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Enantioselective Michael reaction of 1,3-dicarbonyl compounds to 3-nitro-2*H*-chromenes catalyzed by chiral nickel complexes

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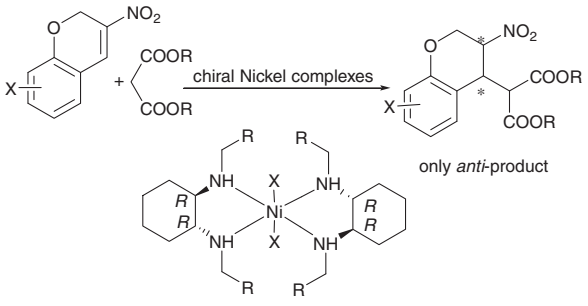
ABSTRACT

A chiral nickel complexes-catalyzed enantioselective Michael addition of 1,3-dicarbonyl compounds to 3-nitro-2*H*-chromenes has been developed; the products could be obtained in high yields and good enantioselectivities.

The Michael addition reaction is widely recognized as one of the most general and versatile methods for formation of C–C bonds in organic synthesis;[1] among which, the Michael reaction of nitroolefins represents a convenient access to nitroalkanes that are versatile intermediates in organic synthesis, because the nitro functionality can be easily transformed into amine, nitrile oxide, ketone or carboxylic acid, hydrogen, etc., providing a wide range of synthetically interesting compounds.[2] Up to now, the development of enantioselective catalytic protocols for this asymmetric Michael addition to nitroalkenes has been a subject of intensive research,[3] for these optically active nitroalkanes are versatile building blocks for agricultural and pharmaceutical compounds.

Although there have been many reports of enantioselective Michael additions with chiral catalysts, including metal-based catalysts and multimetallic catalysts as well as organic catalysts, practical Michael additions of 1,3-dicarbonyl compounds to nitroalkenes remain largely unexplored except for reactions with chiral Mg catalysts[4] and optically active thioureas as efficient catalysts.

However, despite the tremendous amount of work and effort devoted to the development of efficient and versatile Michael reactions, the structure of the electrophile has been restricted to nitroalkenes, enones,[5] and unsaturated imides,[6] and the enantioselective Michael reaction using cyclic nitroalkenes[7] as the acceptors has been relatively unexplored. Here, we have developed a highly enantio- and anti-selective Michael reaction of 1,3-dicarbonyl compounds and readily available cyclic nitroalkenes with chiral nickel complexes[8] as the catalysts (indicated by NMR spectroscopy). The reactions could afford highly functionalized products with two adjacent stereogenic carbon atoms in high levels of enantio- and diastereoselectivities, and the Michael products are interesting cyclic β-amino acid derivatives.



Our initial studies began with the catalytic asymmetric Michael addition of 3-nitro-2*H*-chromene (**2a**) with dimethyl malonate (**3a**) in the catalytic amount of chiral nickel complexes (**1a–h**). The chiral complexes were prepared by reacting nickel salts and chiral diamine ligands smoothly, and it was found that the expected Michael addition products could be obtained by aqueous workup and column chromatography in good yields. The results are summarized in Table 1.

First, the effects of a number of different counterions were surveyed. The asymmetric Michael addition reaction carried out at

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room temperature in DCM afforded the product in high yields and good enantioselectivities (Table 1, entries 1–4). Among which, the use of $NiBr_2$, catalyst **1b** turned out to be the best catalyst in terms of yield and enantioselectivity.

Next, the effects of the solvent and temperature were also investigated (Table 1, entries 5–12). The Michael addition reaction carried out at 0 °C in toluene afforded the desired product with 92% yield and 95% ee. Slight decrease of selectivities and yields were found when the reactions were carried out in other solvents or at other temperatures. It was found that the reaction could also proceed smoothly in polar solvent; however, the product was obtained with just 78% ee. Meanwhile, the amount of catalyst had been optimized to 5 mol %, there was no significant increase in the yield and enantioselectivity by increasing the catalyst amount to 10 mol %; the reaction proceeded sluggishly with a slight drop in enantioselectivity when the catalyst loading was reduced to 2 mol %. Therefore, the optimum reaction conditions were achieved by performing the reaction of 1 equiv of 3-nitro-2*H*-chromene with 1.5 equiv of dimethyl malonate and 5 mol % catalyst loading at 0 °C in toluene.

Prompted by these results, several other chiral diamine ligands were synthesized, and their catalytic activities were also screened with $NiBr_2$ under the optimized reaction conditions (Table 1, entries 13–16). From the results, it was found that the products could be obtained in comparable yields and enantioselectivities, lower catalytic activity and stereoselectivity toward the reaction was observed.

Through this screening process, the following points could be established: (1) The use of chiral nickel complexes, which were prepared from chiral diamine ligands and nickel salts, gave the Michael addition products in good yields with high enantioselectivities. Of these complexes surveyed, the chiral nickel complex (**1b**) provided superior levels of asymmetric induction, affording the Michael addition product in 95% ee (Table 1, entry 11). (3) In all cases tested, only *anti*-selective Michael addition products were obtained (indicated by NMR spectroscopy), no undesired side products were found under these reaction conditions; and this method did not require any other additives to promote the reaction.

Having optimized the reaction conditions, we extended the catalytic enantioselective Michael addition to a wide variety of 3-nitro-2*H*-chromenes (Fig. 1) in the presence of the optimized chiral nickel complex (**1b**). The results obtained are shown in Table 2.

As shown in Table 2, under the optimized reaction conditions, all of the 3-nitro-2*H*-chromenes could furnish the corresponding products in high enantioselectivities (80–95% ee) and good yields, and only the *anti*-products were observed in the reactions. In contrast to the 3-nitro-2*H*-chromene derivatives, substrates bearing an electron-donating substituent on the aromatic ring tended to decrease their reactivity without affecting the good enantioselectivity. Other 1,3-dicarbonyl compounds, such as acetylacetone and dibenzoylmethane, were also tested under the optimized reaction conditions; unfortunately, only the *rac*-products were obtained with high yields. Meanwhile, due to the steric demands of the malonate residue, longer reaction times were needed when dibenzyl malonate was applied as the starting material.

The **1b**-catalyzed enantioselective Michael reaction of 1,3-dicarbonyl compounds to 3-nitro-2*H*-chromene was also applicable to chiral cyclo γ-amino butylic acid (Scheme 1). The ability of **1b** to promote enantioselective Michael reaction should facilitate the preparation of a wide variety of optically active cyclo γ-amino butylic acid.

In conclusion, this Letter has described an efficient method for the asymmetric direct Michael addition that employs 3-nitro-2*H*-chromenes as the acceptors in the presence of a catalytic amount of air- and moisture-stable chiral nickel complexes. The chiral

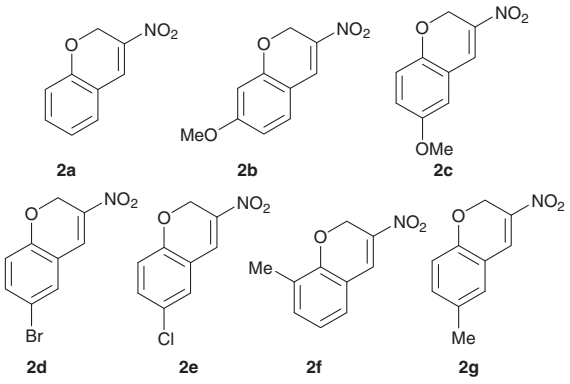
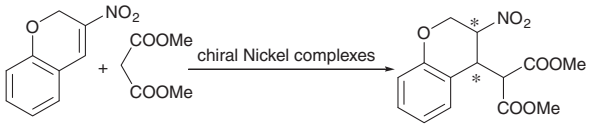


Figure 1. Structures of 3-nitro-2*H*-chromenes.

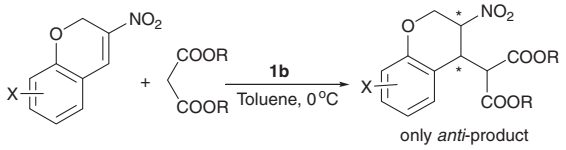
Table 1
Optimization of the reaction conditions[a]



Entry	R	X	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	Cl	DCM	20	10	90	86
2	Ph (**1b**)	Br	DCM	20	10	92	89
3	Ph (**1c**)	Ac	DCM	20	48	84	85
4	Ph (**1d**)	TfO	DCM	20	20	88	87
5	Ph (**1b**)	Br	THF	20	10	86	89
6	Ph (**1b**)	Br	EA	20	10	90	87
7	Ph (**1b**)	Br	Toluene	20	10	92	90
8	Ph (**1b**)	Br	EtOH	20	30	88	78
9	Ph (**1b**)	Br	Toluene	50	4	94	89
10	Ph (**1b**)	Br	Toluene	10	15	91	93
11	Ph (**1b**)	Br	Toluene	0	24	92	95
12	Ph (**1b**)	Br	Toluene	−20	48	48	96
13	4-FC_6H_4 (**1e**)	Br	Toluene	20	24	75	86
14	4-ClC_6H_4 (**1f**)	Br	Toluene	20	24	79	84
15	4-BrC_6H_4 (**1g**)	Br	Toluene	20	24	82	85
16	4-$MeOC_6H_4$ (**1h**)	Br	Toluene	20	10	84	82

[a] All reactions were performed on a 0.5 mmol scale with 5 mol % of catalyst at a 1 M concentration using 1.5 equiv of dimethylmalonate.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column.

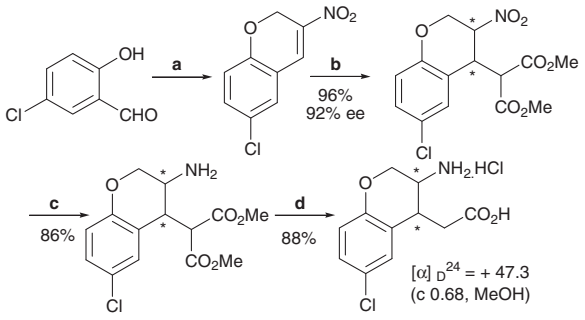
Table 2
Enantioselective Michael addition reaction of malonates to 3-nitro-2*H*-chromenes[a]



2a-g **3a-b** **4**

Entry	2	R	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	Me (**3a**)	**4aa**	24	92	95
2	**2b**	Me (**3a**)	**4ba**	30	82	80
3	**2c**	Me (**3a**)	**4ca**	30	81	88
4	**2d**	Me (**3a**)	**4da**	20	91	92
5	**2e**	Me (**3a**)	**4ea**	20	96	92
6	**2f**	Me (**3a**)	**4fa**	24	88	84
7	**2g**	Me (**3a**)	**4ga**	24	91	86
8	**2a**	Bn (**3b**)	**4ab**	30	88	91
9	**2c**	Bn (**3b**)	**4cb**	36	80	91
10	**2d**	Bn (**3b**)	**4db**	30	90	90
11	**2f**	Bn (**3b**)	**4fb**	30	88	92
12	**2g**	Bn (**3b**)	**4gb**	30	91	92

[a] All reactions were performed with 0.5 mmol of **2**, 0.6 mmol of **3**, 5 mol % of catalyst in 0.5 mL of toluene at 0 °C.
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis using Chiralcel AD-H column.



Scheme 1. Asymmetric synthesis of chiral cyclo γ-amino butylic acid (see Supplementary data for details). Reagents and conditions: (a) *n*-Bu_4NCl/nitroethanol; (b) dimethyl malonate, **1b**, toluene; (c) $NaBH_4$, $NiCl_2{\cdot}6H_2O$; (d) 6 N HCl, reflux.

nickel complex **1b** exhibited high stereoselectivity and catalytic activity in the asymmetric Michael addition. The corresponding Michael addition products were obtained in high yields and good diastereo- and enantioselectivities. We believe that this method could provide an efficient route for the preparation of chiral cyclo γ-amino butylic acid derivatives, and the availability of these compounds may facilitate medicinal chemical studies in various fields. Further work on applying this kind of chiral nickel complexes for other organic transformations is in progress.

Typical procedure for asymmetric conjugate addition of 1,3-dicarbonyl compounds **2** to 3-nitro-2*H*-chromenes **3**: To a stirred mixture of chiral nickel catalyst (5 mol %) and **3** (0.5 mmol) in toluene (0.5 mL) was added **2** (0.6 mmol) at 0 °C, and the resulting mixture was stirred for the amount of time indicated. Then, the reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel to afford the desired product **4**. Compound **4aa** $[\alpha]_D^{24}$ = +50.6 (*c* 0.33, DCM), 95%ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.16 (m, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.26 (q, *J* = 6.8 Hz, 1H), 4.77–4.73 (m, 1H), 4.49–4.47 (m, 1H), 4.41–4.37 (m, 1H), 3.94 (d, *J* = 7.2 Hz, 1H), 3.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 167.5, 153.8, 129.2, 128.6, 122.1, 118.4, 117.6, 80.9, 64.5, 55.2, 53.04, 53.03, 35.9; Exact mass calcd for $[C_{14}H_{15}NO_7+H]$: 310.2793, found 310.2788; The enantiomeric ratio was determined by HPLC on Chiralpak AD-H column (10% 2-propanol/hexane, 1 mL/min), t_{minor} = 12.217 min, t_{major} = 13.575 min.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.111.

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