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Bifunctional thiourea-catalyzed enantioselective double Michael reaction of γ,δ-unsaturated β-ketoester to nitroalkene: asymmetric synthesis of (−)-epibatidine

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Abstract—The asymmetric synthesis of 4-nitrocyclohexanone derivatives has been accomplished by enantioselective double Michael additions of γ,δ-unsaturated β-ketoesters to nitroalkenes using a catalytic amount of bifunctional thiourea and TMG. The three contiguous stereogenic centers of the obtained products were constructed with good to high diastereoselectivity and up to 92% ee. The biologically active natural product, (−)-epibatidine, has been synthesized from the intermediate **11a** in seven steps in 30% overall yield.
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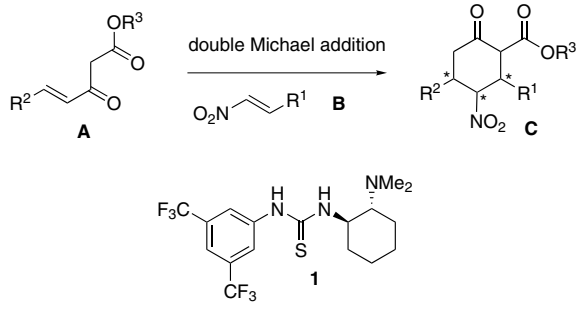
The catalytic asymmetric formation of a carbon–carbon bond represents one of the most challenging fields in organic chemistry. In particular, the enantioselective construction of multiple stereogenic centers in a single reaction has been the subject of intensive research over the past several years.[1] Among the various reactions, the direct Michael addition of 1,3-dicarbonyl compounds to electron-deficient alkenes may be an ideal reaction in terms of operational simplicity, atom economy, and versatile utility of the products.[2] Thus far, various types of enantioselective reactions have been reported by employing chiral catalysts such as a Lewis acid, a Lewis base, or a bimetallic complex.[3,4] Although substantial progress has been realized in the development of asymmetric Michael addition reactions, few of these reactions succeeded in the enantioselective construction of contiguous stereogenic centers.[4a,5] On the other hand, due to their versatility as synthetic intermediates for natural products,[6–9] various methods such as Diels–Alder reaction,[6,7] intramolecular and intermolecular Michael reactions,[8,9] have been developed to synthesize chiral nitrocyclohexanes. However, there are few successful reports using catalytic asymmetric reaction.[9] Recently, we reported that the bifunctional thiourea **1**-catalyzed Michael reaction of malonates to nitroalkenes proceeded with high enantioselectivity up to 93% ee.[10] We then planed to apply this method to a domino reaction,[1] that is, double Michael reactions to synthesize optically active 4-nitrocyclohexanones **C** (Scheme 1). Herein we present a thiourea/TMG-catalyzed double Michael reactions of γ,δ-unsaturated-β-ketoesters **A** to nitroalkenes **B** and also an asymmetric synthesis of (−)-epibatidine from the resultant intermediate bearing three stereogenic centers.

We first investigated the double Michael reactions of γ,δ-unsaturated-β-ketoesters**3a–d** to nitrostyrene **2a** (Table 1).



Scheme 1. Double Michael reaction of **A** and **B** with thiourea **1**.

Keywords: Thiourea; Organocatalyst; Michael reaction; Asymmetric synthesis; γ,δ-Unsaturated β-ketoester; (−)-Epibatidine.
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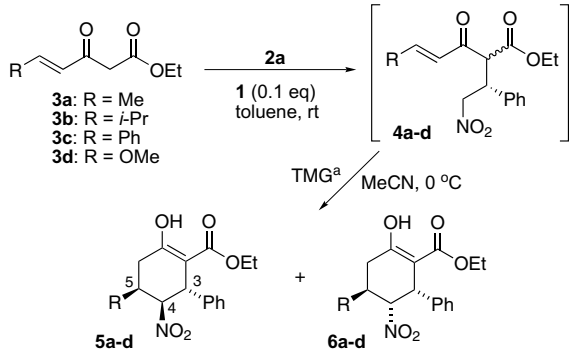
Table 1. Thiourea **1** and TMG-catalyzed enantio- and diastereoselective double Michael reaction of **2a** and **3a–d**



Entry	**3** (R)	Temp (°C)	Yield (%)[b]	de (%)[c]	ee (%)[d]
1[e]	**3a** (Me)	rt	65	>99	86
2	**3a** (Me)	−20	87	>99	92
3	**3b** (*i*-Pr)	rt	71	>99	88
4	**3c** (Ph)	−40	79	90	89
5	**3d** (OMe)	rt	63	64	85

[a] 1,1,3,3,-Tetramethylguanidine.
[b] Isolated yield.
[c] The ratio of **5/6** was determined by ^{1}H NMR.
[d] Determined by HPLC analysis.
[e] The reaction was carried out without TMG.

When **2a** and **3a** were combined in toluene in the presence of 10 mol% of bifunctional thiourea **1**, the domino reaction proceeded at room temperature, giving the cyclic adduct **5a** in 65% yield as the single isomer (entry 1). The enantioselectivity of **5a** was revealed to be 86% ee by chiral HPLC analysis. In contrast to **3a**, no domino reaction of **3b–d** with **2a** occurred, providing acyclic adducts **4b–d** in good yields (entries 3–5). Although we could not succeed in the domino reaction with **1**, subsequent treatment of the obtained products **4b–d** with 0.1 equiv of 1,1,3,3-tetramethylguanidine (TMG) at 0 °C furnished the desired cyclic adducts **5b–d** with good enantioselectivity (85–89% ee). Similarly, the reaction of **3a** under the same two-step conditions provided **5a** in better yield with 92% ee (entry 2). The relative configurations of **5a–d** were determined by ^{1}H NMR analysis (Fig. 1). All the major products **5a–d** possess the same configuration (3,4-*trans*-4,5-*cis*), whereas the 3,4-*cis*-4,5-*trans*-diastereoisomers **6c** and **6d** were produced as minor products in the cases of **3c** and **3d** bearing phenyl and methoxy groups at the δ-position. The stereoselective formation of **5a–d** would be rationally explained by considering the plausible reaction mechanism shown in Figure 2. Namely, the transition state **D**, giving the major isomer **5**, would be energetically more stable than the transition state **E**, due to the steric hindrance between the phenyl ring and the nitronate anion in **E**. This is the first report that succeeds in asymmetric synthesis of three contiguous stereogenic centers by the double Michael reactions with nitroalkenes.

Having established the asymmetric synthesis of 4-nitrocyclohexanones, we next applied this method to the total synthesis of (−)-epibatidine **6**, an alkaloid isolated from the skin of the Ecuadorian frog *Epibatidores tricolor*[11] Although many syntheses of **6** have been reported,[12] only a few full syntheses are enantioselective.[13] In particular, the only catalytic version by Trost and Cook is known.[13f] Our synthetic approach to **6** relies on the double Michael reactions of γ,δ-unsaturated-β-ketoester **7** to nitroalkene **8**. By taking advantage of the axial methoxy group, the corresponding cyclic adduct **9** would be stereoselectively converted into *trans*-nitroalcohol **10a**, which is a key intermediate for the synthesis of (−)-epibatidine (Scheme 2).

The synthesis of **9** began with a condensation of *trans*-4-methoxy-3-buten-2-one and allyl cyanoformate using LHMDS as a base, giving the desired product **7** in 73% yield (Scheme 3). Successive treatment of **7** and a known compound **8**[14] with thiourea **1** and TMG at 0 °C provide the cyclic product **11a** in 67% yield along with diastereomer **11b** (20% yield). The diastereomer **11b** seemed to be generated by a base-catalyzed epimerization of the major product **11a**. Fortunately, replacement of TMG with KOH in EtOH suppressed the

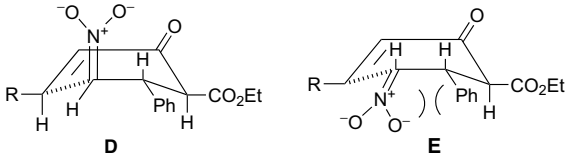
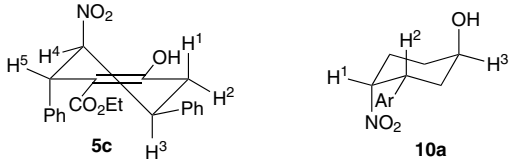


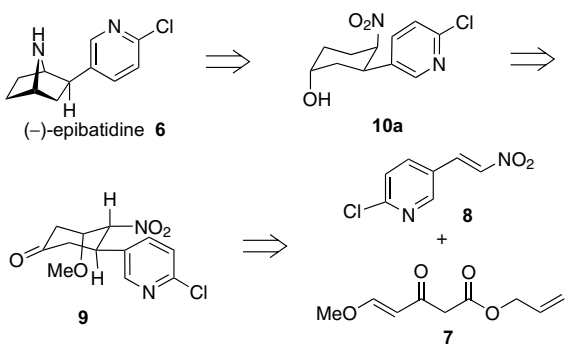
Figure 2. Diastereoselective formation of **5a-d**.



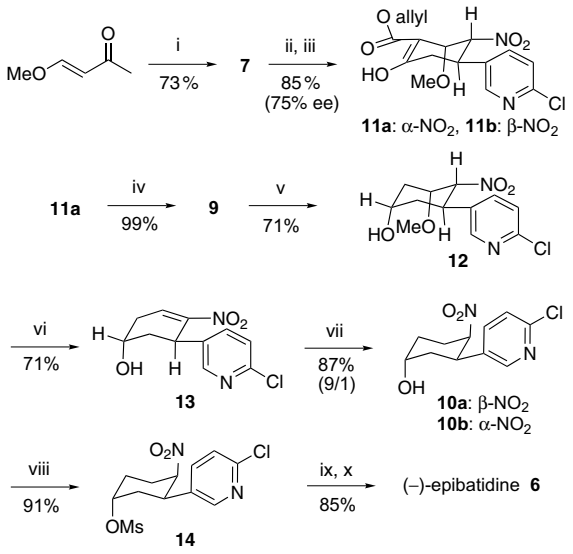
coupling constant (Hz)	NOE (%)
H^1: 18.3, 11.7	H^3 - H^4: 7.8
H^2: 18.3, 6.5	H^4 - H^5: 7.8
H^3: 11.7, 6.5, 3.5	H^3 - H^5: 0.0
H^4: br s ($W_{1/2}$ = 6.6)	
H^5: br s ($W_{1/2}$ = 5.2)	

coupling constant (Hz)
H^1: br s ($W_{1/2}$ = 9.9)
H^2: 13.1, 4.0
H^3: br s ($W_{1/2}$ = 9.8)

Figure 1. Relative configurations of **5c** and **10a**.



Scheme 2. Retrosynthetic analysis of (−)-epibatidine **6**.



Scheme 3. Enantioselective total syntheis of (−)-epibatidine **6**. Reagents and conditions: (i) LHMDS, THF; allyl cyanoformate, −78 °C; (ii) **8**, **1** (10 mol%), toluene, 0 °C; (iii) KOH, EtOH, 0 °C; (iv) $Pd(OAC)_2$, PPh_3, HCO_2H, Et_3N, THF, rt; (v) L-Selectride, THF, −78 °C; (vi) NaOMe, *t*-BuOH, rt; (vii) $NaBH_3CN$, AcOH, MeOH, −20 °C; (viii) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (ix) Zn, AcOH, THF, rt; (x) $CHCl_3$, 60 °C.

epimerization of **11a** into **11b**, affording **11a** in 85% yield as a single isomer. Subsequent decarboxylation of **11a** using Tsuji conditions [$Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, rt][15] gave rise to the desired adduct **9** in good yield, but the ee of **9** was revealed to be only 75% ee. In spite of various screenings of the reaction conditions for the thiourea-catalyzed Michael reaction of **7** and **8**, we could not improve the ee of **9**. The remaining key task for the total synthesis of **6** is conversion of 3,4-*trans*-adduct **9** to 3,4-*cis* adduct **10a**. For this purpose, we planed to employ the axial methoxy group of **9** for the stereoselective reduction of the ketone of **9** and formation of the requisite nitroalkene **13**. Initial treatment of **9** with L-Selectride gave the aimed axial alcohol **12** as a single isomer.[8d] The subsequent elimination of methanol from **12** with NaOMe (1.5 equiv) in *tert*-BuOH afforded nitrocycloalkene **13** in 71% yield (80% yield based on the consumed starting material) as colorless crystals. At this stage, the ee of **13** could be improved to 99% ee by recrystallization from $CHCl_3$. We finally investigated the 1,4-hydride reduction of nitrocycloalkene **13** to obtain 1,4-*cis*-nitroalcohol **10a** (Table 2). Initial attempt to reduce **13** utilized sterically demanding hydride reagent 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester, HEH),[16a]

Table 2. Diastereoselective 1,4-reduction of nitroalkene **13**

Entry	Reagent	Temp (°C)	Time (h)	Yield (%)[a]	Ratio (**10a/10b**)[b]
1	HEH	80	12	0	
2	$NaBH_4$	−78	0.25	45	2.5:1
3	$NaBH_3CN$	0	1.0	78	9:1
4	$NaBH_3CN$	−20	6.5	87	9:1

[a] Isolated yield.
[b] Determined by ^1H NMR analysis.

resulting in recovery of the starting material (entry 1). Although the hindered reagent did not give the products, relatively smaller reducing agents such as $NaBH_4$ and $NaBH_3CN$[16b] did afford the axial nitroalkane **10a** as a major product (entries 2–4).[9c,d,17] The best result (87% yield, **10a/10b** = 9:1) was obtained by reduction with $NaBH_3CN$ in AcOH and MeOH at −20 °C. The structural assignment of **10a** was confirmed by ^1H NMR analysis (Fig. 1).

To complete the total synthesis of **6**, alcohols **10a/10b** were converted into the corresponding mesylates (MsCl, Et_3N, DMAP), from which **14** was isolated in 91% yield. Successive treatment of **14** with zinc/AcOH in THF and refluxing in $CHCl_3$ gave enantiomerically pure (−)-epibatidine [**6**, $[\alpha]_D^{25}$ −6.0 (*c* 0.58, $CHCl_3$)] in 85% yield. The structure of synthetic **6** was confirmed by comparison to reported literature data (^1H, ^{13}C NMR, IR, Mass).[11]

In summary, we have developed a catalytic enantioselective synthesis of 4-nitrocyclohexanone derivatives bearing three contiguous stereogenic centers by using thiourea/TMG-catalyzed double Michael reactions of γ,δ-unsaturated-β-ketoesters to nitroalkenes, and the synthetic utility of these products has been demonstrated by the asymmetric synthesis of (−)-epibatidine.

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