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Chiral Brønsted acid catalyzed enantioselective intermolecular allylic aminations†

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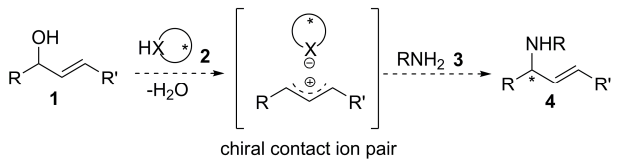
This paper describes an enantioselective intermolecular allylic amination catalyzed by a chiral Brønsted acid via a possible chiral contact ion pair intermediate. A variety of symmetrical or unsymmetrical allylic alcohols can be smoothly aminated to afford the desired products in moderate to high yields with good enantioselectivities and/or regioselectivities.

The substitution reaction of allylic alcohols and their derivatives with diverse nucleophiles and its asymmetric versions have become an extremely useful tool for the construction of carbon-carbon and carbon-heteroatom bonds. This field has long been dominated by the transition-metal catalysis.[1] Allylic alcohol derivatives, such as allylic carboxylates, carbonates, and phosphates, are often used as substrates for this transformation.[1] However, the direct use of allylic alcohols as substrates with the hydroxyl group as the leaving group and water as the only side product has been less developed owing to the poor leaving ability of the hydroxyl group and the poor tolerance of metal catalysts for water.[2] Accordingly, various strategies through the in situ activation of the hydroxyl group and/or the development of efficient catalysts have been adopted to improve the reactivity.[3,4] In contrast to the intensive studies on the metal catalysis, metal-free allylic substitution, especially for the asymmetric transformation, has less been investigated.[5,6]

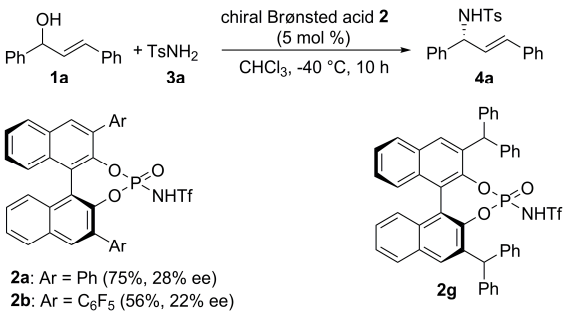
The Brønsted acid catalysis provides a powerful approach for the metal-free direct substitution of allylic alcohols.[7] A variety of reactions with carbon, oxygen, and nitrogen nucleophiles have been successfully described using either stoichiometric or catalytic amount of Brønsted acids as catalysts.[6] However, chiral Brønsted acid catalyzed asymmetric versions of this reaction have rare been reported. In 2011, Rueping and co-workers reported the first highly enantioselective Brønsted acid catalyzed intramolecular allylic substitution based on the concept of chiral ion-pair catalysis with the assumption of forming a chiral contact ion pair between the carbocation and chiral Brønsted acid anion.[8,9] In 2014, Gong and co-workers described the first chiral Brønsted acid catalyzed intermolecular allylic alkylation of allylic alcohols with 1,3-dicarbonyls.[10] Despite these important advances, the asymmetric substitution of allylic alcohol catalyzed by chiral Brønsted acids is still not well solved.

Recently, our group reported a chiral phosphoramide catalyzed asymmetric 1,2-rearrangement of racemic epoxides for the synthesis of enantioenriched aldehydes, in which the contact ion pair of carbocation and chiral phosphoramide anion is likely involved.[11] Since the direct intermolecular amination of allylic alcohols catalyzed by simple achiral Brønsted acids has already been reported,[6e] we wish to examine the chiral Brønsted acid **2** catalyzed asymmetric allylic amination of alcohols **1** with amine **3** via a proposed chiral contact ion pair intermediate (Scheme 1). Herein, we report our preliminary results on this subject.



Scheme 1 Strategy for asymmetric allylic aminations

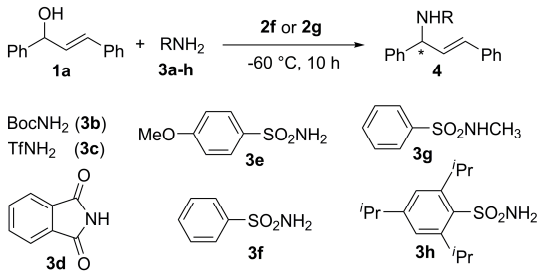
Initially, we selected the allylic amination of allylic alcohol **1a** with *p*-toluenesulfonamide (**3a**) as the model reaction to test the feasibility of chiral Brønsted acid catalysis (Scheme 2).We were pleased to find that the reaction using chiral phosphoramide **2a** as a catalyst went cleanly to give the desired product **4a** in 75% yield with 28% ee. Further searching for more effective catalysts were conducted, and some selected results are summarized in Scheme 2. Phosphoramide **2b** with strong electron-withdrawing groups can not improve the enantioselectivity. Using **2c** and **2f** containing 1-naphthyl or 9-phenanthrenyl at the 3,3'-positions gave higher ee's. The bulky phosphoramide **2e** led a low yield and ee, in which a side reaction with alcohol **1a** itself as a nucleophile was involved. Interestingly, a novel chiral phosphoramide **2g** proved to be effective for this transformation to give amine **4a** in 81% yield with 65% ee (Scheme 2).



Scheme 2 Selected Brønsted acids for asymmetric aminations[12]

The reaction conditions using phosphoramide **2f** and **2g** as catalysts were examined to further improve the enantioselectivity. Lowering the temperature to -60 ℃ led a little higher ee's (Table 1, entries 1 and 2). Increasing the catalyst loading to 10 mol %, up to 75% ee was obtained (Table 1, entry 4). Solvents were found to influence this reaction significantly, and $CHCl_3$ gave the optimal results (Table 1, entries 4-8). Various amine nucleophiles were screened for this reaction. $BocNH_2$ (**3b**), $TfNH_2$ (**3c**), and phthalimide (**3d**) only gave trace amount of products (Table 1, entries 9-11). In comparison with *p*-toluenesulfonamide (**3a**), similar results were obtained with the use of amines **3e** and **3f** as nucleophiles (Table 1, entries 4 vs 12 and 13). However, using amine **3g** bearing one methyl group on the nitrogen atom furnished a racemic product in 93% yield. When a bulky amine **3h** was employed as a nucleophile, the desired product was obtained in 82% yield with 84% ee (Table 1, entry 15).

Table 1 Optimization of Reaction Conditions [a]

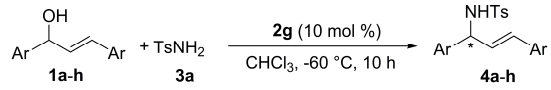


Entry	BA (loading)	Amine	Solvent	Yield (%)[b]	Ee (%)[c]
1	**2f** (5 mol %)	**3a**	$CHCl_3$	68	68
2	**2g** (5 mol %)	**3a**	$CHCl_3$	79	69
3	**2f** (10 mol %)	**3a**	$CHCl_3$	75	71
4	**2g** (10 mol %)	**3a**	$CHCl_3$	88	75
5	**2g** (10 mol %)	**3a**	CH_2Cl_2	83	51
6[d]	**2g** (10 mol %)	**3a**	toluene	38	45
7	**2g** (10 mol %)	**3a**	THF	trace	nd[e]
8	**2g** (10 mol %)	**3a**	hexane	50	20
9	**2g** (10 mol %)	**3b**	$CHCl_3$	trace	nd[e]
10	**2g** (10 mol %)	**3c**	$CHCl_3$	trace	nd[e]
11	**2g** (10 mol %)	**3d**	$CHCl_3$	trace	nd[e]
12	**2g** (10 mol %)	**3e**	$CHCl_3$	72	72
13	**2g** (10 mol %)	**3f**	$CHCl_3$	78	72
14	**2g**(10 mol %)	**3g**	$CHCl_3$	93	2
15	**2g** (10 mol %)	**3h**	$CHCl_3$	82	84

[a] All reactions were carried out with allylic alcohol **1a** (0.40 mmol), amine **3** (0.60 mmol), at -60 ℃ for 10 h unless other noted. [b] Isolated yield. [c] The ee was determined by chiral HPLC. [d] Toluene (2.0 mL) was used. [e] Not determined.

Encouraged by the results obtained with phosphoramide catalyst **2g**, asymmetric allylic amination of various symmetrical allylic alcohols with amine **3a** were subsequently examined. As shown in Table 2, a variety of alcohols **1a-h** can be directly aminated to give the desired products **4a-h** in 60-88% yields with 18-86% ee's. The substituents on the phenyl groups can influence both reactivity and enantioselectivity. Unfortunately, alcohols bearing electron-withdrawing substituents at the *meta* or *ortho* position of phenyl groups were not suitable substrates for this reaction.

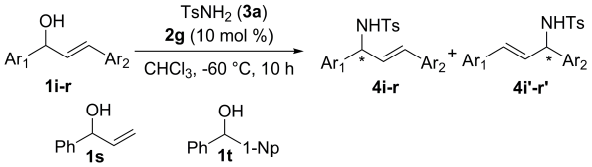
Table 2 Chiral Brønsted Acid Catalyzed Asymmetric Allylic Amination [a]



Entry	Product **4**	Yield (%)[b]	Ee (%)[c]
1	**4a**: Ar = Ph	88	75
2	**4b**: Ar = 4-FC_6H_4	82	70
3	**4c**: Ar = 4-ClC_6H_4	61	85
4	**4d**: Ar = 4-BrC_6H_4	60	86
5	**4e**: Ar = 4-MeC_6H_4	77	66
6	**4f**: Ar = 3-MeC_6H_4	80	62
7	**4g**: Ar = 2-MeC_6H_4	80	22
8	**4h**: Ar = 1-naphthyl	63	18

[a] All reactions were carried out with allylic alcohol **1a-h** (0.40 mmol), amine **3a** (0.60 mmol), and **2g** (0.04 mmol) in $CHCl_3$ (1.0 mL) at -60 ℃ for 10 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC.

Table 3 Chiral Brønsted Acid Catalyzed Asymmetric Allylic Amination [a]



Entry	Allylic alcohol **1**	Yield (%)[b]	Rr (**4**/**4'**)[c]	**4** (ee) (%)[d]	**4'** (ee) (%)[d]
1	**1i**: Ar_1 = 4-MeC_6H_4, Ar_2 = 4-ClC_6H_4	68	4.3/1	82	69
2	**1j**: Ar_1 = 4-MeC_6H_4, Ar_2 = 3-ClC_6H_4	70	8/1	66	nd[e]
3	**1k**: Ar_1 = 3-ClC_6H_4, Ar_2 = 4-MeC_6H_4	75	1/8	nd[e]	68
4	**1l**: Ar_1 = Ph, Ar_2 = 3-ClC_6H_4	56	3.5/1	67	58
5	**1m**: Ar_1 = 4-MeC_6H_4, Ar_2 = 3-BrC_6H_4	87	6.7/1	70	76
6	**1n**: Ar_1 = 4-MeC_6H_4, Ar_2 = 2-BrC_6H_4	87	3/1	13	94
7	**1o**: Ar_1 = 4-MeC_6H_4, Ar_2 = 2,6-$Cl_2C_6H_3$	16	>20/1	60	nd[e]
8	**1p**: Ar_1 = 4-FC_6H_4, Ar_2 = 3-ClC_6H_4	63	3/1	59	73
9	**1q**: Ar_1 = 3-MeC_6H_4, Ar_2 = 3-BrC_6H_4	64	6.9/1	76	53
10	**1r**: Ar_1 = 2-MeC_6H_4, Ar_2 = 3-BrC_6H_4	52	3.8/1	71	55

[a] All reactions were carried out with allylic alcohol **1i-r** (0.40 mmol), amine **3a** (0.60 mmol), and **2g** (0.04 mmol) in $CHCl_3$ (1.0 mL) at -60 ℃ for 10 h. [b] Isolated yield for two regioisomers. [c] The regioisomer ratio (rr) was determined by crude ^1H NMR. [d] The ee was determined by chiral HPLC. [e] Not determined.

Besides the enantioselectivity, the regioselectivity is also a challenge for the chiral Brønsted acid catalyzed allylic amination of unsymmetrical allylic alcohols. Hence, the reaction of various unsymmetrical allylic alcohols **1i-r** under the same conditions was then investigated. As shown in Table 3, all the reactions can proceed smoothly to give the corresponding products in 16-87%

yields with 3/1->20/1 regioselectivity and 13-94% ee's.[13] It was found that the amination site was mainly determined by the electronic effect, and the reaction occurred at the carbon adjacent to the electron-rich aryl group owing to a carbocation intermediate involved in this process (Table 3, entries 1-7,9,10). Moreover, the steric hindrance of substituents on phenyl groups also had an obvious impact effect for this reaction. For example, alcohol **1o** containing a bulky group gave a low yield but with an excellent regioselectivity (Table 3, entry 7). However, phenylpropenol **1s** and diarylmethanol **1t** were not suitable substrates for the current catalytic system.

Conclusions

In summary, we have developed the first chiral Brønsted acid catalyzed asymmetric intermolecular allylic amination of allylic alcohols. Under the catalysis of phosphoramide **2g**, a variety of optically active allylic amines can be obtained in 16-88% yields with 13-94% ee's. In particular, for the challenging unsymmetrical allylic alcohols, moderate to high levels of regioselectivities were achieved. The electronic effect played a crucial role for the regioselectivity owing to a carbocation intermediate involved in this transformation. Further efforts on the exploring more efficient catalysts and expanding the substrate scope are underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: The characterization and data for the determination of enantiomeric excess of products along with the NMR spectra. See DOI: 10.1039/b000000x/

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