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Asymmetric organocatalytic nitroaldol reaction of α-ketoesters: stereoselective construction of chiral tertiary alcohols at subzero temperature

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Abstract

Asymmetric nitroaldol reaction of α-ketoesters was explored using a guanidine–thiourea bifunctional organocatalyst at temperatures below the freezing point of water. The new reaction protocol can be applied to the nitroaldol reaction of nitroalkanes and α-ketoesters to construct the adjacent stereocenters of the chiral tertiary alcohol product with high diastereo- and enantioselectivity.

The challenge of constructing a tetrasubstituted stereogenic center via direct carbon–carbon bond-forming reaction is of ongoing interest in modern synthetic chemistry.[1] Since chiral tertiary alcohols are potentially attractive for the design of medicinal leads,[2] considerable efforts have been devoted to the development of nucleophilic addition to ketones.[3] Catalytic asymmetric nitroaldol reaction of α-ketoesters with nitroalkanes is one of the most straightforward methods to synthesize highly functionalized chiral tertiary alcohols.[4,5] Several effective strategies using chiral Cu-[5a–e] or Mg-complexes[5f] and cinchona alkaloids[5g] to afford chiral tertiary alcohols from α-ketoesters and nitromethane have been reported. We have recently developed a series of asymmetric nitroaldol reactions with aldehyde utilizing the guanidine–thiourea bifunctional catalyst **1** in a biphasic system.[6–11] In these reactions, the retro-mode of reaction is effectively suppressed by the addition of potassium iodide.[6d] Herein, we describe the synthesis of chiral *tert*-nitroaldols **4** from α-ketoesters by the use of newly developed protocol. Stereoselective synthesis of the tertiary alcohols **7**, which have stereocenters adjacent to the tetrasubstituted carbon, was also achieved (Table 1).[12]

Initial trials were conducted with the guanidine–thiourea catalyst **1**, bearing various substituents, under the previously developed biphasic conditions to gain insight into the reaction profile of α-ketoesters. We found that catalyst **1** effectively promotes the nitroaldol reaction of α-ketoester **2a** with nitromethane (**3a**) to afford the nitroaldol adduct **4a**. Catalyst **1b**, featuring an octadecyl group on guanidine and a benzyl group on the chiral spacer, gave the best result in terms of enantioselectivity (entry 2, 55% ee). The results of this reaction were broadly similar to those of the previous nitroaldol reaction with aldehydes, that is (i) a longer alkyl chain or a terminal aromatic ring on guanidine moiety (R^1) is crucial for both reactivity and selectivity and (ii) a benzyl group is the most effective substituent on the chiral spacer (R^2). These findings are consistent with the proposed self-assembly mechanism in the case of aldehydes.[6d] The finding that no catalytic activity was observed in the case of compounds **5** and **6** supports our proposed chemoselective dual activation mode of **1b**-catalyzed nitroaldol reactions (Fig. 1).[6d,13]

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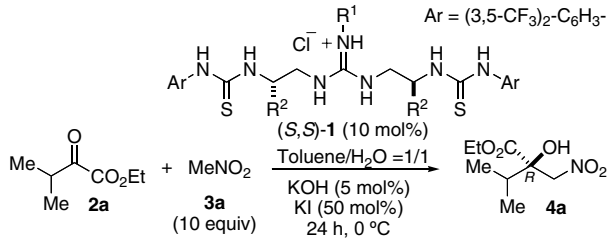
Table 1
Substituent effects on catalyst **1**[a]



Entry	Cat	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	**1a**	$C_{22}H_{45}$	Bn	97	40
2	**1b**	$C_{18}H_{37}$	Bn	82	55
3	**1c**	$C_{15}H_{31}$	Bn	72	55
4	**1d**	$C_{12}H_{25}$	Bn	1	53
5	**1e**	C_8H_{17}	Bn	25	9
6	**1f**	C_4H_9	Bn	11	13
7	**1g**	(4-OMe)–Ph–C_3H_6	Bn	89	49
8	**1h**	(4-CF_3)–Ph–C_3H_6	Bn	92	42
9	**1i**	(1-Naph)-C_3H_6	Bn	99	57
10	**1j**	(2-Naph)-C_3H_6	Bn	94	35
11	**1k**	$C_{18}H_{37}$	Me	68	17
12	**1l**	$C_{18}H_{37}$	*i*-Pr	0	—
13	**1m**	$C_{18}H_{37}$	*t*-Bu	73	22

[a] Reactions were carried out on a 0.1 mmol scale in 1.0 mL of toluene and 1.0 mL of H_2O.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis. The absolute configurations of **4a** were determined to be (*R*) by X-ray analysis. See Scheme 1.

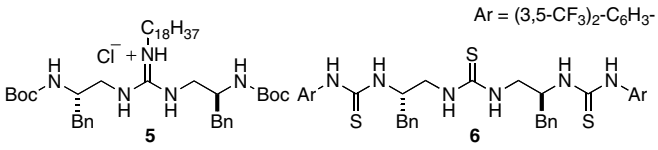
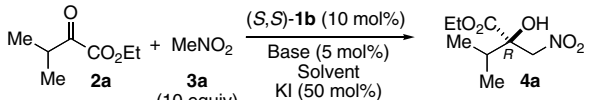


Fig. 1. The structures of compounds **5** and **6**.

Encouraged with these results, we carefully optimized the reaction conditions using α-ketoester **2a** (Table 2). We first investigated a solid–liquid biphasic protocol. In the absence of water, the inorganic bases we examined failed to improve the enantioselectivity (entries 1–8). At lower temperature, the reaction rate drastically decreased, although the ee value was not improved (entry 9). On the other hand, significant improvements of catalytic activity and selectivity were observed upon the addition of a small amount of water at low temperature (entry 9 vs entry 11). At subzero temperature, the reaction was proceeded on ice.[14] Under these conditions, we found that the selectivity increased as the reaction temperature was decreased (entries 10–12), and the ee value improved to 80% (entry 12).[15] However, both chemical yield and enantioselectivity drastically dropped to 4% yield and 14% ee in the absence of potassium iodide (entry 13). These observations suggested that the addition of water and potassium iodide is mandatory, and may favor dissociation of the complex of

Table 2
Reaction conditions screening[a]



Entry	Solvent	Base	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	Toluene	Li_2CO_3	0	62	13
2	Toluene	K_2CO_3	0	99	6
3	Toluene	Cs_2CO_3	0	96	24
4	Toluene	$LiOH·H_2O$	0	98	26
5[d]	Toluene	NaOH	0	84	18
6	Toluene	RbOH	0	11	5
7	Toluene	$CsOH·H_2O$	0	98	16
8	Toluene	KOH	0	92	14
9	Toluene	KOH	−20	8	15
10	Toluene/H_2O = 5:1	KOH	−10	98	51
11	Toluene/H_2O = 5:1	KOH	−20	99	68
12	Toluene/H_2O = 5:1	KOH	−30	62	80
13[e]	Toluene/H_2O = 5:1	KOH	−30	4	14

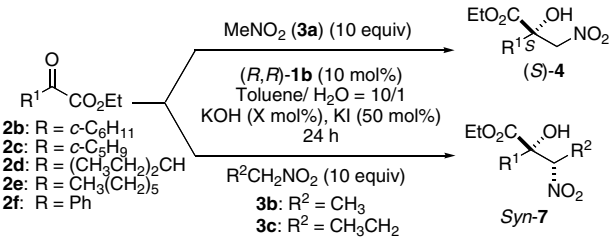
[a] Reactions were carried out on a 0.1 mmol scale in 1.0 mL of toluene.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] (S)-**4a** was obtained as the major product.
[e] Reaction was performed in the absence of potassium iodide.

1b and **4a**, thereby suppressing the retro-mode of the reaction.[6d,14,15]

The new protocol was applied to various aliphatic α-ketoesters **2** and nitroalkanes **3** (Table 3). In most cases, we utilized (*R*,*R*)-**1b** as a catalyst. The enantioselective nitroaldol reaction of aliphatic α-ketoesters with nitromethane (**3a**) proceeded to give *tert*-nitroaldol **4** in moderate to good yields. Thus, cyclic, branched-type, and linear α-ketoesters **2b–e** gave the corresponding nitroaldol products **4** with good enantioselectivities (entries 1–4). When aromatic α-ketoesters were subjected to the reaction, however, unsatisfactory selectivities were obtained (a typical result is shown in entry 5). It is noteworthy that this catalytic system, based on multiple non-covalent bonding interactions, can be employed to construct a stereocenter adjacent to a tertiary alcohol (entries 6–10). The diastereo- and enantioselective nitroaldol reaction proceeded to generate highly functionalized products **7** with high diastereoselectivity and good enantioselectivity (entries 6–10).[16] Although there is still room to improve the catalytic activity, these results represent remarkable examples of the construction of contiguous stereogenic centers, which contain a chiral *tert*-alcohol in a highly stereoselective manner by means of a direct-type catalytic nitroaldol reaction.[12]

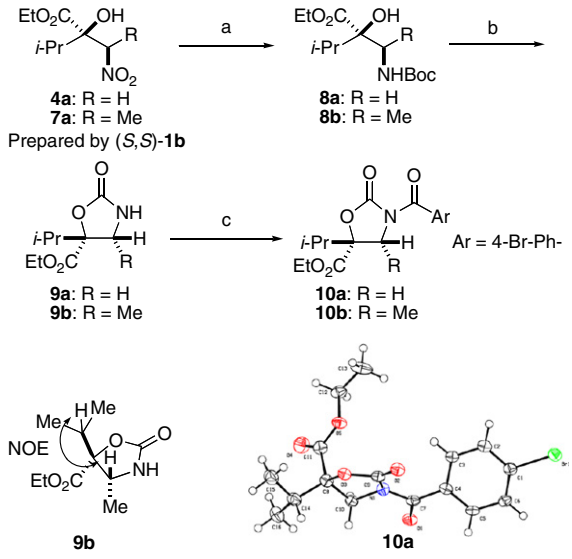
To confirm the stereochemistry, facile transformations of the nitroaldol products **4a** and **7a**, which were synthesized by utilizing (*S*,*S*)-**1b**, were performed as shown in Scheme 1. Reduction of the nitro group of **4a** and **7a** and

Table 3
Catalytic asymmetric nitroaldol reaction of α-ketoesters **2** with nitroalkanes **3**[a]



Entry	α-Ketoester	Nitroalkane	KOH (mol %)	Temperature (°C)	Product[c] (%)	ee[d] (%)	dr[e]
1	**2b**	**3a**	10	−25	**4b** (90)	93	—
2[b]	**2c**	**3a**	10	−20	**4c** (83)	80	—
3	**2d**	**3a**	10	−25	**4d** (89)	78	—
4	**2e**	**3a**	10	−25	**4e** (60)	83	—
5	**2f**	**3a**	10	−35	**4f** (56)	5	—
6[f]	**2a**	**3b**	10	−35	**7a** (43)	81	86:14
7[f,g,h]	**2a**	**3b**	10	−35	**7a** (45)	80	85:15
8	**2b**	**3b**	10	−30	**7b** (45)	91	97:3
9	**2b**	**3c**	10	−30	**7c** (35)	83	92:8
10	**2e**	**3b**	20	−30	**7d** (36)	93	79:21

[a] Reactions were carried out on a 0.1 mmol scale in 1.0 mL of toluene.
[b] Toluene/H_2O = 5:1.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.
[e] Determined by ^1H NMR.
[f] **1b** (20 mol %), KI (100 mol %).
[g] When (*S*,*S*)-**1b** was used as a catalyst, the opposite enantiomer was obtained.
[h] The relative stereochemistry of **7a** was determined to be *syn* by NOE experiments. See Scheme 1.



Scheme 1. Transformations of nitroaldol products. Reagents and conditions: (a) $NiCl_2$, $NaBH_4$, MeOH, then Boc_2O, 0 °C, 30 min, **8a**: 88%, **8b**: 74%; (b) (i) 50% TFA/CH_2Cl_2, rt, 1 h; (ii) CDI, CH_3CN, reflux, 20 h, **9a**: 80 % in 2 steps, **9b**: 93% in 2 steps; (c) *p*-bromobenzoyl chloride, NaH, CH_2Cl_2, rt, 1 h, **10a**: 93%, **10b**: 87%.

subsequent reaction with Di-*tert*-butyl dicarbonate gave the corresponding *N*-Boc-protected amines **8**.[17] Removal of the Boc group, followed by treatment with *N*,*N*-carbonyldiimidazole (CDI), gave the cyclic carbamates **9**. The relative stereochemistry of contiguous stereocenters of **9b** was determined to be *syn* by NOE experiments of **9b**. Carbamates **9** were readily reacted with *p*-bromobenzoyl chloride to give *N*-acyl-oxazolidinones **10**. The absolute stereochemistry of **10a** was determined by X-ray crystal structure analysis.[18]

The stereochemistries of **4** and **7** obtained during the nitroaldol process can be explained by the transition state based on the chemoselective dual activation concept.[6,13] The larger substituent of the R^1 group on α-ketoester and R^2 group of nitroalkane is considered to favor *anti* relationships with respect to nitroalkane and ketone, to minimize steric repulsion, as shown in Figure 2, and so *syn*-**7** is obtained preferentially.

In summary, we have explored the asymmetric nitroaldol reaction of α-ketoesters utilizing the guanidine–thiourea bifunctional organocatalyst **1b** under the novel condition of subzero temperature. Various aliphatic α-ketoesters afforded chiral *tert*-nitroaldols. Direct-type

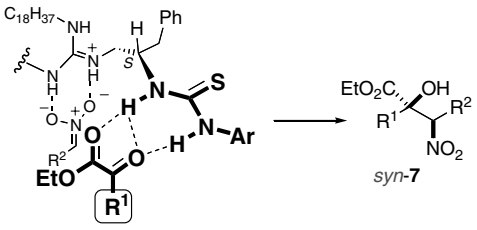


Fig. 2. Plausible transition state in the nitroaldol reaction with α-ketoester and nitroalkane utilizing (*S*,*S*)-**1b**.

catalytic diastereo- and enantioselective nitroaldol reactions of α-ketoesters were also demonstrated. Further studies aimed at the improvement of the catalytic efficiency and gaining insight into the mechanistic role of the subzero temperature condition are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.030.

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