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Enantioselective radical addition reactions to imines using binaphthol-derived chiral *N*-triflyl phosphoramides

Sunggi Lee, Sunggak Kim *

Department of Chemistry, School of Molecular Science (BK 21), Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea

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ABSTRACT

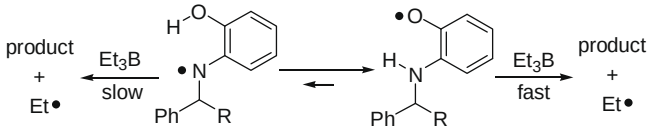
Binaphthol-derived chiral phosphoric acid catalysts were applied to enantioselective radical addition reactions of imines and provided chiral amines with good enantioselectivities (73–84% ee). Furthermore, the enantioselectivities were not affected by either electronic properties of phenyl imines or radical precursors.

Stereoselective radical addition reactions have been investigated with great attention because of unique characteristics of radical chemistry.[1] Most of enantioselective radical addition reactions were focused on conjugative additions to α,β-unsaturated carbonyl compounds. Despite synthetic usefulness of chiral amines, there were several examples to prepare optically active chiral amines by enantioselective radical addition reactions to imines.[2]

Recently, chiral Brønsted acid-mediated organic reactions have proved to be synthetically useful due to their broad applicability, high enantioselectivity, and environmentally friendly conditions.[3] Among several different types of Brønsted acid catalysts, binol-derived phosphoric acid[4] and *N*-triflyl phosphoramide catalysts[5] have been actively studied in various enantioselective reactions such as the Mannich reaction,[4] the Diels–Alder reaction,[5] alkylation of α-diazoetser,[6] aza-ene-type reaction,[7] the Friedel–Crafts alkylation,[8] carbonyl-ene reaction,[9] and hydrogenation.[10,11] Herein, we report our preliminary result on catalytic enantioselective radical addition reactions to imines using binol-derived chiral *N*-triflyl phosphoramide catalysts.

We began our study with 2-hydroxy imine **1** for radical addition reactions because the transition state of **1** was well defined as two-point binding mode.[12] When **1** was reacted with isopropyl iodide and *n*-tributyltin hydride using Et_3B initiator at room temperature for 1 h, the reaction proceeded smoothly and desired product **2** was obtained in 66% yield along with byproduct **3** (16%). The reaction worked well even at −78 °C, but the amount of **3** was increased to some extent due to a slow iodine atom transfer process at −78 °C (entry 2). When the reaction was carried out in the presence of diphenyl phosphate, the amount of **3** was increased up to 33%, indicating that the phosphoric acid could activate the imine substrate **1** through the hydrogen bond so that a less nucleophilic ethyl radical could add to **1** more readily. (entry 3). In the absence of *n*-tributyltin hydride, **3** was obtained as a major product, clearly showing that addition of an ethyl radical to **1** is faster than iodine atom transfer process (entry 4). Since intramolecular hydrogen atom transfer would generate a reactive phenoxy radical which would react faster with triethylborane to generate the ethyl radical, the formation of byproduct **3** might be unavoidable with **1** (Scheme 1).[13] When the reaction was carried out using phosphoramide catalyst **4a** in toluene at −78 °C, the reaction proceeded cleanly and was complete within 1 h (Scheme 2). However, the product **3** was obtained as a racemic mixture. A similar result was realized in dichloromethane. Apparently, the present result obtained here resulted from the fast background reaction of **1** in the absence of catalyst **4a** (Table 1).

Thus, we turned our attention to less reactive imine acceptors to exhibit the catalytic ability of chiral phosphoric acid derivatives



Scheme 1. Intramolecular hydrogen atom transfer from N to O.

* Corresponding author. Tel.: +82 42 350 2820; fax: +82 42 350 2810.
E-mail address: skim@kaist.ac.kr (S. Kim).

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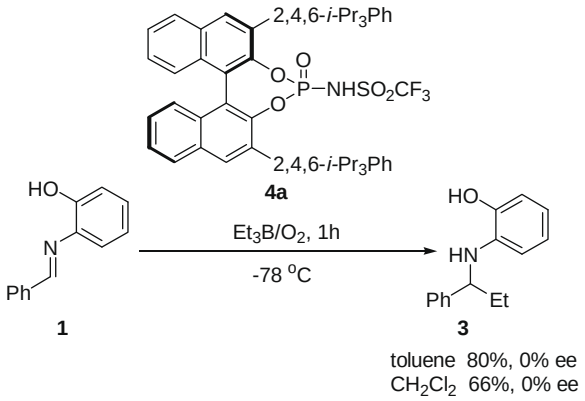
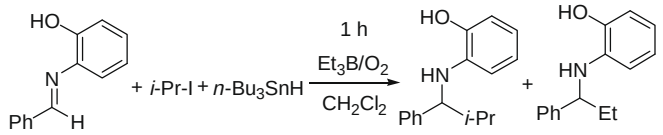


Scheme 2. Phosphoramide-catalyzed reactions.

Table 1
Radical addition reactions to 2-HO-phenyl imine



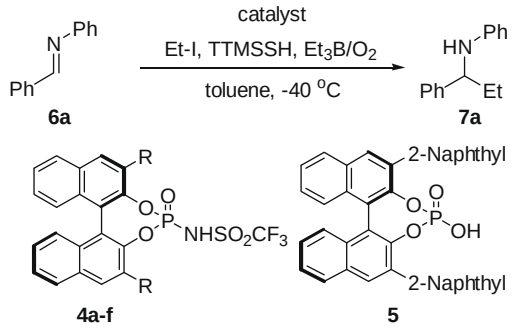
Entry	Temp (°C)	Catalyst	Yield (%)	
			2	**3**
1	rt	None	66	16
2	−78	None	57	28
3	−78	$(PhO)_2POOH$	42	33
4	−78	None[a]	9	68

Reaction condition: 0.3 equiv catalyst, 5.0 equiv *i*-Pr-I, 3.0 equiv *n*-Bu_3SnH, and 2.0 equiv Et_3B were used.
[a] Without *n*-Bu_3SnH.

by activating the imino group. We began our study using simple phenyl imine **6a** and tris(trimethylsilyl)silane (TTMSSH) in toluene at −40 °C.[14] To check the efficiency of chiral phosphoric acid catalysts, various binol-derived phosphoric acids having substituents at 3 and 3′ position, starting from 4-naphthyl group to the bulkiest triphenylsilyl group were examined. As shown in Table 2, when the reaction was carried out using 2-naphthyl-substituted phosphoric acid **5**, the racemic product was obtained in 37% yield along with recovery of the starting material (45%) (entry 1). Since the reaction was slow and did not go to completion even after 18 h, the reaction was repeated using more acidic phosphoramide catalysts **4** and the enantioselectivities and chemical yields were improved significantly. The same level of enantioselectivities was observed among **4b**, **4c**, and **4d** (entries 2–4). Bulkier triphenylsilyl and 3,5-bis(trifluoromethyl)phenyl groups might not block the one of the imine face effectively (entries 5 and 6). The slightly better selectivity was obtained with 2,4,6-triisopropylphenyl-substituted **4a** (entry 7). Furthermore, it was gratifying to find that the enantioselectivity was improved considerably up to 58% ee when dichloromethane was used as solvent (entry 8).

Since the enantioselectivity seemed to be sensitive to the solvent, the effect of the solvent was examined (Table 3). Although the reactions were complete within 3 h in chloroform and chlorobenzene, the enantioselectivities were reduced to 10% ee and 20% ee, respectively (entries 2 and 3). When the reaction was carried out in ethereal solvents, the reaction slowed down significantly and required 24 h for completion (entries 4–6). When diethyl ether was employed, the ee was as high as 49%, whereas the ee value

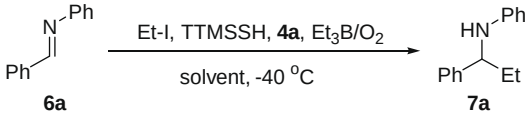
Table 2
Effect of catalysts



Entry	Catalyst (R)		Time (h)	Yield (%)	ee (%)
1	**5**	2-Naphthyl	12	37 (45)[a]	3
2	**4b**	2-Naphthyl	12	61 (8)[a]	21
3	**4c**	4-Ph–Ph	6	57 (10)[a]	20
4	**4d**	9-Anthryl	12	50	21
5	**4e**	$SiPh_3$	12	73	9
6	**4f**	3,5-$(CF_3)_2$Ph	12	33	19
7	**4a**	2,4,6-*i*-Pr_3Ph	12	57	26
8	**4a**[b]	2,4,6-*i*-Pr_3Ph	18	75	58

Reaction condition: 0.3 equiv of catalyst, 5.0 equiv EtI, 3.0 equiv of TTMSSH, and 2.0 equiv of Et_3B were used.
[a] Remained starting material by ^1H NMR analysis using mesitylene as internal standard.
[b] Reaction was carried out in dichloromethane.

Table 3
Effect of solvents



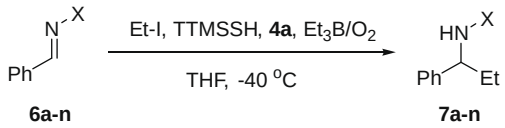
Entry	Solvent	Time (h)	Yield (%)	ee (%)
1	CH_2Cl_2	18	75	58
2	$CHCl_3$	3	82	10
3	C_6H_5Cl	3	66	20
4	Et_2O	24	77	49
5	iPr_2O	24	76	25
6	THF	24	42	77
7	Acetone	18	29	40
8	CH_3COOCH_3	24	90	12
9	CH_3CN	18	16 (23)[a]	14

Reaction condition is the same as the condition in Table 2.
[a] Remained starting material by ^1H NMR using mesitylene as internal standard.

dropped to 25% in diisopropyl ether. The highest 77% ee was obtained in tetrahydrofuran (entry 6). In addition, when the reaction was carried out in several other solvents, low ee was obtained (entries 7–9). Thus, remaining reactions were performed using catalyst **4a** in tetrahydrofuran at −40 °C.

To improve the enantioselectivity of the reaction, we tried to modify the structure of the imino group and the results are summarized in Table 4. When electron-donating and electron-withdrawing groups were introduced in 2-, 3-, and 4-positions, the enantioselectivities were not improved. The methyl substituent at 2-, 3-, and 4-positions did not improve the ee (entries 2–4) and particularly, 2-methyl substituent lowered the ee significantly (19% ee). A 4-methoxy-substituted phenyl imine **6e** gave a very low chemical yield with 53% ee (entries 5). In halogen-substituted phenyl imines, 4-chloro- and 4-bromo-phenyl imines **6g** and **6h** gave the product in 62% and 61% yields with 64% ee and 65% ee, respectively, but 2-chlorophenyl imine **6f** gave a very low ee (entry

Table 4
Modification on imines



6a-n **7a-n**

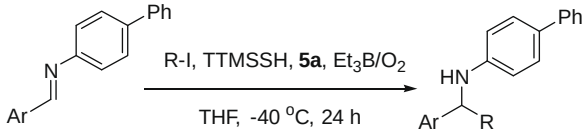
Entry		X	Time (h)	Yield (%)	ee (%)
1	**6a**	Ph	24	42	77
2	**6b**	2-MePh	24	36 (27) [a]	19
3	**6c**	3-MePh	24	29 (15) [a]	68
4	**6d**	4-MePh	24	23	76
5	**6e**	4-MeOPh	24	12	53
6	**6f**	2-ClPh	24	24 (16) [a]	23
7	**6g**	4-ClPh	6	62	64
8	**6h**	4-BrPh	12	61	65
9	**6i**	1-Naph	24	10	19
10	**6j**	2-Naph	24	34	60
11	**6k**	4-Ph–Ph	24	56	83
12	**6l**	Tosyl	6	30 (39) [b]	1
13	**6m**	OBn	24	NR	
14	**6n**	NHNTs	24	NR	

Reaction condition is the same as that in Table 2.
[a] Benzaldehyde from decomposition by ^{1}H NMR with mesitylene as internal standard.
[b] Reduction product ($PhCH_2NHX$).

6). The low chemical yields with 2-substituted imines seemed to result from their instability (entries 2 and 6). Furthermore, 1- and 2-naphthyl imines **6i** and **6j** were not attractive in chemical yield and the ee. The best ee was achieved with 4-biphenyl imine **6k** (83% ee) (entry 11). In addition, more electrophilic tosyl imine **6l** afforded a mixture of the desired addition product along with the direct reduction product (30%) (entry 12). In the cases of *O*-benzyl imine **6m** and *N*-tosyl hydrazone **6n**, the reaction did not proceed.

To determine the scope and limitation of the present method, the reaction was carried out with several phenyl imine derivatives using several alkyl radicals and the experimental results are summarized in Table 5. When isopropyl iodide and *tert*-butyl iodide were used, the same level of enantioselectivities was obtained (entries 2 and 3). The enantioselectivities were not altered by modifying the electronic properties of the benzene ring (entries 4–9) and ranged from 73% ee to 84% ee. Another important issue associated

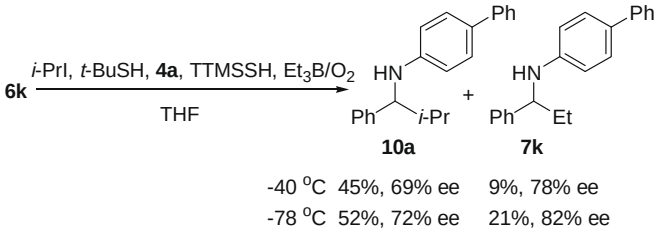
Table 5
Radical addition reactions of various substrates[15]



6k, 8, 9 **7k, 10a-b, 11a-c, 12a-c**

Entry		Ar	R	Pdt	Yield (%)	ee (%)
1	**6k**	Ph	Et	**7k**	56	83
2	**6k**	Ph	*i*-Pr	**10a**	35 (20)[a]	75 (75)[a]
3	**6k**	Ph	*t*-Bu	**10b**	36 (31)[a]	80 (83)[a]
4	**8**	4-MeOPh	Et	**11a**	77	73
5	**8**	4-MeOPh	*i*-Pr	**11b**	46 (35)[a]	81 (65)[a]
6	**8**	4-MeOPh	*t*-Bu	**11c**	56 (33)[a]	74 (4)[a]
7	**9**	4-ClPh	Et	**12a**	71	84
8	**9**	4-ClPh	*i*-Pr	**12b**	43 (29)[a]	75 (81)[a]
9	**9**	4-ClPh	*t*-Bu	**12c**	31 (29)[a]	78 (85)[a]

Reaction condition is the same as that in Table 2.
[a] Ethyl addition product.



10a **7k**

Scheme 3. Effect of polarity-reversal catalyst.

with the present reaction is the formation of the ethyl radical addition byproduct (20–35%), which is due to competition between the iodine atom transfer and the direct addition of the ethyl radical to the imine.

In order to reduce the formation of the byproduct, *tert*-butyl mercaptan was employed as a polarity-reversal catalyst.[16] Since the hydrogen atom transfer from an alkyl mercaptan to a nucleophilic alkyl radical ($k = 7.2 \times 10^6\ M^{-1}s^{-1}$)[17] is much faster than that from TTMSSH ($k = 7.0 \times 10^3\ M^{-1}s^{-1}$),[18] the ethyl radical would be captured by the alkyl mercaptan prior to its addition onto the imine. As we expected, in the presence of 2.0 equiv of *tert*-butyl mercaptan, the ratio of the ethyl addition product **7k** to the desired product **10a** was increased to 5 to 1 from 1.75 to 1, but at the same time the enantioselectivity was reduced to 69% ee at −40 °C (Scheme 3). At −78 °C the enantioselectivity was slightly increased to 72% ee but 21% of **7k** was isolated.

In summary, we have developed the enantioselective radical addition reactions to imines using chiral *N*-triflyl phosphoramide catalyst **4a** with various substrates. The enantioselectivities were ranged from 73% to 84% and were not affected by electronic properties of imines. To obviate the problem of the ethyl radical addition byproduct along with higher ee, further studies are underway.

Acknowledgments

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14. When *n*-Bu_3SnH was used, the imino group of **6a** was directly reduced to give phenyl benzyl amine.
15. *Typical procedure*: A mixture of phosphoramide (0.3 equiv, 0.015 mmol) and imine (1.0 equiv, 0.05 mmol) was dissolved in tetrahydrofuran (2.0 mL) at room temperature and the resulting mixture was cooled down to −40 °C. Alkyl iodide (5.0 equiv), TTMSSH (3.0 equiv), and Et_3B (2.0 equiv) were added and air (5.0 mL) was introduced via syringe. After being stirred at −40 °C for 12 h, additional Et_3B (2.0 equiv) and air were added. After completion of reaction, the solvent was evaporated and the residue was purified by column chromatography on basic alumina.
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