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Organocatalytic Sequential Michael Reactions: Stereoselective Synthesis of Multifunctionalized Tetrahydroindan Derivatives

Peng He, Xiaohua Liu,* Jian Shi, Lili Lin, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China

liuxh@scu.edu.cn; xmfeng@scu.edu.cn

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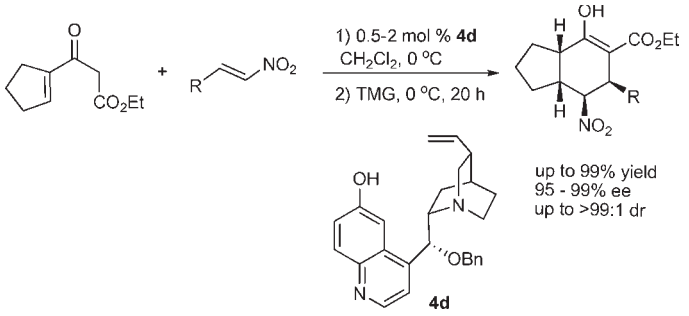
ABSTRACT



Multifunctionalized tetrahydroindan derivatives with four stereocenters were constructed via two sequential Michael reactions between cyclic γ,δ-unsaturated-β-ketoester and nitroalkenes initiated with 0.5−2 mol % of cinchona alkaloid based bifunctional organocatalysts and then with 1 equiv of tetramethylguanidine for cyclization. The desired products could be obtained in high yields (up to 99% yield) with excellent enantioselectivities (95−99% ee) as well as diastereoselectivities (up to >99:1 dr) even on a gram scale.

Multifunctionalized bicyclic indan derivatives[1] possess structural features typical of the natural and unnatural biologically interesting compounds such as tridemethylisovelleral,[2] indanomycin,[3] amaminols,[4] etc. Thus, remarkable attention has been attracted to pursue an efficient synthetic methodology for this class of compounds.[5] However, only a few examples have succeeded in the enantioselective construction of this highly substituted bicyclo[4.3.0]nonane.[6] Besides cycloadditions, the asymmetric organocatalytic double Michael reaction[7] has emerged as a powerful protocol for the synthesis of multifunctionalized chiral cyclopentane and cyclohexanone derivatives.[8,9] Nonetheless, an efficient catalytic

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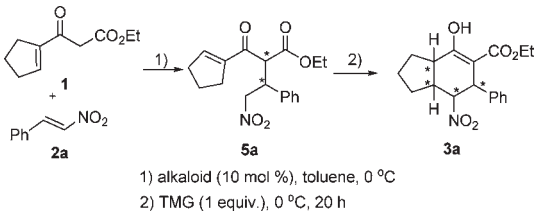
asymmetric synthesis of nitrosubstituted bicyclic indans with four stereocenters[10] has not been reported, although they could be conveniently transformed into a variety of useful compounds.[6b,11] Herein, we report a highly stereoselective sequential Michael reactions of cyclic γ,δ-unsaturated β-ketoester with nitroalkenes to address the issue, giving the indan derivatives in moderate to good yields with excellent diastereo- and enantioselectivities under 0.5−2 mol % organocatalyst.

Scheme 1. Proposed Process of the Sequential Michael Additions



Cinchona alkaloids and their derivatives have been revealed as efficient bifunctional organocatalysts for asymmetric conjugate addition of 1,3-dicarbonyl compounds with electrophillic reagents, pioneered by Deng's group.[12] Considering the effective activation, our initial screening reaction between cyclic γ,δ-unsaturated β-ketoester **1** and nitroalkene **2a** was performed in the presence of 10 mol % of cinchona alkaloid derivatives **4** in toluene. However, no domino Michael reaction occurred, with only acyclic adduct **5a** provided (Scheme 1).

The matter could be addressed by subsequent treatment of the first Michael adduct with 1,1,3,3-tetramethylguanidine (TMG) similar to the synthesis of 4-nitrocyclohexanone derivatives.[9b] The desired cyclic adduct **3a** could be furnished exclusively and quantitatively with maintained enantioselectivity at the C6 position, regardless of the diastereoselectivity of intermediate **5a** due to the complete enolization of the final bicyclic product **3a**. The high stereoselective attack of nitro carbon on the cyclopentene led to the formation of bicyclic isomers with high diastereoselectivity. Even in the preparation of racemic products, high diastereoselectivity was also found for most of the tetrahydroindan products, and only two enantiomers were achieved. Therefore, the stereoselective control in the first Michael reaction is crucial for the final outcome.

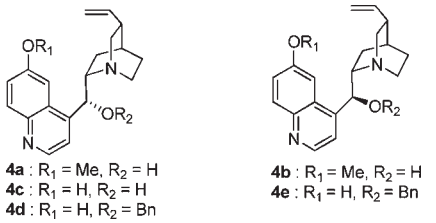


Figure 1. Catalysts used in the first Michael reaction.

Initially, commercially available quinine **4a** and quinidine **4b** (Figure 1) catalyzed the reaction smoothly but exhibited poor asymmetric induction (Table 1, entries 1 and 2). When 6′-demethylquinine **4c** was tested, remarkable improvement in ee was observed (Table 1, entry 3, 90% ee, 21% yield). Encouraged by this result, we further explored 6′-OH-modified quinine **4d** and quinidine **4e** as catalysts for this reaction. To our delight, the yield was improved significantly when a benzyl ether group was introduced at the C9 position of **4d** (Table 1, entry 4). Although comparable ee value with reversed configuration was obtained with quinidine-based catalyst **4e**, the reaction was sluggish and afforded the adduct **3a** in lower yield (Table 1, entry 5 vs entry 4). It indicated that the free phenolic hydroxyl group played a crucial role in activating and fixing substrate to accomplish good stereoinduction, while the steric structure around C9 affected the activity greatly. To further improve the yield, solvent and temperature were optimized (Table 1, entries 6−10). It was found that the best result was obtained in CH_2Cl_2 at 0 °C (98% yield, 97% ee) (Table 1, entry 7). With the best catalyst in hand, the effect of the catalyst loading was further investigated. When the amount of **4d** was lowered from 10 to 1 mol %, the excellent yields and ee values were maintained (Table 1, entries 7, 11 and 12). Nevertheless, further decreasing the amount of **4d** to 0.5 mol % led to a drop in the yield, without any influence of the ee value (Table 1, entry 13).

Using the optimized conditions (Table 1, entry 12), the substrate scope of the sequential Michael reactions was then examined (Table 2). Regardless of the electronic

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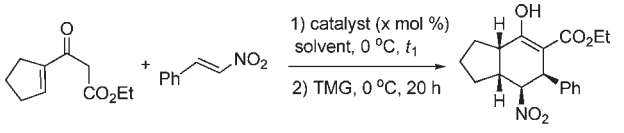
Table 1. Optimization of the Reaction Conditions[a]



1 2a 3a

entry	catalyst (mol %)	solvent	t_1 (h)[b]	yield (%)[c]	ee (%)[d]
1	**4a** (10)	toluene	69	99	9
2	**4b** (10)	toluene	69	90	−13
3[e]	**4c** (10)	toluene	47	21	90
4	**4d** (10)	toluene	20	81	95
5[e]	**4e** (10)	toluene	82	30	−95
6	**4d**(10)	THF	20	99	60
7	**4d** (10)	CH_2Cl_2	20	98	97
8[e]	**4d** (10)	Et_2O	43	60	96
9	**4d** (10)	DMF	20	90	93
10[f]	**4d** (10)	CH_2Cl_2	20	98	93
11	**4d** (5)	CH_2Cl_2	20	98	97
12	**4d** (1)	CH_2Cl_2	20	97	97
13	**4d** (0.5)	CH_2Cl_2	50	84	97

[a] Unless otherwise noted, the reaction was carried out with **1** (0.15 mmol, 1.5 equiv), **2a** (0.1 mmol), catalyst **4** (0.5−10 mol %), and solvent (0.5 mL) at 0 °C for the indicated time, then TMG (1.0 equiv) was added, and the mixture was stirred for 20 h. [b] The reaction time of the first step. [c] Isolated yield after two steps. [d] Determined by HPLC and dr >99:1. [e] Unreacted nitroolefin should be separated to avoid the byproduct in the second Michael reaction, then CH_2Cl_2 (1.5 mL) and TMG (1.0 equiv) were added, and the reaction mixture was stirred for 20 h. [f] The reaction was carried out at room temperature.

properties or steric hindrance of the substituents on the aromatic ring of nitroalkenes, bicyclic indans were obtained in good to excellent yields with excellent enantioselectivities (95−98% ee) and diastereoselectivities (up to >99:1 dr) (Table 2, entries 1−11). When 4-CN substituted nitroolefin was surveyed, the diastereoselectivity was unexpectedly decreased (Table 2, entry 10). In addition, nitrodiene also worked well to give the desired adduct in good yield and 97% ee (Table 2, entry 12). In the case of fused-ring aromatic nitroolefins, the catalyst was also efficient (95−98% ee, Table 2, entries 13−15). Furthermore, the heteroaromatic nitroolefins were competent candidates for the reaction, affording the corresponding cyclization products in high yields and 95−97% ee (Table 2, entries 16−17). It is noteworthy that excellent ee and dr values have been achieved with aliphatic nitroolefins (Table 2, entries 18−19, 99% ee) for which the corresponding adducts have proven both versatile and unique as synthetic intermediates.[13] In the presence of 0.5 mol % of catalyst **4d**, equivalent enantioselectivities could also be achieved with somewhat lower reactivity (Table 2, entries 1, 3, 6−8, 15). The acyclic γ,δ-unsaturated β-ketoester **1b** and **1c** also provided the chiral nitrocyclohexanone derivatives with moderate diastereoselectivities but high yields and enantioselectivities for both isomers (Scheme 2).[9b,c]

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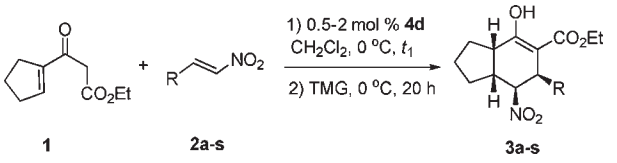
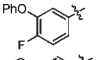
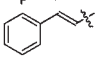
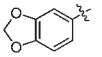
Table 2. Sequential Michael Reactions of Cyclic γ,δ-Unsaturated β-Ketoester **1** and Nitroolefins **2**[a]



1 2a-s 3a-s

entry	R	t_1 (h)[b]	yield (%)[c]	dr[d]	ee (%)[e]
1	Ph	20	**3a,**97 (84)	>99:1	97 (97)
2[f]	2-MeC_6H_4	70	**3b,** 64	>99:1	98
3	4-MeC_6H_4	20	**3c,** 98 (92)	>99:1	95 (94)
4	2-MeOC_6H_4	20	**3d,** 80	>99:1	96
5	3-MeOC_6H_4	20	**3e,** 80	98:2	96
6	4-PhC_6H_4	20	**3f,** 95 (90)	>99:1	96 (96)
7	4-FC_6H_4	20	**3g,** 95 (80)	>99:1	97 (98)
8	4-ClC_6H_4	20	**3h,** 96 (90)	>99:1	97 (97)
9	4-BrC_6H_4	20	**3i,** 85	>99:1	96
10	4-CNC_6H_4	33	**3j,** 70	88:12	97
11		20	**3k,** 86	>99:1	97
12[f]		60	**3l,** 60	>99:1	97
13[f]		60	**3m,** 66	>99:1	98
14	1-naphthyl	20	**3n,** 73	>99:1	95
15	2-naphthyl	20	**3o,**99 (95)	>99:1	95 (95)
16	2-furyl	20	**3p,** 80	>99:1	95
17	2-thienyl	33	**3q,** 72	>99:1	97
18[f,g]	c-hexyl	84	**3r,** 62	99:1	99
19[f,g]	^{i}Pr	70	**3s,** 50	97:3	99

[a] Unless otherwise noted, the reaction was carried out with **1** (0.15 mmol, 1.5 equiv), **2** (0.1 mmol), **4d** (1 mol %), and CH_2Cl_2 (0.5 mL) at 0 °C for the indicated time, then TMG (1.0 equiv) was added, and the reaction was stirred for 20 h. The data in parentheses were obtained with 0.5 mol % of catalyst **4d** for 50 h. [b] Reaction time of the first step. [c] Isolated yield after two steps. [d] Determined by NMR and HPLC analysis. [e] Determined by HPLC. [f] Unreacted nitroolefin should be separated before TMG was added. [g] 2 mol % of catalyst was used.

To test the synthetic potential of the present approach, a gram-scale synthesis of the chiral nitrosubstituted tetrahydroindan was performed. The product could be isolated in 85% yield (2.25 g) with 97% ee. After a recrystallization,[14] the enantioselectivity was raised to 99% ee with 65% yield (1.72 g). Notably, through a simple reduction of nitro group,[15] product **3a** was successfully converted into the useful intermediate of amino ketoester[11b] in excellent yield without any loss of stereoselectivity (Scheme 2).

The absolute configuration of product **3i** was determined as (3a*S*,6*R*,7*S*,7a*R*) by X-ray diffraction analysis (Scheme 3).[16] The ring junction in product **3** was in favor of *cis*-fused isomer, and the phenyl group and nitro

(14) Recrystallization was carried out in CH_2Cl_2 and petroleum ether (CH_2Cl_2/petroleum ether = 1:10).

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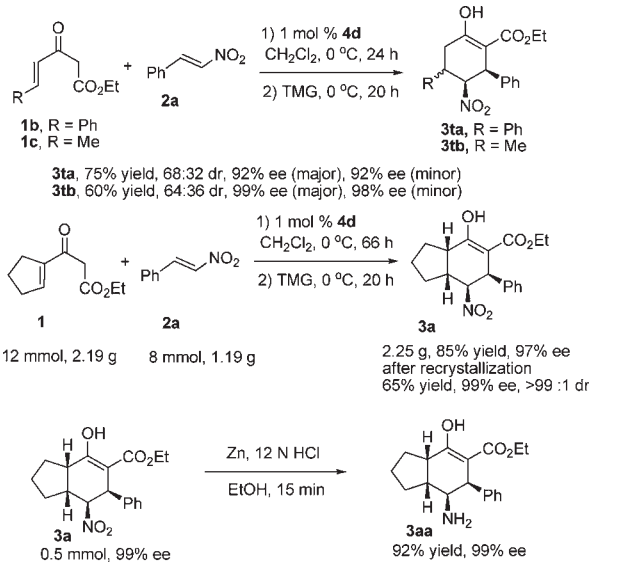
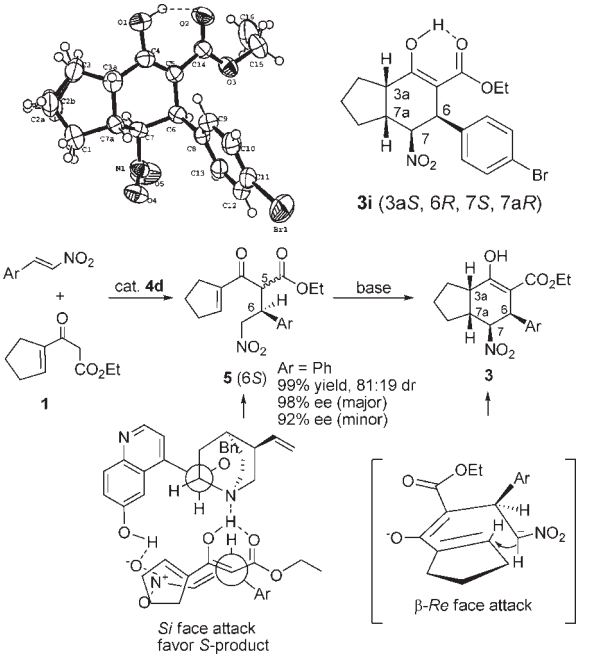
(16) CCDC-803725 contains the supplementary crystallographic data of **3i**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Substrate Extension, Scaled-Up Version of the Sequential Michael Reactions, and Synthetic Transformations of the Product



Scheme 3. X-ray Crystallographic Structure of **3i** and Proposed Process of the Sequential Michael Additions



group oriented also on the same side. This *cis*-fused ring is more stable than the *trans*-fused stereoisomer, which is in agreement with the equilibration results for tetrahydroindanon derivatives.[5a] The steric repulsive force between the nitro and methylene group of the cyclopentenyl resulted the (7aα,7α) arrangement. The bulky C6-substituent preferred the pseudoaxial conformation due to the severe A[1,3] strain with ester group. Therefore, the relative configuration of other products would undergo analogous configuration. The first Michael adduct **5a** was also isolated (Scheme 3, Ar = Ph, >99% yield, 81:19 dr, 98% ee for major isomers and 92% ee for minor ones). When the parent mixture was treated with TMG, nearly single diastereomer of **3a** was obtained with 97% ee which accordingly implied that the absolute configuration of the major isomers at C6 was the same as 6*S*.

A possible catalytic process is summarized in Scheme 3. The hypothetical transition state of bifunctional activation was that tertiary amine part of **4d** activated the enolized cyclic γ,δ-unsaturated β-ketoester **1**, while the 6′-OH activated the nitro group via H-bond.[12c] The stereoselective formation of (6*S*)-intermediate **5** would be rationally explained by the favorable *Si*-face attack of nitroolefin while the steric hindrance between the Ar group of nitroolefin and quinuclidine moiety resulted in the disfavored (6*R*)-**5** as the minor isomer.[17] Consequently, in the presence of base, a stereospecific nucleophilic attack of the nitronate anion to the β-*Re* face of the double bond would lead to the multisubstituted tetrahydroindan derivative **3** in high stereoselectivity.

In summary, a highly enantioselective and diastereoselective organocatalytic sequential Michael reactions has been developed to provide multisubstituted bicyclic tetrahydroindans. Low catalyst loading (0.5−1 mol %), high yields (up to 99%), excellent enantioselectivities (95−99% ee), diastereoselectivities (up to >99:1) and broad synthetic utility of the nitrosubstituted bicyclic indan product render this methodology appealing for asymmetric synthesis. Further applications of this reaction are underway.

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Supporting Information Available. Experimental procedures and spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For details, see the Supporting Information.