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Enantioselective amination of acyclic α-alkylated β-keto esters catalyzed by chiral lithium binaphtholate

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ABSTRACT

The enantioselective amination of α-alkylated β-keto esters with azodicarboxylates using a chiral dilithium binaphtholate as catalyst affords optically active α,α-disubstituted α-amino acid derivatives in high enantioselectivities of up to 95% ee. A stoichiometric amount of lithium hydroxide accelerates the amination. This method provides easy access to various chiral α,α-disubstituted α-amino acids in high yields and with high enantioselectivities from readily available starting materials and chiral sources.

Introduction

α,α-Disubstituted α-amino acids bearing a quaternary stereogenic center often possess attractive bioactivities;[1] however, these α-amino acids do not occur in nature. Therefore, the development of asymmetric syntheses for α,α-disubstituted α-amino acids is a popular research area, and many asymmetric reactions have been developed over the past several decades. Although carbon–carbon bond forming reactions involving Strecker reactions[2] and Mannich reactions[3] are the most conventional strategies for synthesizing α,α-disubstituted α-amino acids, these amino acids can also be accessed by carbon–nitrogen bond formation, realizing amino-functionalization of substrates. In 2003, Jørgensen and coworkers reported the asymmetric amination of α-alkylated β-keto esters with electrophilic azodicarboxylates using a chiral Ph-bis (oxazoline) (box)-copper complex as a chiral metal catalyst.[4,5] In particular, great efforts toward asymmetric amination with azodicarboxylates have been made using chiral organocatalysts involving cinchona alkaloids,[6] ureas,[7] guanidines,[8] phase transfer catalysts,[9] squaramides,[10] imidazolines,[11] and primary amines.[12] However, many of the substrates used in these asymmetric aminations are cyclic α-alkylated β-keto esters, such as cyclohexanone carboxylates and 1-indanone carboxylates.[13] There are few examples of successful aminations using acyclic substrates, and this topic has received little attention to date (Fig. 1a).[5,9a,12,13a,f]

We have recently reported the sufficient catalysis of asymmetric conjugate addition to vinyl ketones by a chiral lithium binaphtholate in highly enantioselective manner.[14] In particular, the lithium binaphtholate catalyst was effective for acyclic α-alkylated β-keto esters. Therefore, it was strongly expected that the lithium binaphtholate catalysis realized the asymmetric amination of acyclic α-alkylated β-keto esters. As part of our ongoing research efforts directed at the development of a chiral lithium binaphtholate catalyst, we herein report on the asymmetric amination of acyclic α-alkylated β-keto esters with azodicarboxylates catalyzed by a chiral lithium binaphtholate.

Results and discussion

We initially studied the amination of α-methylated β-keto ester **1a** to *tert*-butyl azodicarboxylate **2x** in the presence of (*R*)-3,3′-Br_2-1,1′-bi-2-naphthol (–BINOL) (10 mol %) and lithium hydroxide (LiOH, 20 mol %) according to the reported conjugate reaction condition.[14] The reaction at 0 °C in diethyl ether afforded the corresponding amino acid derivative **3ax** in high yield and with good enantioselectivity (6 h, 98% yield, 74% ee). The use of the parent (*R*)-BINOL diminished the enantioselectivity (95% yield, 5% ee). (*R*)-3,3′-Cl_2-BINOL and (*R*)-3,3′-I_2-BINOL gave the product **3ax** in 61% ee and 64% ee, respectively. A strong solvent effect was observed. Et_2O was the best choice for the solvent (*tert*-butyl methyl ether (TBME): 92% yield, 54% ee; cyclopentyl methyl ether (CPME): 90% yield, 71% ee; tetrahydrofuran (THF): 35% yield, 65% ee; 1,4-dioxane: 82% yield, 17% ee). The enantioselectivity was

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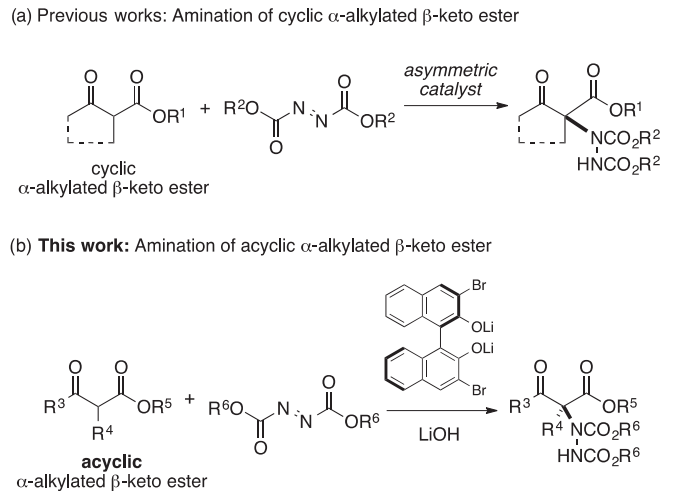


Figure 1. Asymmetric aminations of α-alkylated β-keto esters with azodicarboxylates reported (a) previously and (b) in this work.

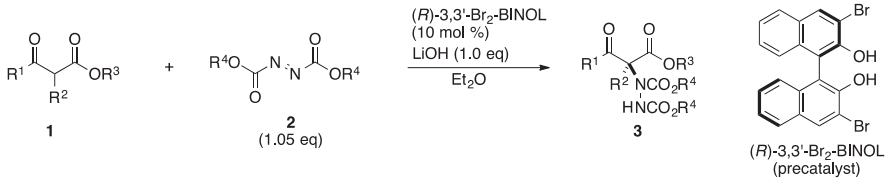
further improved by lowering the reaction temperature to −60 °C (24 h, 99% yield, 80% ee).[15] We then investigated several reaction conditions in detail and found that the use of a stoichiometric amount of LiOH facilitated the amination in a highly enantioselective manner (24 h, 90% yield, 87% ee).[16]

Selected data for the asymmetric amination of α-alkylated β-keto esters **1** with azodicarboxylates **2** are summarized in Table 1.[17] Methyl azodicarboxylate **2y** and benzyl azodicarboxylate **2z** reacted smoothly to give the corresponding adducts, albeit in lower enantioselectivities (entries 2 and 3). We then examined the substrate scope for various acyclic α-alkylated β-keto esters **1** with *tert*-butyl azodicarboxylate **2x** (entries 4–8). The reaction of isopropyl ketone **1b** reached completion in 2 hours but gave lower selectivity (entry 4). β-Keto ester **1c** bearing an electron-withdrawing atom on the aromatic ring reacted well at −60 °C, giving **3cx** with good enantioselectivity (entry 5). Although β-keto esters **1d–f** bearing electron-donating groups required higher temperatures, high enantioselectivities were observed in **3dx–3fx** (entries 6–8). These results indicated that the electronic environment of the aromatic ring affected the selectivities as well as reactivities. Keto esters **1g** and **1h** afforded the products **3gy** and **3hy** with good enantioselectivities by using methyl azodicarboxylate **2y** instead of **2x** (entries 9 and 10).[18] These results indicated that a steric interaction between the R^2 and R^4 substituents dramatically influenced the asymmetric induction. The highest enantioselectivity (95% ee) was obtained in the reaction of α-benzylated β-keto ester **1h** with azodicarboxylate **3x**. The absolute configurations of **3az** and **3fx** were identified as *R* by comparison with the literature values for the specific optical rotation or high-performance liquid chromatography (HPLC) retention time.[5,13e] The other substrates were analogously estimated to be *R*.

Based on the absolute configuration of product **3**, the proposed transition state is shown in Figure 2. An equilibrium exists between (*R*)-3,3′-Br_2-BINOL and lithium binaphtholates in the reaction medium. Considering that a stoichiometric amount of LiOH sufficiently improved both the reactivity and enantioselectivity, dilithium binaphtholate may be the most reactive species, though the detailed structure is unclear. This effect may be related to the ability of the azodicarboxylate **2** to participate in a two-point binding with the lithium complex.[19] In the formation of the *S*-isomer, a steric hindrance between the R^2 substituent on keto ester **1** and the R^4 substituent on azodicarboxylate **2** might interrupt the formation of the *S*-isomer, preferentially producing the *R*-isomer.

The proposed catalytic cycle is presented in Figure 3. The dilithium binaphtholate **4** coordinates with keto ester **1** to form a chiral lithium complex **5** in the presence of excess LiOH relative to the catalyst. The complex **5** then engages with the azodicarboxylate **2**, followed by an enantioselective carbon–nitrogen bond formation. The dilithium binaphtholate **4** is dislocated from complex **6** and reformed along with lithium amidate **7**. In the case of a catalytic amount of LiOH, monolithium binaphtholate gradually accumulates during the reaction, leading to a slower and less selective conversion. Excess LiOH may retain a high concentration of dilithium binaphtholate **4** in the reaction medium, resulting in a highly enantioselective transformation.

Table 1
Enantioselective amination of acyclic α-alkylated β-keto ester **1** and azodicarboxylate **2**[a]



Entry	1	R^1	R^2	R^3	2	R^4	Temp., °C	Time, h	3	Yield, %	Ee, %[b]
1	**1a**	Ph	Me	Et	**2x**	*t*-Bu	−60	24	**3ax**	90	87
2	**1a**	Ph	Me	Et	**2y**	Me	−60	24	**3ay**	99	64
3	**1a**	Ph	Me	Et	**2z**	Bn	−60	24	**3az**	92	54[c]
4	**1b**	*i*-Pr	Me	Et	**2x**	*t*-Bu	−60	2	**3bx**	85	54
5	**1c**	4-F-C_6H_4	Me	Me	**2x**	*t*-Bu	−60	24	**3cx**	98	78
6	**1d**	4-MeO-C_6H_4	Me	Me	**2x**	*t*-Bu	−40	24	**3dx**	96	80
7[d]	**1e**	3,5-$(MeO)_2$-4-Br-C_6H_2	Me	Me	**2x**	*t*-Bu	−20	24	**3ex**	93	88
8	**1f**	3,4-$(MeO)_2$-C_6H_3	Me	Me	**2x**	*t*-Bu	−30	24	**3fx**	95	89[c]
9	**1g**	Ph	Allyl	Et	**2y**	Me	−60	24	**3gy**	86	82
10	**1h**	Ph	$PhCH_2$	Et	**2y**	Me	−60	24	**3hy**	82	95

[a] Unless otherwise noted, the reaction was conducted by adding a solution of an azodicarboxylate **2** (1.05 equiv) in Et_2O to a solution of a keto ester **1** (0.50 mmol), (*R*)-3,3′-Br_2-BINOL (10 mol %), and LiOH (1.0 equiv) in Et_2O (1 mL).
[b] Determined by HPLC.
[c] The absolute configuration is *R*.
[d] The reaction was conducted with 1.14 mmol scale of **1e**.

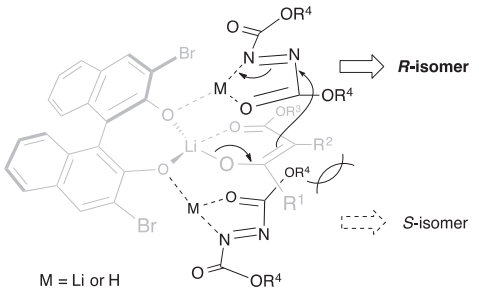


Figure 2. Possible transition state in the asymmetric amination of α-alkylated β-keto esters.

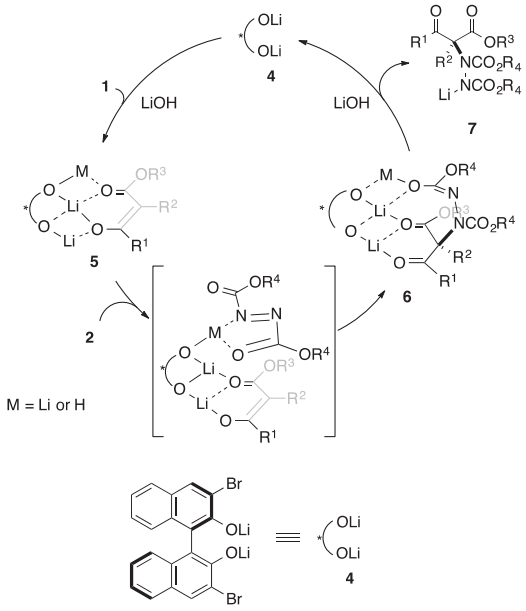


Figure 3. Plausible catalytic cycle for the asymmetric amination of α-alkylated β-keto esters.

Conclusions

We report the development of a lithium binaphtholate-catalyzed asymmetric amination of acyclic α-alkylated β-keto esters with azodicarboxylate, affording optically active α,α-disubstituted amino acid derivatives. This reaction can extend the substrate scope for the amination to acyclic α-alkylated β-keto esters. The use of a stoichiometric amount of LiOH dramatically enhanced the reactivity, realizing a highly stereoselective transformation. This method provides access to various chiral α,α-disubstituted amino acids from readily available starting materials and chiral sources. We are presently developing a method for synthesizing bioactive compounds using this asymmetric amination.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.013.

References and notes

1. Reviews of asymmetric synthesis of α,α-disubstituted α-amino acids, see: (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127–5143; (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623; (c) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349–358; (d) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430; (e) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1–7.
2. Reviews regarding catalytic asymmetric Strecker reactions, see: (a) Shibasaki, M.; Kanai, M.; Mita, T. *Org. React. (Hoboken, NJ, U.S.)* **2008**, *70*, 1–119; (b) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176–1178; (c) Liu, Y.-L.; Zhou, J. *Synthesis* **2015**, *47*, 1210–1226; (d) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764–1766; (e) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947–6983.
3. Reviews regarding catalytic asymmetric Mannich reactions, see: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112; (b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41; (c) Cai, X.-H.; Hui, G.; Bing, X. *Eur. J. Chem.* **2012**, *3*, 258–266.
4. Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *123*, 2420–2421.
5. (a) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367–1369; (b) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.
6. (a) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115–2118; (b) Liu, X.; Sun, B.; Deng, L. *Synlett* **2009**, 1685–1689.
7. (a) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137–140; (b) Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. *Chem. Eur. J.* **2011**, *17*, 10470–10477; (c) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527–5530.
8. (a) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044–16045; (b) Trillo, P.; Gómez-Martinez, M.; Alonso, D. A.; Baeza, A. *Synlett* **2015**, 95–100.
9. (a) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9466–9468; (b) He, R.; Maruoka, K. *Synthesis* **2009**, 2289–2292; (c) Lan, Q.; Wang, X.; He, R.; Ding, C.; Maruoka, K. *Tetrahedron Lett.* **2009**, *50*, 3280–3282.
10. Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028–2031.
11. Murai, K.; Fukushima, S.; Nakamura, A.; Shimura, M.; Fujioka, H. *Tetrahedron* **2011**, *67*, 4862–4868.
12. Xu, C.; Zhang, L.; Luo, S. *J. Org. Chem.* **2014**, *79*, 11517–11526.
13. (a) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565–4568; (b) Nandakumar, M. V.; Ghosh, S.; Schneider, C. *Eur. J. Org. Chem.* **2009**, 6393–6398; (c) Ghosh, S.; Nandakumar, M. V.; Krautscheid, H.; Schneider, C. *Tetrahedron Lett.* **2010**, *51*, 1860–1862; (d) Comelles, J.; Pericas, A.; Moreno-Manas, M.; Vallribera, A.; Drudis-Sole, G.; Lledos, A.; Parella, T.; Roglans, A.; Garcia-Granda, S.; Roces-Fernandez, L. *J. Org. Chem.* **2007**, *72*, 2077–2087; (e) Pericas, A.; Shafir, A.; Vallribera, A. *Org. Lett.* **2013**, *15*, 1448–1451; (f) Kumar, A.; Ghosh, S. K.; Gladysz, J. A. *Org. Lett.* **2016**, *18*, 760–763.
14. Kotani, S.; Moritani, M.; Nakajima, M. *Asian J. Org. Chem.* **2015**, *4*, 616–618.
15. The reactivity dramatically diminished at −78 °C, giving no products.
16. Increasing the equivalent of LiOH (1.3 equiv) did not improve the result (24 h, 99% yield, 86% ee).
17. *Representative procedure for the asymmetric amination:* To a suspension of (*R*)-3,3′-Br_2-BINOL (22.2 mg, 0.05 mmol) and LiOH (12.0 mg, 0.5 mmol) in Et_2O (1 mL) was added an Et_2O solution of α-methyl-β-keto ester **1a** (0.25 M, 2 mL, 0.50 mmol) at 0 °C under argon atmosphere. A solution of azodicarboxylate **2x** in Et_2O (0.525 M, 1 mL, 0.525 mmol) was added to the reaction mixture at −60 °C and further stirred for 24 h at the same temperature. The reaction was quenched with aqueous sat. NH_4Cl (5 mL), and the aqueous layer were extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), and dried over Na_2SO_4. Concentration and column chromatographic purification gave the corresponding product **3ax** in 90% yield with 87% ee.
18. In the reaction of β-keto esters of **1g** bearing larger substituents at α-position (R^2) with azodicarboxylate **2x**, the enantioselectivity was suddenly dropped to 13% ee.
19. It might be difficult to make a stable complex from dibenzyl azodicarboxylate **2z** due to the rotation of the benzyl moieties, resulting in obtaining lower enantioselectivity.