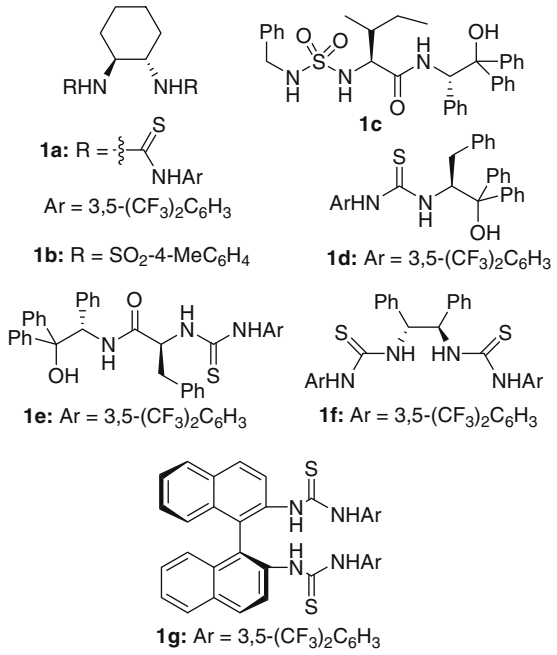
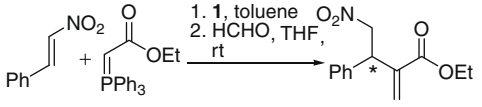


Figure 1. Chiral Brønsted acid catalysts.

Table 1
Optimization of reaction conditions for enantioselective Michael-type reaction[a]



3a 2a 4a

Entry	Catalyst	Mol%	Temp (°C)	Time (d)	Yield (%)	ee[b] (%)
1	**1a**	10	rt	1	59	10
2	**1a**	10	0	2	54	15
3	**1a**	10	−20	5	25	35
4	**1a**	20	−20	5	34	37
5	**1a**	30	−20	4	47	39
6	**1a**	30	−20	5	46	47[c]
7	**1b**	30	−20	5	25	15[c]
8	**1c**	30	−20	3	44	−11[c]
9	**1d**	30	−20	4	49	24[c]
10	**1e**	30	−20	3	35	39[c]
11	**1f**	30	−20	3	35	−37[c]
12	**1g**	30	−20	2	38	36[c]

[a] Reactions were carried out with 0.16 mmol of **2**, and 0.24 mmol of **3** in 0.5 mL of solvent. Then excess of HCHO was added and stirred at room temperature for 24 h.
[b] Determined by chiral HPLC. The absolute configurations have not been assigned yet.
[c] 4 Å molecular sieves were added for this reaction (Table 2, entry 5).

ity (Table 1, entries 3–5). It was gratifying to note that an addition of 4 Å molecular sieves showed positive effect on the enantioselectivity of the reaction (Table 1, entry 6). After optimizing the reaction conditions, various chiral Brønsted acid catalysts **1b**–**g** with different hydrogen bond-donating arms were screened in the above-mentioned reaction, and the results are summarized in Table 1. The poor enantioselectivity with catalysts having sulfonamide[13b] and sulfamide group as hydrogen bond-donating arms clearly indicates that the presence of thiourea group is crucial to get asymmetric induction in this reaction (Table 1, entries 7 and 8). It was also observed that the catalysts bearing both thiourea and hydroxyl group[13a] on their skeleton afforded the product in moderate yield and enantioselectivities (Table 1, entries 9 and 10). In order to see the effect of cyclohexyl backbone of bisthiourea catalyst **1a** on the enantioselectivity, catalysts with diphenyl[9,12e] (**1f**) and binapthyl[12d] (**1g**) backbone were then studied, but the corresponding Michael adduct was obtained in moderate enantioselectivities (Table 1, entries 11 and 12). In view of this study, the catalyst **1a** was chosen for further study.

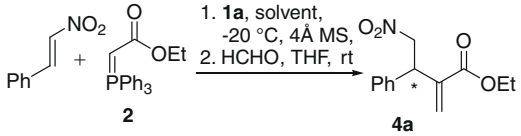
The effect of solvent on the enantioselectivity of the reaction was then studied (Table 2). Among the different solvents screened, non polar solvents were found to be superior in comparison to the polar ones. Of the different non polar solvents tested, *o*-xylene was the optimum choice. Finally, we were pleased to find that cooling the reaction mixture to −40 °C had a positive effect on the enantioselectivity and the product **4a** was obtained in 63% ee while a good level of conversion was maintained (Table 2, entry 9).

Having identified the optimized condition for this reaction, we evaluated the effect of ester substituent of P-ylides[14] on yield and enantioselectivity (Table 3). Ethyl ester **2a** turned out to be the suitable ylide for the reaction (Table 3, entry 1).

Ylides **2b** and **2c** led to the addition product in low yield and enantioselectivity (Table 3, entries 2 and 3). Reaction with bulky *tert*-butyl ester **2d** afforded the Michael adduct in excellent yield and moderate enantioselectivity (Table 3, entry 4).

The scope and limitations of the Michael-type reaction catalyzed by bisthiourea **1a** were then examined. A wide range of nitroolefins including both aromatic and aliphatic nitroolefins reacted smoothly with **2a** under optimized condition to give Michael adduct in moderate to good yield and enantioselectivity (Table 4). It was observed that the electronic nature of the substituents at the aromatic ring shows significant effect on the enantioselectivity (Table 4, entry 2 vs 6). Heteroaromatic nitroolefin also gave the Michael adduct in moderate yield and enantioselectivity (Table 4, en-

Table 2
Effect of solvent on enantioselectivity[a]

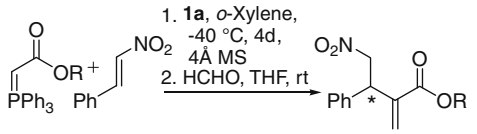


2 4a

Entry	Solvent	Time (d)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	2	25	14
2	$CHCl_3$	2	25	32
3	THF	2	33	33
4	Toluene	5	46	47
5	*o*-Xylene	5	52	53
6	Benzene	‘6	44	22[d]
7	DMF	1	35	08
8	CH_3CN	1	—	—[e]
9	*o*-Xylene	6	54	63[f]

[a] Reactions were carried out at 0.16 mmol scale in 0.5 mL solvent, **2**:**3**:**1a** = 1:1.5:0.3.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Reaction was carried out at −5 °C.
[e] Complex mixture.
[f] Reaction was carried out at −40 °C.

Table 3
Effect of ylides on enantioselectivity[a]

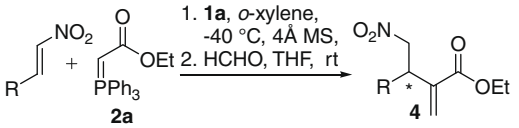


2a-d 4a-d

Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Et	**4a**	54	63
2	Me	**4b**	56	36
3	^{i}Pr	**4c**	30	14
4	^{t}Bu	**4d**	72	41

[a] Reactions were carried out at 0.16 mmol scale in 0.5 mL *o*-xylene, **2**:**3**:**1a** = 1:1.5:0.3.
[b] Isolated yield.
[c] Determined by chiral HPLC. The absolute configurations have not been assigned yet.

Table 4
Enantioselective Michael-type addition of P-ylide with different nitroolefins[a]



2a 4

Entry	R	Time (d)	Product	Yield[b] (%)	ee[c] (%)
1	C_6H_5	6	**4a**	54	63
2	4-ClC_6H	6	**4e**	63	63
3	4-FC_6H_4	6	**4f**	27	46
4	3-ClC_6H_4	6	**4g**	26	39
5	3-FC_6H_4	6	**4h**	25	35
6	4-OMeC_6H_4	6	**4i**	35	24
7	3-MeC_6H_4	6	**4j**	35	42
8	4-MeC_6H_4	6	**4k**	35	41
9	3,5-MeC_6H_3	6	**4l**	29	59
10	3,4-Methylene dioxy-C_6H_3	4	**4m**	52	11
11	2-Thioenyl	6	**4n**	40	43
12	PhCH_2CH_2	6	**4o**	60	16
13	Cyclohexyl	4	**4p**	43	19

[a] Reactions were carried out at 0.16 mmol scale in 0.5 mL *o*-xylene, **2**:**3**:**1a** = 1:1.5:0.3.
[b] Isolated yield.
[c] Determined by chiral HPLC. The absolute configurations have not been assigned yet.

try 11). With aliphatic nitroolefins, the addition products were obtained in low ee (Table 4, entries 12 and 13).

In conclusion, we have developed the first asymmetric Michael-type reaction of stabilized phosphorus ylides with nitroalkenes, followed by its reaction with formaldehyde to provide optically active γ-nitro-α-methylene carboxylic esters in moderate to good yields and enantioselectivities (up to 63% ee). The reaction is catalyzed by simple thiourea-based organocatalyst, which can be readily synthesized from commercially available starting materials. The procedure is operationally very simple and provides versatile synthetic intermediates. Further elaboration of this novel transformation, its synthetic application to determine the absolute stereochemistry and mechanistic studies are ongoing in our laboratory.

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References and notes

1. For selected examples on thiourea catalysis, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (c) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103; (d) Yoon, T. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *44*, 466–468.
2. For a review on thiourea catalysis, see: (a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418–5427; (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743; (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; (d) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296.
3. For examples of Brønsted acid catalyzed enantioselective reactions, see: (a) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095; (b) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419.
4. For a review on Brønsted acid catalysis, see: (a) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432; (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064; (c) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758–1763; (d) Yamamoto, H.; Fustatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924–1942; (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010; (f) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543; (g) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758.
5. For a review, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.
6. Maya, V.; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117–1119.
7. (a) Asunskis, J.; Shechter, H. *J. Org. Chem.* **1968**, *33*, 1164–1168; (b) von Strandtmann, M.; Cohen, M. P.; Puchalski, C.; Shavel, J., Jr. *J. Org. Chem.* **1968**, *33*, 4306–4309; (c) Connor, D. T.; von Strandtmann, M. *J. Org. Chem.* **1973**, *38*, 1047–1049.
8. For selected examples of stabilized sulfur ylides in organocatalytic reactions, see: (a) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430–1433; (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433–1436; (c) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241.
9. Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. *J. Am. Chem. Soc.* **2008**, *130*, 2456–2457.
10. For selected examples see: (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125; (b) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; (c) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451–1453; (d) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 2047–2050; (e) Wang, J.; Heikkinen, L. D.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1052–1056; (f) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524–13525; (g) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862–13863; (h) Gao, P.; Wang, C.; Wu, Y.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2008**, 4563–4566.
11. Dadwal, M.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothri, I. N. N. *Chem. Commun.* **2006**, 338–340.
12. (a) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed* **2005**, *44*, 6576–6579; (b) Herrera, R. P.; Monge, D.; Martin-Zomora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303–3306; (c) Martin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976–8977; (d) Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785–1790; (e) Sohtome, Y.; Takemura, N.; Takagi, R.; Hashimoyo, Y.; Nagasawa, K. *Tetrahedron* **2008**, *64*, 9423–9429.
13. (a) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064–8065; (b) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784–3786.
14. Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977–2980.