ORGANIC LETTERS

2010
Vol. 12, No. 10
2278−2281

Primary Amine/(+)-CSA Salt-Promoted Organocatalytic Conjugate Addition of Nitro Esters to Enones

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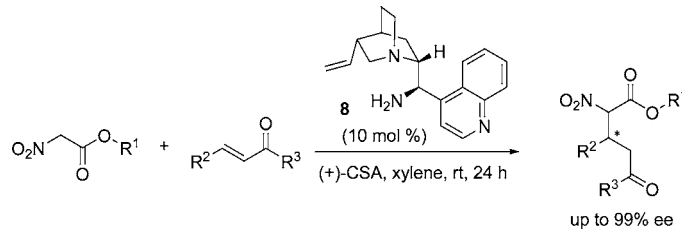
Received March 18, 2010

ABSTRACT



The combination of 9-amino-9-deoxy-*epi*-cinchonine and (+)-CSA resulted in a novel primary amine-based organocatalyst for effective iminium activation of α,β-unsaturated ketones. Such a catalytic system could catalyze the conjugate addition of nitroacetate to enones in a highly enantioselective manner, affording the desired adducts in high yields and with up to 99% ee.

The conjugate addition of the stabilized carbanions to α,β-unsaturated carbonyl compounds represents one fundamental carbon−carbon bond-forming reaction in organic synthesis, and the development of chiral catalysts for the asymmetric version of this reaction constitutes an important research field and has been well-explored in recent years.[1] In particular, small organic molecules have been found to be extremely useful in promoting asymmetric conjugate addition reactions.[2] Since MacMillan's introduction of iminium catalysis as a general mode of activation in asymmetric catalysis,[3] this LUMO-lowering strategy has been firmly established and has found wide applications in asymmetric synthesis.[4] It should be noted that catalysts used for the iminium activations in the early days are mostly chiral secondary amines and have been utilized mainly for the activation of α,β-unsaturated aldehydes. Primary amine-based organocatalytic synthetic methods have emerged as powerful and versatile tools in asymmetric synthesis recently.[5] In particular, chiral primary amines are extremely useful in iminium catalysis, and reactions catalyzed by primary amines in many cases are better than or complementary to those achieved with reactions promoted by pyrrolidine-based secondary amine catalysts.[6] As part of our research program toward the development of primary amine-based asymmetric synthetic methods,[7] we became interested in the design of novel organocatalytic reactions utilizing primary amine-induced iminium activation.

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(2) For recent reviews on organocatalytic conjugate additions, see: (a) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

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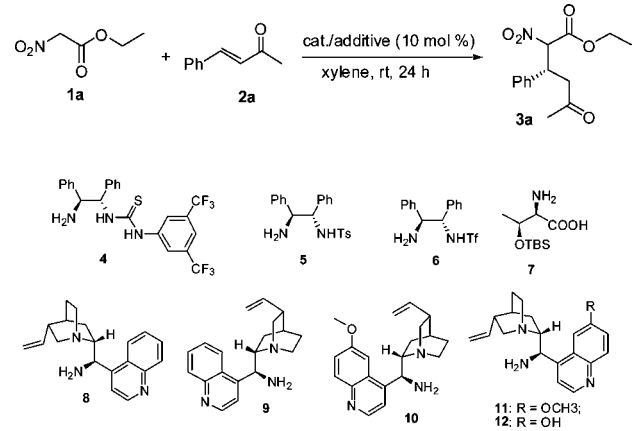
10.1021/ol1006407
Published on Web 04/22/2010

Nitro esters are valuable sources of stabilized carbanions in organic synthesis, and they have been used as masked amino acids in various organic transformations.[8] However, enantioselective reactions employing nitro esters are currently very limited.[9] In this context, we were intrigued to develop an organocatalytic asymmetric addition of nitro esters to α,β-unsaturated ketones, as examples of this type of enantioselective conjugate additions are scarce in the literature. Ikariya and co-workers reported enantioselective addition of ethyl nitroacetate to cyclopentenone, catalyzed by a chiral ruthenium complex.[10] Jørgensen et al. prepared a number of novel secondary amine organocatalysts and applied them in the Michael addition of nitroacetate to α,β-unsaturated ketones. The products were formed with good enantioselectivities, and no diastereoselectivity was observed.[11] Although very interesting, those reported reactions suffered from very low reaction rates, and virtually no reaction scope was explored in these studies. We envisaged that an enantioselective conjugate addition of nitro esters to enones may be achieved via efficient iminium activation of enones by primary amine-based organocatalysts. Herein, we show that the combination of (+)-camphorsulfonic acid (CSA) with cinchonidine results in an effective organic catalyst, which catalyzed the enantioselective conjugate addition of nitroacetate to α,β-unsaturated ketones, affording the desired adducts with excellent enantiomeric excesses.

The reaction between ethyl nitroacetate **1a** and *trans*-4-phenyl-3-buten-2-one **2a** was chosen as a model reaction, and the catalytic effects of various primary amine catalysts were examined. The results are summarized in Table 1.

Table 1. Screening of Organocatalysts for the Conjugate Addition of Ethyl α-Nitro Acetate to *trans*-4-Phenyl-3-buten-2-one[a]



entry	cat.	additive	t (h)	yield[b] (%)	dr[c]	ee[d] (%) *syn/anti*
1	**4**	*p*-NO_2PhCO_2H	24	74	1:1	77/80
2	**5**	*p*-NO_2PhCO_2H	9	91	1:1	66/65
3	**6**	*p*-NO_2PhCO_2H	48	97	1:1	83/83
4	**7**	*p*-NO_2PhCO_2H	14	99	1:1	0/13
5	**8**	*p*-NO_2PhCO_2H	24	39	1:1	98/98
6	**8**	TsOH	24	59	1:1	91/90
7	**8**	(−)-CSA	24	89	1:1	94/93
8	**8**	**(+)-CSA**	**24**	**94**	**1:1**	**99/99**
9	**9**	(+)-CSA[e]	24	80	1:1	−77/−86
10	**10**	(+)-CSA	24	80	1:1	−77/−84
11	**11**	(+)-CSA	24	89	1:1	99/99
12	**12**	(+)-CSA	20	87	1:1	97/86

[a] Reactions were performed with 4-phenyl-but-3-en-2-one (0.1 mmol), ethyl nitroacetate (0.2 mmol), and primary amine (0.01 mmol) in xylene (0.1 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the products. [d] The ee value was determined by chiral HPLC analysis. [e] 20 mol % additive.

(1*S*,2*S*)-1,2-Diphenylethane-1,2-diamine-derived primary amine catalysts containing thiourea (**4**) and sulfonamides (**5** and **6**), in combination with *p*-nitrobenzoic acid, were found to be effective, affording the desired products in excellent yields and with moderate to good enantioselectivities (entries 1−3). *O*-TBS-L-Threonine **7** gave almost racemic products (entry 4). Cinchona alkaloids are privileged chrial structural scaffolds in asymmetric catalysis,[12] and various cinchona alkaloids were next investigated. 9-Amino-9-deoxy-*epi*-cinchonine (**8**), combining with *p*-nitrobenzoic acid or *p*-toluenesulfonic acid, afforded the products in low yields (entries 5 and 6). We reasoned the nature of the counteranion might be important in the asymmetric induction.[13] We thus

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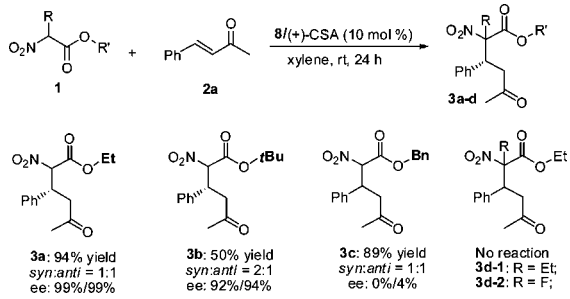
(12) For a recent book, see: Song, C. E., Ed. *Cinchoan Alkaloids in Synthesis & Catalysis: Ligands, Immobilization and Organocatalysis*; Wiley-VCH: Weinheim, 2009.

decided to introduce chiral acid to the catalytic system, and camphorsulfonic acid (CSA) was selected. While (−)-CSA salt of **8** gave very good results, (+)-CSA salt of **8** turned out to be an even better catalyst, affording the desired adducts in excellent yield and with 99% ee, although little diastereoselectivity was observed (entry 8). Primary amines derived from cinchonidine (**9**) and quinine (**10**) were less effective (entries 9 and 10), and quinidine or 6′-demethylated quinidine (**11**)-based primary amine was equally effective (entries 11 and 12). A catalytic system comprising **8** and (+)-CSA was chosen as the catalyst for the further reactions since such a system gave marginally higher yield of the product.

The influence of ester moieties of different nitro esters on the reactions was next examined (Scheme 1). *tert*-Butyl

Scheme 1. Conjugate Addition of Various Nitro Esters to *trans*-4-Phenyl-3-buten-2-one



nitroacetate offered slightly improved diastereoselectivity; however, the chemical yield dropped significantly. Benzyl nitroacetate turned out to be completely ineffective, affording the adducts in nearly racemic form. In contrast to unbranched nitro esters, α-substituted ethyl nitroacetate was unsuitable for the conjugate addition reaction, and no desired product was obtained. We previously employed fluorinated nucleophiles[14] for the asymmetric generation of fluorinated quaternary chiral centers, and when α-fluorinated nitroacetate was employed, the conjugate addition also could not proceed.

To establish the reaction scope, a number of enones were employed as acceptors, and the results are summarized in Table 2. Reactions are applicable to various *β*-aryl-substituted butenones, and conjugate addition products were obtained with very high enantioselectivity; however, virtually no diastereoselectivities were observed (entries 1−7). Cyclic enones, such as cyclohexenone and cycloheptenone, were also excellent acceptors for the conjugation additions, affording the desired products in high yields and with excellent enantioselectivity (entries 8 and 9).

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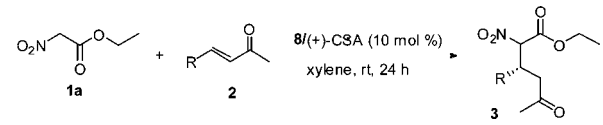
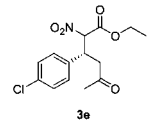
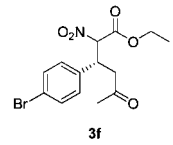
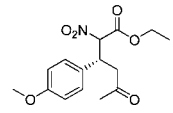
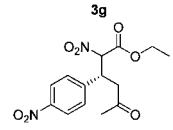
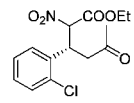
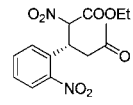
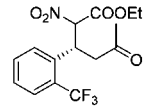
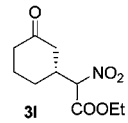
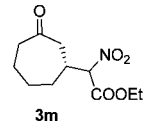
Table 2. Conjugate Addition of Ethyl Nitroacetate to α,*β*-Unsaturated Ketones[a]

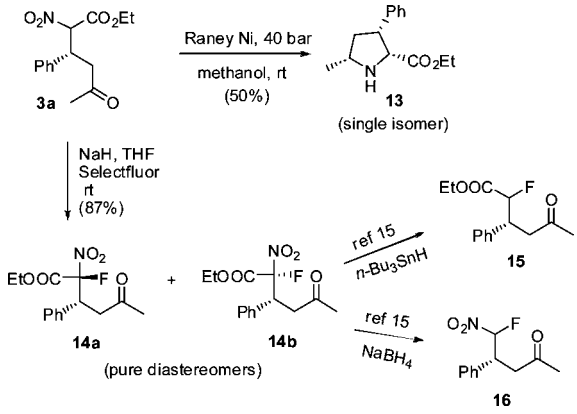


entry	product	yield[b] (%)	dr[c] (anti/syn)	ee[d] (%)
1	 3e	92	1.6:1	82/95
2	 3f	86	1.3:1	95/98
3	 3g	89	1:1	92/97
4	 3h	77	1.4:1	98/94
5	 3i	86	1.6:1	90/93
6	 3j	93	1.5:1	96/97
7	 3k	88	1.2:1	96/97
8	 3l	91	1:1	99/99
9	 3m	83	1:1	96/99

[a] Reactions were performed with enone (0.1 mmol), ethyl nitroacetate (0.2 mmol), **8** (0.01 mmol), and (+)-CSA (0.01 mmol) in xylene (0.1 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the products. [d] The ee value was determined by chiral HPLC analysis.

The Michael adducts obtained from the catalytic enantioselective conjugate addition of ethyl nitroacetate to α,β-unsaturated ketones are rich in functionality and ready to be converted into useful chiral building blocks (Scheme 2). The

Scheme 2. Synthetic Manipulations of Adduct **3a**



facile reduction of the nitro group, followed by in situ reductive amination, afforded chiral pyrrolidine **13** as a single stereoisomer.[11a] To partially circumvent the low diastereoselectivities of our reactions, adduct **3a** was subjected to electrophilic fluorination reaction to yield **14** with fluorinated quaternary centers. The two diastereomers of **14** can be easily separated by column chromatographic purification, which can be further converted to optically pure α-fluorinated ester **15** or α-fluorinated nitro compound **16** following the procedures reported in the literature.[15]

In summary, we discovered that a combination of 9-amino-9-deoxy-*epi*-cinchonine **8** and (+)-CSA resulted in a novel primary amine-based catalyst for efficient activation of α,β-unsaturated ketones via iminium intermediates. The CSA salt of **8** was capable of catalyzing the conjugate addition of nitro acetate to enones in a highly enantioselective manner, affording the desired adducts in excellent yields and with up to 99% ee. Extension of this useful iminium catalyst to other catalytic asymmetric reactions, particularly those involving enone substrates, is under investigation in our laboratory.

Acknowledgment. We thank the National University of Singapore and the Ministry of Education (MOE) of Singapore (R-143-000-362-112) for the generous financial support.

Supporting Information Available: Representative experimental procedures, HPLC chromatogram, and NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1006407

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