Tetrahedron Letters 53 (2012) 6569–6572

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective decarboxylative Michael addition of β-ketoacids to nitroalkenes catalyzed by binaphthyl-derived organocatalysts

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ARTICLE INFO

Article history:
Received 13 August 2012
Revised 13 September 2012
Accepted 21 September 2012
Available online 28 September 2012

Keywords:
Asymmetric catalysis
Organocatalysis
Michael addition
γ-Nitro ketones
Nitroalkenes

ABSTRACT

The catalytic enantioselective decarboxylative Michael addition reaction promoted by chiral bifunctional organocatalysts has been developed, allowing facile synthesis of the corresponding γ-nitro ketones with excellent enantioselectivity (up to 97% ee). The method reported represents a valuable approach utilizing β-ketoacids as synthetic equivalents of aryl methyl ketones.

The Michael addition reaction is widely recognized as one of the most important and fundamental methods for the formation of C–C bonds in organic synthesis,[1] and the development of asymmetric version of this reaction has been a subject of intensive research.[2] In addition to the great success of catalysis with metal complexes, the environmentally friendly organocatalyst-mediated asymmetric Michael reaction has been explored in depth in recent years.[3,4] The Michael addition of nucleophiles to nitroalkenes represents a direct and appealing approach to the synthesis of chiral nitroalkanes that are versatile intermediates in organic synthesis, which can be transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen group, and so on.[5] In recent years, the enantioselective decarboxylative additions of malonic acid half-thioesters as ester enolate equivalents have received much attention.[6] Although a number of reactions of malonic acid half-thioesters as carbon nucleophiles to various electrophiles have been reported,[7] the corresponding β-ketoacids have received relatively little attention as carbon nucleophiles. There have been a few reported examples of decarboxylative aldol, alkylation, and Mannich reactions of β-ketoacids as surrogates of ketones.[8] The Evans group has reported the first catalytic enantioselective decarboxylative reaction of β-ketoacids with nitroalkenes in the presence of chiral Ni(II) complexes.[9] Very recently, The Ma and Lu groups described organocatalytic enantioselective decarboxylative aldol-type reactions of β-ketoacids with trifluoromethyl ketones and isatins.[10] Recently, several groups have reported the direct catalytic enantioselective Michael addition of aryl methyl ketones to nitroalkenes.[11] There are still some drawbacks to the previously reported procedures, such as the high catalyst loading and long reaction time required for good enantioselectivity. Accordingly, the development of alternative catalysts for the direct organocatalytic enantioselective decarboxylative Michael addition of β-ketoacids to nitroalkenes is highly desirable. We envisioned that the assembly of a structurally well-defined chiral 1,2-diamine and binaphthyl scaffold with a H-bonding motif could activate nitroalkenes and ketoacids as bifunctional organocatalysts. The rigid binaphthyl structure can serve as an efficient stereocontrolling axial chiral element.

As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[12] we recently reported enantioselective Michael additions of active methylenes and methines.[13] Herein, we wish to describe the direct enantioselective decarboxylative Michael addition of β-keto acids to nitroalkenes catalyzed by bifunctional organocatalysts bearing both central and axial chiral elements (see Fig. 1.).

To determine suitable reaction conditions for the catalytic enantioselective decarboxylative Michael addition reaction of β-ketoacids, we initially investigated the reaction system with nitrostyrene (**1a**) and benzoylacetic acid (**2a**) in the presence of 10 mol % of catalyst in THF at room temperature. We first examined the impact of the structure of catalysts **I–VI** on the enantioselectivities (21–85% ee, Table 1, entries 1–6). The best results were obtained with catalyst **III** which is a binaphthyl-modified squaramide bifunctional organocatalyst bearing central and axial chiral

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0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.09.100

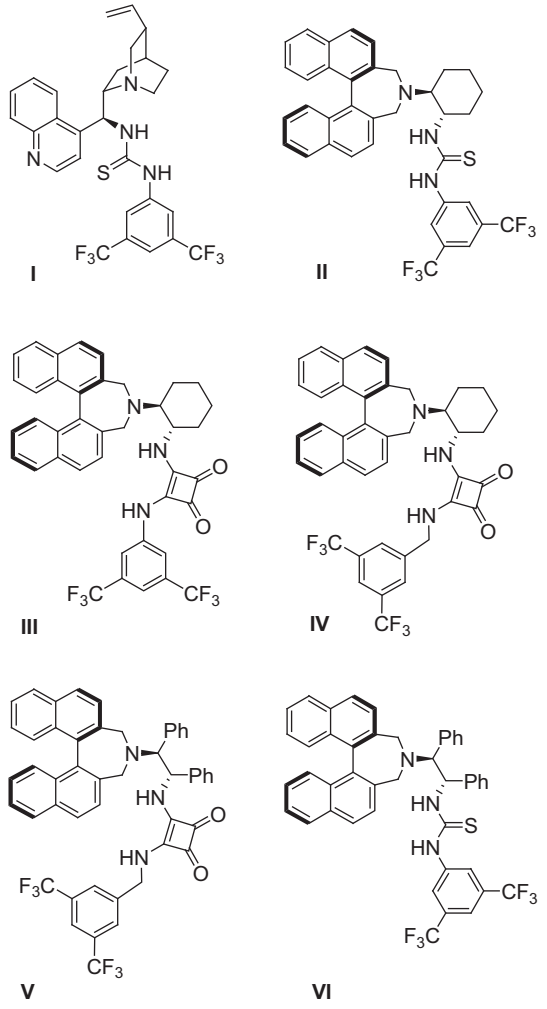
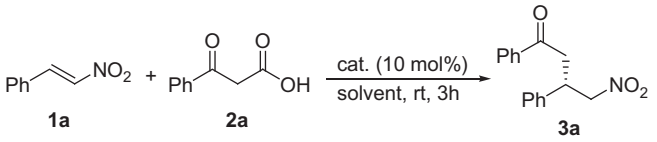


Figure 1. Structures of chiral organocatalysts.

Table 1
Optimization of the reaction conditions[a]



Entry	Cat.	Solvent	Yield[b] (%)	ee[c] (%)
1	I	THF	60	21
2	II	THF	67	55
3	III	THF	70	85
4	IV	THF	60	69
5	V	THF	56	57
6	VI	THF	54	27
7	III	Et_2O	76	67
8	III	Dioxane	75	81
9	III	EtOAc	63	75
10	III	PhMe	80	65
11	III	CH_2Cl_2	78	71
12	III	$CHCl_3$	74	85
13	III	$CHCl_2CH_2Cl$	76	81
14	III	MeOH	77	56
15	III	*i*-PrOH	78	45
16	III	$CHCl_3$/THF (1:1)	83	93
17	III	$CHCl_3$/THF (4:1)	83	97
18	III	$CHCl_3$/THF (9:1)	80	93
19	III	$CHCl_3$/THF (1:4)	81	93
20[d]	III	$CHCl_3$/THF (4:1)	82	97
21[e]	III	$CHCl_3$/THF (4:1)	83	96
22[f]	III	$CHCl_3$/THF (4:1)	84	96
23[g]	III	$CHCl_3$/THF (4:1)	83	97
24[h]	III	$CHCl_3$/THF (4:1)	62	80

[a] Reaction conditions: β-nitrostyrene (**1a**, 0.2 mmol), benzoylacetic acid (**2a**, 0.24 mmol), catalyst (0.02 mmol), $CHCl_3$/THF (4:1, 2.0 mL) at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using Chiralpak AD-H column.
[d] 5 mol % Catalyst loading.
[e] 1 mol % Catalyst loading.
[f] 0.25 mol % Catalyst loading for 6 h.
[g] 0.1 mol % Catalyst loading for 6 h.
[h] 0.05 mol % Catalyst loading for 6 h.

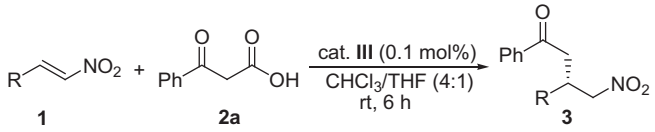
elements.[13f] Different solvents were then tested in the presence of 10 mol % of catalyst **III** together with benzoylacetic acid (**2a**) and β-nitrostyrene (**1a**) in order to improve the selectivity of the reaction further. Aprotic solvents, such as THF, diethyl ether, ethyl acetate, toluene, dichloromethane, chloroform, and 1,1,2-trichloroethane were tolerated well in this conjugate addition without a significant decrease in the enantioselectivities (65–85% ee, Table 1, entries 3 and 7–13). Protic polar solvents also afforded products in good yields, but the selectivities dropped significantly (Table 1, entries 14 and 15). Remarkably, the use of co-solvent of chloroform and THF gave high yields and excellent enantioselectivities (entries 16–19). Among the solvents probed, the best results (83% yield and 97% ee) were achieved when the reaction was conducted in chloroform/THF (4:1) (Table 1, entry 17). The present catalytic system tolerates catalyst loading down to 5, 1, 0.25, or 0.1 mol % without compromising the yield or the enantioselectivity (Table 1, entries 20–24).

We then explored the possibility of using a wide range of nitroalkene derivatives **1** with benzoylacetic acid (**2a**) in the presence of 0.1 mol % of catalyst **III** in THF at room temperature (Table 2).[14] A range of electron-donating and electron-withdrawing substituents on the aryl ring of the nitrostyrenes **1b–g** provided the reaction products in high yields (78–89%) and with excellent enantioselectivities (87–97%, Table 2, entries 1–7). The heteroaryl- and naphthyl-substituted nitroalkenes **1h–j** provided the products with high selectivity (Table 2, entries 8–10). However, diminished yield and enantioselectivity was observed with alkyl-substituted nitroalkene **1k** (Table 2, entry 11). The absolute configuration of the adducts **3** was determined for some derivatives by comparison of their optical and HPLC properties with literature values.[11]

To examine the generality of the catalytic enantioselective decarboxylative Michael addition reaction of the β-ketoacid derivatives **2** by using chiral bifunctional organocatalyst **III**, we studied the Michael addition of various β-ketoacids **2b–h** with β-nitrostyrene (**1a**). As seen from the results summarized in Table 3, the corresponding γ-nitro ketones **3l–r** were obtained in excellent yields with excellent enantioselectivities. A range of electron-donating and electron-withdrawing substitutents on the β-aryl ring of the β-ketoacids **2b–e** provided reaction products in high yields and excellent enantioselectivities (87–97% ee, Table 3, entries 1–4). The heteroaryl- and naphthyl-substituted β-ketoacids **2f** and **2g** provided the products with high selectivity (93% and 83% ee, Table 3, entries 5 and 6). The β-alkyl-substituted β-ketoacid, 3-oxobutanoic acid (**2h**), was also an acceptable starting material and provided the corresponding Michael adducts in high yield and with excellent enantioselectivity (91% ee, Table 3, entry 7).

The present method is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As shown in Scheme 1, when benzoylacetic acid (**2a**) was treated with nitroalkene **1g** under the optimal reaction conditions, the reaction proceeded smoothly to afford the desired γ-nitro ketone **3g** at the gram scale with 76% yield and 91% ee. (Scheme 1).

Table 2
Variation of the nitroalkenes **1**[a]

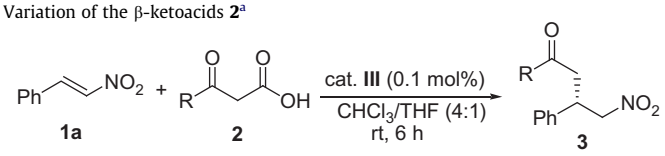


1 2a 3

Entry	**1**, R	Yield[b] (%)	ee[c] (%)
1	**1a**, Ph	**3a**, 83	97
2	**1b**, 2-$NO_2C_6H_4$	**3b**, 82	93
3	**1c**, 4-FC_6H_4	**3c**, 88	90
4	**1d,** 4-ClC_6H_4	**3d**, 89	93
5	**1e**, 4-BrC_6H_4	**3e**, 87	87
6	**1f**, 4-MeC_6H_4	**3f**, 80	91
7	**1g**, 4-$MeOC_6H_4$	**3g**, 78	90
8	**1h**, 2-Furyl	**3h**, 80	92
9	**1i**, 2-Thienyl	**3i**, 83	91
10	**1j**, 2-Naphthyl	**3j**, 81	93
11[d]	**1k**, $PhCH_2CH_2$	**3k**, 70	76

[a] Reaction conditions: nitroalkene **1** (0.2 mmol), benzoylacetic acid (**2a**, 0.24 mmol), catalyst (0.2 μmol), $CHCl_3$/THF (4:1, 2.0 mL) at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using Chiralpak AD-H (for **3a** and **3c**–**k**) and IA (for **3b**) columns.
[d] This reaction was conducted using 10 mol % catalyst at room temperature for 15 h.

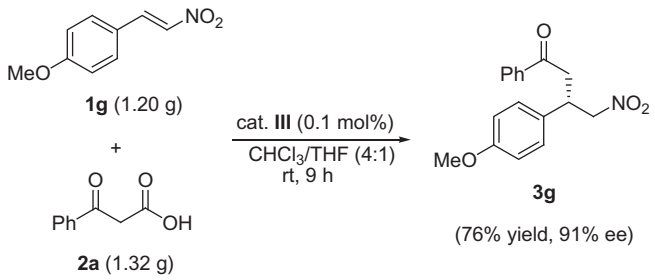
Table 3
Variation of the β-ketoacids **2**[a]



1a 2 3

Entry	**2**, R	Yield[b] (%)	ee[c] (%)
1	**2b**, 4-MeC_6H_4	**3l**, 83	97
2	**2c**, 4-$MeOC_6H_4$	**3m**, 80	87
3	**2d**, 4-BrC_6H_4	**3n**, 80	95
4	**2e**, 2-ClC_6H_4	**3o**, 84	91
5	**2f**, 2-Thienyl	**3p**, 85	93
6	**2g**, 2-Naphthyl	**3q**, 84	83
7	**2h**, Me	**3r**, 87	91

[a] Reaction conditions: β-nitrostyrene (**1a**, 0.2 mmol), β-ketoacid **2** (0.24 mmol), catalyst (0.2 μmol), $CHCl_3$/THF (4:1, 2.0 mL) at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using Chiralpak AD-H (for **3l**–**q**) and (*S*,*S*)-Whelk-O1 (for **3r**) columns.



Scheme 1. Gram scale Michael addition of benzoylacetic acid (**2a**) with nitroalkene **1g**.

In conclusion, we have developed a highly efficient catalytic enantioselective decarboxylative Michael addition reaction of β-ketoacids to nitroalkenes using 0.1 mol % of a binaphthyl-derived chiral bifunctional organocatalyst. The desired γ-nitro ketones were obtained in good to high yields, and excellent enantioselectivities (up to 97% ee) were observed for all the substrates examined in this work. We believe that this method provides a practical entry for the preparation of chiral γ-nitro ketone derivatives. Further study of this catalytic enantioselective decarboxylative addition reaction of β-ketoacids with various carbon electrophiles is in progress.

Acknowledgment

This research was supported in part by the Soonchunhyang University Research Fund.

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14. *Typical procedure for the Michael addition reaction of benzoylacetic acid (**2a**) with β-nitrostyrene (**1a**)*: To a stirred solution of nitrostyrene (**1a**, 29.8 mg, 0.2 mmol) and catalyst **III** (100 μL, 2×10^{-3} M, 0.2 μmol) in chloroform/THF (4:1, 2.0 mL) was added benzoylacetic acid (**2a**, 39.4 mg, 0.24 mmol) at room temperature. The reaction mixture was stirred for 6 h at room temperature. After completion of the reaction, the resulting solution was concentrated in vacuo and the obtained residue was purified by flash chromatography (EtOAc/Hexane, 1:5) to afford the 44.7 mg (83%) of the Michael adduct **3a.** *(S)-4-nitro-1,3-diphenylbutan-1-one (**3a**)*: $[\alpha]_D^{23} = -10.3$(c = 1.00, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.93–7.89 (m, 2H), 7.62–7.37 (m, 3H), 7.35–7.20 (m, 5H), 4.84 (dd, J = 12.2, 6.1 Hz, 1H), 4.70 (dd, J = 12.2, 7.8 Hz, 1H), 4.31–4.15 (m, 1H), 3.50–3.40 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.82, 139.05, 136.31, 133.56, 129.02, 128.70, 127.98, 127.84, 127.42, 79.52, 41.48, 39.24; HPLC (90:10, *n*-hexane: *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 8.6 min (major), t_R = 10.5 min (minor), 97% ee.