Phase-Transfer Catalysis

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Asymmetric Neutral Amination of Nitroolefins Catalyzed by Chiral Bifunctional Ammonium Salts in Water-Rich Biphasic Solvent**

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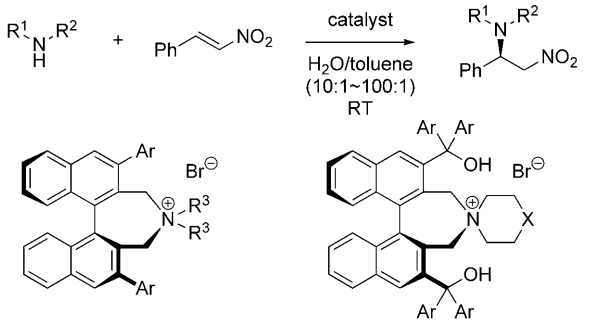
The development of new, catalytic asymmetric transformations using a chiral metal-free catalyst in water solvent under neutral conditions with excellent atom economy is one of the most ideal approaches in current asymmetric synthesis in view of environmental awareness.[1] Accordingly, we are interested in the possibility of realizing such an ideal transformation, and hence want to develop an environmentally benign asymmetric conjugate amination to nitroolefins[2,3] under essentially neutral conditions to fulfill the ideals of the four important keywords—metal-free, water, neutral, and atom economy—as described above. This transformation allows the efficient asymmetric synthesis of chiral 1,2-diamino compounds, which are useful chiral building blocks in pharmaceutical areas.[4] Herein, we report our initial study on this subject by developing an asymmetric neutral amination to nitroolefins catalyzed by chiral bifunctional tetraalkylammonium salts of type **2** with very low catalyst loading (0.05 mol%) in water-rich biphasic solvent (Scheme 1).



Scheme 1. Asymmetric neutral amination catalyzed by chiral ammonium salts.

At first, we examined the screening of binaphthyl-modified chiral ammonium salts as phase-transfer catalysts[5] for conjugate amination[6–8] of nitroolefins under neutral conditions in water-rich biphasic solvent (Scheme 1).[9] An attempted reaction of *tert*-butyl benzyloxycarbamate and β-nitrostyrene in H_2O/toluene (10:1) with 1 mol% of (*S*)-**1a**[10] as chiral phase-transfer catalyst at room temperature (25°C) for 24 hours afforded an amination product in low yield with low enantioselectivity (Table 1, entry 1). Replacing 3,4,5-trifluorophenyl groups of catalyst (*S*)-**1a** by 3,5-bis(trifluoromethyl)phenyl groups (**1b**) did not improve the result (Table 1, entry 2). The use of a morpholine-derived catalyst (*S*)-**1c** slightly improved the enantioselectivity but with low yield (39% *ee*; Table 1, entry 3). Next, we examined bifunctional ammonium bromides of type **2**[9,11] possessing diarylhydroxymethyl groups. Pleasingly, a dramatic improvement in both the yield and enantioselectivity was attained in the reaction with a bifunctional-type catalyst (*S*)-**2a** (69% yield, 75% *ee*; Table 1, entry 4). Exchange of the morpholine skeleton of catalyst (*S*)-**2a** to the piperidine skeleton improved the yield and enantioselectivity (91% yield, 82% *ee*; Table 1, entry 5). Switching the catalyst to (*S*)-**2c**, which possesses radially extended aromatic substituents (Ar), further improved the selectivity (88% *ee*; Table 1, entry 6).[12]

Table 1: Screening of the optimum condition.[a]

Entry	Catalyst (mol%)	Amination agent (R^1NHR^2)	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*S*)-**1a** (1)	BocNHOBn	24	5	16
2	(*S*)-**1b** (1)	BocNHOBn	24	17	14
3	(*S*)-**1c** (1)	BocNHOBn	24	12	39
4	(*S*)-**2a** (1)	BocNHOBn	24	69	75
5	(*S*)-**2b** (1)	BocNHOBn	13	91	82
6	(*S*)-**2c** (1)	BocNHOBn	4	90	88
7[d]	(*S*)-**2c** (1)	BocNHOBn	4	90	88
8[e]	(*S*)-**2c** (1)	BocNHOBn	4	82	84
9[f]	(*S*)-**2c** (1)	BocNHOBn	36	90	93
10	(*S*)-**2c** (1)	$BocNH_2$	4	≈0	–
11	(*S*)-**2c** (1)	$BnONH_2$	4	99	≈0
12	(*S*)-**2c** (1)	TsNHOBn	4	56	3[g]
13	(*S*)-**2c** (1)	$MeO_2CNHOBn$	4	73	25[g]
14	(*S*)-**2c** (0.05)	BocNHOBn	8	91	90
15	(*S*)-**2c** (0.01)	BocNHOBn	72	76	91

[a] Reaction conditions: β-nitrostyrene (0.050 mmol) and amination agent (0.25 mmol) in the presence of phase-transfer catalyst in H_2O (2.0 mL)/toluene (0.20 mL) at room temperature (25°C). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction was performed in H_2O/toluene = 50:1. [e] Reaction was performed in H_2O/toluene = 100:1. [f] Reaction was performed at 0°C. [g] Absolute configuration of the major isomer was not determined. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Ts = 4-toluenesulfonyl.

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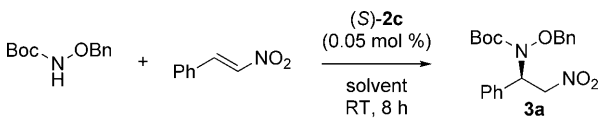
Additionally, even in the further water-rich biphasic solvent system (H_2O/toluene = 50:1–100:1), catalyst (*S*)-**2c** efficiently promoted the reaction and gave an amination product with high enantioselectivity (Table 1, entries 7 and 8).[13] The highest enantioselectivity was attained when lower temperature (0 °C) was employed with catalyst (*S*)-**2c** (93 % *ee*; Table 1, entry 9).

Other amination agents were also examined in the asymmetric amination of β-nitrostyrene in the presence of chiral ammonium bromide (*S*)-**2c**. The use of *tert*-butyl carbamate did not give any amination product (Table 1, entry 10). On the other hand, the reaction using *N*-benzyloxyamine proceeded smoothly and amination product was obtained in high yield, however, with almost no selectivity (Table 1, entry 11). The reactions with *N*-benzyloxytosylamine or methyl benzyloxycarbamate also gave the corresponding amination products with low enantioselectivities (Table 1, entries 12 and 13). These results indicate that both a *tert*-butoxycarbonyl and benzyloxy group on the nitrogen atom of the amination agent are necessary to obtain high yield with high selectivity.

The practicability of the present reaction was shown in decreasing the catalyst loading of chiral ammonium bromide (*S*)-**2c**. The reaction using only 0.05 mol % of catalyst (*S*)-**2c** promoted the amination efficiently at room temperature, and gave the product in high yield with high enantioselectivity (91 % yield, 90 % *ee*; Table 1, entry 14). Further decrease of the catalyst loading to 0.01 mol % still gave the product in good yield (76 % yield, TON 7600) and high selectivity (91 % *ee*) with prolonged reaction time (Table 1, entry 15).

It should be noted that the present reaction does not work well under the ordinary phase-transfer reaction conditions using aqueous base solutions, such as aqueous solutions of KOH, K_2CO_3, and PhCOOK, and under the homogeneous reaction conditions without aqueous solution (Scheme 2).

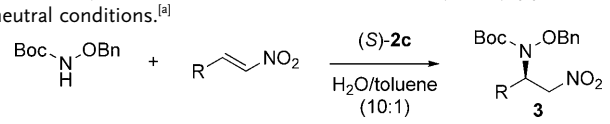


Scheme 2. Effect of a base and aqueous solution.

Hence, the highly enantioselective conjugate amination of nitroolefins was only achieved when the reaction was performed under the base-free, neutral phase-transfer conditions in water-rich biphasic solvent.

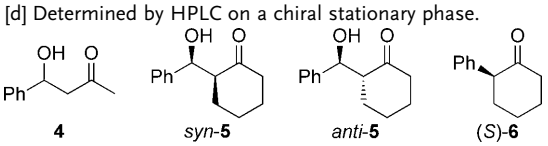
With optimal reaction conditions in hand, we further studied the generality of the asymmetric conjugate amination to nitroolefins under the neutral conditions in the presence of chiral bifunctional ammonium bromide (*S*)-**2c**. Two standard reaction conditions were examined for each substrate (conditions A and B in Table 2). Various types of nitroolefins were found to be employable for the reaction with low catalyst

Table 2: Asymmetric amination of nitroolefins catalyzed by (*S*)-**2c** under neutral conditions.[a]



Entry	R	Conditions[b]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	Ph	A	8	91 (**3a**)	90
2	Ph	B	36	90 (**3a**)	93
3	4-MeC_6H_4	A	16	93 (**3b**)	90
4	4-MeC_6H_4	B	36	90 (**3b**)	91
5	4-BrC_6H_4	A	16	91 (**3c**)	91
6	4-BrC_6H_4	B	36	89 (**3c**)	94
7	3-FC_6H_4	A	36	70 (**3d**)	90
8	3-FC_6H_4	B	72	62 (**3d**)	93
9	4-TBSOC_6H_4	A	10	94 (**3e**)	92
10	4-TBSOC_6H_4	B	68	92 (**3e**)	95
11	2-naphthyl	A	15	85 (**3f**)	90
12	2-naphthyl	B	72	70 (**3f**)	91
13	2-thienyl	A	18	93 (**3g**)	90
14	2-thienyl	B	72	81 (**3g**)	94
15	2-furyl	A	16	90 (**3h**)	90
16	2-furyl	B	48	82 (**3h**)	93
17	$(CH_3)_2CHCH_2$	A	8	95 (**3i**)	77
18	$(CH_3)_2CHCH_2$	B	32	99 (**3i**)	82
19	*t*Bu	A	6	97 (**3j**)	79
20	*t*Bu	B	17	99 (**3j**)	83

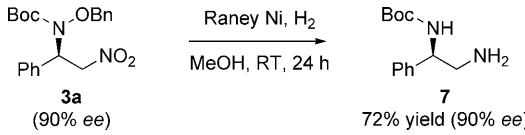
[a] Reaction conditions: nitroolefin (0.050 mmol) and *tert*-butyl benzyloxycarbamate (0.25 mmol) in the presence of catalyst (*S*)-**2c** (0.05 or 1 mol %) in H_2O (2.0 mL)/toluene (0.20 mL) at room temperature or 0 °C. [b] Conditions A: (*S*)-**2c** (0.05 mol %) at room temperature (25 °C); conditions B: (*S*)-**2c** (1 mol %) at 0 °C. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase.



loading (0.05 mol %; conditions A). The reactions of nitroolefins having various aromatic and heteroaromatic groups under the conditions A gave the corresponding amination products **3** in high enantioselectivities (90–92 % *ee*) with good to high yields (Table 2, entries 1–15 (odd-number entries)). The reactions with nitroolefins possessing alkyl group gave the products in good enantioselectivities (77–79 % *ee*) with high yields (Table 2, entries 17 and 19). The reactions at lower temperature (0 °C) with 1 mol % of catalyst (*S*)-**2c** (conditions B) slightly improved the enantioselectivities and gave the amination products **3** in 91–95 % *ee* for nitroolefins with aromatic and heteroaromatic groups, and 82–83 % *ee* for nitroolefins with alkyl group (Table 2, entries 1–15 (even-numbered entries)). Notably, substrates containing unstable functional groups under basic and acidic conditions, such as siloxy groups,[14] are tolerated in the present neutral phase-transfer conditions (Table 2, entries 9 and 10). Furthermore, the amination was examined in the presence of other compounds containing base- and/or acid-sensitive functional groups, such as **4**–**6**, and we found that the asymmetric amination was performed without any decomposition (e.g. retro-aldol reaction, dehydration) and loss of stereochemical information in the presence of compounds **4**–**6** under the

neutral phase-transfer conditions. These results support the fact that complex substrates containing base- and/or acid-sensitive functional groups can be applied to this neutral phase-transfer reaction system.

The resulting amination products **3** can be readily transformed into the corresponding 1,2-diamines, which are versatile chiral building blocks from synthetic as well as pharmaceutical viewpoints.[4] For example, exposure of a mixture of **3a** in MeOH to a hydrogen atmosphere in the presence of Raney Nickel at room temperature for 24 hours resulted in the formation of *N*-Boc-protected 1,2-diamine **7**[15] in 72% yield with complete preservation of the enantiopurity (Scheme 3).



3a (90% *ee*) → **7** 72% yield (90% *ee*)

Scheme 3. Transformation of the amination product into 1,2-diamine.

To obtain insights into a transition-state structure for the present asymmetric amination, we carried out X-ray crystal structure analysis of ammonium amides prepared from chiral bifunctional ammonium salts of type **2**. Several kinds of ammonium amides were prepared to obtain crystals suitable for X-ray diffraction analysis, and finally we succeeded to obtain a single-crystal X-ray structure of (*S*)-**2d** (Figure 1).[16] The crystal structure of (*S*)-**2d** provides important structural information. The bond lengths of amide moiety (O1-C1: 1.304 Å, N1-C1: 1.309 Å) indicate that the negative charge of the amide anion is delocalized as shown in Figure 1. Importantly, the hydrogen-bonding interaction between the hydroxy group in the binaphthyl unit and the oxygen atom of amide anion (O1) is clearly observed in the crystal structure of (*S*)-**2d**.

Based on the X-ray structure of (*S*)-**2d**, plausible transition-state models have been proposed to account for the observed absolute configuration of amination products **3** (Figure 1). In the generation of a chiral ammonium amide derived from *tert*-butyl benzyloxycarbamate and the catalyst (*S*)-**2c** under neutral conditions, the amide anion would be stabilized by both the ionic interaction of the ammonium amide and the hydrogen bond between the hydroxy group in catalyst (*S*)-**2c** and the oxygen atom of the amide moiety (**A** in Figure 1). Then, nitrostyrene might approach from the upper side, thereby avoiding the steric repulsion between *tert*-butoxycarbonyl group of amide and phenyl group of nitrostyrene (**B** ≫ **C** in Figure 1), to account for the observed absolute configuration in **3a**.[17] This explanation on the steric effect of the *tert*-butoxycarbonyl group for obtaining the high enantioselectivity was supported by the result of the reaction using less-hindered methyl benzyloxycarbamate, which gave low enantioselectivity (Table 1, entry 13).

In summary, we have successfully developed a highly efficient catalytic asymmetric amination of nitroolefins under neutral phase-transfer conditions under the influence of a chiral bifunctional tetraalkylammonium bromide in water-rich biphasic solvent. The advantage of the base-free, neutral phase-transfer reaction system for asymmetric amination was clearly demonstrated in comparison with the reaction under ordinary phase-transfer conditions using aqueous base solution. Furthermore, the role of hydroxy groups in the bifunctional catalyst was clearly shown in the transition-state model of the reaction based on the single-crystal X-ray structure of an ammonium amide. Further application to other asymmetric reactions and the mechanistic study of the neutral phase-transfer reaction system using a chiral bifunctional ammonium salt are currently underway.

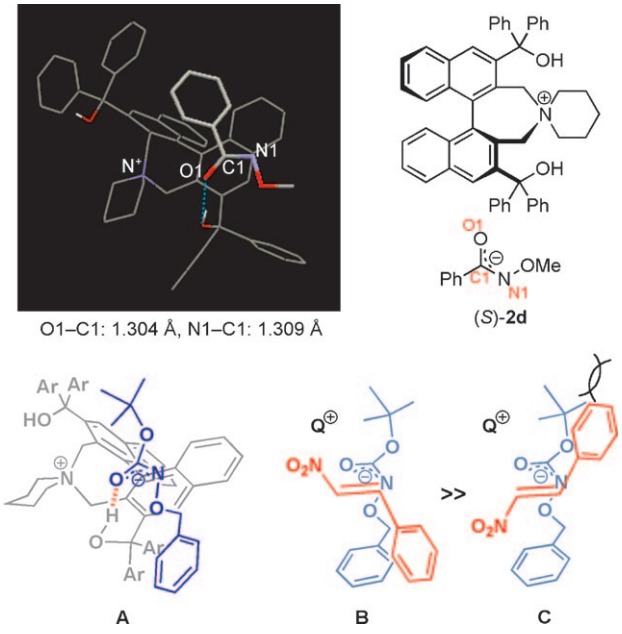


Figure 1. X-ray crystal structure of (*S*)-**2d** and plausible transition-state models.

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