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Asymmetric α-amination of β-keto esters using a guanidine–bisurea bifunctional organocatalyst

Minami Odagi*, Yoshiharu Yamamoto and Kazuo Nagasawa*

Full Research Paper

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Address:
Department of Biotechnology and Life Science, Tokyo University of Agriculture and Technology, 2-24-16, Naka-cho, Koganei city, 184-8588, Tokyo, Japan

Email:
Minami Odagi* - odagi@cc.tuat.ac.jp;
Kazuo Nagasawa* - knaga@cc.tuat.ac.jp

* Corresponding author

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Abstract

An asymmetric α-amination of β-keto esters with azodicarboxylate in the presence of a guanidine–bisurea bifunctional organocatalyst was investigated. The α-amination products were obtained in up to 99% yield with up to 94% ee.

Introduction

Asymmetric α-amination of β-keto esters is an important synthetic route to optically active α-amino acid derivatives with chiral quaternary stereocenters [1,2]. Since an α-amino acid moiety is frequently found in biologically active compounds, considerable efforts have been made to achieve a stereoselective synthesis of this structure [3,4]. In particular, catalytic asymmetric α-amination of β-keto esters has been widely explored, using both metal catalysts and organocatalysts [5-18].

We have developed a series of guanidine–bis(thio)urea bifunctional organocatalysts, and have used them in a variety of asymmetric reactions [19,20]. Recently, we disclosed an α-hydroxylation of tetralone-derived β-keto esters **2** using guanidine–bisurea bifunctional organocatalyst **1a** in the presence of cumene hydroperoxide (CHP) as an oxidant (Figure 1a) [21]. This reaction provides the corresponding α-hydroxylation products **3** in high yield with high enantioselectivity. A computational study of the transition state of this reaction revealed that inter- and intramolecular hydrogen-bonding networks between catalyst and substrate are critical for obtaining high enantioselectivity [22]. Based upon these insights, we expected that guanidine–bisurea bifunctional organocatalyst **1** would be effective in promoting α-amination of β-keto esters as a result of interactions between guanidine and enolate of the β-keto ester, and between urea and azodicarboxylate (Figure 1b). Herein, we describe the catalytic asymmetric α-amination of β-keto esters with azodicarboxylates as a nitrogen source in the presence of **1**.

Results and Discussion

The reaction conditions for α-amination of β-keto ester **4a** in the presence of diethyl azodicarboxylate (DEAD) were optimized

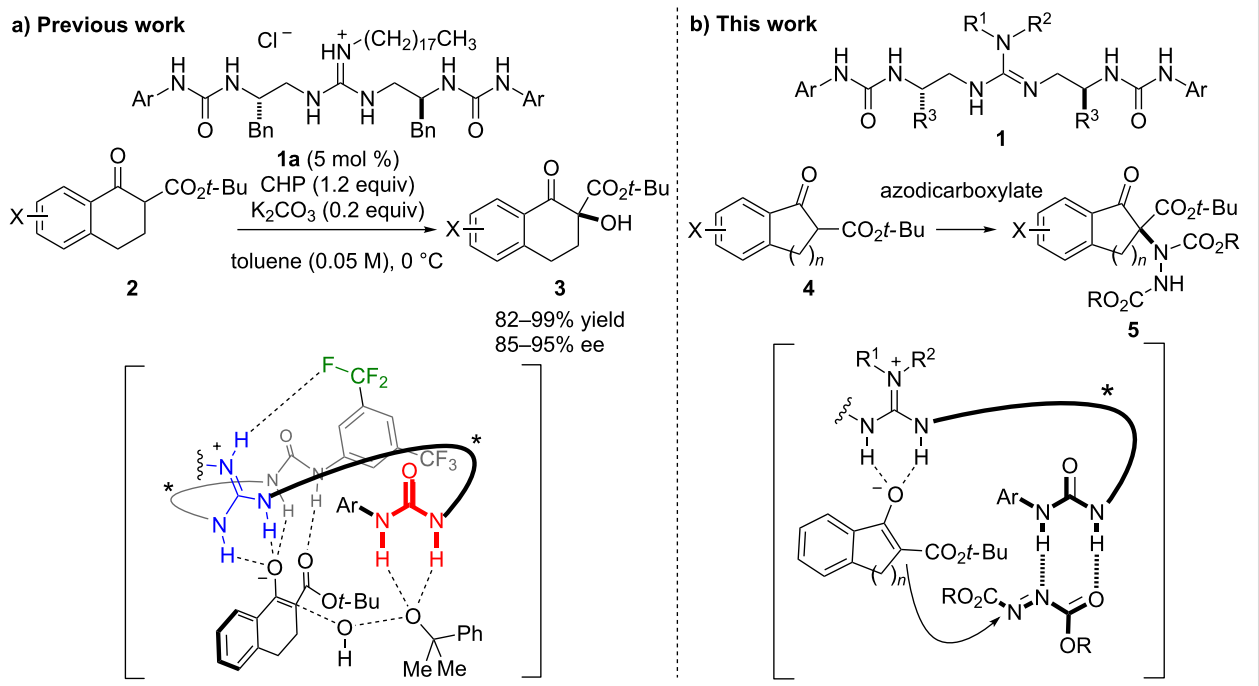
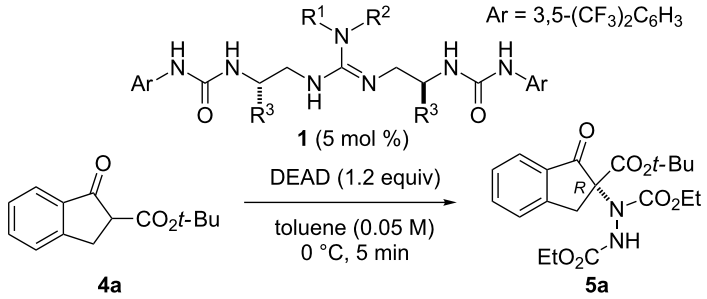


Figure 1: a) Asymmetric α-hydroxylation of **2** in the presence of **1a**. b) Asymmetric α-amination of **4** explored in this study.

as follows. First, we focused on the catalyst structure (Table 1) [23]. Initially, the R^3 substituent on the chiral spacer of the catalyst **1** was optimized (Table 1, entries 1–4). The catalyst with a benzyl group at R^3 (**1a**) afforded **5a** in excellent yield with moderate enantioselectivity for *R* configuration (Table 1, entry 1) [24,25]. When R^3 was changed to a phenyl group, the enantioselectivity was slightly increased to 59% ee (Table 1, entry 2). In the case of a methyl group, **5a** was obtained in 98%

Table 1: Optimization of catalyst structure.[a]



entry		catalyst **1**		α-amination product **5a**	
		R^1, R^2	R^3	yield (%)[b]	ee (%)[c]
1	**1a**	H, $-(CH_2)_{17}CH_3$	Bn	99	53
2	**1b**	H, $-(CH_2)_{17}CH_3$	Ph	94	59
3	**1c**	H, $-(CH_2)_{17}CH_3$	Me	98	50
4	**1d**	H, $-(CH_2)_{17}CH_3$	iPr	97	66
5	**1e**	$-(CH_2)_5-$	iPr	93	27
6	**1f**	$-(CH_2)_4-$	iPr	99	80

[a]Reaction conditions: **4a** (0.1 mmol), DEAD (0.12 mmol) and **1** (5 mol %) in toluene (2.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. DEAD = diethyl azodicarboxylate.

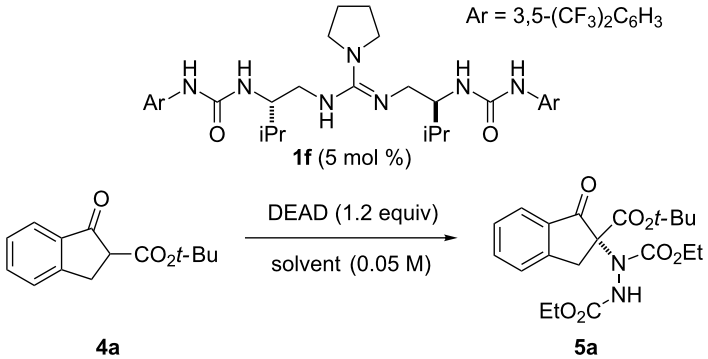
yield with 50% ee (Table 1, entry 3). An isopropyl group as R^3 group was most effective, affording **5a** with 66% ee (Table 1, entry 4). Next, we optimized R^1 and R^2 on the guanidine moiety (Table 1, entries 5 and 6). A catalyst bearing a six-membered ring at R^1 and R^2 (**1e**) gave excellent yield, but with only 27% ee (Table 1, entry 5). Interestingly, catalyst **1f** bearing a pyrrolidine ring at R^1 and R^2 showed the highest selectivity, and **5a** was obtained in 99% yield with 80% ee (Table 1, entry 6). Thus, we chose **1f** as the optimized catalyst for the reaction [26].

Next, we investigated various solvents, such as ethyl acetate, dichloromethane, acetonitrile and diethyl ether (Table 2, entries 1–5) for the reaction in the presence of catalyst **1f** (Table 2). The best result was obtained with diethyl ether, and **5a** was isolated in 95% yield with 85% ee (Table 2, entry 5). The enantioselectivity was improved to 90% ee by decreasing the reaction temperature to −40 °C without decrease in the yield (Table 2, entry 6). When the reaction was performed at −78 °C, the yield of **5a** was dropped to 91% (Table 2, entry 7).

As a further investigation, we optimized the ester moiety of the azodicarboxylate (Table 3). In addition to the ethyl ester (Table 3, entry 1), we examined benzyl, isopropyl, and *tert*-butyl ester as azodicarboxylate (Table 3, entries 2–4). By changing the ethyl ester to a benzyl or isopropyl ester, the amination products **6a** and **7a** were obtained in excellent yield, but the enantioselectivity was dropped to 64 and 79% ee, respectively (Table 3, entries 2 and 3). In the case of the *tert*-butyl ester, the reactivity of the azodicarboxylate was drastically decreased, and the reaction has not been completed after 48 h. The enantioselectivity of **8a** was also poor (Table 3, entry 4).

With the optimal reaction conditions in hand (Table 2, entry 6), we investigated the substrate scope for α-amination of β-keto esters (Scheme 1). First, various indanone-derived β-keto esters were examined. With electron-donating substituents such as methoxy and methyl, the corresponding amination products **5b**–**f** were obtained in high yield (72–99%) with high enantioselectivity (77–94% ee). In the case of substrates bearing electron-withdrawing groups, such as halogen atoms, the amination products **5g**–**j** were obtained with high enantioselectivity (73–86% ee). On the other hand, in the case of tetralone derivative **4k** and cyclopentanone derivative **4l**, the enantioselectivity of the products **5k** and **5l** was moderate to low (61% ee and 38% ee, respectively).

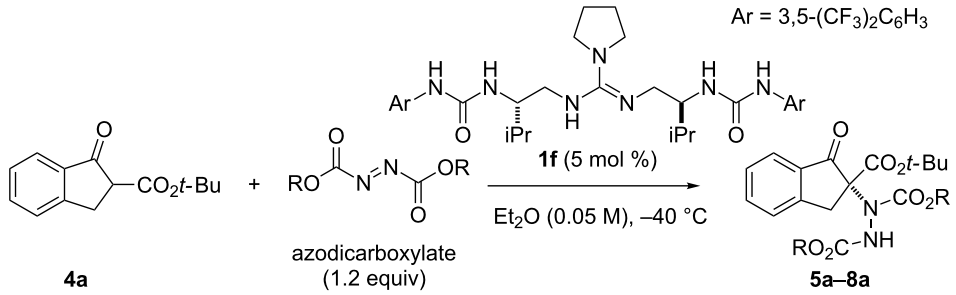
Table 2: Investigation of solvent effect.[a]



entry	solvent	time (min)	temp (°C)	α-amination product **5a**	
				yield (%)[b]	ee (%)[c]
1	toluene	5	0	99	80
2	EtOAc	5	0	99	78
3	DCM	30	0	99	75
4	MeCN	30	0	97	58
5	Et_2O	5	0	95	85
6	Et_2O	5	−40	99	90
7	Et_2O	30	−78	91	89

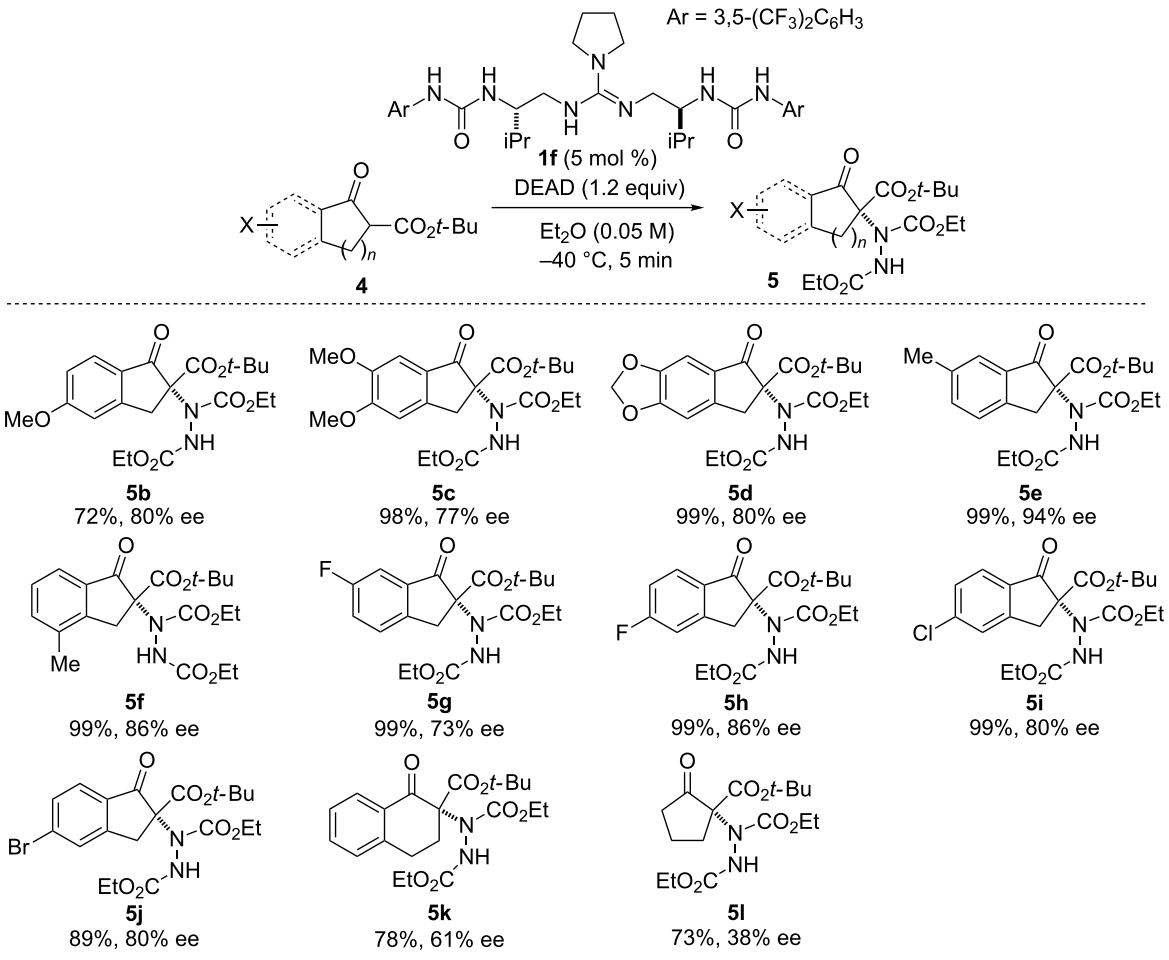
[a]Reaction conditions: **4a** (0.1 mmol), DEAD (0.12 mmol) and **1f** (5 mol %) in solvent (2.0 mL). [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. DEAD = diethyl azodicarboxylate. EtOAc = ethyl acetate. DCM = dichloromethane. MeCN = acetonitrile. Et_2O = diethyl ether.

Table 3: Optimization of the ester moiety of azodicarboxylate.[a]



entry	azodicarboxylate	time	α-amination product		
	R			yield (%)[b]	ee (%)[c]
1	Et	5 min	**5a**	99	90
2	Bn	5 min	**6a**	98	64
3	iPr	30 min	**7a**	98	79
4	*t*-Bu	48 h	**8a**	58	44

[a]Reaction conditions: **4a** (0.1 mmol), azodicarboxylate (0.12 mmol) and **1f** (5 mol %) in Et_2O (2.0 mL) at −40 °C. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase.



Scheme 1: Substrate scope of α-amination.

To get insight into the transition state of the reaction, we performed a nonlinear effect (NLE) study (Figure 2) [27]. We found a linear relationship between % ee of **1f** and **5a** in the reaction. This result suggests that the stereoselectivity is controlled by the monomeric structure of **1f** [28-31]. Furthermore, to confirm the requirement of bifunctionality in catalyst **1**, we performed the α-amination reaction in the presence of carbamate **9** or triurea **10** as a catalyst (Scheme 2). In both cases, the enantioselectivity of the α-amination product **3a** was drastically decreased. These results clearly show that the guanidine and urea moieties in the catalyst **1f** are mandatory for obtaining high enantioselectivity, presumably interacting with the enolate of **4a** and DEAD, respectively.

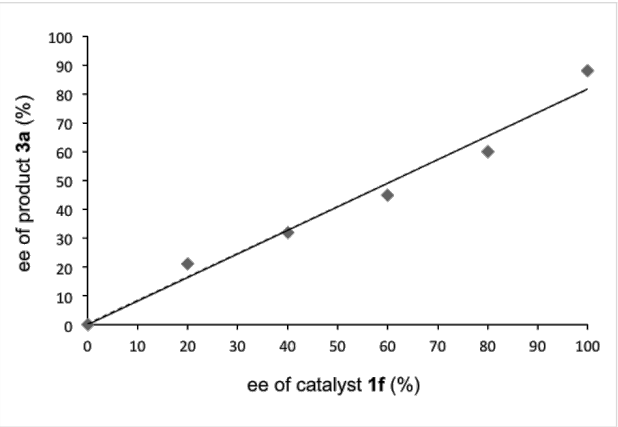


Figure 2: NLE study of α-amination.

Conclusion

In conclusion, we have developed an asymmetric α-amination of β-keto esters **4** by using guanidine–bisurea bifunctional organocatalyst **1f** in the presence of diethyl azodicarboxylate (DEAD). The α-amination of various indanone-derived β-keto esters proceeded in high yield (up to 99% yield) and with high enantioselectivity (up to 94% ee).

Supporting Information

Supporting Information File 1

Experimental procedures, copies of NMR spectra and HPLC chromatograms.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-22-S1.pdf]

Acknowledgements

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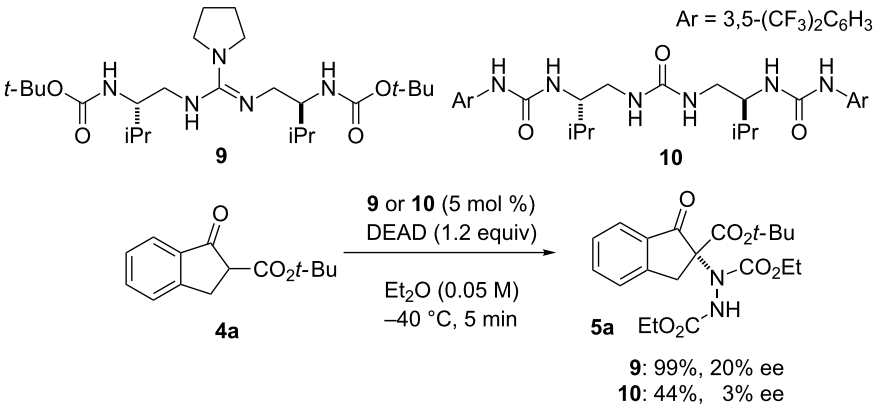

Scheme 2: α-Amination of **4a** using **9** or **10** as catalyst.

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23. Guanidine–bisthiourea bifunctional organocatalyst was not suitable for the reaction. For details, see Tables S2 and S3 in Supporting Information File 1.
24. The absolute stereochemistry of **5a** was assigned by comparison with a known compound (ref. [17]).
25. Based on previously reported transition states (Figure 1a), we expected that the α-amination product would be the *S* conformer. However, the reaction afforded the *R* conformer. This result suggests that the reaction proceeds through a different transition state from previously reported reactions. Further investigation of the transition state is on-going.
26. The results of optimization of substituents on the aromatic ring are summarized in Table S1 in Supporting Information File 1.
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