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Enantioselective amination of nitroolefins under base-free and water-rich conditions by chiral bifunctional phase-transfer catalysts

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The direct enantioselective amination of nitroolefins has been performed with L-tert-leucine-derived squaramide-scaffold bifunctional phase-transfer catalysts under base-free and water-rich conditions with low catalyst-loading (0.5~1 mol%) to provide 2-aminonitroalkanes in good yields (up to 96%) and enantioselectivities (up to 93% *ee*).

Introduction

The Chiral phase-transfer catalysis (CPTC) plays an important role in modern organic synthesis both in academies and industries for providing numerous chiral intermediates and building blocks[1]. However, most of phase-transfer catalytic reactions such as alkylation and Michael addition were usually performed under basic conditions, some substrates and chiral phase-transfer catalysts such as ammonium and phosphonium salts are unstable in the presence of these basic additives[2]. In order to overcome this problem, neutral phase-transfer catalytic reactions have been discovered by chemists, but this type of reactions is less investigated except Maruoka and colleagues' research works[3].

On one hand, the synthesis and application of bifunctional chiral phase-transfer catalysts with various privileged skeletons including Cinchona alkaloids, binols, 1,2-diaminocyclohexane and amino acids are booming in recent years (Figure 1)[4, 5]. Commonly, this type of catalysts not only possess quaternary onium salt centre but also hydrogen-bonding functional group such as free OH, (thio)urea and squaramide, which are used in asymmetric Henry reaction, epoxidation, Michael addition, alkylation, Mannich reaction and so on to achieve good enantioselectivities. On the other hand, the organocatalyzed amination of active carbonyl compounds at α-position with azodicarboxylates has provided an efficient strategy for C-N bond formation[6, 7], and the direct

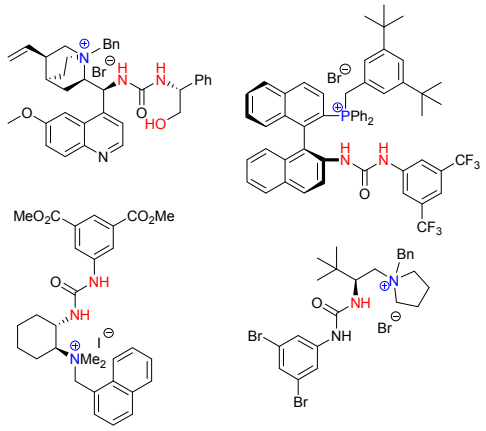

Figure 1. The representative chiral bifunctional phase-transfer catalysts developed in recent literatures.

neutral amination of nitroolefins in water-rich solvents has also been found to afford 2-aminonitroalkanes in high yields and enantioselectivities with chiral binaphthyl-based bifunctional tetraalkylammonium salts (Scheme 1a, **CPTC-1**) under phase-transfer conditions[8]. Although the latter is regarded as a powerful and environmental benign C-N formation reaction, it is rarely investigated except this above-mentioned example, and the catalysts used in this reported amination were synthesized over 10 steps with a low overall yield[9]. Herein we have prepared a plenty of chiral bifunctional phase-transfer catalysts in good yields from commercially available materials in simple synthetic routes through 3~5 steps with easily handling reagents, and the direct enantioselective aminations of nitroolefins have been performed by using these chiral bifunctional phase-transfer catalysts under base-free and water-rich conditions with only 0.5-1.0 mol% of catalyst-loading to generate 2-aminonitroalkanes in good to excellent yields and enantioselectivities (Scheme 1b, **OC-11**).

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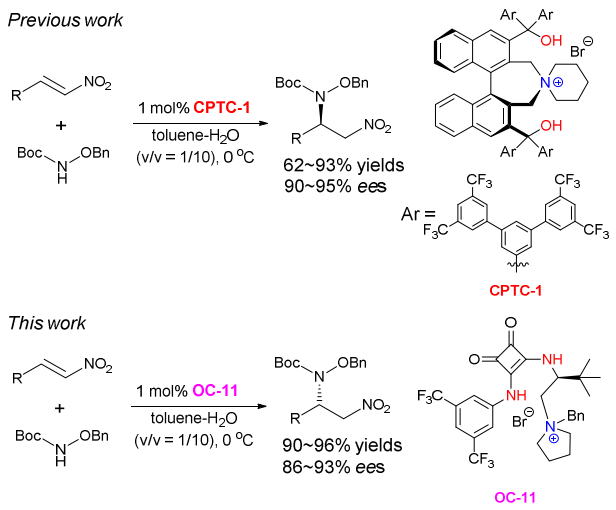

Scheme 1. Enantioselective amination by chiral bifunctional phase-transfer catalysts.

Results and discussion

As illustrated in Figure 2, twelve chiral phase-transfer catalysts (**OC-1** to **OC-12)** are synthesized from commercially available reagents such as L-tartaric acid, cinchonine, ugi's amine, (*R*)-3-amino-1-benzylpyrrolidine, L-valine and L-tert-leucine in good yields (see the Supplementary Information for details), respectively. All synthetic catalysts are screened in model reaction of BocNHOBn **1** and *trans*-β-nitrostryene **2a** under neutral water-rich conditions, and the results are listed in Table 1. The racemic product **3a** was obtained in moderate yield (45%) by using catalyst **OC-1** from L-tartaric acid. **OC-2** was prepared by masking two hydroxyl groups in **OC-1** with MsCl, and only trace amination product was detected from TLC under the same base-free conditions with **OC-2** as catalyst. These results clearly indicate that free hydroxyl groups of catalyst **OC-1** is essential for obtaining good yield in this reaction (Table 1, entry 1 *vs* entry 2). When cinchonine-derived **OC-3** was used as phase-transfer catalyst, **3a** was obtained in moderate yield (56%) and low enantiselectivity (Table 1, entry 3). In our previous reports[10], a series of ferrocene-based organocatalysts have been prepared for enantioselective Michael reaction and Morita–Baylis–Hillman reaction to afford good performance, these researches demonstrate that ferrocene could be an excellent scaffold for construction of chiral organocatalysts. With the continuation of our works, the ferrocene-based chiral bifunctional quaternary phosphonium salts **OC-4** and **OC-5** are synthesized and tested in this direct amination, respectively. Unexpectedly, these two phase-transfer catalysts have shown low efficiency in this amination to produce **3a** with moderate yields and low enantiselectivities. Interestingly, **OC-5** with a thiourea group generated **3a** in an opposite configuration which compared to **OC-4** with a urea group (Table 1, entries 4 and 5) in this reaction. Kowalczyk[11] and Oriyama[12] have reported asymmetric Michael reaction of thiols to electro-deficiency alkenes by using chiral (thio)urea and squaramide organoccatalysts derived from commercially available (*S*)- or (*R*)-3-amino-1-benzylpyrrolidine. We have prepared four chiral bifunctional quaternary ammonium salts **OC-6** to **OC-9** based (*R*)-3-amino-1-benzylpyrrolidine and these phase-transfer catalysts are also applied in the water-rich amination reaction of **1** and **2a**. **OC-6** containing a urea motif with *p*-trifluoromethyl group at phenyl ring afforded **3a** in moderate yield but low *ee* value (Table 1, entry 6). By replacing *p*-trifluoromethylphenyl with 3,5-bistrifluoromethylphenyl in **OC-6** to furnish **OC-7**, and **OC-7** results in no significant increase of enantioselectivity but with higher yield of **3a** than **OC-6** under the same conditions (Table 1, entry 7 *vs* entry 6). **OC-8** with a thiourea group as a catalyst has provided **3a** in good yield and moderate *ee* value (Table 1, entry8). When squaramide-containing catalyst **OC-9** has been used in the amination reaction of **2a**, an expected increase

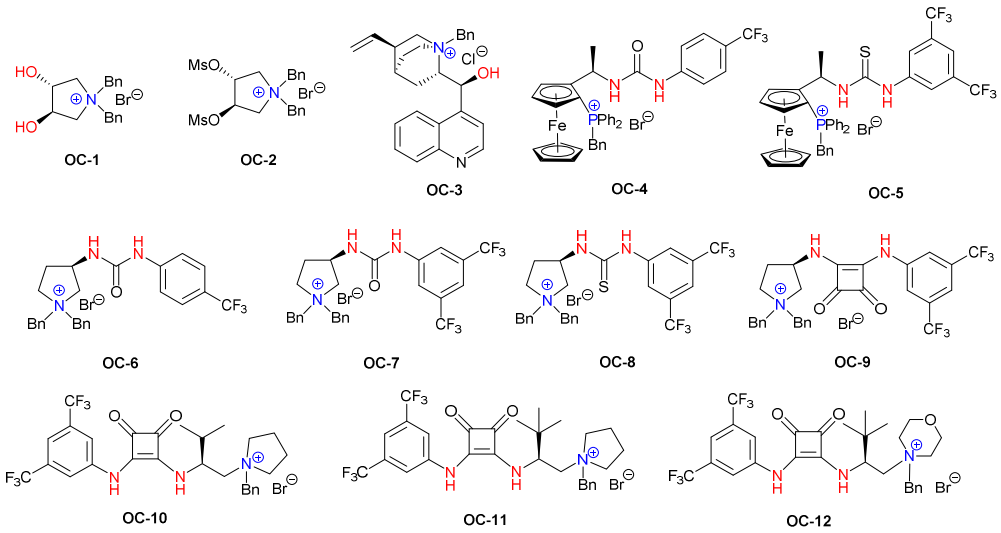

Figure 2. Chiral bifunctional phase-transfer catalysts.

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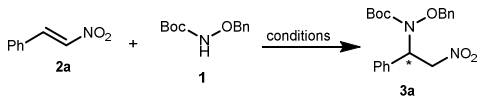
Table 1. The screening of catalysts.



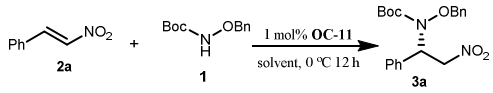
Entry[a]	NH(eq.)[b]	Cat.	*T*[c]	Yield[d][%]	*ee*[e][%]
1	5.0	**OC-1**	r.t.	45	*rac*-
2	5.0	**OC-2**	r.t.	trace	-
3	5.0	**OC-3**	r.t.	56	-21(*R*)
4	3.0	**OC-4**	r.t.	53	19(*S*)
5	3.0	**OC-5**	r.t.	50	-21(*R*)
6	3.0	**OC-6**	r.t.	62	31(*S*)
7	3.0	**OC-7**	r.t.	70	30(*S*)
8	3.0	**OC-8**	r.t.	78	40(*S*)
9	3.0	**OC-9**	r.t.	90	45(*S*)
10	3.0	**OC-10**	r.t.	93	60(*S*)
11	3.0	**OC-10**	0°C	90	67(*S*)
12	3.0	**OC-11**	r.t.	96	84(*S*)
13	**3.0**	**OC-11**	**0°C**	**91**	**87(*S*)**
14	5.0	**OC-11**	0°C	92	87(*S*)
15	1.5	**OC-11**	0°C	85	88(*S*)
16	3.0	**OC-12**	r.t.	96	83(*S*)
17	**3.0**	**OC-12**	**0°C**	**92**	**89(*S*)**

[a]Reaction was performed using 1 mol% of catalysts in a 0.1 mmol scale in the 2.2 mL mixed solvent of toluene/H_2O = 1/10 (v/v); [b]NH = BocNHOBn; [c]Reaction time: 8 h for r.t. and 12 h for 0°C; [d]Isolated yield based on **2a**; [e]Determined by HPLC on a chiral stationary phase and the absolute configuration of **3a** was assigned according to ref. 8.

in yield and enantioselectivity of product **3a** is observed, and this reveals that quaternary ammonium salts with a squaramide motif are beneficial to this water-rich amination both in yield and enantioselectivity (Table 1, entry 9 *vs* entry 8). Jiang and coworkers[13] have developed a category of (thio)urea- and squaramide-tertiary amine organocatalysts for asymmetric conjugated additions in high efficiency, and they have also prepared L-tert-leucine-derived urea-ammonium salts as chiral phase-transfer catalysts for enantioselective alkylation of 5*H*-oxazol-4-ones. Inspired by Jiang's work, three squaramide-containing catalysts **OC-10**, **OC-11** and **OC-12** have been prepared from L-valine or L-tert-leucine with pyrrolidine or morpholine in five steps, respectively. To our delight, **OC-10** derived from L-valine and pyrrolidine has shown good catalytic performance to give **3a** in high yield and acceptable enantioselectivity at 0 °C (Table 1, entries 10 and 11 *vs* entry 9, 67% *ee* vs 45% *ee*). Instead of L-valine in **OC-10**, L-tert-leucine is introduced to generate **OC-11**, the yield and enantioselectivity of **3a** are enhanced remarkably (Table 1, entry 12 *vs* entry 11). When the reaction was performed at 0 °C, the ee value of **3a** was promoted slightly from 84% to 87% with a little decrease of yield and an acceptable prolongation of reaction time (Table 1, entry 13 *vs* entry 12). Increasing the amount of amination reagent from 3.0 eq. to 5.0 eq., no significant improvement of enantioselectivity of **3a** was observed (Table 1, entry14 *vs* entry 13). The decrease of the amount of amination reagent from 5.0 eq. to 1.5 eq. resulted in somewhat lower yield of **3a** but with a very little enhancement of *ee* value (Table 1, entry 15 *vs* entry 14). Besides pyrrolidine, morpholine was also embedded in the structure of catalyst to furnish **OC-12**, which demonstrated a similar catalytic ability with **OC-11** in this direct amination reaction at room temperature. A slight increase of enantioselectivity was found when the reaction was performed at 0 °C to give **3a** in 89% *ee* (Table 1, entries 16 and 17 *vs* entry 15). Based on the results of screening of catalysts, **OC-11** and **OC-12** have shown very similar catalytic and enantioselective abilities in this water-rich amination.

Next, we have performed the model reaction of 2a and 1 in various solvent systems (Table 2). The hydrophobic organic sol-

Table 2. The screening of solvents and additives.



Entry[a]	solv.	Yield[h][%]	*ee*[i][%]
1	CH_2Cl_2/H_2O (v/v = 1/10)	85	89
2	$CHCl_3/H_2O$ (v/v = 1/10)	89	85
3	Et_2O/H_2O (v/v = 1/10)	90	83
4	EtOAc/H_2O(v/v = 1/10)	89	84
5	CH_3CN/H_2O(v/v = 1/10)	68	81
6	EtOH/H_2O(v/v = 1/10)	62	77
7	THF/H_2O(v/v = 1/10)	56	82
8	toluene	87	88
9[b]	toluene/H_2O(v/v = 1/10)	92	76
10[c]	toluene/H_2O(v/v = 1/10)	95	*rac*-
11[d]	H_2O	n.r.[e]	-
12[f]	brine	n.r.	-
13[g]	toluene/H_2O(v/v = 1/10)	90	89

[a]Reaction was performed using 1 mol% of **OC-11** in a 0.1 mmol scale in the various solvents; [b]1 mol% solid K_2CO_3 as an additive; [c]1 mol% solid KOH as an additive; [d]The reaction was performed in 2.2 mL of water; [e]n.r. means no reaction under these conditions. [f]The reaction was performed in 2.2 mL of brine; [g]1 mol% solid KI as an additive; [h]Isolated yield based on **2a**; [i]Determined by HPLC on a chiral stationary phase and the absolute configuration of **3a** was assigned according to ref. 8.

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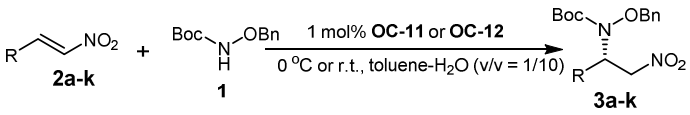
vent systems (Table 2). The hydrophobic organic solvents such as dichloromethane (DCM), chloroform, ether, and ethyl acetate provide good results both in yields and enantioselectivites of amination product **3a** (Table 2, entries 1~4). However, when hydrophilic organic solvents like ethanol, acetonitrile or THF was used as a component of reaction solvent system, both yields and enantioselectivities of **3a** are found to be obviously decreased (Table 2, entries 5~7). The high yield and enantioselectivity of **3a** were obtained with toluene as sole solvent (Table 2, entry 8). When 1 mol% solid K_2CO_3 was used as an additive under standard reaction conditions, **3a** was obtained in high yield but with a moderate *ee* value (Table 2, entry 9), and instead of K_2CO_3 with solid KOH, the racemic product of **3a** was obtained (Table 2, entry 10). Unfortunately, the reaction was performed in water or brine to result in no reaction (Table 2, entries 11 and 12) due to the insolubilities of substrates and catalysts in water. Interestingly, the amination product **3a** was furnished both in high yield and enantioselectivity by using 1 mol% solid KI as an additive (Table 2, entries 13). The reaction is not sensitive to the change of reaction temperature from 0 °C to room temperature. Therefore, the optimum reaction conditions were established as follows: 1 mol% **OC-11** or **OC-12**, 0.1 mmol trans-β-nitrostyrene, 0.3 mmol BocNHOBn, 2.2 mL mixed solvent of toluene/H_2O = 1/10 (v/v).

With the optimal reaction conditions in hand, various trans-β-nitrostryenes (**2b-m**) were used as substrates for water-rich enantioselective amination reactions. Because of the comparative catalytic abilities of **OC-11** and **OC-12**, both of them were applied as chiral bifunctional phase-transfer

Table 3. Substrates scope of the direct enantioselective amination.



Ent.[a]	R	Cat.	*T*.	Time	Yield[b][%]	*ee*[c][%]	Ent.[a]	R	Cat.	*T*.	Time	Yield[b][%]	*ee*[c][%]
1	**2a**, Ph	**OC-11**	0 °C	8 h	**3a**, 91	87	24	**2f**, 3-$CF_3C_6H_4$	**OC-12**	r.t.	8 h	**3f**, 85	85
2	**2a**, Ph	**OC-11**	r.t.	4 h	**3a**, 96	84	25	**2g**, 4-MeC_6H_4	**OC-11**	0 °C	8 h	**3g**, 90	92
3	**2a**, Ph	**OC-12**	0 °C	8 h	**3a**, 92	89	26	**2g**, 4-MeC_6H_4	**OC-11**	r.t.	8 h	**3g**, 91	87
4	**2a**, Ph	**OC-12**	r.t.	4 h	**3a**, 96	83	27	**2g**, 4-MeC_6H_4	**OC-12**	0 °C	8 h	**3g**, 91	90
5	**2b**, 4-FC_6H_4	**OC-11**	0 °C	4 h	**3b**, 94	86	28	**2g**, 4-MeC_6H_4	**OC-12**	r.t.	8 h	**3g**, 90	82
6	**2b**, 4-FC_6H_4	**OC-11**	r.t.	4 h	**3b**, 95	85	29	**2h**, 4-$OMeC_6H_4$	**OC-11**	0 °C	8 h	**3h**, -[d]	89
7	**2b**, 4-FC_6H_4	**OC-12**	0 °C	4 h	**3b**, 92	86	30	**2h**, 4-$OMeC_6H_4$	**OC-11**	r.t.	8 h	**3h**, -[d]	75
8	**2b**, 4-FC_6H_4	**OC-12**	r.t.	4 h	**3b**, 96	84	31	**2h**, 4-$OMeC_6H_4$	**OC-12**	0 °C	8 h	**3h**, -[d]	91
9	**2c**, 4-ClC_6H_4	**OC-11**	0 °C	4 h	**3c**, 92	91	32	**2h**, 4-$OMeC_6H_4$	**OC-12**	r.t.	8 h	**3h**, -[d]	80
10	**2c**, 4-ClC_6H_4	**OC-11**	r.t.	4 h	**3c**, 96	85	33	**2i**, 2-furyl	**OC-11**	0 °C	8 h	**3i**, 93	91
11	**2c**, 4-ClC_6H_4	**OC-12**	0 °C	4 h	**3c**, 92	89	34	**2i**, 2-furyl	**OC-11**	r.t.	8 h	**3i**, 92	82
12	**2c**, 4-ClC_6H_4	**OC-12**	r.t.	4 h	**3c**, 95	84	**35**	**2i**, 2-furyl	**OC-12**	0 °C	8 h	**3i**, 93	**93**
13	**2d**, 4-BrC_6H_4	**OC-11**	0 °C	4 h	**3d**, 93	90	36	**2i**, 2-furyl	**OC-12**	r.t.	8 h	**3i**, 95	74
14	**2d**, 4-BrC_6H_4	**OC-11**	r.t.	4 h	**3d**, 96	88	37	**2j**, piperonyl	**OC-11**	0 °C	8 h	**3j**, -[d]	89
15	**2d**, 4-BrC_6H_4	**OC-12**	0 °C	4 h	**3d**, 96	88	38	**2j**, piperonyl	**OC-11**	r.t.	8 h	**3j**, -[d]	84
16	**2d**, 4-BrC_6H_4	**OC-12**	r.t.	4 h	**3d**, 96	85	39	**2j**, piperonyl	**OC-12**	0 °C	8 h	**3j**, -[d]	89
17	**2e**, 3-ClC_6H_4	**OC-11**	0 °C	12 h	**3e**, 82	89	40	**2j**, piperonyl	**OC-12**	r.t.	8 h	**3j**, -[d]	82
18	**2e**, 3-ClC_6H_4	**OC-11**	r.t.	8 h	**3e**, 90	86	**41**	**2k**, ^{i}Pr	**OC-11**	0 °C	8 h	**3k**, 92	**93**
19	**2e**, 3-ClC_6H_4	**OC-12**	0 °C	12 h	**3e**, 81	87	42	**2k**, ^{i}Pr	**OC-11**	r.t.	8h	**3k**, 95	92
20	**2e**, 3-ClC_6H_4	**OC-12**	r.t.	8 h	**3e**, 91	82	43	**2k**, ^{i}Pr	**OC-12**	0 °C	8h	**3k**, 92	92
21	**2f**, 3-$CF_3C_6H_4$	**OC-11**	0 °C	12 h	**3f**, 82	91	44	**2k**, ^{i}Pr	**OC-12**	r.t.	8h	**3k**, 93	90
22	**2f**, 3-$CF_3C_6H_4$	**OC-11**	r.t.	8 h	**3f**, 86	88	45	**2l**, 2,4-$Cl_2C_6H_3$	**OC-11**	0 °C	36 h	n.r.[e]	-
23	**2f**, 3-$CF_3C_6H_4$	**OC-12**	0 °C	12 h	**3f**, 84	87	46	**2l**, 2,4-$Cl_2C_6H_3$	**OC-12**	r.t.	36 h	n.r.	-

[a]Reaction was performed in a 0.1 mmol scale with 3.0 eq. of BocNHOBn; [b]Isolated yields based on **2a-k**; [c]Determined by HPLC on a chiral stationary phase and the absolute configurations of **3a-k** were assigned according to ref. 8; [d]The pure products **3h** and **3j** couldn't be separated through a flash column chromatography, but all TLC results indicated full conversion of various substrates in amination processes; [e]n.r. means no reaction under the optimal conditions.

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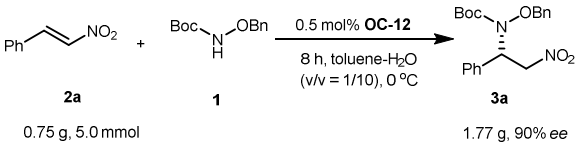
catalysts in the reactions. The corresponding amination products were obtained both in excellent yields and enantioselectivities in most cases and the results are summarized in Table 3. Substrates with an electron-withdrawing group at para-position of phenyl ring (**2b**, **2c** and **2d**) furnished the corresponding products (**3b**, **3c** and **3d**) in excellent yields and ee values within 4 hours except substrate **2m** with a *para*-nitro group at phenyl ring. Substrates with an electron-donating group at para-position of phenyl ring (**2g** and **2h**) were fully converted to be the corresponding amination products (**3g** and **3h**) in high enantioselectivities within 8 hours (Table 2, entries 25~32). However, the pure **3h** couldn't be separated from a flash column chromatography even though TLC results indicated full conversion of substrate **2h** in amination processes. The product **3h** and amination reagent BocNHOBn were eluted at the same time in 1/1 ratio which can be found in ^{1}NMR spectrum. Substrates with an electron-withdrawing group at meta-position of phenyl ring (**2e** and **2f**) need longer reaction time than the other substrates to give the amination products **3e** and **3f** in good yields and enantioselectivities (Table 3, entries 17~24). 2-Furyl and piperonyl trans-β-nitrostryenes **2i** and **2j** are also suitable to this water-rich neutral amination reaction to generate the corresponding products **3i** and **3j** in excellent *ee* values (Table 3, entries 33~40). Although TLC results showed full conversion of **2j**, the pure amination product **3j** was not obtained from a flash column chromatography with various ratios of petroleum and EtOAc as eluent systems. Alkyl substituted substrate (*E*)-3-methyl-1-nitrobut-1-ene **2k** was underwent amination smoothly to afford **3k** in excellent yield and enantioselectivity (Table 3, entries 41~44). Unfortunately, substrate **2l** couldn't provide the corresponding product even with the prolongation of reaction time up to 36 hours (Table 3, entries 45 and 46) under the same conditions, and it is probably due to the repulsive effect between bulky Boc group in amination reagent **1** and ortho-Cl at phenyl ring of substrate **2l**.

We proposed that dual activation of both nitroolefin **2a** and BocNHOBn by **OC-12** is responsible for the highly efficient chiral induction in this amination process. The substrate **2a** was activated by the hydrogen-bonding interactions between the two NH in squaramide catalyst **OC-12** and the nitro-group in substrate **2a**, while BocNHOBn was activated through the static electronic interaction of the cationic ammonium center in **OC-12** to attack from the *Si*-face to produce **3a** in high yield and enantioselectivity (Figure 3). When hydrophilic organic solvents like ethanol, acetonitrile or THF was used as a component of reaction solvent system, the yields and enantioselectivities of **3a** are found to be significantly decreased (Table 2, entries 5~7), because the hydrogen-bonding interactions between **OC-12** and **2a** of the biphasic interface were deteriorated by these hydrophilic solvent systems.

In order to demonstrate the practicability of this above enantioselective amination protocol, 5.0 mmol of **2a** has been used in the reaction under optimal conditions with only 0.5 mol% catalyst-loading to deliver the corresponding product **3a** in 95% yield and 90% *ee* (Scheme 2).



Scheme 2. Gram-scale preparation of **3a**.

Experimentals

General procedure for the neutral asymmetric amination of *trans*-β-nitrostyrenes

Catalysts **OC-11** or **OC-12** (0.65 mg for **OC-11** or 0.67 mg for **OC-12**, 1 mol%), *trans*-β-nitrostyrenes **2** (0.1 mmol) and BocNHOBn **1** (67 mg, 0.3 mmol) were added to a 10-mL vial equipped with a stirring bar, the mixed solvent of toluene (0.2 mL) and H_2O (2.0 mL) was added subsequently. The mixture was stirred at 0 °C or room temperature for the indicated time which illustrated in Table 2 and then the mixture was extracted by EtOAc (3×5.0 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield a light yellow glue which was purified by flash column chromatography on silica gel, eluting with mixtures of petroether/EtOAc (50/1 to 20/1, v/v). The *ee* of pure product was determined by HPLC using a chiral column (Daicel Chiralpak AS-H, see details in the supplementary information).

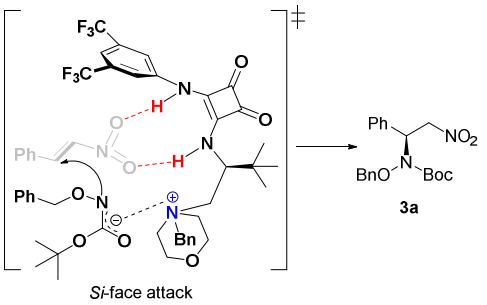


Figure 3. The proposed transition state model of this amination.

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Conclusions

In conclusion, we have prepared a series of chiral bifunctional phase-transfer catalysts based various skeletons and their performances in asymmetric neutral amination of *trans*-β-nitrostyrenes under water-rich conditions are investigated to produce 2-aminonitroalkanes in high yields and enantioselectivities. Applications of these chiral bifunctional phase-transfer catalysts in other neutral C-C or C-X bond formation processes are currently under studied and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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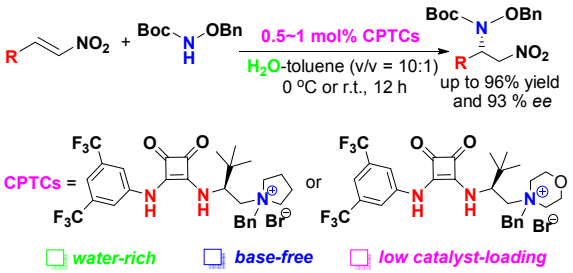

The direct enantioselective amination of nitroolefins has been performed with L-tert-leucine derived squaramide-scaffold bifunctional phase-transfer catalysts under base-free and water-rich conditions to provide 2-aminonitroalkanes in excellent yields and enantioselectivities.