Tetrahedron 73 (2017) 5975–5982

Contents lists available at ScienceDirect

Tetrahedron

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

Chiral lithium binaphtholate for enantioselective amination of acyclic α-alkyl-β-keto esters: Application to the total synthesis of L-carbidopa

Toshifumi Asano [a], Miyuki Moritani [a], Makoto Nakajima [a], Shunsuke Kotani [a, b, *]

[a] Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto, 862-0973, Japan
[b] Priority Organization for Innovation and Excellence, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto, 862-0973, Japan

ARTICLE INFO

Article history:
Received 16 June 2017
Received in revised form
2 August 2017
Accepted 10 August 2017
Available online 13 August 2017

Keywords:
Asymmetric catalysis
Amination
Chiral binaphtholate
Enantioselectivity
β-Keto ester

ABSTRACT

A chiral lithium binaphtholate catalyzes the enantioselective amination of α-alkyl-β-keto esters with azodicarboxylates to produce optically active α,α-disubstituted α-amino acid derivatives in high yields and with good to high enantioselectivities. A stoichiometric amount of lithium hydroxide efficaciously improved both the reactivity and enantioselectivity of amination. The resulting aminated product is readily convertible to L-carbidopa.

1. Introduction

Optically active amino acids are one of the most representative constituents of living organisms. However, α,α-disubstituted α-amino acids are found only in unnatural amino acids, some of which possess unique biologically activity.[1] Therefore, a number of asymmetric transformations for synthesizing such optically active α,α-disubstituted α-amino acids have been developed over the past several decades.[2] One conventional strategy to generate optically active α,α-disubstituted α-amino acids is the asymmetric addition of a tertiary carbanion equivalent to an electrophilic nitrogen.[3] In 2003, Jørgensen and co-workers were the first to demonstrate a chiral Ph-bis(oxazoline)copper complex catalyzed enantioselective amination of α-alkyl-β-keto esters with azodicarboxylates to produce optically active α,α-disubstituted α-amino acids in high enantioselectivity.[4] Recent advances on metal catalyses and organocatalysis have also provided us with many asymmetric variations.[5–8] Indeed, cyclic α-alkyl-β-keto esters such as cyclohexanone carboxylates and 1-indanone carboxylates afforded high stereoselectivity, however, less attention has been paid to acyclic α-alkyl-β-keto esters, except for acetylpropionates. In this regard, our group has explored the utilities of the conjugate base of binaphthol (i.e., binaphtholate) and has recently reported asymmetric conjugate additions of acyclic α-alkyl-β-keto esters using dilithium binaphtholate catalysis.[9,10] In this publication, we report the full details of the enantioselective amination of acyclic α-alkyl-β-keto esters catalyzed by chiral lithium binaphtholate,[10] and the asymmetric short-step synthesis of L-carbidopa using the enantioselective amination as a key step.

2. Results and discussion

2.1. Enantioselective amination of α-alkyl-β-keto esters catalyzed by chiral lithium binaphtholate.

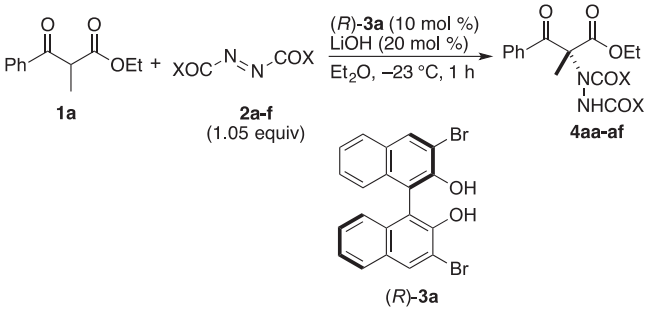
We began examining the asymmetric amination of β-keto ester **1a** with various azodicarbonyl compounds **2a-f** in the presence of 10 mol % of (*R*)-3,3′-Br_2-BINOL (**3a**) as a precatalyst and 20 mol % of lithium hydroxide (LiOH) in diethyl ether at −23 °C (Table 1). Azodicarboxylate esters **2a-e** showed sufficient reactivity to afford the corresponding aminated adducts **4aa-ae** in high yields (entries 1–5). *tert*-Butyl azodicarboxylate **2c** gave the best enantioselectivity of 74% ee (entry 3). Azodicarbonamide **2f** was less reactive under these reaction conditions, yielding no product (entry 6).

To improve the enantioselectivities, we next examined the amination reaction with various BINOLs **3a-f** (Table 2). Parent (*R*)-

* Corresponding author. Priority Organization for Innovation and Excellence, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto, 862-0973, Japan.
E-mail address: skotani@gpo.kumamoto-u.ac.jp (S. Kotani).

http://dx.doi.org/10.1016/j.tet.2017.08.015
0040-4020/

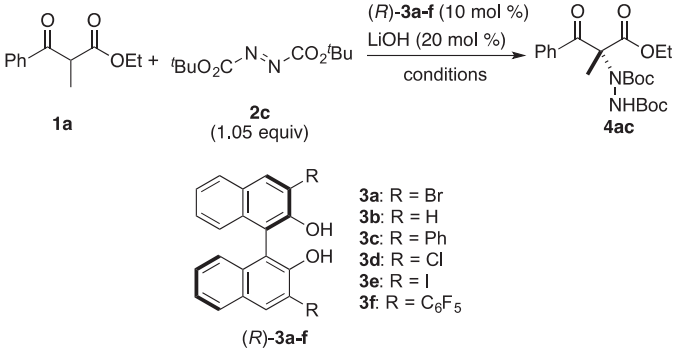
Table 1
Enantioselective amination of **1a** with **2** catalyzed by chiral lithium binaphtholate under various reaction conditions.[a]



Entry	2	X	Yield, %	ee, %[b]
1	**2a**	OMe	96	62
2	**2b**	OEt	96	64
3	**2c**	O^{t}Bu	98[c]	74
4	**2d**	OBn	92	54[d]
5	**2e**	OCH_2CCl_3	89	4
6	**2f**	NMe_2	0	–

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and LiOH (20 mol %) in Et_2O (4 mL) at −23 °C.
[b] Determined by HPLC analysis.
[c] For 0.5 h.
[d] The absolute configuration is *R*.

Table 2
Screening of (*R*)-BINOLs.[a]



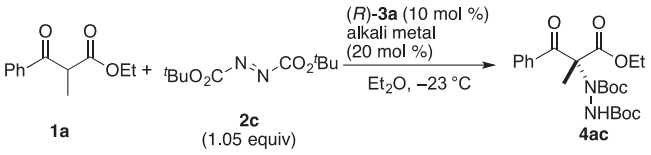
Entry	3	Time, h	Yield, %	ee, %[b]
1	**3a**	0.5	98	74
2	**3b**	1	95	5
3	**3c**	1	92	4
4	**3d**	0.5	97	61
5	**3e**	0.5	97	64
6	**3f**	1	92	8

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3** (10 mol %) and LiOH (20 mol %) in Et_2O (4 mL) at −23 °C.
[b] Determined by HPLC analysis.

BINOL (**3b**) and (*R*)-3,3′-Ph_2-BINOL (**3c**) were ineffective, giving very low selectivities (entries 2 and 3). Higher enantioselectivities were obtained with (*R*)-3,3′-dihaloBINOLs, with a significant acceleration of the reaction rate (entries 1, 4, and 5). To clarify the effects of the halogen substituents, we conducted the amination reaction with (*R*)-3,3′−$(C_6F_5)_2$−BINOL (**3f**, entry 6). Similar to (*R*)-3,3′-Ph_2-BINOL (**3c**), low enantioselectivity (8% ee) was obtained, despite the higher conversion. This result indicates that the steric effect of the substituents affect the asymmetric induction, whereas the electron deficiency increased the catalytic activity.

To investigate the effect of the bases, we examined the reaction

Table 3
Screening of alkali metals.[a]



Entry	Alkali metal	Time, h	Yield, %	ee, %[b]
1	LiOH	0.5	98	74
2	^{n}BuLi	1	96	68
3	LiO^{t}Bu[c]	1	99	71
4	NaOH	1	54	8
5	KOH	1	34	4

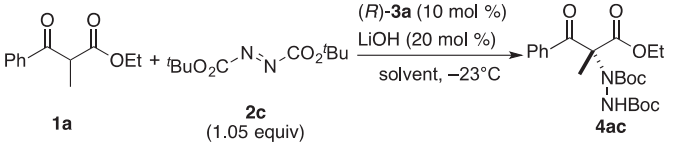
[a] Unless otherwise noted, the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and an alkali metal (20 mol %) in Et_2O (4 mL) at −23 °C.
[b] Determined by HPLC analysis.
[c] 1.0 M LiO^{t}Bu/THF was used.

with various alkali metals (Table 3). Other lithium bases such as butyllithium and lithium *tert*-butoxide afforded good enantioselectivities (entries 2 and 3). Sodium hydroxide and potassium hydroxide gave the lower yields and selectivities (entries 4 and 5). These results implied that the enantio-determining step involves lithium metals.

We next investigated solvent effects (Table 4). Less polar solvents such as dichloromethane and toluene were ineffective for both the yields and selectivities (entries 2 and 3). Regarding coordinative solvents, tetrahydrofuran afforded the aminated adduct **4ac** in good enantioselectivity, albeit in low yield (entry 4). Acyclic ethers such as *tert*-butyl methyl ether (TBME) and cyclopentyl methyl ether (CPME) afforded good yields and enantioselectivities (entries 5 and 6). In contrast, 1,4-dioxane and 1,2-dimethoxyethane (DME) decreased selectivity (entries 7 and 8). Bidentate coordination might prevent substrates from accessing lithium atom, resulting in lower enantioselectivities.

We performed the amination at various temperatures (Table 5). At 0 °C, the reaction was completed within 10 min, but the enantioselectivity was decreased (entry 2). Thus, conducting the reaction at lower temperatures increased the enantioselectivities (entries 3 and 4). At −60 °C, the highest enantioselectivity (80% ee) was obtained (entry 4), whereas, at −78 °C, both reactivity and

Table 4
Screening of solvents.[a]



Entry	Solvent	Time, h	Yield, %	ee, %[b]
1	Et_2O	0.5	98	74
2	CH_2Cl_2	2	22	2
3	toluene	2	22	11
4	THF	2	35	65
5	TBME	1	92	54
6	CPME	1	90	71
7	1,4-dioxane	2	82	17
8	DME	2	18	10

[a] All the reactions were performed by treating **1a** (0.5 mmol) with **2c** (1.05 equiv) in the presence of (*R*)-**3a** (10 mol %) and LiOH (20 mol %) in a solvent (4 mL) at −23 °C.
[b] Determined by HPLC analysis.