Organocatalysis

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

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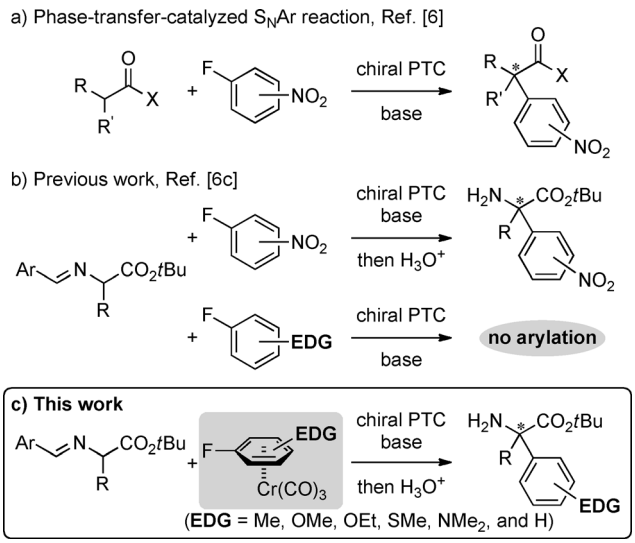
Abstract: *Although phase-transfer-catalyzed asymmetric S_NAr reactions provide unique contribution to the catalytic asymmetric α-arylations of carbonyl compounds to produce biologically active α-aryl carbonyl compounds, the electrophiles were limited to arenes bearing strong electron-withdrawing groups, such as a nitro group. To overcome 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 been 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, the 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 1 a).[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 1 b). As a solution to this problem, we are interested in S_NAr reaction of the chromium complexes of fluoroarenes, which activate the arenes through η^6-coordination to $Cr(CO)_3$.[7,8] Here we report a valuable example of a 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 1 c).



Scheme 1. Phase-transfer-catalyzed asymmetric S_NAr reactions. PTC = phase-transfer catalyst.

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 the 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 alkylation reactions 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 was 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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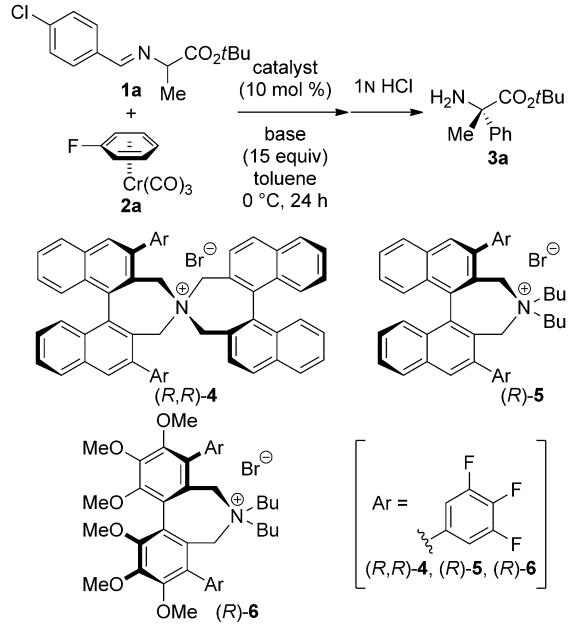
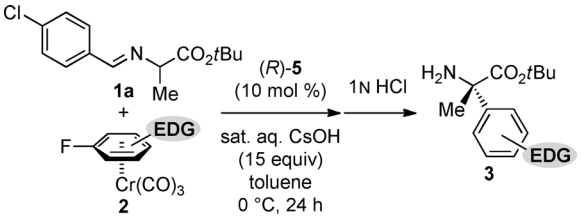
Table 1: Optimization of the reaction conditions.[a]



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_2O	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 the amount of **2a**. [c] Determined by HPLC analysis on a chiral stationary phase.

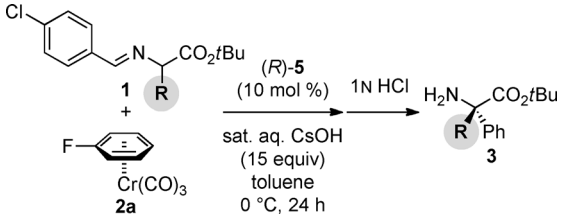
Table 2: Asymmetric arylation of alanine derivative **1a**.[a]



Entry	EDG (**2**)	Yield [%][b]	*ee* [%][c]
1	H (**2a**)	70 (**3a**)	97
2	*p*-Me (**2b**)	71 (**3b**)	98
3	*m*-Me (**2c**)	69 (**3c**)	98
4	*o*-Me (**2d**)	62 (**3d**)	94
5	*p*-OMe (**2e**)	70 (**3e**)	98
6	*m*-OMe (**2f**)	68 (**3f**)	99
7	*p*-OEt (**2g**)	61 (**3g**)	98
8	*p*-SMe (**2h**)	65 (**3h**)	99
9	*p*-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 the amount of **2**. [c] Determined by HPLC analysis on a chiral stationary phase.

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*Bu (**1c**)	60 (**3k**)	88
4	CH_2Ph (**1d**)	68 (**3l**)	95
5	$CH_2CH{=}CH_2$ (**1e**)	74 (**3m**)	96
6	CH_2CH_2SMe (**1f**)	76 (**3n**)	90
7	CH_2OtBu (**1g**)	73 (**3o**)	96
8	$CH_2CH_2CO_2tBu$ (**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 HPLC analysis on a chiral stationary phase.

With the optimal reaction conditions identified, 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*-, and *o*-fluorotoluene derivatives (**2b**–**2d**) proceeded efficiently, and gave the products (**3b**–**3d**) in good yields with high enantioselectivities (94–98% *ee*, entries 2–4). Other electron-donating group (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]

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 suitable for the reaction to give the corresponding products **3n**–**3p** in high enantioselectivities (90–96% *ee*, entries 6–8).

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.

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[14] For the preparation of saturated aqueous CsOH (80 wt% aq. CsOH), see Ref. [12].

[15] The reaction on larger scale (10 times) gave a similar result (74% yield, 97% *ee*).

[16] For details of the determination of the absolute configuration of **3a**, see the Supporting Information.

[17] Racemic arene chromium complexes **2c**, **2d**, and **2f** were used for the reaction.

