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Reactive Ketimino Radical Acceptors: Intermolecular Alkyl Radical Addition to Imines with a Phenolic Hydroxyl Group

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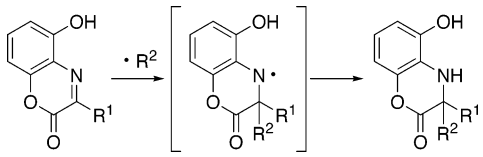

Intermolecular carbon radical addition to the carbon−nitrogen double bond of ketimines was studied. In the study on the reactivity of various aldimines, we found that the aldimine **7** having a phenolic hydroxyl group shows an excellent reactivity toward nucleophilic carbon radicals. A remarkable effect of phenolic hydroxyl group is assumed to be the stabilization of intermediate aminyl radical provided by a hydroxyl group. The screening of reactive ketimino acceptors showed that ketimines **15**, **17**, and **19** having a phenolic hydroxyl group exhibit excellent reactivities. The radical addition to ketimines **15**, **17**, and **19** took place regioselectively at the imino carbon to give the *C*-alkylated products without the formation of *N*-alkylated products. Enantioselective ethyl radical addition to ketimine **15** using chiral box ligand and $Zn(OTf)_2$ gave the diethylated product **30** in 80% ee.

Introduction

Free radical reactions have been developed as a powerful method for constructing the carbon−carbon bond, providing many advantages over ionic chemistry.[1,2] Although the use of radical reaction in organic synthesis has continued to increase, the intermolecular radical addition to the carbon atom of imine derivatives has received much less attention until recently.[3] Most synthetically useful carbon−carbon bond-forming reactions of imines are restricted to the use of organometallic reagents.[4] However, the addition of organometallic reagents is frequently plagued by the enolization of the substrates with acidic α-hydrogens, poor electrophilicity of the imino group, and the formation of reductive coupling products. The addition of a strictly neutral species such as an uncharged free radical would provide a highly general solution to the fundamental problems that are associated with the strong basicity of organometallic reagents.

Hart's group reported the first study on intermolecular radical addition to formaldoxime ether.[5] Recently, the intermolecular radical reactions of α-sulfonyl oxime ethers, aldoxime ethers, hydrazones, glyoxylic imine derivatives, nitrones, and *N*-sulfonylimines have been investigated mainly by the groups of Kim,[6] Bertrand,[7] Friestad,[8] and ourselves.[9,10] However, these studies on the intermolecular radical addition to the carbon atom of imines have concentrated on the reaction of aldimines. The difficulty in achieving the construction of an all-substituted sp^3-

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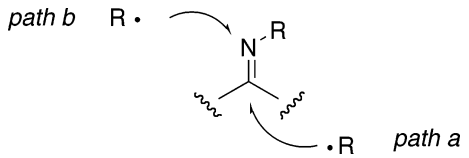


FIGURE 1. Regiochemical course of radical addition to ketimines.

carbon center based on the intermolecular radical addition to the carbon atom of ketimines has remained unresolved (*path a*), due to the low reactivity of ketimines and the regiochemical course of carbon radical addition to ketimines (Figure 1). In fact, the regioisomeric carbon−nitrogen bond formation based on intramolecular radical addition to the nitrogen atom of ketimines has been investigated, although there are no intermolecular examples of this process (*path b*).[11]

For an example of intermolecular radical addition to the carbon atom of ketimines, Shono's group reported the electroreductive intermolecular coupling of ketoxime ethers with ketones.[12] More recently, the photoinduced intermolecular reaction of ketoxime ethers with α-alkoxy carbon radical was achieved by the group of Alonso.[13] However, nothing is known about the radical addition to ketimines using a conventional radical initiator such as Et_3B or AIBN.[14] Therefore, the screening of reactive ketimino acceptors is the new focus of our efforts. Our recent studies showed that ketimines having a 2-phenolic hydroxyl group have excellent reactivities toward nucleophilic alkyl radicals under mild aqueous-medium reaction conditions using Et_3B.[15a] We also reported the results of experiments to test the viability of several ketimines in Et_3B-induced intermolecular radical reactions.[15b] In this paper, we report, in detail, the Et_3B-induced reaction of imines having a 2-phenolic hydroxyl group in organic solvent. This reaction was applied to the first reported example of intermolecular enantioselective radical addition to ketimine.[16]

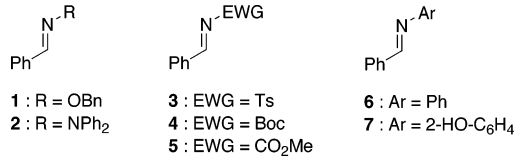
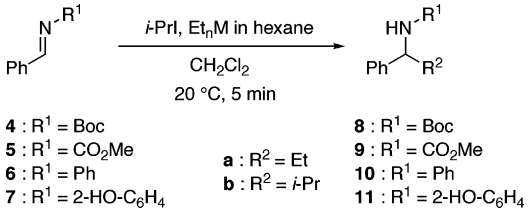


FIGURE 2. Aldimine derivatives prepared from benzaldehyde.

SCHEME 1



Results and Discussion

Reactivity of *N*-Aromatic Aldimine Having a Phenolic Hydroxyl Group. To compare the effect of substituent of nitrogen atom of C═N bond, our experiments began with the investigation of intermolecular radical addition to several aldimines (Figure 2). In our previous studies, we reported that the Et_3B-induced radical addition to oxime ether **1** and hydrazone **2** did not proceed in the absence of Lewis acid and the activation of C═N bond with $BF_3{\cdot}OEt_2$ was essential to achieve the intermolecular radical addition to **1**.[9b,d,e] More recently, we reported that electron-deficient *N*-sulfonyl imine **3** exhibits an excellent reactivity and the radical addition to **3** proceeded smoothly even in the absence of Lewis acid.[9h]

The substrates of choice were different types of aldimines **4**−**7** prepared from benzaldehyde to identify the reactivity of aldimine **7** having a phenolic hydroxyl group. The reactions were run in undegassed CH_2Cl_2 at 20 °C for 5 min by using Et_3B as an ethyl radical source (Scheme 1). In contrast to *N*-sulfonyl imine **3**,[9h] the reaction of similar electron-deficient imines **4** and **5** gave not only the inferior yields of products **8a**

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(16) For the intermolecular enantioselective radical addition to aldimines, see refs 8b,c and 9f.

TABLE 1. Radical Addition to Aldimines 4−7

entry	imine	RI	initiator	product	yield (%)[a]
1[b]	**4**	none	Et_3B	**8a**	23
2[b]	**5**	none	Et_3B	**9a**	21
3[b]	**6**	none	Et_3B	**10a**	40
4[b]	**7**	none	Et_3B	**11a**	85
5[b]	**7**	none	Et_2Zn		no reaction
6[c]	**7**	*i*-PrI	Et_3B	**11b**	90

[a] Isolated yields. [b] Reactions were carried out using 1 M Et_3B or Et_2Zn in hexane (2.5 equiv). [c] Reaction was carried out using *i*-PrI (30 equiv) and 1 M Et_3B in hexane (2.5 equiv).

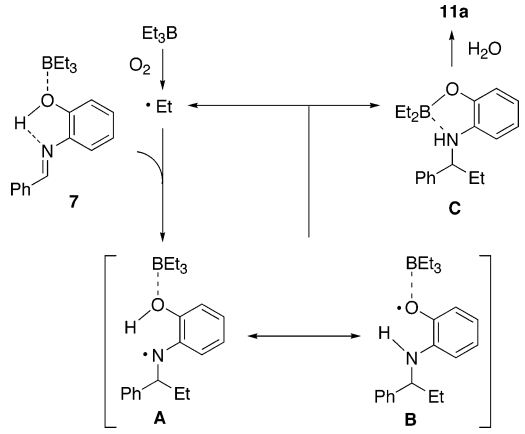


FIGURE 3. Effect of 2-hydroxyl group and reaction pathway.

and **9a** but also significant amounts of starting materials and hydrolysis products due to the unstable C═N bond (Table 1, entries 1 and 2). Although moderate chemical yield was observed in the reaction of *N*-aromatic imine **6**, it is important to note that the reaction of *N*-aromatic imine **6** proceeded even in the absence of Lewis acid under mild reaction conditions using Et_3B (entry 3). These results suggested that the C═N bonds of both **6** and its intermediate aminyl radical were stabilized by the conjugation with *N*-aromatic ring. We then examined the *N*-aromatic aldimine **7** capable of forming an intramolecular hydrogen bond. The aldimine **7** having a phenolic hydroxyl group was extremely reactive, and the radical reaction proceeded within 5 min to give the desired product **11a** in 85% yield, because of the effective activation of the C═N bond and extra stabilization of the intermediate aminyl radical provided by the intramolecular hydrogen bond (entry 4). The role of a phenolic hydroxyl group has not yet been completely clear; however, the stabilization of intermediate aminyl radical **A** would be provided by a hydroxyl group, giving the accelerated addition rates (Figure 3). In this reaction, Et_3B worked as not only a radical initiator but also a radical chain terminator to trap the intermediate radical **A** or **B** to give a chain-propagating ethyl radical. In the case of the reaction using Et_2Zn as an ethyl radical source,[17] no reaction occurred (entry 5). This result suggests that a hydroxyl group of **7** was reacted with Et_2Zn to give zinc alkoxide,[18] which did not have a good reactivity. The reaction of **7** with isopropyl radical was conducted under tin-free iodine atom-transfer conditions using *i*-PrI and Et_3B.

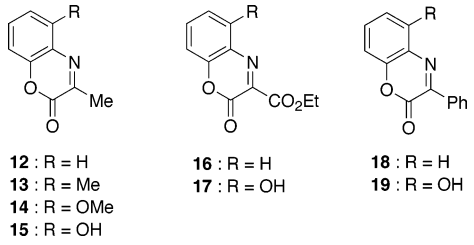
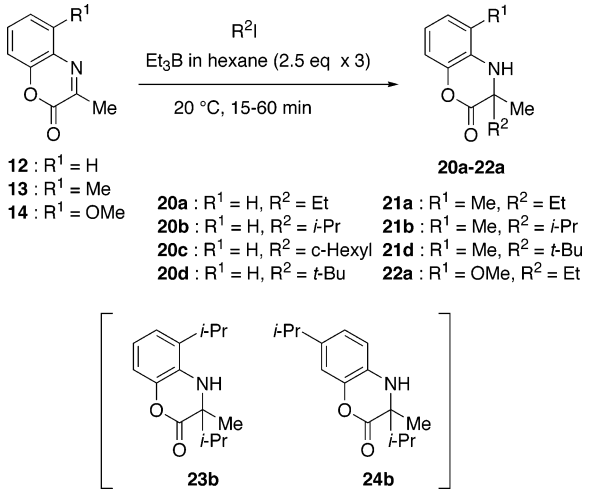


FIGURE 4. Cyclic *N*-aromatic ketimine derivatives.

SCHEME 2



Isopropyl radical addition reaction was also facile, and the desired isopropylated product **11b** was isolated in 90% yield (entry 6). Results from these studies show that aldimine **7** having a hydroxyl group is a highly promising imino radical acceptor, comparable to *N*-sulfonyl imine **3** having a strong *N*-electron-withdrawing substituent reported in our previous studies.[9h]

Reactivity of *N*-Aromatic Ketimines. The development of reactive ketimino acceptors is a challenging problem. On the basis of the above results of aldimines, we hoped that *N*-aromatic ketimines would serve as radical acceptors, as a result of the stabilization of intermediate aminyl radical by the delocalization on adjacent *N*-aromatic ring. Therefore, we decided to explore the reactivity of *N*-aromatic ketimines **12**−**19** (Figure 4).[19] We also expected that the electron-withdrawing carbonyl moiety of the ketimines **12**−**19** activates the C═N bond, and cyclic structure of **12**−**19** enhances the stabilization of C═N bond toward hydrolysis. Moreover, the intermolecular radical addition to ketimines **12**−**19** provides a new method for the synthesis of α,α-disubstituted amino acids.

All reactions of ketimines **12**−**14** were carried out in undegassed solvent under a nitrogen atmosphere (Scheme 2).[20] Several trends in Table 2 are noteworthy. The ethyl radical addition to *N*-aromatic ketimine **12** proceeded effectively to give a 77% yield of the desired *C*-ethylated product **20a** even in the absence of Lewis acids, although a large amount of Et_3B (2.5 equiv × 3) was required (entry 1). In contrast, the isopropyl radical addition reaction using isopropyl iodide gave the mixture of products, and a careful product analysis showed that the diisopropylated products **23b** and **24b** were also formed (entries

(17) Ryu and Komatsu reported that Et_2Zn can serve as a radical initiator. See: Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335.

(18) (a) Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369. (b) Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630.

(19) The preparation method of required starting materials **12**−**19** is reported in Supporting Information.

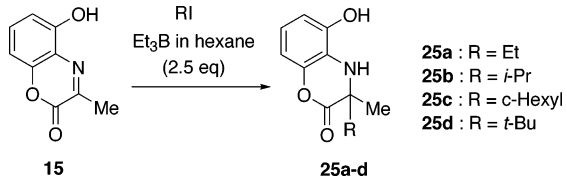
(20) The [2 + 2] photocycloaddition of ketimine **12** was reported. See: Nishio, T.; Omote, Y. *J. Org. Chem.* **1985**, *50*, 1370.

TABLE 2. Alkyl Radical Addition to Ketimines 12−14

entry	imine	R^2I (equiv)	solvent	Lewis acid	time (min)	product (% yield)[a]
1[b]	**12**	none	CH_2Cl_2	none	60	**20a** (77)
2[c]	**12**	*i*-PrI (10)	CH_2Cl_2	none	60	**20b** (24), **20a** (10)[f]
3[c]	**12**	*i*-PrI (15)	CH_2Cl_2	none	60	**20b** (26), **20a** (3)[g]
4[d]	**12**	*i*-PrI (10)	CH_2Cl_2	$Yb(OTf)_3$	15	**20b** (54), **20a** (5)[h]
5[d]	**12**	*i*-PrI (10)	THF−CH_2Cl_2	$Yb(OTf)_3$	15	**20b** (64), **20a** (20)
6[d]	**12**	*i*-PrI (15)	THF−CH_2Cl_2	$Yb(OTf)_3$	15	**20b** (75), **20a** (trace)
7[d]	**12**	c-Hexyl I (10)	THF−CH_2Cl_2	$Yb(OTf)_3$	15	**20c** (60), **20a** (21)
8[d]	**12**	c-Hexyl I (15)	THF−CH_2Cl_2	$Yb(OTf)_3$	15	**20c** (66), **20a** (19)
9[d]	**12**	*t*-BuI (10)	THF−CH_2Cl_2	$Yb(OTf)_3$	15	**20d** (89), **20a** (7)
10[d]	**12**	*t*-BuI (15)	THF−CH_2Cl_2	$Yb(OTf)_3$	15	**20d** (96)
11[b]	**13**	none	CH_2Cl_2	none	60	**21a** (32)
12[e]	**13**	none	THF−CH_2Cl_2	$Yb(OTf)_3$	20	**21a** (73)
13[d]	**13**	*i*-PrI (15)	THF−CH_2Cl_2	$Yb(OTf)_3$	20	**21b** (76), **21a** (trace)
14[d]	**13**	*t*-BuI (15)	THF−CH_2Cl_2	$Yb(OTf)_3$	20	**21d** (84)
15[b]	**14**	none	CH_2Cl_2	none	60	**22a** (13)
16[e]	**14**	none	THF−CH_2Cl_2	$Yb(OTf)_3$	20	**22a** (63)

[a] Isolated yields. [b] Reactions were carried out using 1 M Et_3B in hexane (2.5 equiv × 3). [c] Reactions were carried out using RI and 1 M Et_3B in hexane (2.5 equiv × 3). [d] Reactions were carried out using RI and 1 M Et_3B in hexane (2.5 equiv × 3) in the presence of $Yb(OTf)_3$ (1.0 equiv). [e] Reactions were carried out using 1 M Et_3B in hexane (2.5 equiv × 3) in the presence of $Yb(OTf)_3$ (1.0 equiv). [f] Products **23b** (9%) and **24b** (10%) were also obtained. [g] Products **23b** (13%) and **24b** (14%) were also obtained. [h] Products **23b** (4%) and **24b** (4%) were also obtained.

SCHEME 3



2−4). A Lewis acid such as $Yb(OTf)_3$, which is sufficiently mild to be compatible with the other reactants, greatly increased the chemical yield of the reaction. THF serves to dissolve the $Yb(OTf)_3$. When a stoichiometric amount of $Yb(OTf)_3$ was employed in THF−CH_2Cl_2, the formation of **23b** and **24b** was remarkably diminished, leading to a 75% yield of the desired product **20b** (entry 6). Under the analogous reaction conditions, cyclohexyl iodide and *t*-BuI worked well (entries 8 and 10). The similar trends were observed in the reaction of ketimine **13** having a methyl group and ketimine **14** having a methoxyl group (entries 11−16). The use of $Yb(OTf)_3$ was found to be optimal for good chemical yields, although substrates **13** and **14** with increased steric size at the 2-position showed slightly lower reactivity. In these reactions, radical addition to the nitrogen atom of ketimines **12**−**14** was not observed. Results were consistent with the fact that simple alkyl radicals are relatively nucleophilic and their additions are uncomplicated by electronic effects or chelation with Lewis acid.

The reaction of ketimine **15** having a hydroxyl group was faster than those of other ketimines **12**−**14** (Scheme 3). Treatment of **15** with only 2.5 equiv of Et_3B furnished the ethylated product **25a** without the formation of any other byproducts (Table 3, entries 1−6). In the absence of Lewis acid additive, the reaction of **15** in CH_2Cl_2 afforded the ethylated product **25a** in 89% yield within 5 min (entry 1). It is important to note that high chemical yields were observed even at −78 °C, although the reaction took a longer time for completion (entries 2, 4, and 6). The replacement of CH_2Cl_2 with a nonpolar aromatic solvent such as toluene was also effective for the reaction of **15** (entries 3 and 4). The use of $Yb(OTf)_3$ led to a small enhancement in chemical yields (entries 5 and 6). We next explored the alkyl radical addition to ketimine **15**. At first, the tin-free reaction of **15** was tested under iodine atom-transfer reaction conditions (entries 7−10). As a result of the enhanced reactivity of **15**, the ethylated product **25a** contaminated the desired alkyl radical addition products, especially when secondary alkyl radicals were used (entries 7−9). The reaction with an isopropyl radical gave a significant amount of the ethylated product **25a**, as a result of competitive addition of an ethyl radical generated from Et_3B (entry 7). Under identical conditions, the addition of more nucleophilic and stable *tert*-butyl radical gave the desired product **25d** with higher selectivity, due to the efficient iodine atom-transfer from *tert*-butyl iodide to ethyl radical (entry 10). We have previously reported that a highly reactive imino radical acceptor, such as glyoxylic oxime ether or BF_3-activated aldoxime ether, gives the ethylated product as a byproduct, whereas a less reactive imino radical acceptor gives the desired alkylated product selectively.[9b−f] Thus, these observations strongly indicate that ketimine **15** having a hydroxyl group has an excellent reactivity. Low selectivity with $Yb(OTf)_3$ lends support to this conclusion (entry 8). To suppress the formation of the undesired ethylated product **25a**, Bu_3SnH was employed as a radical mediator (entries 11−16). The effect of temperature on selectivity was also examined, and it was found that outstanding levels of selectivity can be obtained at 20 °C (entries 14−16). In the case of the reaction using isopropyl iodide and Bu_3SnH, the formation of **25a** diminished remarkably, leading to an excellent yield of the isopropylated product **25b** after being stirred in CH_2Cl_2 at 20 °C for 5 min (entry 14). Other radical precursors such as cyclohexyl iodide and *t*-BuI worked well under similar reaction conditions to give the desired products **25c** and **25d** selectively (entries 15 and 16).

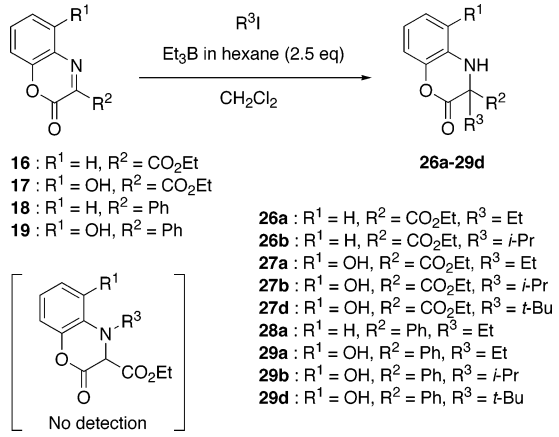
To gain further insight into the effect of a phenolic hydroxyl group, the next radical acceptors of choice were ketimines **16**−**19** (Scheme 4). All reactions were carried out by using 2.5 equiv of Et_3B. The influence of the substituent R^2 on reactivity is shown in Table 4, and several entries are noteworthy. Since ketimines **16** and **17** ($R^2 = CO_2Et$) have two electrophilic centers (carbon and nitrogen atoms of the C=N bond), we are interested in regiochemical course of radical addition to **16** and **17**. Additionally, we expected that the reactivity of **16** and **17** is enhanced by the electron-withdrawing substituent R^2, which would lower the LUMO energy of a radical acceptor. However, increasing the size of R^2 affected the reactivity of acceptor toward radical additions, and the reaction of ketimine **16** did not proceed effectively (entries 1−5). In contrast, ketimine **17** having a hydroxyl group had shown reactivity higher than that

TABLE 3. Alkyl Radical Addition to Ketimine 15[a]

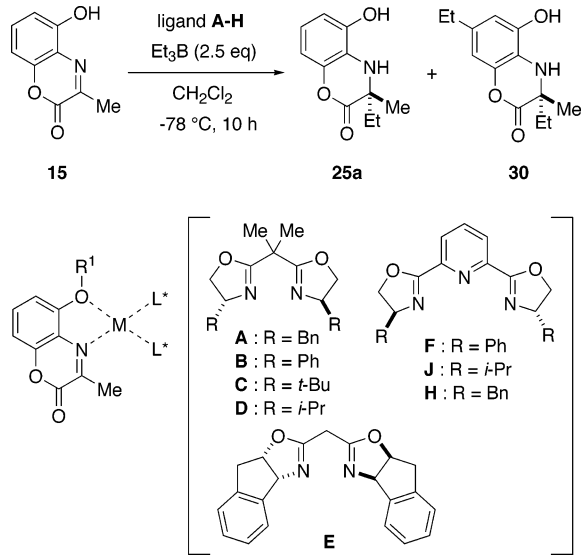
entry	RI	solvent	additive	*T* (°C)	time (min)	product[b]	% yield[c] (selectivity)[d]
1	none	CH_2Cl_2	none	20	5	**25a**	89
2	none	CH_2Cl_2	none	−78	60	**25a**	82
3	none	toluene	none	20	5	**25a**	93
4	none	toluene	none	−78	60	**25a**	84
5[e]	none	THF−CH_2Cl_2	$Yb(OTf)_3$	20	5	**25a**	95
6[e]	none	THF−CH_2Cl_2	$Yb(OTf)_3$	−78	60	**25a**	90
7	*i*-PrI	CH_2Cl_2	none	20	5	**25b**	87 (4:1)
8[e]	*i*-PrI	THF−CH_2Cl_2	$Yb(OTf)_3$	20	5	**25b**	86 (1:1)
9	c-Hexyl I	CH_2Cl_2	none	20	5	**25c**	76 (3.5:1)
10	*t*-BuI	CH_2Cl_2	none	20	5	**25d**	89 (16:1)
11[f]	*i*-PrI	CH_2Cl_2	Bu_3SnH	−78	60	**25b**	95 (1.8:1)
12[f]	c-Hexyl I	CH_2Cl_2	Bu_3SnH	−78	60	**25c**	95 (1.6:1)
13[f]	*t*-BuI	CH_2Cl_2	Bu_3SnH	−78	60	**25d**	92 (10:1)
14[f]	*i*-PrI	CH_2Cl_2	Bu_3SnH	20	5	**25b**	96 (>30:1)
15[f]	c-Hexyl I	CH_2Cl_2	Bu_3SnH	20	5	**25c**	95 (13:1)
16[f]	*t*-BuI	CH_2Cl_2	Bu_3SnH	20	5	**25d**	97 (>30:1)

[a] Reactions were carried out using RI (30 equiv) and 1 M Et_3B in hexane (2.5 equiv). [b] Major products. [c] Isolated yields. [d] Selectivity for **25b**−**d**:**25a** is determined by ^1H NMR analysis. [e] Reactions were carried out in the presence of $Yb(OTf)_3$ (1.0 equiv). [f] Reactions were carried out in the presence of Bu_3SnH (3 equiv).

SCHEME 4



SCHEME 5



of ketimines **16** and **15** (entries 6−9). The ethyl radical addition to ketimine **17** proceeded cleanly and efficiently even in the absence of Lewis acid, giving the *C*-ethylated product **27a** uncontaminated by starting material and any other products (entry 6). However, as observed with an isopropyl radical addition, the highly reactive acceptor **17** gave the reduced selectivity as a result of the competitive addition of an ethyl radical (compare entry 7 in Table 4 with entry 7 in Table 3). Past results on optimizing selectivity indicated that Bu_3SnH was good chain carrier for the alkyl radical addition to ketimine **15** (entries 14−16 in Table 3). It was again found that Bu_3SnH gave the high selectivity when ketimine **17** was used (entry 8). It is important to note that the regioselective radical addition took place at the carbon atom of C═N bond, and the formation of *N*-alkylated Michael-type adducts was not observed. We next investigated the bulky ketimines **18** and **19**, highly stabilized by conjugation with phenyl group (R^2 = Ph). The radical addition to **18** was extremely slow, and ethyl radical did not add in the absence of Lewis acid (entry 10). In contrast to **18**, the reaction of **19** having a hydroxyl group took place even in the absence of Lewis acid (entry 13). Use of zinc Lewis acid led to high yields (entries 14−17), and the ethyl radical addition to **19** proceeded even at −78 °C (entry 15). It was observed that the substrate reactivity followed the order R^2 = CO_2Et (**17**) > Me (**15**) > Ph (**19**).

Enantioselective Reaction of Ketimines. In recent years, studies on enantioselective radical reactions have achieved some remarkable success, particularly in radical additions to C═C bonds.[1] Direct asymmetric synthesis of amines by enantioselective addition to the C═N bond of imines provides an efficient method for introducing the stereogenic center and carbon−carbon bond in one step.[4,21] We previously reported the first enantioselective radical addition to aldimino acceptor mediated by chiral Lewis acid.[9f] Similar study was carried out using a chiral Lewis acid derived from Cu(I) and Tol-BINAP with less success.[22] Recently, highly enantioselective radical addition to aldimine was achieved by Friestad's group.[8c] However, nothing has been known about the enantioselective radical addition to ketimines. Therefore, the stereocontrol in the intermolecular reaction of ketimines has been a subject of current interest.

Several combinations of chiral box ligands **A**−**H** and Lewis acids were initially evaluated in the ethyl radical addition to

(21) For reviews, see: (a) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.

(22) Halland, N.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290.

TABLE 4. Alkyl Radical Addition to Ketimines 16−19[a]

entry	imine	R^3I	Lewis acid	additive	T (°C)	time (min)	product[b]	% yield[c] (selectivity)[d]
1	**16**	none	none	none	20	60	**26a**	12
2[e]	**16**	none	$Zn(OTf)_2$	none	20	60	**26a**	56
3[e]	**16**	none	$Zn(OTf)_2$	none	−78	900	**26a**	35
4[e]	**16**	*i*-PrI	$Zn(OTf)_2$	none	20	60	**26b**	17 (>30:1)
5[e,f]	**16**	*i*-PrI	$Zn(OTf)_2$	Bu_3SnH	20	60	**26b**	35 (>30:1)
6	**17**	none	none	none	20	5	**27a**	94
7	**17**	*i*-PrI	none	none	20	5	**27b**	94 (1:1)
8[f]	**17**	*i*-PrI	none	Bu_3SnH	20	5	**27b**	91 (11:1)
9	**17**	*t*-BuI	none	none	20	5	**27d**	83 (8:1)
10	**18**	none	none	none	20	60	**28a**	trace
11[e]	**18**	none	$Zn(OTf)_2$	none	20	60	**28a**	24
12[e]	**18**	none	$Zn(OTf)_2$	none	−78	900	**28a**	13
13	**19**	none	none	none	20	20	**29a**	88
14[e]	**19**	none	$Zn(OTf)_2$	none	20	5	**29a**	91
15[e]	**19**	none	$Zn(OTf)_2$	none	−78	60	**29a**	80
16[e]	**19**	*i*-PrI	$Zn(OTf)_2$	none	20	5	**29b**	96 (7:1)
17[e,f]	**19**	*i*-PrI	$Zn(OTf)_2$	Bu_3SnH	20	5	**29b**	88 (>30:1)
18	**19**	*t*-BuI	none	none	20	5	**29d**	96 (>30:1)

[a] Reactions were carried out using RI (30 equiv) and 1 M Et_3B in hexane (2.5 equiv) in CH_2Cl_2. [b] Major products. [c] Isolated yields. [d] Selectivity for the alkylated products **26b**−**29d**:the ethylated products **26a**−**29a** is determined by ^1H NMR analysis. [e] Reactions were carried out in the presence of $Zn(OTf)_2$ (1.0 equiv). [f] Reactions were carried out in the presence of Bu_3SnH (3 equiv).

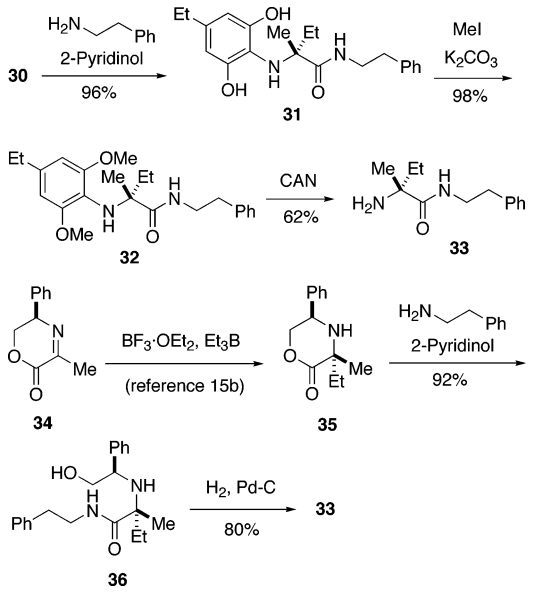
TABLE 5. Enantioselective Radical Addition to Ketimine 15[a]

			25a		**30**	
entry	ligand	Lewis acid	yield (%) [b]	ee (%) [c]	yield (%) [b]	ee (%) [c]
1	**A**	$Mg(OTf)_2$	72	2	trace	
2	**A**	$Zn(OTf)_2$	49	33	35	78 (*R*)
3	**A**	$Cu(OTf)_2$	32	−72	trace	
4	**B**	$Zn(OTf)_2$	19	23	63	80 (*R*)
5	**C**	$Zn(OTf)_2$	50	6	38	22 (*R*)
6	**D**	$Zn(OTf)_2$	36	3	31	racemic
7	**E**	$Zn(OTf)_2$	19	2	34	racemic
8	**F**	$Zn(OTf)_2$	34	8	19	racemic
9	**G**	$Zn(OTf)_2$	41	7	10	33 (*R*)
10	**H**	$Zn(OTf)_2$	32	3	16	14 (*R*)

[a] Reactions were carried out using 1 M Et_3B in hexane (2.5 equiv), ligand (1 equiv), and Lewis acid (1 equiv) in CH_2Cl_2 at −78 °C for 10 h. [b] Isolated yields. [c] Enantioselectivity was determined by HPLC analysis.

two-point-binding ketimine **15** (Scheme 5). The reactions of the highly reactive acceptor **15** were run in CH_2Cl_2 at −78 °C, and then the enantiomeric purities of products were checked by chiral HPLC analysis (Table 5). We expected that the coordination of the Lewis acid would be activating the substrate **15** for radical addition step. However, the enantioselective radical reaction of **15** was relatively slow as evidenced by low conversions after a short time. Increasing the reaction time to 10 h improved the chemical yields, and the formation of diethylated product **30** was newly observed in the presence of chiral Lewis acid. Therefore, it is assumed that the trapping step of the intermediate radical with Et_3B is suppressed by a bulky chiral Lewis acid. The formation of **30** may result from the accumulation of intermediate radical and enough time to couple with an ethyl radical. In general, the enantiomeric ratio of diethylated product **30** was better than that of ethylated product **25a**. The best result was obtained with the zinc Lewis acid and phenyl-substituted ligand **B** to afford the highest 80% ee of the diethylated product **30** in 63% yield, accompanied by a 19% yield of the ethylated product **25a** (entry 4).[23] The absolute configuration at the stereocenter of **30** was determined to be *R* by converting the adduct **30** into the amino acid derivative **33**, which was also synthesized from known chiral

SCHEME 6



compound **34** (Scheme 6).[15b,24] A *re* face radical addition to the zinc complex with octahedral geometry accounts for the observed product configuration (Figure 5).[25]

Next, the ethyl radical addition to ketimine **14** having a methoxy group was investigated under several reaction conditions using chiral box ligands and Lewis acids (Scheme 7). The reactions of the less reactive acceptor **14** were run at 20 °C for 15 h to give a mixture of ethylated product **22a** and diethylated product **37**. The results obtained by using $Cu(OTf)_2$ and box ligand **A** having a benzyl group are shown in Table 6. The

(23) The similar trends were observed in other radical reactions. In general, the phenyl-substituted box ligand **B**−zinc Lewis acid combination gives high selectivity, whereas the aliphatic substituted box ligands give high selectivity in combination with magnesium Lewis acid. See: (a) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (b) Porter, N. A.; Wu, J. H. L.; Zhang, G. R.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702. (c) Sibi, M. P.; Zimmerman, J.; Rheault, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4521.

(24) Harwood: L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051.

(25) For zinc-box ligand complex, see: (a) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955. (b) Sibi, M. P.; Zhang, R.; Manyem, S. *J. Am. Chem. Soc.* **2003**, *125*, 9306.

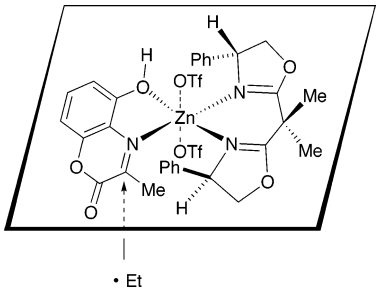


FIGURE 5. Model to explain enantioselectivity and absolute stereochemistry.

SCHEME 7

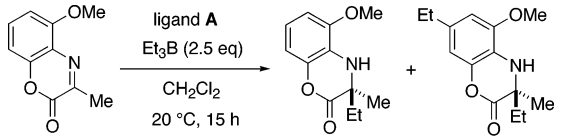


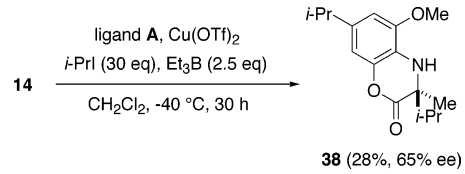
TABLE 6. Enantioselective Radical Addition to Ketimine 14[a]

			37[b]	
entry	Lewis acid	solvent	yield (%) [c]	ee (%) [d]
1	$Zn(OTf)_2$	CH_2Cl_2	31	−28 (*R*)
2	$Cu(OTf)_2$	CH_2Cl_2	35	54 (*S*)
3	$Cu(OTf)_2$	benzene	37	57 (*S*)
4	$Cu(OTf)_2$	toluene	31	56 (*S*)
5	$Cu(OTf)_2$	benzene/CH_2Cl_2	40	65 (*S*)

[a] Reactions were carried out using 1 M Et_3B in hexane (2.5 equiv), ligand **A** (1 equiv), and Lewis acid (1 equiv) at 20 °C for 15 h. [b] The monoethylated product **22a** was also obtained in 21−34% yields. [c] Isolated yields. [d] Enantioselectivity was determined by HPLC analysis.

combination of zinc Lewis acid and box ligand was less effective for the reaction of **14** (entry 1). Copper Lewis acid, which is generally unsuccessful under reductive radical conditions,[26] was quite efficient in radical addition to **14**. The copper Lewis acid mediated reaction of **14** proceeded slowly to give 65% ee of the diethylated product **37** in 40% yield, accompanied by the monoethylated product **22a**, after being stirred in benzene−CH_2Cl_2 (entry 5). The absolute configuration at the stereocenter of **37** was determined to be *S* by comparison with the chiral HPLC analysis and the optical rotation value of *R*-**37**, which was prepared from the *R*-adduct **30** by methylation of a phenolic hydroxyl group. Although the selectivity differs depending on substrates, ligands, and Lewis acids, the most noteworthy outcome of these experiments was that the opposite sense of stereoinduction is found between the zinc- and copper-mediated reactions (compare entries 2−5 in Table 6 with Table 5 and entry 1 in Table 6).[27] The reversal in enantioselectivity of copper-mediated reaction remains unclear; however, the similar reversal of stereochemistry was observed.[26−28] The distortion of square planar geometry of copper(II) center may be responsible for the reversal in enantioselectivity.[29] Finally, the chiral copper-mediated reaction of **14** with isopropyl radical was

SCHEME 8



conducted under tin-free iodine atom-transfer conditions using *i*-PrI and Et_3B (Scheme 8). Although the competitive reaction with ethyl radical and isopropyl radical gave a complex mixture, 65% ee of diisopropylated product **38** was isolated in 28% yield.

Conclusion

We have demonstrated the utility of aldimine and ketimines having a 2-phenolic hydroxyl group in intermolecular radical reactions. In addition to the radical reaction of aldimine derivatives, the radical addition to ketimine derivatives disclosed a broader aspect of the utility of imino radical acceptor for the synthesis of various types of amines.

Experimental Section

General Procedure for Enantioselective Radical Addition to Ketimines 15 and 14. A solution of ketimine **14** or **15** (0.5 mmol), Lewis acid (0.5 mmol), and ligand (0.5 mmol) in benzene/CH_2Cl_2 (1:2, v/v, 3 mL, for **14**) or CH_2Cl_2 (3 mL, for **15**) was stirred for 30 min under nitrogen atmosphere at 20 °C. To the reaction mixture was added Et_3B (1.0 M in hexane, 1.25 mL, 1.25 mmol) at 20 °C (for **14**) or −78 °C (for **15**). After being stirred at the same temperature for 10−15 h, the reaction mixture was diluted with saturated $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by column chromatography (hexane/AcOEt 4:1) afforded **30** or **37** along with **25a** or **22a**. Under similar reaction conditions, the isopropyl radical addition to ketimine **14** gave the diisopropylated product **38**.

(*R*)-3,7-Diethyl-3,4-dihydro-5-hydroxy-3-methyl-2*H*-1,4-benzoxazin-2-one (30). A colorless oil. IR ($CHCl_3$) 3597, 1760 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.47 (1H, s), 6.46 (1H, s), 5.41 (1H, br s), 3.61 (1H, br s), 2.53 (2H, q, J = 7.5 Hz), 1.79 (1H, m), 1.67 (1H, m), 1.45 (3H, s), 1.19 (3H, t, J = 7.5 Hz), 0.96 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 169.4, 145.3, 143.4, 137.8, 116.8, 110.5, 107.8, 57.7, 29.6, 28.3, 22.6, 15.4, 7.5. MS (EI^+): *m*/*z* 235 (M^+, 13), 178 (100). HRMS (EI^+): calcd for $C_{13}H_{17}NO_3$ (M^+) 235.1208, found 235.1217. HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, 254 nm) t_R (major, *R*) = 17.8 min, t_R (minor, *S*) = 25.9 min. A sample of 80% ee by HPLC analysis gave $[\alpha]^{22}_D$ −8.2 (*c* 1.1, $CHCl_3$).

(*R*)-3-Ethyl-3,4-dihydro-5-hydroxy-3-methyl-2*H*-1,4-benzoxazin-2-one (25a). A colorless oil. IR ($CHCl_3$) 1762 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.72 (1H, br t, J = 8.3 Hz), 6.62 (1H, br d, J = 8.3 Hz), 6.60 (1H, br d, J = 8.3 Hz), 5.53 (1H, br s), 3.86 (1H, br s), 1.83 (1H, m), 1.68 (1H, m), 1.47 (3H, s), 0.97 (3H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 170.1, 144.5, 141.9, 120.4, 119.4, 111.3, 108.4, 57.7, 29.7, 22.7, 7.4. MS (EI^+): *m*/*z* 207 (M^+, 40), 150 (100). HRMS (EI^+): calcd for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0892. HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, 254

(26) For few examples of chiral copper Lewis acid catalyzed radical reaction, see: Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. Also see ref 8c.

(27) For discussion on the reversal of stereochemistry, see: (a) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719. (b) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879. (c) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

(28) For a discussion of a square planar geometry model relative to copper, see: (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (b) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444. (c) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

(29) A working hypothesis for the reversed sense of stereoinduction is shown in Supporting Information.

nm) t_R (major, *R*) = 15.2 min, t_R (minor, *S*) = 19.9 min. A sample of 33% ee by HPLC analysis gave $[\alpha]^{24}_D$ −13.4 (*c* 1.3, $CHCl_3$).

(*S*)-3,7-Diethyl-3,4-dihydro-5-methoxy-3-methyl-2*H*-1,4-benzoxazin-2-one (37). A colorless oil. IR ($CHCl_3$) 3390, 1763 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.50 (1H, s), 6.47 (1H, s), 3.96 (1H, br s), 3.86 (3H, s), 2.57 (2H, q, *J* = 7.3 Hz), 1.83 (1H, m), 1.65 (1H, m), 1.44 (3H, s), 1.21 (3H, t, *J* = 7.3 Hz), 0.94 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 168.9, 147.3, 140.9, 135.3, 119.2, 107.8, 106.2, 57.7, 55.7, 30.0, 28.5, 23.0, 15.5, 7.5. MS (EI^+): *m*/*z* 249 (M^+, 29), 220 (100). HRMS (EI^+): calcd for $C_{14}H_{19}NO_3$ (M^+): 249.1365. Found: 249.1362. HPLC (Chiralcel AD-H, hexane/2-propanol 98/2, 0.5 mL/min, 254 nm) t_R (minor, *R*) = 13.5min, t_R (major, *S*) = 15.1 min. A sample of 65% ee by HPLC analysis gave $[\alpha]^{24}_D$ +9.6 (*c* 1.1, $CHCl_3$).

(*S*)-3-Ethyl-3,4-dihydro-5-methoxy-3-methyl-2*H*-1,4-benzoxazin-2-one (22a). A colorless oil. IR ($CHCl_3$) 1764 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.75 (1H, t, *J* = 7.9 Hz), 6.66 (1H, d, *J* = 7.9 Hz), 6.62 (1H, d, *J* = 7.9 Hz), 4.08 (1H, br s), 3.87 (3H, s), 1.84 (1H, m), 1.66 (1H, m), 1.45 (3H, s), 0.95 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 168.7, 147.5, 140.9, 121.7, 118.5, 108.9, 106.3, 57.6, 55.9, 30.2, 23.1, 7.6. MS (EI^+): *m*/*z* 221 (M^+, 23), 192 (100). HRMS (EI^+): calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1052, found 221.1059. HPLC (Chiralcel AD-H, hexane/2-propanol 98/2, 0.5 mL/min, 254 nm) t_R (minor, *R*) = 17.3 min, t_R (major, *S*) = 18.8 min. A sample of 21% ee by HPLC analysis gave $[\alpha]^{22}_D$ +4.2 (*c* 1.2, $CHCl_3$).

(*S*)-3,4-Dihydro-3,7-diisoproyl-5-methoxy-3-methyl-2*H*-1,4-benzoxazin-2-one (38). A colorless oil. IR ($CHCl_3$) 3403, 1762 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.51 (1H, s), 6.49 (1H, s), 4.10 (1H, br s), 3.87 (3H, s), 2.82 (1H, m), 2.10 (1H, m), 1.39 (3H, s), 1.22 (6H, d, *J* = 6.7 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ 168.7, 147.1, 141.0, 140.1, 119.1, 106.4, 104.9, 60.4, 55.9, 33.9, 31.4, 24.1, 19.2, 17.0, 15.9. MS (EI^+): *m*/*z* 277 (M^+, 37), 234 (100). HRMS (EI^+): calcd for $C_{16}H_{23}NO_3$ (M^+) 277.1678, found 277.1681. HPLC (Chiralcel AD-H, hexane/2-propanol 98/2, 0.5 mL/min, 254 nm) t_R (minor, *R*) = 11.1 min, t_R (major, *S*) = 13.5 min. A sample of 65% ee by HPLC analysis gave $[\alpha]^{20}_D$ +8.9 (*c* 1.3, $CHCl_3$).

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Supporting Information Available: Experimental procedure and characterization data for other compounds **8a**−**21d**, **23b**, **24b**, **25b**−**29d**, and **31**−**36**, and ^1H and ^{13}C NMR spectrum of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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