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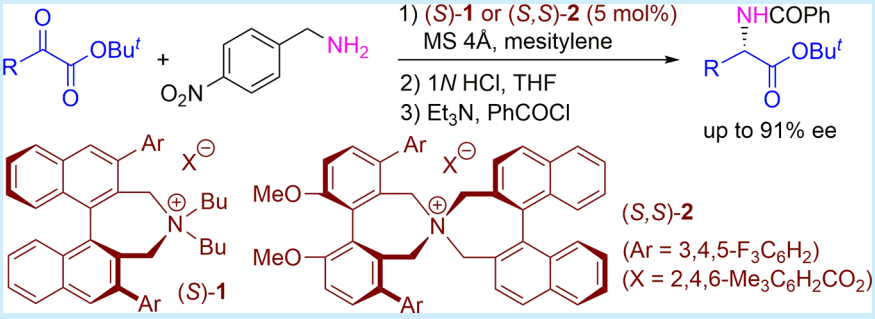
Asymmetric Synthesis of α-Amino Acids by Organocatalytic Biomimetic Transamination

Qi-Kai Kang,[†] Sermadurai Selvakumar,[†] and Keiji Maruoka*[,†,‡]

[†]Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

[‡]School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, China

Supporting Information

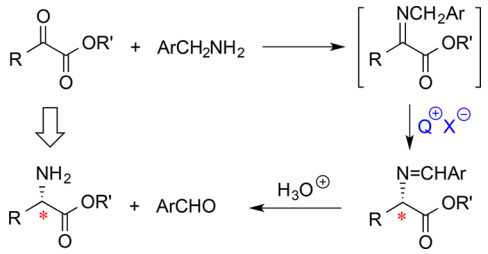


ABSTRACT: A biomimetic enantioselective transamination of α-keto ester derivatives can be realized under mild conditions by using chiral quaternary ammonium arenecarboxylates in the absence of base additives. The corresponding α-amino acids can be used as versatile intermediates for further synthetic transformations that furnish chiral pyrrolidine and octahydroindolizine derivatives.

The development of new catalytic asymmetric transformations based on chiral metal-free catalysts[1] in the absence of acid and/or base additives is one of the most desirable approaches in current asymmetric synthesis, especially from the viewpoint of green sustainable chemistry. We have thus been interested in the possibility of realizing such asymmetric transformations and studied the environmentally benign asymmetric organocatalytic transamination[2] of α-keto esters into the corresponding α-amino acid derivatives under very mild conditions. Although ordinary phase-transfer reactions using quaternary ammonium salts as phase-transfer catalysts are generally believed to require base additives,[3] we found that even in the absence of any external base additives[4] the enantioselective phase-transfer transamination of α-keto esters into the corresponding α-amino acid derivatives proceeds smoothly and with high enantioselectivity in the presence of chiral quaternary ammonium carboxylates (Q^+X^-) under mild conditions in organic solvents (Scheme 1).

Initially, the asymmetric transamination of α-keto ester **1a** with *p*-nitrobenzylamine (**2a**) as the amine donor was carried out in the presence of simplified Maruoka catalyst (*S*)-**4a** in toluene to furnish the corresponding product (**3a**) in 33% yield and 17% ee (entry 1, Table 1). We then examined the effect of the counteranion of the phase-transfer catalysts (*S*)-**4a** in order to influence the reactivity and selectivity on the asymmetric transamination.[5] When acetate was used as the anion, both the chemical yield and the enantioselectivity of the product **3a** improved (entry 2), while the use of benzoate (*S*)-**4c** accelerated the transamination (entry 3). Among several

Scheme 1. Biomimetic Enantioselective Transamination of α-Keto Esters



aromatic carboxylates, 2,4,6-trimethylbenzoate exhibited the best performance in this transamination (entry 4 vs entries 3 and 5). Among the solvents tested, dichloromethane (DCM) and *tert*-butyl methyl ether (TBME) decreased the enantioselectivity (entries 6 and 7). In contrast, aromatic solvents such as *o*-xylene and mesitylene slightly increased the enantioselectivity (entries 8 and 9). Dilution of the reaction mixture enhanced the enantioselectivity to 86% ee (entry 10), while the use of 1.5 equiv of **2a** improved the chemical yield without loss of enantioselectivity (entry 11). We also examined different amine donors **2**, and similar or less satisfactory results were obtained from using *p*-(methoxycarbonyl)benzylamine (**2b**), *p*-cyanobenzylamine (**2c**), or *p*-(aminomethyl)pyridine (**2d**) (entries 12−14). Biphenyl- and spiro-type phase-transfer

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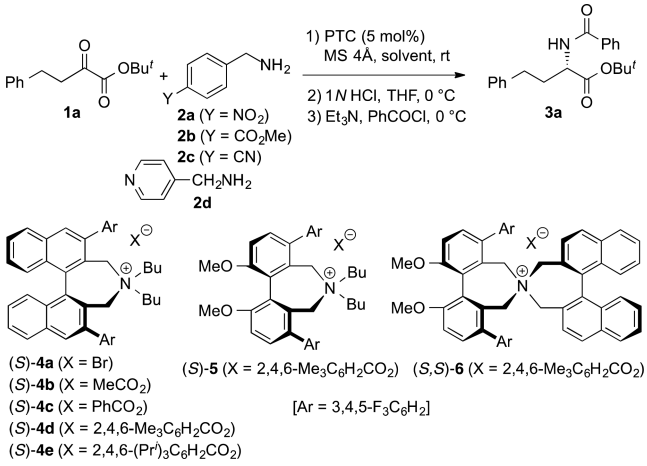
Table 1. Optimization of the Reaction Conditions for the Biomimetic Enantioselective Transamination of α-Keto Esters[a]



entry	PTC	solvent	amine	time (h)	% yield[b] (% ee)[c]
1	(*S*)-**4a**	toluene	**2a**	36	33 (17)
2	(*S*)-**4b**	toluene	**2a**	36	48 (42)
3	(*S*)-**4c**	toluene	**2a**	36	58 (40)
4	(*S*)-**4d**	toluene	**2a**	24	60 (74)
5	(*S*)-**4e**	toluene	**2a**	24	52 (58)
6	(*S*)-**4d**	DCM	**2a**	12	59 (14)
7	(*S*)-**4d**	TBME	**2a**	12	51 (63)
8	(*S*)-**4d**	*o*-xylene	**2a**	12	53 (76)
9	(*S*)-**4d**	mesitylene	**2a**	12	79 (78)
10[d]	(*S*)-**4d**	mesitylene	**2a**	12	63 (86)
11[d,e]	(*S*)-**4d**	mesitylene	**2a**	12	80 (86)
12[d,e]	(*S*)-**4d**	mesitylene	**2b**	12	72 (85)
13[d,e]	(*S*)-**4d**	mesitylene	**2c**	12	44 (78)
14[d,e]	(*S*)-**4d**	mesitylene	**2d**	12	65 (85)
15[d,e,f]	(*S*)-**5**	mesitylene	**2a**	12	87 (88)
16[d,e,g]	(*S,S*)-**6**	mesitylene	**2a**	12	93 (89)
17[d,e,g,h]	(*S,S*)-**6**	mesitylene	**2a**	24	70 (91)

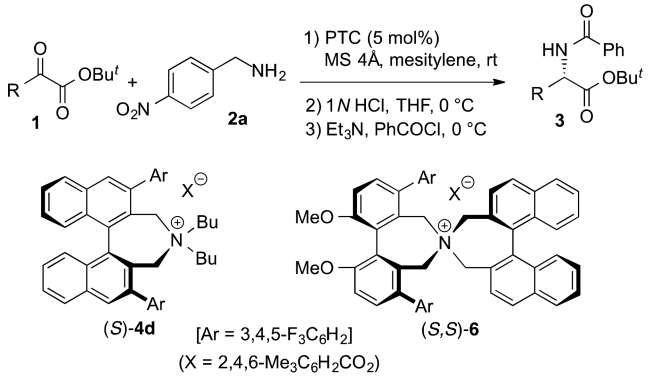
[a]Unless otherwise specified, the asymmetric transamination of **1a** (0.1 mmol) was carried out at room temperature in the specified solvent (0.5 mL) with benzylic amine (1.0 equiv) and MS 4 Å (20 mg) in the presence of the chiral PTC (5 mol %). [b]Determined by ^{1}H NMR spectroscopy using TCE as the internal standard after derivatization of the product. [c]Determined by chiral HPLC after derivatization of the product. [d]2.0 mL of solvent was used. [e]1.5 equiv of benzylamine was used. [f]PTC (*S*)-**5** (5 mol %) was used. [g]PTC (*S,S*)-**6** (5 mol %) was used. [h]The reaction was carried out at 10 °C.

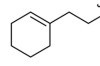
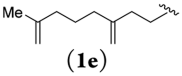
catalysts (*S*)-**5** and (*S,S*)-**6** exhibited an increased enantioselectivity (entries 15 and 16). Lowering the reaction temperature in the presence of (*S,S*)-**6** further improved the enantioselectivity (entry 17).

As shown in Table 2, α-keto esters **1b**–**e**, which contain C═C bonds, showed moderate reactivity and good enantioselectivity (entries 3–7). Functional groups such as *tert*-butoxycarbonyl and benzyloxy substituents were also tolerated under the optimized conditions (entries 8 and 9). Alkyl-substituted α-keto esters **1h**–**j** furnished the corresponding amino ester derivatives in 40–72% yield and 76–86% ee (entries 10–13). Unfortunately, phenyl-substituted α-keto ester **1** (R = Ph) afforded only trace amounts of the target product **3** (R = Ph).

In order to examine the tolerance of acid- or base-labile substrates under the previously determined optimized organo-

Table 2. Substrate Scope for the Biomimetic Enantioselective Transamination of α-Keto Esters 1[a]



entry	R	PTC	time (h)	% yield[b]	% ee[c]
1[d]	$PhCH_2CH_2$ (**1a**)	(*S*)-**4d**	24	65	88
2[d]	$PhCH_2CH_2$ (**1a**)	(*S,S*)-**6**	24	70	91
3	CH_2=$CHCH_2CH_2$ (**1b**)	(*S*)-**4d**	16	58	86
4	CH_2=$CHCH_2CH_2$ (**1b**)	(*S,S*)-**6**	18	40	82
5	CH_2=$CHCH_2CH_2CH_2$ (**1c**)	(*S*)-**4d**	48	56	80
6	 (**1d**)	(*S,S*)-**6**	48	40	86
7	 (**1e**)	(*S*)-**4d**	42 / 42[d]	46 / 48[d]	78 / 86[d]
8	^{t}BuO$_2$CCH$_2$CH$_2$ (**1f**)	(*S,S*)-**6**	48	40	80
9	BnOCH$_2$CH$_2$CH$_2$ (**1g**)	(*S,S*)-**6**	24	64	72
10	Me (**1h**)	(*S*)-**4d**	16	72	80
11	Me (**1h**)	(*S,S*)-**6**	16	49	76
12[d]	^{n}Bu (**1i**)	(*S,S*)-**6**	36	44	86
13[d]	^{i}Bu (**1j**)	(*S,S*)-**6**	72	40	79

[a]Unless otherwise specified, the asymmetric transamination of **1** (0.05 mmol) was carried out at room temperature in mesitylene (1.0 mL) with **2a** (0.075 equiv) and MS 4 Å (20 mg) in the presence of PTC (5 mol %). [b]Isolated yield. [c]The enantioselectivity was determined by chiral HPLC analysis. [d]The reaction was carried out at 10 °C.

catalytic transamination conditions, we carried out the reaction in the presence of **7a** and **7b** (Scheme 2), which afforded **3a** in 90% (89% ee) and 80% yields (88% ee), respectively. Under the applied reaction conditions, 95% of **7a** and 90% of **7b** survived.

The obtained transamination products can be easily derivatized. For example, **3b** was readily transformed into pyrrolidine derivative **8** under concomitant slight loss of enantioselectivity via a halogen-mediated cyclization (Scheme 3A). Moreover, ozonolysis of product **3e** generated **9**, which could be converted into (+)-monomorine, which is a trail pheromone of the tropical pharao ant *Monomorium pharaonis L.* (Scheme 3B).[6,7]

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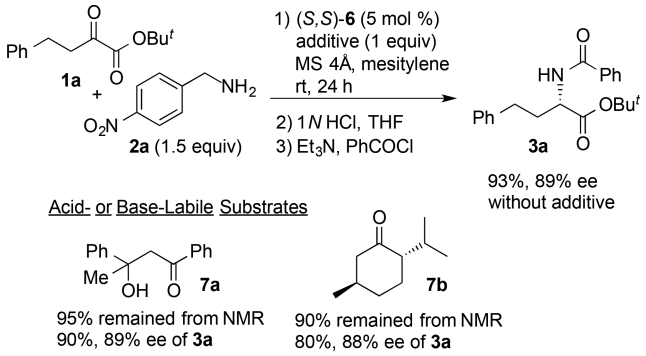
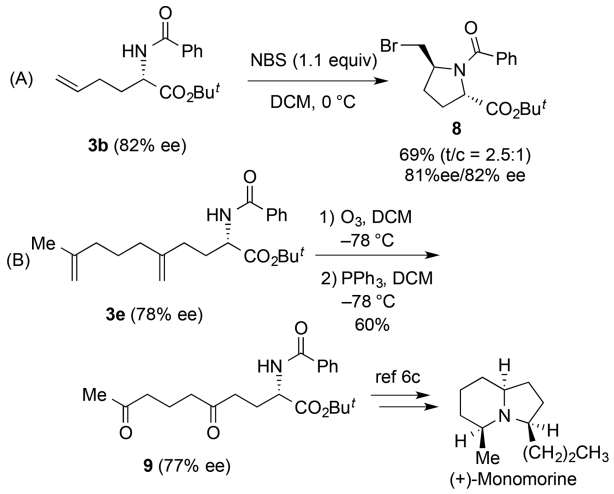
Scheme 2. Tolerance of Acid- or Base-Labile Substrates under the Applied Mild Reaction Conditions

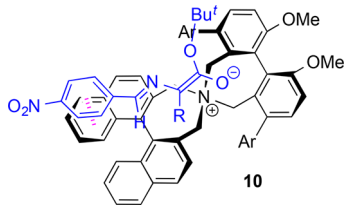


Scheme 3. Subsequent Transformations of the Obtained Transamination Products



Based on the absolute configuration of the transamination products (**3**),[8] a plausible structure for the transition state is proposed in Scheme 4. First, the α-keto ester would be

Scheme 4. Proposed Transition State for the Asymmetric Transamination of α-Keto Esters



transformed into the corresponding α-imino ester via a condensation with amine **2**. In the presence of a weak base (amine **2** or its imine),[9] this α-imino ester could afford the corresponding *E*-enolate, which could react with the chiral PTC (*S*,*S*)-**6** to furnish the ion pair **10**. Here, the effective shielding of one face of the enolate with the PTC by the $\pi-\pi$ interactions between the aryl and the binaphthyl groups implies that the protonation should occur from the upper side, which would lead to the enantioenriched amino acid **3** with *S*-configuration.[8]

In conclusion, we have developed an enantioselective transamination of α-keto esters in the presence of chiral quaternary ammonium carboxylate (*S*)-**4d** and (*S*,*S*)-**6**, which proceeds in the absence of base additives. The reaction exhibits good reactivity and affords high enantioselectivity under mild conditions. Further applications of this catalytic system are currently under investigation in our group, and the corresponding results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00588.

Details of the effect of PTC counteranion; effect of solvent and its concentration; PTC screening and effect of temperature; synthesis of catalysts; general procedure for transamination; general procedure for checking tolerance of acid- or base-labile substrates under standard conditions; general procedure for transformation of product; ^{1}H NMR and ^{13}C NMR spectra; HPLC spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: maruoka@kuchem.kyoto-u.ac.jp. Fax: (+81) 75-753-4041

ORCID

Keiji Maruoka: 0000-0002-0044-6411

Notes

The authors declare no competing financial interest.

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(8) Given the specific rotation of **3a** ($[\alpha]_D^{20.0}$ = +13.0 (*c* 1.12, $CHCl_3$), 88% ee), the absolute configuration was assigned as *S* by comparison with previous reports (*R*: $[\alpha]_D^{20.0}$ = − 21.9 (*c* 0.95, $CHCl_3$), 94% ee); cf. Xiao, X.; Liu, M.; Rong, C.; Xue, F.; Li, S.; Xie, Y.; Shi, Y. An Efficient Asymmetric Biomimetic Transamination of α-Keto Esters to Chiral α-Amino Esters. *Org. Lett.* **2012**, *14*, 5270.

(9) Amine **2** or its imine may act as a base, rather than the carboxylate anion, which is a weaker base in comparison. The influence of the carboxylate anion on the reactivity and enantioselectivity may be due to its participation in the formation and subsequent protonation of ion pair **10**.

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