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Organocatalytic Enantioselective Michael Reaction of Malononitrile with β,β-Disubstituted Nitroalkenes

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Abstract: We have developed and optimized an enantioselective Michael reaction of malononitrile with β,β-disubstituted nitroalkenes. This reaction was catalyzed by a cinchona alkaloid derived thiourea catalyst, producing products of high yields (up to 98%) and stereoselectivities (up to 93% *ee*). One of the adducts was used as an intermediate for the synthesis of dihydropyrrole derivative bearing a synthetically valuable quaternary chiral center.

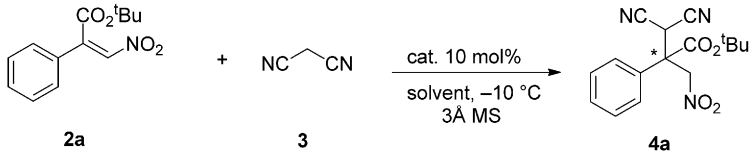
Keywords: asymmetric; malononitrile; Michael reaction; organocatalysis; β,β-disubstituted nitroalkenes

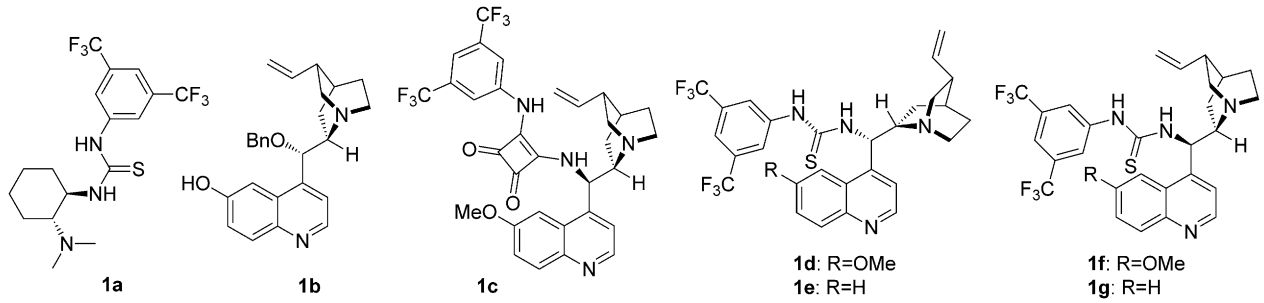
The catalytic asymmetric conjugate addition reaction of nucleophiles to electron-deficient alkenes has garnered attention due to its wide applicability in the synthesis of biologically relevant compounds.[1] One of the most extensively studied asymmetric conjugate addition reactions is the Michael reaction of nitroolefins, which represents a convenient access to nitroalkanes that are versatile intermediates in organic synthesis.[2] However, the studies reported to date have primarily focused on more reactive β-monosubstituted[3] or α,β-disubstituted[4] nitroolefins. The catalytic asymmetric Michael reaction of β,β-disubstituted nitroalkenes is less studied, primarily because steric hindrance poses a potential problem. Particularly noteworthy is that the synthetically important quaternary chiral centers could be generated through the Michael reaction of β,β-disubstituted nitroolefins with nucleophiles. However, only a handful of studies have focused on this particular reaction, likely due to low activity profiles.[5–6]

α-Substituted β-nitroacrylate has recently been documented as a Michael reaction acceptor with a variety of nucleophiles, with the corresponding adduct readily transformable to β-amino acids that are an important motif for β-peptides, β-lactams, and other biologically important compounds.[7] Enones,[6a] aldehydes,[6b] indoles,[6c–e] oximes,[6f] and thiols[6g] have been documented as ideal nucleophiles for this asymmetric Michael addition process. Despite those recent advances, there is still a need for the development of new nucleophilic reagents that are capable of generating structurally diverse quaternary chiral centers through Michael reaction with α-substituted-β-nitroacrylate.

Malononitrile is an equivalent to a 1,3-dicarbonyl compound, and the nitrile group is a versatile functional group for many further transformations.[8] Organocatalytic asymmetric Michael reactions using malononitrile as the nucleophile are relatively less explored due to its high reactivity and incapability of two-point binding with the catalyst. Most of the efforts in this field have been focused on the employment of α,β-unsaturated carbonyls as electrophiles.[9] There have been very few studies using nitroolefins as Michael reaction acceptors. Takemoto[10a] and Yuan,[10b] respectively, reported the bifunctional thiourea catalyzed Michael reactions of malononitrile to nitroolefins with modest enantioselectivity. Arai[10e] synthesized a neural, chiral bis(imidazolidine)-derived NCN-type palladium pincer complex and was able to show an improved stereoselectivity. Although those impressive reports have been published about this reaction, the introduction of new electrophiles for the synthesis of structurally more diversified compounds with high enantioselectivity remains a challenging task. Taking advantage of the high reactivity of malononitrile, we envisaged that the use of the more sterically congested β,β-disubstituted nitroolefins, such as α-substituted-β-nitroacrylate (**2**), as Michael reaction acceptors might improve the stereoselectivity of this reaction.

Table 1. Reaction condition optimization.[a]





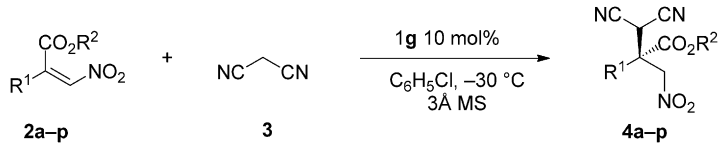
Entry	Catalyst	Solvent	Time [h]	Yield [%][b]	ee [%][c, g]
1	**1a**	toluene	20	93	79 (*S*)
2	**1b**	toluene	20	64	31 (*S*)
3	**1c**	toluene	20	67	20 (*R*)
4	**1d**	toluene	20	79	85 (*R*)
5	**1e**	toluene	20	92	86 (*R*)
6	**1f**	toluene	20	95	83 (*S*)
7	**1g**	toluene	20	92	86 (*S*)
8[d]	**1g**	toluene	20	93	83 (*S*)
9	**1g**	EA	24	trace	–
10	**1g**	CH_2Cl_2	12	89	87 (*S*)
11	**1g**	THF	18	trace	–
12	**1g**	Et_2O	18	44	81 (*S*)
13	**1g**	CH_3CN	18	67	4 (*S*)
14	**1g**	C_6H_5Cl	13	98	90 (*S*)
15	**1g**	$ClCH_2CH_2Cl$	20	73	86 (*S*)
16	**1g**	CH_3Cl	13	95	89 (*S*)
17	**1g**	*m*-xylene	20	95	88 (*S*)
18[e]	**1g**	C_6H_5Cl	27	96	91 (*S*)
19[f]	**1g**	C_6H_5Cl	32	98	92 (*S*)

[a] Unless noted reactions were performed with **2a** (0.1 mmol), **3** (0.2 mmol), **1a–g** (10 mol%), and 3 Å MS (40 mg) in 0.5 mL of solvent at −10 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase.
[d] Conducted without 3 Å MS.
[e] Conducted at −25 °C.
[f] Conducted at −30 °C.
[g] The absolute configurations were determined by comparing the specific rotations of adducts with **4g**.

To begin our investigation, the reaction of (*Z*)-*tert*-butyl 3-nitro-2-phenylacrylate (**2a**) and malononitrile (**3**) was chosen as an initial model. This asymmetric Michael reaction was evaluated with 10 mol% of bifunctional organocatalysts (**1a–g**)[11] in toluene under −10 °C with 3 Å molecular sieves as additive. The results are summarized in Table 1. The thiourea moiety is essential for the high stereoselectivity of this reaction; replacing the thiourea group with a squaramide moiety resulted in a low enantioselectivity of the adduct **4a** (Table 1, entry 3). The tertiary amine group of the catalysts is also an important factor for the reaction to proceed smoothly.[9] Organocatalysts having both a thiourea moiety and tertiary amino group allowed the corresponding adduct to have both a high yield and high stereoselectivity (Table 1, entries 1, 4–7). The best result was obtained when cinchonine-derived thiourea **1g** was used, producing a 92% yield and 86% *ee* (Table 1, entry 7).

Having identified the best catalyst (**1g**), the effects of solvent and temperature were also investigated to further improve the efficiency of this Michael reac-

Table 2. Substrate scope of nitroacrylate.[a]



Entry	R^1	R^2	Product	Time [h]	Yield [%][b]	ee [%][c]
1	C_6H_5	*t*-butyl	**4a**	32	98	92
2	C_6H_5	isopropyl	**4b**	32	90	86
3	C_6H_5	benzyl	**4c**	40	95	73
4	3-MeC_6H_4	*t*-butyl	**4d**	32	85	90
5	3-$MeOC_6H_4$	*t*-butyl	**4e**	40	98	91
6	3-FC_6H_4	*t*-butyl	**4f**	45	87	89
7	3-ClC_6H_4	*t*-butyl	**4g**	45	86	90
8	4-MeC_6H_4	*t*-butyl	**4h**	48	92	92
9	4-$MeOC_6H_4$	*t*-butyl	**4i**	33	95	93
10	4-FC_6H_4	*t*-butyl	**4j**	32	78	89
11	4-ClC_6H_4	*t*-butyl	**4k**	36	83	90
12	4-BrC_6H_4	*t*-butyl	**4l**	48	89	90
13	4-$CF_3C_6H_4$	*t*-butyl	**4m**	45	70	87
14	2-naphthyl	*t*-butyl	**4n**	42	98	92
15	2-thienyl	*t*-butyl	**4o**	48	84	92
16	2-phenylethyl	*t*-butyl	**4p**	36	80	7

[a] Unless noted reactions were performed with **2a–p** (0.1 mmol), **3** (0.2 mmol), **1g** (10 mol%) and 3 Å MS (40 mg) in 0.5 mL of chlorobenzene at −30 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase.

tion. As shown in Table 1, the reaction media has a substantial influence on the reactivity and stereoselectivity. The reaction proceeded sluggishly in tetrahydrofuran and ethyl acetate; only trace amounts of product **4a** were detected. A less polar solvent like chlorobenzene was shown to be the optimal solvent for this transformation with the highest enantioselectivity (Table 1, entry 14). The temperature also slightly affected the stereoselectivity of this reaction. At −30 °C with a prolonged reaction time, the reaction gave the product in 98% yield and 92% *ee* (Table 1, entry19).

Using those optimized reaction conditions, we investigated the asymmetric Michael reactions of malononitrile with a variety of α-substituted-β-nitroacrylates (**2a-p**), with the results presented in Table 2. In general, the electronic nature of the substituents on the phenyl ring of α-aryl-β-nitroacrylates (**2d–m**) had little effect on the reactivity and stereoselectivity of the reaction; both the electron-donating and electron-withdrawing groups were well tolerated and produced the corresponding products in excellent yields and enantioselectivities (Table 2, entries 4–13). It is noteworthy that 2-naphthyl and 2-thienyl substrates reacted smoothly to afford the products in 98 and 84% yields, respectively, both in 92% *ee* (Table 2, entries 14 and 15). However, alkylated substrate **2p** reacted well with malononitrile (**3**), but the stereoselectivity was low (Table 2, entry 16). The ester group on the α-position of **2** affected the stereoselectivity significantly as a result of steric hindrance. Use of isopropyl and benzyl α-phenyl-β-nitroacrylate (**2b** and **2c**) yielded products with low stereoselectivities (Table 2, entries 2 and 3).

The absolute configuration of **4g** was determined to be *S* based on the single crystal X-ray structure analysis (Figure 1).[12] A plausible transition state is depicted in Figure 2, based on this analysis and previous reported results on cinchona alkaloid derived thiourea catalysis. As we have described in the catalyst screening part, the thiourea moiety and tertiary amine group of the catalyst **1g** are important factors for the high yields and stereoselectivities of this reaction. The α-aryl-β-nitroacrylate (**2**) is activated through double hydrogen bonding of the thiourea moiety to the nitro group, while the deprotonated malononitrile becomes a pronucleophile through hydrogen bonding with the protonated tertiary amine of **1g**. The *Re* face attack at the α-position of α-aryl-β-nitroacrylate (**2**) is favored to afford the corresponding product in *S* configuration.

Finally, the synthetic utility of the asymmetric Michael reaction was investigated. The reaction was scaled up to 4 mmol of **2a** and 8 mmol of malononitrile (**3**). Product **4a** was isolated with an 86% yield retaining high enantioselectivity (Scheme 1). The cor-

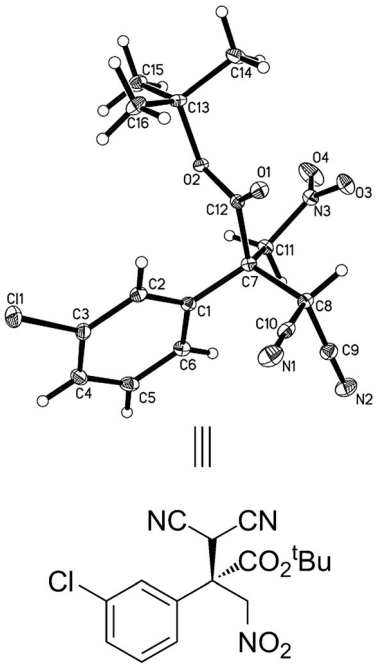


Figure 1. X-ray structure of **4g**.

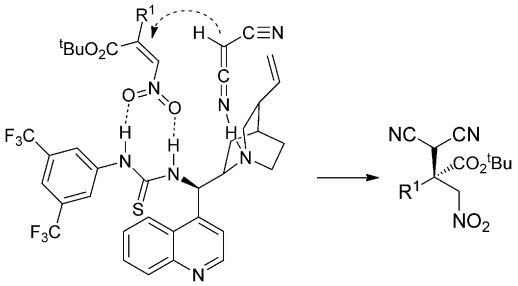
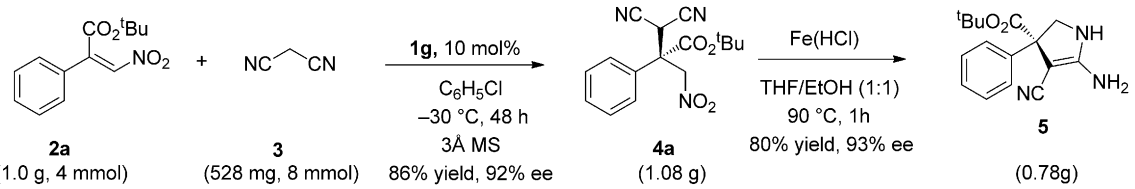


Figure 2. Proposed transition state of this Michael reaction.

responding dihydropyrrole **5** was readily obtained in an 80% yield by the reduction of the nitro group with reduced iron and concentrated hydrochloric acid in THF/EtOH (1:1, v/v) under 90 °C. The dihydropyrrole moiety is a functional core of various natural products and pharmaceutical agents[13] and could be used as an intermediate for the synthesis of various nitrogen-containing biologically relevant heterocyclic compounds.[14]



Scheme 1. Scale up reaction and transformation of **4a.**

In conclusion, we have developed an enantioselective Michael reaction of malononitrile to α-substituted-β-nitroacrylates. This reaction was catalyzed efficiently by a cinchonine-derived bifunctional thiourea catalyst, and the corresponding adducts bearing quaternary chiral centers were obtained in high yields and enantioselectivities. More importantly, this strategy could be used for the synthesis of dihydropyrrole derivatives for biological and pharmaceutical applications.

Experimental Section

Typical Procedure for the Asymmetric Michael Reaction

A sample bottle equipped with a magnetic stirring bar was charged with **2** (0.1 mmol), **3** (13.2 mg, 0.2 mmol, 2.0 equiv), chlorobenzene (0.5 mL) and 3 Å molecular sieve (40 mg). After the temperature had been cooled down to −30 °C, **1g** (5.6 mg, 0.01 mmol, 0.1 equiv) was added. The reaction mixture was stirred at −30 °C until **2** was consumed (determined by TLC). The reaction mixture was directly purified by silica gel column chromatography (petroleum ether/ethyl acetate = 15:1 v/v as eluent) to give the product **4**.

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