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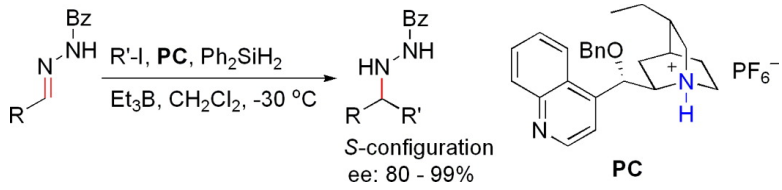

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Highly Enantioselective Radical Addition to *N*-Benzoyl Hydrazones Using Chiral Ammonium Salts

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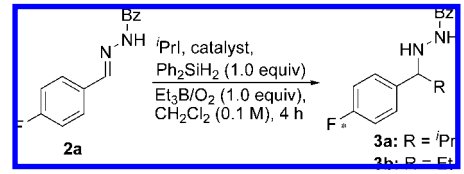
Radical reactions have become a powerful and versatile tool for organic chemists since the reactions provide mild and neutral conditions in which a wide range of functional groups are tolerated.[1] Stereochemical outcomes in radical reactions have been relying mainly on utilizing chiral auxiliaries.[2] Although they allow the diastereoselectivity of products, additional cleavage steps are required to obtain the desired products. Recent years have witnessed significant progress in chiral Lewis acid mediated enantioselective radical reactions.[3,4] The chiral Lewis acids interact with substrates noncovalently and provide the chiral environment as well as the reactivity enhancement of substrates. During the past several years, organocatalysts have drawn considerable attention, playing an important role in nonradical enantioselective reactions.[5,6] However, little has been reported on the development of organocatalysts for enantioselective radical reactions.[7] With several advantages such as low toxicity, low cost, and ease of manipulation, organocatalysts are an attractive alternative to chiral Lewis acids in enantioselective radical reactions.

We present a highly enantioselective radical-mediated C−N bond forming reaction that uses organocatalysts under tin-free conditions. This reaction provides access to highly enantioenriched chiral amines that are important chiral building blocks.[8] We assumed that protonated cinchona alkaloid derivatives (PC) might interact with substrates that are capable of being hydrogen-bonding acceptors through hydrogen bonding and provide a chiral environment (Scheme 1).

We initiated our work with **2a** as a model substrate to establish the optimal conditions for the enantioselective radical addition to the C═N bond of *N*-benzoyl hydrazones. The results are tabulated in Table 1. An isopropyl radical addition reaction of **2a** was performed in the presence of 1.0 equiv of **1a** at room temperature. The reaction proceeded smoothly and was completed in 4 h, affording the addition adduct **3a** in 82% with 82% ee (entry 1). Diphenylsilane played a role as the radical chain carrier and also as the hydrogen atom donor.[9] We chose diphenylsilane instead of organotin hydrides that are generally used as the radical chain carrier to avoid their disadvantages such as high toxicity and difficulty in purifying the product. Triethylborane was chosen since it allowed reactions to be initiated at low temperatures. The enantioselectivity was improved by conducting the reaction at lower temperature. The reaction at −30 °C gave more than 99% ee (entry 3). To evaluate the potency of an asymmetric catalyst, we examined the turnover by lowering the catalyst loading. As the amount of **1a** decreased to 0.3 equiv, the yields remained almost the same, while the enantioselectivity decreased, suggesting a catalyst turnover (entries 3−6). In the case of a reaction with 0.1 equiv of **1a**, the enantioselectivity decreased significantly without affecting the chemical yield, showing that at least 0.3 equiv of **1a** is required to obtain the high enantioselectivity (entry 7). The reaction with an excess of **1a** did not affect the efficiency and the selectivity (entry 8). The addition reaction of **2a** with an ethyl radical generated from triethylborane took place as a background reaction, giving **3b** in ∼10% yields along with the desired product **3a**. By optimizing the reaction further, we were able to reduce the amount of isopropyl iodide to a stoichiometric amount at no expense to the yield and selectivity of the product (entry 9). We examined the reactivity of catalysts **1b**−**e** having a different counteranion for the radical addition reactions to C═N bonds (entries 10−13). The chiral ammonium salts afforded comparable chemical yields with lower enantioselectivity. It proved that **1a** is a good choice.

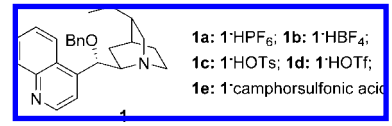
Table 1. Addition of Isopropyl Radical to **2a** under Various Reaction Conditions



entry	catalyst (equiv)	^{i}PrI (equiv)	temp (°C)	yield (%)[a] of **3a** (**3b**)[b]	ee (%)[c] of **3a**
1	**1a** (1.0)	5.0	RT	82 (9)	82
2	**1a** (1.0)	5.0	0	81 (9)	90
3	**1a** (1.0)	5.0	−30	81 (9)	99
4	**1a** (0.7)	5.0	−30	80 (10)	92
5	**1a** (0.5)	5.0	−30	80 (9)	92
6	**1a** (0.3)	5.0	−30	79 (10)	84
7	**1a** (0.1)	5.0	−30	78 (11)	40
8	**1a** (3.0)	5.0	−30	81 (9)	99
9	***1a*** *(1.0)*	*1.5*	*−30*	*82 (9)*	*99*
10	**1b** (0.5)	5.0	−30	76 (11)	40
11	**1c** (0.5)	5.0	−30	77 (11)	20
12	**1d** (0.5)	5.0	−30	76 (11)	40
13	**1e** (0.5)	5.0	−30	78 (10)	40

[a] Isolated yield. [b] The yield in parentheses is for **3b**. [c] Determined by chiral HPLC analysis and compared with authentic racemic material.

Scheme 1



Under optimal conditions, we investigated the efficiency of reaction toward different kinds of alkyl halides. The results are presented in Table 2. As demonstrated earlier, the addition reaction of a secondary isopropyl radical gave high yields with excellent enantioselectivity (see Table 1). Similar results were obtained in the addition of a cyclohexyl radical (Table 2, entry 1). When tertiary radicals such as *tert*-butyl and 1-adamantyl radicals were added, good chemical yields and extremely high enantioselectivity were obtained (entries 2 and 3). Addition of a primary octyl radical gave a moderate yield and reduced enantioselectivity (entry 4).

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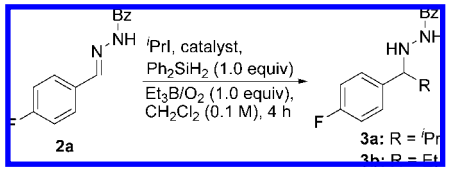
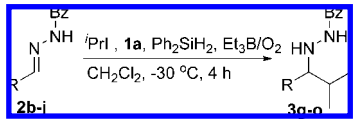
Table 2. Alkyl Radical Addition to **2a** in the Presence of **1a**[a]



entry	R	product	yield (%)[b]	ee (%)[c]
1	[c]hexyl	**3c**	80	99
2	[t]butyl	**3d**	71	99
3	1-adamantyl	**3e**	70	99
4	[n]octyl	**3f**	55	81

[a] Reactions were run with **1a** (0.4 mmol), **2a** (0.4 mmol), RI (0.6 mmol), Ph_2SiH_2 (0.4 mmol), and Et_3B (0.4 mmol) in CH_2Cl_2 (4 mL) with addition of air (80 mL) at −30 °C for 4 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis and compared with authentic racemic material.

Table 3. Scope of Isopropyl Radical Addition to *N*-Benzoyl Hydrazones Catalyzed by **1a**[a]



entry		R	product	yield (%)[b]	ee (%)[c]
1	**2b**	4-Cl-Ph-	**3g**	81	99
2	**2c**	4-MeC(O)-Ph-	**3h**	80	99
3	**2d**	4-NO_2-Ph-	**3i**	81	99
4	**2e**	Ph-	**3j**	81	99
5	**2f**	4-OH-Ph-	**3k**	79	98
6	**2g**	4-OMe-Ph-	**3l**	80	98
7	**2h**	4-MeC(O)NH-Ph-	**3m**	77	99
8	**2i**	4-Et-Ph-	**3n**	81	99
9	**2j**	$CH_3(CH_2)_6$-	**3o**	72	80

[a] Reactions were run with **1a** (0.4 mmol), **2a** (0.4 mmol), RI (0.6 mmol), Ph_2SiH_2 (0.4 mmol), and Et_3B (0.4 mmol) in CH_2Cl_2 (4 mL) with addition of air (80 mL) at −30 °C for 4 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis and compared with authentic racemic material.

To evaluate the generality and the scope of the reaction, a wide range of *N*-benzoyl hydrazones derived from aldehydes were subjected to optimized conditions. Table 3 presents the results. Radical addition reactions to aryl aldehyde derived *N*-benzoyl hydrazones were all highly enantioselective (Table 3, entries 1−8). In these cases, the trace of minor enantiomer was hardly detectable in the chiral HPLC analysis. Aryl aldehyde derived *N*-benzoyl hydrazones with an electron-poor benzene ring or an electron-rich benzene ring gave similar results in terms of chemical yield and enantioselectivity, showing the generality of reaction. The addition reaction to *N*-benzoyl hydrazone derived from an aliphatic aldehyde gave a moderate yield and reduced enantioselectivity (entry 9). Radical addition to *N*-benzoyl hydrazone derived from a ketone did not take place under the reaction conditions.

Although high loading of **1a** was required to attain a high level of enantioselectivity, **1a** was readily recovered after a simple aqueous workup in more than 95% yield. When the recovered **1a** was reused in the isopropyl radical addition reaction to **2a**, the chemical yield and enantioselectivity were as high as when the freshly prepared **1a** was used. The product **3j** was converted to 1-phenylpropane-1-amine using SmI_2.[10] The absolute configuration of **3j** was determined to be *S* by comparing the optical rotation with that reported in the literature.

In conclusion, we have developed a chiral ammonium salt mediated radical addition reaction with high enantioselectivity that offers a method of approaching enantioenriched chiral amines. To the best of our knowledge, the level of enantioselectivity and generality reported herein is the highest among those previously reported. The radical reactions can be performed under metal-free, especially tin-free conditions. The chiral ammonium salts are recyclable after a simple aqueous workup, and the reaction conditions are environmentally benign. Further work to expand the scope of the reaction is underway.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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