Phase-Transfer-Catalyzed Asymmetric S_NAr Reaction of α -Amino Acid Derivatives with Arene Chromium Complexes

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Dedication ((optional))

Abstract: Although phase-transfer-catalyzed asymmetric S_NAr reactions provide unique contribution to the catalytic asymmetric α -arylations of carbonyl compounds to produce biologically active α -aryl carbonyl compounds, the electrophiles were limited to arenes bearing strong electron-withdrawing groups, such as a nitro group. To solve this limitation, we examined the asymmetric S_NAr reactions of α -amino acid derivatives with arene chromium complexes derived from fluoroarenes, including those containing electron-donating substituents. The arylation was efficiently promoted by binaphthyl-modified chiral phase-transfer catalysts to give the corresponding α,α -disubstituted α -amino acids containing various aromatic substituents with high enantioselectivities.

Catalytic asymmetric α -arylation of carbonyl compounds has extensively studied over the last decade to prepare biologically interesting α -aryl carbonyl compounds.^[1,2] Several catalytic asymmetric methods for α -arylation have been developed using chiral metal complexes.^[3] As another method for asymmetric α -arylation, phase-transfer-catalyzed nucleophilic aromatic substitution (S_NAr) reaction provides an efficient means to realize enantioselective α -arylations (Scheme 1).^[4,5] Jørgensen's and our groups have reported highly enantioselective phase-transfer-catalyzed S_NAr reactions of carbonyl compounds with nitro group-bearing fluoroarenes as electrophiles (Scheme 1a).^[6] The drawback of this method is the limited scope of fluoroarenes that can be used, as only electron-deficient arenes are effective substrates. The S_NAr reactions using fluoroarenes with electron-donating groups (EDG), did not work under the phase-transfer conditions (Scheme 1b). As a solution to this problem, we are interested in S_NAr reaction of the chromium complexes of fluoroarenes, which activate the arenes via η^6 -coordination to $Cr(CO)_3$.^[7,8] Here we report a valuable example of phase-transfer-catalyzed asymmetric S_NAr reaction of α -amino acid derivatives with arene chromium complexes, which produces enantioenriched α,α -disubstituted α -amino acids^[9] including those containing an electron-rich aromatic substituents (Scheme 1c).

Scheme 1. Phase-transfer-catalyzed asymmetric S_NAr reactions.

We first examined the asymmetric S_NAr reaction of alanine derivative **1a** with chromium complex **2a** derived from fluorobenzene, promoted by biaryl-modified chiral quaternary ammonium salts **4–6** as promising chiral phase-transfer catalysts (Table 1).^[5] Attempted reaction of **1a** and fluorobenzene derivative **2a** with solid KOH in toluene under the influence of chiral phase-transfer catalyst (*R,R*)-**4**^[10] at 0 °C for 24 h, followed by treatment with aqueous HCl for hydrolysis of imine moiety and removal of chromium, afforded the corresponding α,α -disubstituted α -amino ester **3a** with moderate yield and enantioselectivity (77% ee, entry 1). The use of simplified catalyst (*R*)-**5**,^[11] which is one of the most effective catalysts for asymmetric alkylations of **1a**,^[11,12] improved the enantioselectivity to give product **3a** in moderate yield with high enantioselectivity (97% ee, entry 2). The use of biphenyl-modified catalyst (*R*)-**6**^[13] caused the decrease of enantioselectivity for the S_NAr reaction (39% ee, entry 3). Changing the base to CsOH improved the yield (entry 4), and the highest yield and enantioselectivity were attained by the use of saturated aqueous CsOH^[14] as base with catalyst (*R*)-**5** (entry 5).^[15] The absolute configuration of product **3a** was determined by comparison of the optical rotation of the *N*-acetylated derivative of **3a**, with the literature value.^[6c,16]

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Table 1. Optimization of the reaction conditions.^[a]

Entry	Catalyst	Base	Yield [%] ^[b]	ee [%] ^[c]
1	(R,R) - 4	KOH	42	77
2	(R) - 5	KOH	39	97
3	(R) - 6	KOH	41	39
4	(R) - 5	CsOH·H ₂ O	70	91
5	(R) - 5	sat. aq CsOH	70	97

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.10 mmol), and base (1.5 mmol) in the presence of phase-transfer catalyst (10 mol %, 0.010 mmol) in toluene (2.0 mL) at 0 °C for 24 h. [b] Yields of isolated product **3a**, which were determined on the basis of amount of **2a**. [c] Determined by chiral HPLC analysis.

With the optimal reaction conditions in hand, we next examined the substrate generality of the asymmetric S_NAr reaction of alanine derivative **1a** with arene chromium complexes **2** under the influence of chiral phase-transfer catalyst (R) -**5** (Table 2). The S_NAr reactions with *p*-, *m*-, *o*-fluorotoluene derivatives (**2b–2d**) proceeded efficiently, and uniformly gave the products (**3b–3d**) in good yields with high enantioselectivities (94–98% ee, entries 2–4). Other electron-donating groups (EDG)-substituted fluoroarene derivatives (**2e–2i**) could also be used in this reaction, thereby providing the products (**3e–3i**) with excellent enantioselectivities (98–99% ee, entries 5–9).^[17]

Table 2. Asymmetric arylation of alanine derivative **1a**.^[a]

Entry	EDG (2)	Yield [%] ^[b]	ee [%] ^[c]
1	H (2a)	70 (3a)	97
2	<i>p</i> -Me (2b)	71 (3b)	98
3	<i>m</i> -Me (2c)	69 (3c)	98
4	<i>o</i> -Me (2d)	62 (3d)	94
5	<i>p</i> -OMe (2e)	70 (3e)	98
6	<i>m</i> -OMe (2f)	68 (3f)	99
7	<i>p</i> -OEt (2g)	61 (3g)	98
8	<i>p</i> -SMe (2h)	65 (3h)	99
9	<i>p</i> -NMe ₂ (2i)	63 (3i)	98

[a] Reaction conditions: **1a** (0.30 mmol), **2** (0.10 mmol), and saturated aqueous CsOH (1.5 mmol) in the presence of (R) -**5** (10 mol %, 0.010 mmol) in toluene (2.0 mL) at 0 °C for 24 h. [b] Yields of isolated products **3**, which were determined on the basis of amount of **2**. [c] Determined by chiral HPLC analysis.

Other α -amino acid derivatives **1** could be employed in the S_NAr reaction with arene chromium complex **2a** (Table 3). Not only simple alkyl-substituted α -amino acid derivatives (**1a–1c**) but also phenylalanine (**1d**) and allylglycine (**1e**) derivatives were tolerated in the reaction to give the corresponding phenylation products **3j–3m** in high enantioselectivities (88–99% ee, entries 1–5). Furthermore, heteroatom-containing α -amino acids, such as methionine (**1f**), serine (**1g**), and glutamic acid derivatives (**1h**) were also employable for the reaction to give the corresponding products **3n–3p** in high enantioselectivities (90–96% ee, entries 6–8).

Table 3. Asymmetric phenylation of α -amino acid derivatives **1**.^[a]

Entry	R (1)	Yield [%] ^[b]	ee [%] ^[c]
1	Me (1a)	70 (3a)	97
2	Et (1b)	78 (3j)	99
3	<i>i</i> Bu (1c)	60 (3k)	88
4	CH ₂ Ph (1d)	68 (3l)	95
5	CH ₂ CH=CH ₂ (1e)	74 (3m)	96
6	CH ₂ CH ₂ SMe (1f)	76 (3n)	90
7	CH ₂ OC <i>t</i> Bu (1g)	73 (3o)	96
8	CH ₂ CH ₂ CO ₂ <i>t</i> Bu (1h)	51 (3p)	92

[a] Reaction conditions: **1** (0.30 mmol), **2a** (0.10 mmol), and saturated aqueous CsOH (1.5 mmol) in the presence of (*R*)-**5** (10 mol %, 0.010 mmol) in toluene (2.0 mL) at 0 °C for 24 h. [b] Yields of isolated products **3**, which were determined on the basis of amount of **2a**. [c] Determined by chiral HPLC analysis.

In summary, we have successfully overcome a major limitation of phase-transfer-catalyzed asymmetric S_NAr reactions by the use of arene chromium complexes. The S_NAr reaction of α -amino acid derivatives with chromium complexes derived from electron-rich fluoroarenes, was efficiently promoted by binaphthyl-modified chiral phase-transfer catalysts to give the corresponding α,α -disubstituted α -amino acids containing various aromatic substituents, in a highly enantioselective manner. This report offers a new option for catalytic asymmetric α -arylation to produce biologically active α -aryl carbonyl compounds.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS and MEXT (Japan).

Keywords: amino acids • arylation • asymmetric synthesis • organocatalysis • phase-transfer catalysis

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- [14] For preparation of saturated aqueous CsOH (80 wt % aq CsOH), see Ref. 12.
- [15] The reaction in larger scale (10 times) gave a similar result (74% yield, 97% ee).
- [16] For details of the determination of absolute configuration of **3a**, see supporting information.
- [17] Racemic arene chromium complexes **2c**, **2d**, and **2f** were used for the reaction.

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The limited substrate scope in phase-transfer-catalyzed asymmetric S_NAr reactions was solved by the use of arene chromium complexes as electrophiles. This report demonstrates an efficient asymmetric synthesis of α , α -disubstituted α -amino acids containing various aromatic substituents.