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Enantioselective synthesis of nitrocyclopropanes via conjugate addition of bromomalonate to nitroalkenes catalyzed by Ni(II) complexes

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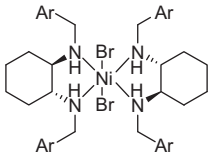
ABSTRACT

A novel one-pot methodology for the catalytic enantioselective synthesis of highly functionalized nitrocyclopropanes promoted by chiral nickel complexes is developed. The treatment of bromomalonates with nitroalkenes under the mild reaction conditions afforded the corresponding Michael adducts which cyclizes to controlled reaction conditions with excellent diasteroselectivities (>99 de) and enantioselectivities (up to 99% ee).

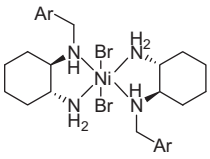
The cyclopropane ring is a important structural motif in a great number of natural products and biologically active agents.[1] In addition, cyclopropyl derivatives are also valuable as synthetic building blocks in organic synthesis.[2,3] Cyclopropanes are susceptible to ring opening reaction with many nucleophilic reagents due to high strain of the cyclopropane ring. A number of efforts have been made to develop efficient synthetic methods of chiral cyclopropanes.[4] Nitrocyclopropanes are a class of special cyclopropane compounds, which are constituent of a diverse assortment of natural products.[5] Furthermore, chiral nitrocyclopropanes can be converted into a wide range of useful chiral compounds.[6] Over the past decade, tremendous effort has been devoted to the development of efficient and stereoselective methodologies for cyclopropanation of alkenes using chiral organometallic carbenoid species and yields[4] and cyclopropanation of α,β-unsaturated aldehydes and ketones using organocatalysts.[7]

On the other hand, the asymmetric synthesis of nitrocyclopropanes via the addition of chloromalonates to nitroalkenes and consequent ring-closure of Michael adducts was reported by Connon and co-workers.[8] This reaction provided the nitrocyclopropanes in moderate yields and enantioselectivities using cinchona alkaloid derived thioureas as the catalysts. The similar approach has been recently developed by Takemoto, Yan, and Lattanzi groups using organocatalysts such as chiral bifunctional thioureas, 6′-demetyl quinine, or α,α-diaryl prolinols to access highly functionalized nitrocyclopropanes (Scheme 1).[9] Among them, Yan and co-workers achieved a highly diastero- and enantioselective synthesis of nitrocyclopropanes via the highly enantioselective conjugate addition of bromomalonates to nitroalkenes using 6′-demetyl quinine as catalyst and consequent DABCO-mediated ring-closure. Nonetheless, the development of alternative catalysts for nitrocyclopropanation via the addition of halomalonates to nitroalkenes would be highly desirable. Recently, the efficient examples of the enantioselective reactions catalyzed by air- and moisture-stable nickel complexes were reported.[10] To the best of our knowledge, nitrocyclopropanation via the addition of bromomalonates to nitroalkenes catalyzed by chiral nickel complexes has not been reported.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[11] we recently reported the catalytic electrophilic amination, fluorination, and Michael addition reaction of active methines promoted by chiral nickel complexes with excellent enantioselectivities.[12] In this Letter, we wish to describe



4a : Ar = phenyl
4b : Ar = 4-fluorophenyl
4c : Ar = 1-naphthyl



4d : Ar = phenyl
4e : Ar = 1-naphthyl

Figure 1. Structures of chiral nickel catalysts.

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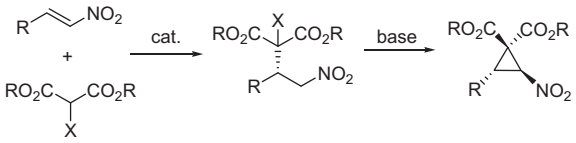


Scheme 1. Route to nitrocyclopropanes.

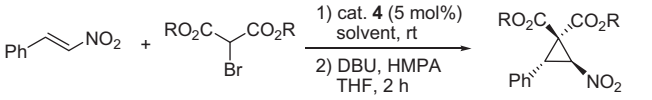
enantioselective conjugate addition of bromomalonates to nitroalkenes catalyzed by air- and moisture-stable chiral nickel complexes (Fig. 1). The consequent intramolecular cyclopropanation provided nitrocyclopropanes in good yields and with excellent enantioselectivities.

To determine suitable reaction conditions for the catalytic enantioselective cyclopropanation reaction of nitroalkenes, we first examined cyclopropanation reaction of nitrostyrene (**1a**) with bromomalonates **2** in the presence of 5 mol % of dicationic nickel complexes **4** in CH_2Cl_2 at room temperature (Table 1). We studied the effect of the ester group of bromomalonates **2** using nickel catalyst **4a** in CH_2Cl_2 (entries 1 and 2). Diethyl bromomalonates (**2b**) showed better enantioselectivity (entry 2). We surveyed the effect of structure of nickel complexes **4**. High yields with excellent enantioselectivities (92–96% ee) were observed for structurally variable nickel catalysts **4a–c** (entries 2–4). Under the standard reaction conditions, catalyst **4b** gave better enantioselectivity (96% ee, entry 3). However, *N*-monobenzyl cyclohexanediamine-derived Ni complexes (**4d–e**) were not effective in this reaction (entries 5 and 6). Next, we examined the reaction in various solvents (entries 3 and 7–11). The use of CH_2Cl_2, toluene, dibromomethane and 1,2-dichloroethane gave the good results, whereas the cyclopropanation reaction in MeOH and acetone gave lower enantioselectivities. The absolute configuration of **3a** was established by comparison of the optical rotation and chiral HPLC analysis with previously reported values.[9]

With optimal reaction condition in hand, we studied the generality of the enantioselective cyclopropanation reaction of aromatic and heteroaromatic nitroalkenes **1** with bromomalonates **2**.[13] As it can be seen by the results summarized in Table 2, the corresponding cyclopropane derivatives **3a–n** were obtained in high yields with enantioselectivities (85–99% ee).

Although the reason for the observed enantioselectivity is still unclear, we suppose that bromomalonates **2** are activated by the nickel catalyst **4** in a bidentate fashion. Then, bromomalonates anion attacks the *si*-face of double bond of nitroalkene as shown in Figure 2.

Table 1
Optimization of the reaction conditions

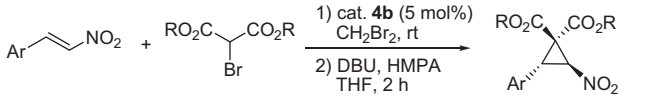


1a 2 3

Entry	**2**, R	Cat. **4**	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**2a**, Me	**4a**	DCM	72	**3a**, 90	92
2	**2b**, Et	**4a**	DCM	72	**3b**, 92	94
3	**2b**, Et	**4b**	DCM	24	**3b**, 98	96
4	**2b**, Et	**4c**	DCM	24	**3b**, 89	92
5	**2b**, Et	**4d**	DCM	72	nr	—
6	**2b**, Et	**4e**	DCM	72	nr	—
7	**2b**, Et	**4b**	Toluene	24	**3b**, 95	95
8	**2b**, Et	**4b**	DBM	24	**3b**, 99	97
9	**2b**, Et	**4b**	DCE	24	**3b**, 95	96
10	**2b**, Et	**4b**	MeOH	24	**3b**, 70	65
11	**2b**, Et	**4b**	Acetone	24	**3b**, 85	75

[a] Isolated yield: Only *trans*-isomer was observed by NMR analysis.
[b] Enantiopurity was determined by chiral HPLC analysis using chiralpak AD–H column.

Table 2
Catalytic enantioselective cyclopropanation



1 2 3

Entry	**1**, Ar	**2**, R	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**1a**, Ph	**2a**, Me	64	**3a**, 87	94
2	**1a**, Ph	**2b**, Et	24	**3b**, 99	97
3	**1b**, *p*-$MeOC_6H_4$	**2a**, Me	64	**3c**, 89	96
4	**1b**, *p*-$MeOC_6H_4$	**2b**, Et	42	**3d**, 96	99
5	**1c**, *p*-MeC_6H_4	**2a**, Me	64	**3e**, 86	97
6	**1c**, *p*-MeC_6H_4	**2b**, Et	17	**3f**, 97	99
7	**1d**, *p*-BrC_6H_4	**2a**, Me	64	**3g**, 85	91
8	**1e**, *p*-ClC_6H_4	**2b**, Et	42	**3h**, 92	98
9	**1f**, *p*-FC_6H_4	**2b**, Et	17	**3i**, 95	98
10	**1g**, *o*-$NO_2C_6H_4$	**2b**, Et	24	**3j**, 93	91
11	**1h**, *o*-BrC_6H_4	**2b**, Et	22	**3k**, 90	93
12	**1i**, 2-thienyl	**2b**, Et	70	**3l**, 89	99
13	**1j**, 2-furyl	**2b**, Et	20	**3m**, 91	91
14	**1k**, 1-naphthyl	**2b**, Et	96	**3n**, 70	85

[a] Isolated yield: Only *trans*-isomer was observed by NMR analysis.
[b] Enantiopurity was determined by HPLC analysis using chiralpak AD–H (for **3a–c**, **3e–g**, and **3m**), AS (for **3d**, **3h**, **3i**, **3k**, **3l**, and **3n**) and chiralcel OD–H (for **3j**) columns.

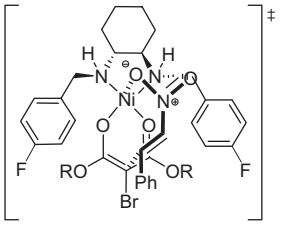


Figure 2. Proposed transition state model for the conjugate addition.

In conclusion, we have developed an efficient catalytic cyclopropanation reaction of nitroalkenes with bromomalonates using air- and moisture-stable chiral nickel complexes at room temperature. The desired cyclopropane derivatives **3** were obtained in high yields, excellent diasteroselectivities (>99 de) and excellent enantioselectivities (85–99% ee) were observed for all the substrates examined in this work. We believe that this report provides a practical method for the preparation of chiral nitrocyclopropane derivatives, and the availability of these compounds should facilitate biochemical and medicinal studies in various fields.

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13. *Typical procedure*: To a stirred solution of methyl bromomalonate (**2a**, 47.2 mg, 0.22 mmol), Ni-catalyst **4b** (8.2 mg, 0.01 mmol) in dibromethane (0.4 mL) was added nitrostyrene (**1a**, 29.8 mg, 0.2 mmol) at room temperature. The reaction mixture stirred for 64 h at room temperature. The reaction mixture was diluted with HMPA (2 mL), and DBU (30.8 μL, 0.21 mmol) in THF (0.2 mL) was added dropwise with vigorous stirring. The reaction mixture was stirred for 2 h, the resulting mixture was extracted with EtOAc (20 mL), then washed with sat. NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (EtOAc/hexane: 1/6) to afford (*2S*,*3R*)-dimethyl 2-nitro-3-phenylcyclopropane-1,1-dicarboxylate (**3a**, 87% yield, 48.5 mg). $[\alpha]_D^{20}$ = +37.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37–7.31 (m, 3H), 7.28–7.25 (m, 2H), 5.39 (d, *J* = 6.2 Hz, 1H), 4.19 (d, *J* = 6.2 Hz, 1H), 3.83 (s, 3H), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.8, 163.6, 130.1, 128.7, 128.6, 128.2, 66.1, 53.9, 53.3, 46.1, 37.8; MS (ESI): *m*/*z* = 280.1 $[M+H]^+$; HPLC (90:10, *n*-hexane/*i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD–H column, t_R = 7.0 min (minor), 8.1 min (major), 94% ee.