

Proline and Lewis base co-catalyzed addition of α,β -unsaturated aldehydes to nitrostyrenes

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Received 5 October 2007; revised 3 December 2007; accepted 12 December 2007

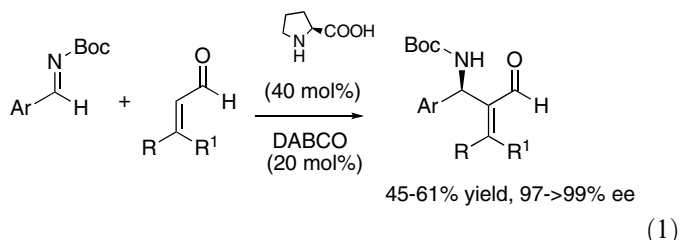
Abstract

A novel proline and DABCO co-catalyzed reaction between unmodified α,β -unsaturated aldehydes and nitrostyrenes, which gives access to α -(1-aryl-2-nitro)ethyl- α,β -unsaturated aldehydes, is presented.

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Continuing development in synthetic organic chemistry relies on discovering new selective reactions. The Morita–Baylis–Hillman (MBH) reaction is an organocatalytic reaction involving the coupling of the α -position of activated alkenes with carbonyl electrophiles such as an aldehyde or ketone via the catalytic influence of a nucleophilic species.^{1,2} The concept of this reaction has been applied to intermolecular reactions between activated alkenes and other electrophiles including imines,³ salicylaldehydes,⁴ azodicarboxylate esters⁵ and activated allyl halides.⁶ Moreover, tertiary phosphine-catalyzed intermolecular MBH reactions have been developed.⁷ Recently, Shi and co-workers reported a dual catalytic system based on the combination of enamine and Lewis base catalysis for the Baylis–Hillman type reaction between methyl vinyl ketone and aryl carbaldehydes.⁸ Miller and co-workers have also applied this strategy for inter- and intramolecular MBH type reactions with aldehydes as electrophiles.⁹ Recently, Barbas reported an enamine and Lewis base co-catalytic system for the reaction between enals and *N*-*p*-methoxyphenyl-(PMP) protected α -imino glyoxylate.¹⁰ We have developed an enamine and Lewis base co-catalyzed aza-MBH type reaction between α,β -unsaturated aldehydes and Boc-protected imines (Eq. 1).¹¹ While a variety of elec-

trophiles have been studied extensively since the first reports of the MBH reaction, the direct organomediated application of nitroolefins as electrophiles in the MBH reaction has not been reported.

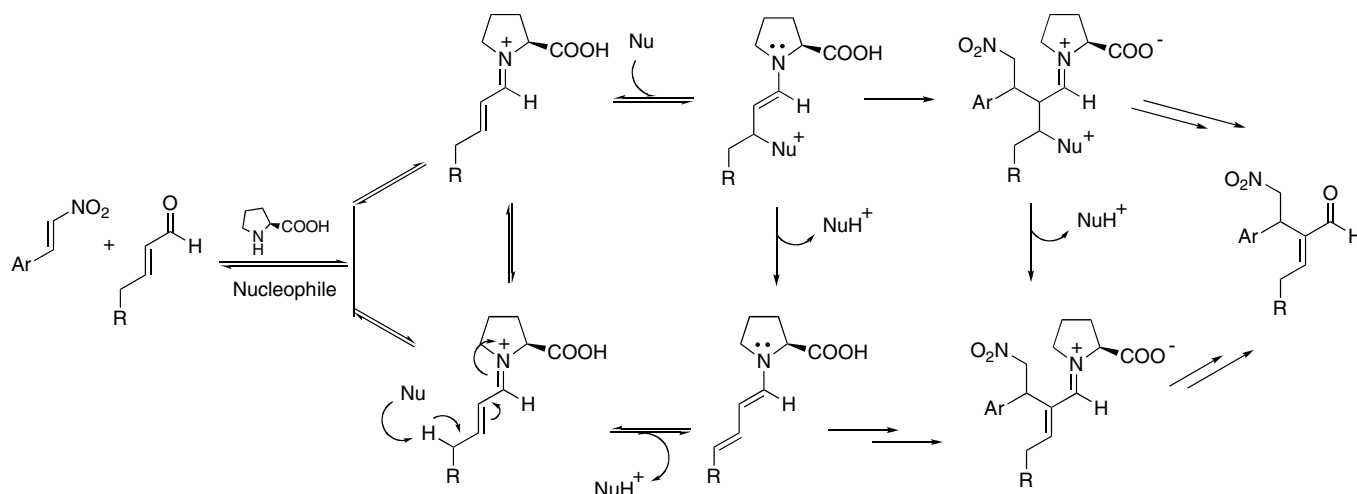


Based on the use of co-catalyst systems involving proline or peptide derivatives and organic nucleophilic amines for mediating asymmetric MBH^{8,9} and aza-MBH reactions,^{10,11} we envisioned the possibility of developing a reaction between α,β -unsaturated aldehydes and nitrostyrenes (Scheme 1).¹²

Thus, we predicted that an iminium intermediate derived from the reaction between the amino acid catalyst and the enal donor could be activated by an amine to form two different possible enamine intermediates (Scheme 1). These in situ generated enamines could subsequently undergo nucleophilic Michael addition to the nitrostyrene and give the corresponding α -(2-nitroethyl)- α,β -unsaturated carbonyl compounds. These types of product are valuable synthons for the preparation of a large variety

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Scheme 1. Suggested activation pathways for the reaction between enals and nitrostyrene catalyzed by a combination of proline and an organic nucleophile.

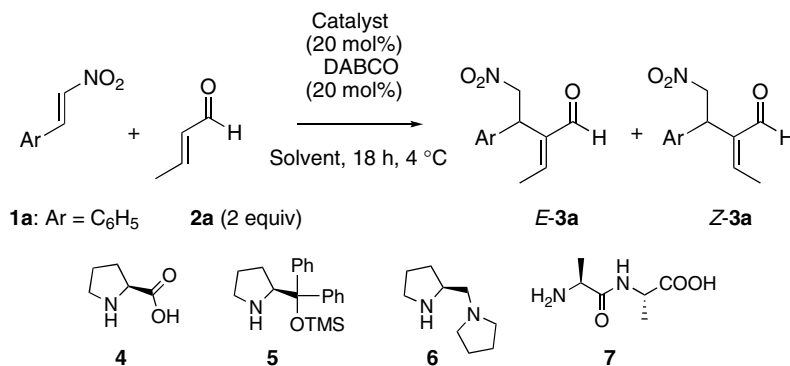
of valuable heterocyclic compounds.¹³ Herein, we present a new intermolecular MBH-type reaction which, for the first time, encompasses nitroolefins as the electrophilic partner in a completely organomediated process.

In an initial catalyst, organic base and solvent screen, we found that the combination of (*S*)-proline **4** and 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed the reaction between nitrostyrene **1a** (0.5 mmol) and buten-2-al **2a**

(0.25 mmol) to give α -2-nitroethyl- α,β -unsaturated aldehyde **3a** (Table 1).

The use of a nucleophilic organic amine base was essential and of the screened bases, imidazole and DABCO, only DABCO enabled the formation of **3a**. We also found that the other chiral amines **5–7** failed to catalyze the formation of **3a** in the presence of DABCO. The combination of (*S*)-proline and DABCO was effective in polar aprotic solvents

Table 1
Screening of the enantioselective reaction between **1a** and **2a**^a



Entry	Catalyst	Solvent	Conv. (%)	Yield ^b (%)	<i>E/Z</i> ^c
1	4	DMF	10	n.d.	>25:1
2	4	DMF	100 ^d	44 ^d	>25:1 ^d
3	4	CHCl ₃	0	—	—
4	5	DMF	0	—	—
5	5	CHCl ₃	0	—	—
6	5	Toluene	0	—	—
7	6	DMF	0	—	—
8	6	THF	0	—	—
9	6	Toluene	0	—	—
10	7	DMF	0	—	—

^a Experimental conditions: A mixture of **1a** (0.50 mmol), buten-2-al **2a** (0.25 mmol), chiral pyrrolidine (40 mol %) and DABCO (20 mol %) in 1.0 mL of solvent was stirred at 4 °C under the conditions displayed in Table.

^b Isolated yield of pure compound **3a**.

^c *E/Z* ratio as determined by ¹H NMR. n.d. = not determined.

^d 40 mol % of catalyst was used.

Table 2

Direct organocatalytic asymmetric reactions between nitrostyrenes **1** and α,β -unsaturated aldehydes **2**^a

Entry	Ar	R	Product	Yield ^b (%)	<i>E/Z</i> ^c
1	Ph	Me	3a	47	>25:1
2	Ph	Et	3b	57	>25:1
3	Ph		3c	53	>25:1
4	Ph	<i>n</i> -Bu	3d	62	>25:1
5	2-BrC ₆ H ₄	Et	3e	41	>25:1
6	3-ClC ₆ H ₄	Et	3f	55	>25:1

^a Experimental conditions: A mixture of **1** (0.50 mmol), enal **2** (0.25 mmol), (*S*)-proline (40 mol %) and DABCO (20 mol %) in 1.0 mL of DMF was stirred at 4 °C.

^b Isolated yield of pure compounds *E/Z*-**3**.

^c *E/Z* ratio determined by ¹H NMR analysis.

such as DMF (entries 1 and 2). For example, (*S*)-proline and DABCO co-catalyzed the formation of α -(1-aryl-2-nitro)ethyl-enal **3a** in 44% yield in DMF (entry 2). The *E/Z* ratio was excellent (>25:1) as determined by ¹H NMR analysis of the crude reaction mixture and the *E*-isomer was formed predominantly. Full conversion of the donor enal **2a** was achieved under these reaction conditions but a small amount of competing self-MBH type reaction of **2a** occurred.¹⁴ Encouraged by these promising results, we decided to investigate the catalytic asymmetric reaction between various nitrostyrenes **1** and different α,β -unsaturated aldehydes **2** with (*S*)-proline as the organocatalyst and DABCO as the organic amine nucleophile (Table 2).¹⁵

The catalytic aza-MBH type reactions proceeded with excellent *E/Z* selectivity (>25:1) and the corresponding α,β -unsaturated aldehydes **3a–f** were obtained in moderate to good yields (41–62%). For example, the combination of (*S*)-proline and DABCO catalyzed the reaction between nitrostyrene **1a** and heptenal **2d** with high *E/Z*-selectivity and nitro-substituted enal **3d** was isolated in 62% yield (entry 4). Moreover, the reaction tolerated α,β -unsaturated aldehyde donors with a terminal olefin functionality (entry 3). It should be pointed out that in all cases the enal products **3** were obtained with very low ees (<10%). For example, **3a** had an ee of <5%.

On the basis of previous proline and DABCO co-catalyzed reactions between enals and imines^{10,11} we propose that the reaction proceeds as outlined in Scheme 1. We are still studying the role of DABCO. It could either work as a base enabling the formation of a conjugated enamine and/or act as a nucleophile to generate an enamine intermediate, which includes DABCO, according to Scheme 1.

In summary, we have reported a simple catalytic reaction between unmodified enals and nitrostyrenes. This is the first example of nitroolefins as electrophiles in MBH-type reactions. The combined proline and DABCO cata-

lyzed transformations furnish the corresponding MBH Michael type adducts with an α -alkylidene group in good yields with excellent *E*-selectivity. Further elaboration of this transformation, mechanistic studies, and application of nitroolefins as electrophiles in MBH-type reactions are ongoing in our laboratory.

Acknowledgements

We gratefully acknowledge the Swedish National Research Council, Wenner–Gren Foundation and Carl–Trygger Foundation for financial support.

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15. *Typical experimental procedure for the organocatalytic Baylis-Hillman reactions:* To a stirred mixture of (*S*)-proline (0.10 mmol, 40 mol %), nitrostyrene **1** (0.50 mmol, 2.0 equiv) and DABCO (0.05 mmol, 20 mol %) in DMF 1.0 mL at 4 °C was added α,β -unsaturated aldehyde **2** (0.25 mmol, 1.0 equiv). The reaction was stirred vigorously for the time and the temperature described in Table 2. Next, the crude product was purified by silica gel chromatography (pentane–EtOAc-mixtures) to give the corresponding enals **3**. Compound **3a** *E*-isomer: Colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 9.38 (d, J = 1.6 Hz, 1H), 7.30–7.26 (m, 5H), 6.80 (q, J = 7.2 Hz, 1H), 5.32 (dd, J = 8.8 Hz, 12.8 Hz, 1H), 5.04 (dd, J = 6.4 Hz, 12.8 Hz, 1H), 4.76–4.71 (m, 1H), 2.12 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): 194.7, 154.8, 137.7, 129.1, 127.9, 127.8, 76.6, 41.3, 15.3. HRMS (ESI): calcd for $[\text{M}+\text{Na}]^+(\text{C}_{12}\text{H}_{13}\text{NO}_3)$ requires m/z 242.0788, found 242.0781. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane–*i*-PrOH = 90:10, λ = 230 nm), 1.0 mL/min; t_{R} = faster enantiomer 20.2 min, slower enantiomer 41.6 min.