DOI: 10.1002/adsc.200600247

Organocatalytic, Enantioselective Conjugate Addition of Nitroalkanes to Nitroolefins

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Received: May 26, 2006; Accepted: July 18, 2006

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Abstract: An organocatalytic, enantioselective conjugate addition reaction of nitroalkanes with nitroolefins has been developed under neat conditions without using an organic solvent. The process, catalyzed by a modified *Cinchona* alkaloid, affords synthetically useful 1,3-dinitro compounds in good yields (70–82%) with good degrees of enantioselectivity (67–88% *ee*).

Keywords: asymmetric catalysis; C–C bond formation; Michael addition; organic catalysis

The Michael addition of stabilized carbanions to electron-deficient α,β-unsaturated systems is one of the important means for the construction of C–C bonds in organic synthesis.[1–3] Versatile nitroalkanes have been demonstrated as a valuable stabilized carbanion for the conjugate addition process. Recently, an organometallic and organocatalytic asymmetric version of conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds has been the subject of intensive investigation. For example, Shibasaki[4] and Jacobsen[5] have reported organometallic-promoted, highly enantioselective Michael additions to α,β-unsaturated ketones. Davis,[6] Hanessian,[7] Soós,[8] Jørgensen,[9] and Maruoka[10] have independently developed the "metal-free" organocatalyzed enantioselective processes. In these approaches, the acceptors employed have been restricted to α,β-unsaturated ketones,[6–9] aldehydes,[10a] and esters.[10b] The use of nitroolefins as Michael acceptors for the asymmetric reaction has proven to be a challenging task despite the fact that nitroolefins are more active than α,β-unsaturated carbonyls[11,12] and the versatile nitro groups can be readily transformed into a variety of functionalities.[2c] A single study has been disclosed recently using a chiral ligand-metal complex as a catalyst for the conjugate addition of nitroalkanes to nitroalkenes in moderate to high enantioselectivity.[13,14] It is noted that the catalytic system requires the use of Et_2Zn (0.25 equivs.) and Ti(O-*i*-Pr)$_4$ (0.8 equivs.) as co-catalysts in addition to the chiral ligand (0.1 equiv.). Moreover, the method suffers from a narrow scope, only working for less hindered linear nitroalkanes. In this communication, we describe the results of an investigation which has led to the development of the first method for carrying out organocatalytic enantioselective Michael-type addition reactions of nitroalkanes with nitroolefins to afford synthetically useful enantiomerically enriched 1,3-dinitro compounds in good yields (70–82%) and good enantioselectivities (67–88% *ee*) under neat conditions without using organic solvent. The process has shown to be applicable for both linear and more steric hindered branch nitroalkanes.

This investigation began with screening several chiral organocatalysts for their ability to promote asymmetric Michael-type addition reactions of 2-nitropropane (**1a**) to *trans*-β-nitrostyrene (**2a**) (Figure 1 and Table 1). The initial reaction was performed in toluene in the presence of 10 mol% of a modified *Cinchona* alkaloid **I**[3c,d] at room temperature with a 10:1 mole ratio of **1a** to **2a** (0.2M). Surprisingly, no reactions occurred after 3 days based on TLC analysis. However, when the reaction was performed under the neat reaction conditions using 2-nitropropane (**1a**) as solvent, the formation of Michael adduct **3a** was observed in 81% yield and 70% *ee* (Table 1, entry 1). Encouraged by the results, we surveyed its analogues **II** and **III**[3c,d] for the same reaction, but very low values of enantioselectivities were observed (entries 4 and 5). This indicates that both -OH groups in **I** may play a role in governing enantioselectivity. Chiral amine thioureas **IV–VI**[3a,b,e,8] have been demonstrated as effective promoters for nitroolefin-associated Michael-type addition processes due to the strong dual hydrogen bond interactions between the thiourea

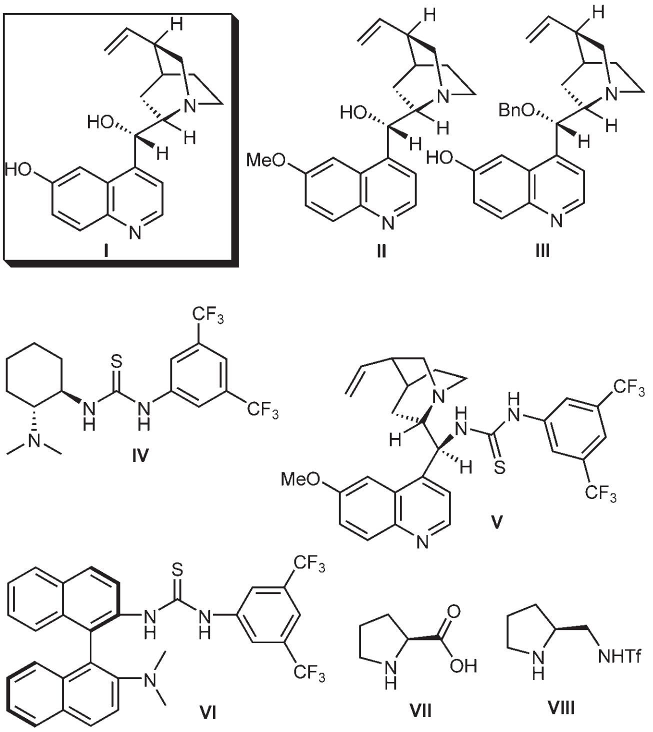
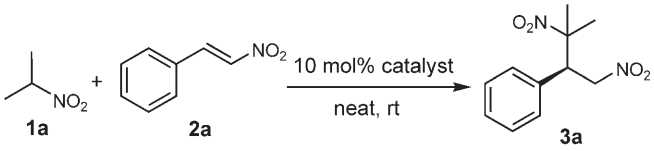


Figure 1. Chiral organocatalysts.

Table 1. Results of exploratory studies on the catalytic asymmetric Michael-type addition reaction of 2-nitropropane (**1a**) to *trans*-β-nitrostyrene (**2a**).[a]



Entry	Catalyst	*t* (d)	Yield[b] [%]	*ee*[c] [%]
1	**I**	2	81	70
2[f]	**I**	6	79	78
3[g]	**I**	4	47(85)[d]	78
4	**II**	9	72	15
5	**III**	2	62	8
6	**IV**	2	41	63
7	**V**	2	73	30
8	**VI**	2	29	48
9	**VII**	2	<5	nd[e]
10	**VIII**	2	<5	nd[e]

[a] Reaction conditions: see Experimental Section.

[b] Isolated yields.

[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

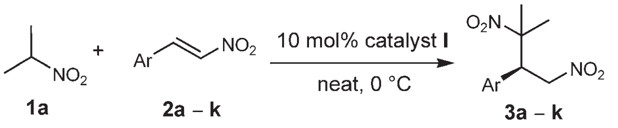
[d] Based on recovered starting material.

[e] Not determined.

[f] Reaction at 0 °C.

[g] Reaction at −25 °C.

Table 2. Catalyst **I**-promoted asymmetric Michael-type addition reactions of 2-nitropropane (**1a**) to nitrostyrenes **2**.[a]



Entry	Nitrostyrene Ar	No.	*t* (d)	Yield[b] [%]	*ee*[c [%]]
1	Ph	**3a**	6	79	78
2	4-F-C_6H_4	**3b**	7	76	73
3	4-Cl-C_6H_4	**3c**	8	70	83
4	2-CF_3-C_6H_4	**3d**	9	78	83
5	2-Cl-C_6H_4	**3e**	10	73	81
6[d]	2,6-Cl_2-C_6H_3	**3f**	7	75	80
7	4-MeO-C_6H_4	**3g**	12	78	67
8	2-MeO-C_6H_4	**3h**	8	73	84
9[d]	2-BnO-C_6H_4	**3i**	7	80	77
10[d]	2,3-$(MeO)_2$-C_6H_3	**3j**	8	78	85
11	2-thiophene	**3k**	10	78	70

[a] Reaction conditions: see Experimental Section.

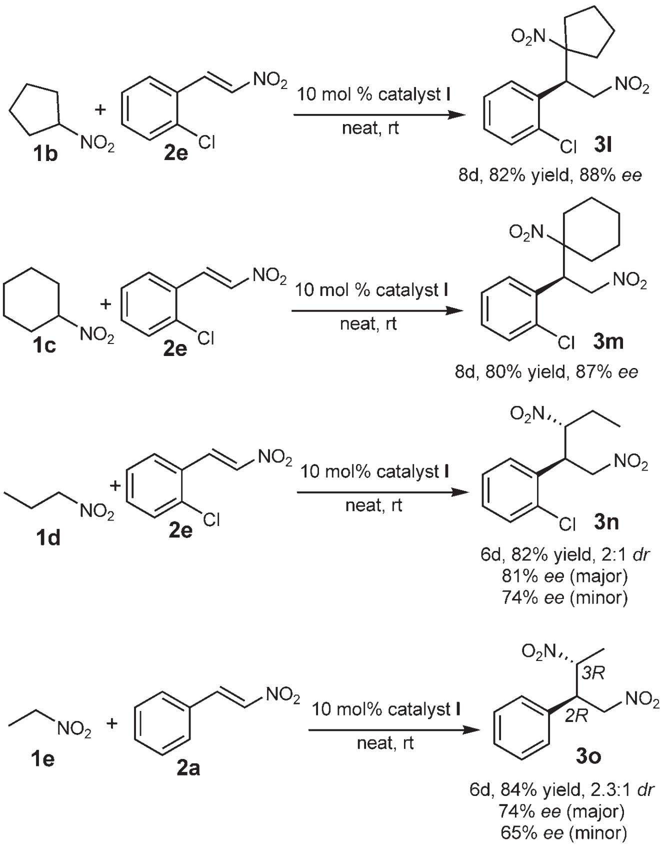
[b] Isolated yields.

[c] Determined by chiral HPLC analysis (Chiralpak AS-H, Chiralcel OD-H, and Chiralcel OJ-H).

[d] Reaction was run at room temperature.

moiety of the catalyst and the nitro group of the substrate. Unfortunately, lower reaction yields and poorer enantioselectivities for the reaction were obtained, as compared with catalyst **I** (Table 1, entries 6–8). L-Proline **VII** and (*S*)-pyrrolidine-sulfonamide **VIII**,[15] a catalyst first developed in our laboratory, were also screened for the process. Unfortunately, no reactions occurred (entries 9 and 10). Lowering the reaction temperature to 0 °C resulted in an improvement of the enantioselectivity (78% *ee*, Table 1, entry 2) of the **I**-catalyzed process without sacrificing yield (79%), albeit with a longer reaction time (6 days). No gain was observed when the reaction temperature was further decreased to −25 °C (entry 3).

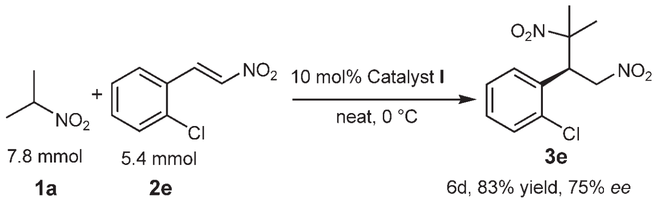
The conditions that proved optimal for the reaction of 2-nitropropane (**1a**) to *trans*-β-nitrostyrene (**2a**), catalyzed by **I** (10 mol%) were applicable for Michael-type additions of other nitroolefins (Table 2). The aromatic rings of nitroolefins bearing electron-neutral (entry 1), electron-withdrawing (entries 2–6) or electron-donating (entries 7–10) substituents underwent reaction smoothly affording the desired products with good yields (70–80%) and good enantioselectivities (67–85% *ee*), indicating that electronic features have a very marginal effect on the processes. Examination of the results of the investigation reveals that the steric effect (entries 4, 5 and 8–10) also plays a minimal role in governing the enantioselectivity and reactivity of the conjugate reactions. A heteroaromatic nitroolefin (e.g., thiophene, entry 11) was able to participate in the reaction as well. Unfortunately, no reaction occurred for less reactive aliphatic nitroolefins.



Scheme 1. Catalyst **I**-catalyzed Michael-type addition reactions of other nitroalkanes.

Structural variation in the Michael donor nitroalkanes **1b–e** was found to be tolerated in the Michael-type addition reactions catalyzed by **I** (Scheme 1). Higher *ee* (87–88% *ee*) and better yields (80–82%) were achieved for cyclic nitroalkanes (**1b** and **1c**) than the acyclic one (**1a**). When 1-nitropropane (**1d**) and 1-nitroethane (**1e**) were used for the reaction, two new stereogenic centers were formed with *ca.* 2:1 *dr* and respective 81 and 74% *ee* for the major isomer and 74 and 65% *ee* for the minor one. The absolute *2R,3R* stereoconfiguration of the major isomer **3o** was determined by comparing its optical rotation {$[\alpha]_D^{25}$: +15.3 (*c* 1.6 in CH_2Cl_2) with the literature data ($[\alpha]_D^{25}$: +21.6 (*c* 1.12 in CH_2Cl_2) (For details, see Supporting Information).[13] The low *dr* is partially due to rapid epimerization at the nitro group attached chiral carbon.

Because of the small-scale synthesis, a large excess of the nitroalkane (56 equivs.) was used under neat conditions (see Experimental Section). We surmised that if a larger scale was practiced, the amount of nitroalkane used could be significantly reduced. To test the possibility, we performed a reaction between 2-nitropropane (**1a**, 7.8 mmol, 1.44 equivs., 0.7 mL) and nitroolefin (**2e**, 5.4 mmol) in the presence of 10 mol% catalyst **I** at 0 °C (Scheme 2). It was found that the reaction proceeded even faster (6 days *vs.* 10 days (Table 2, entry 5) in a higher yield (83%), albeit with a slightly drop in enantioselectivity (75%).



Scheme 2. Catalyst **I**-catalyzed Michael-type addition reaction under solvent-free conditions.

In summary, this investigation has resulted in a new organocatalytic Michael-type addition reaction of nitroalkanes with *trans*-β-nitrostyrenes. This process, catalyzed by modified *Cinchona* alkaloid **I**, affords synthetically useful 1,3-dinitro compounds in good yields and with good levels of enantioselectivity without using an organic solvent. In a preliminary study, we have demonstrated that the process can be carried out in solvent-free conditions. Further studies of the mechanistic features, scope and synthetic applications of this valuable reaction are underway.

Experimental Section

Typical Procedure

Catalyst **I** (7 mg, 0.02 mmol) was added to a vial containing 2-nitropropane (**1a**) (1 mL, 11.2 mmol) and *trans*-β-nitrostyrene (**2a**) (30 mg, 0.20 mmol) at 0 °C. After 6 days of stirring, TLC analysis indicated completion of the reaction. The reaction mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ethyl acetate/hexane = 1:20 to 1:10) to afford the adduct **3a** as a clear oil; yield: 38 mg (79%); 78% *ee*, as determined by HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 30/70, flow rate 0.5 mL min^{-1}, $\lambda = 254$ nm): $t_{minor} = 18.5$ min, $t_{major} = 19.2$ min; $[\alpha]_D^{25}$ (major): +15.7 (*c* 1.2 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, TMS): $\delta = 7.32–7.24$ (m, 3H, Ar), 7.17–7.07 (m, 2H, Ar), 4.91 (dd, $^3J_{H,H} = 13.0$ Hz, $^3J_{H,H} = 11.5$ Hz, 1H, CH), 4.72 (dd, $^3J_{H,H} = 13.0$ Hz, $^2J_{H,H} = 4.0$ Hz, 1H, CH_2), 4.07 (dd, $^3J_{H,H} = 11.0$ Hz, $^2J_{H,H} = 4.0$ Hz, 1H, CH_2), 1.52 (s, 3H, CH_3), 1.51 (s, 3H, CH_3).

Acknowledgements

The financial support by the Department of Chemistry and the Research Allocation Committee, University of New Mexico, NIH-INBRE (P20 RR016480) and from the American Chemical Society-PRF (G1 type) is gratefully acknowledged.

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