Radical Additions to C=N Bonds

Enantioselective Radical Addition to *N*-Acyl Hydrazones Mediated by Chiral Lewis Acids**

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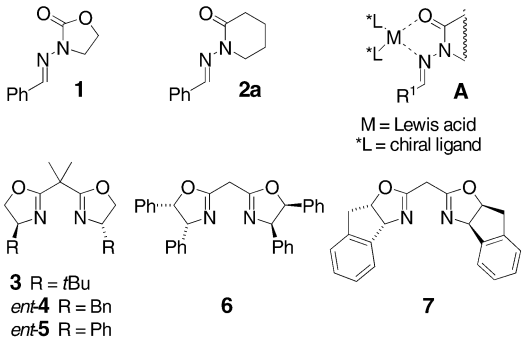
Radical addition reactions can generate new carbon–carbon bonds under mild, nonbasic conditions that may be compatible with a broad range of functionality within either the radical precursor or acceptor.[1] In recent years, campaigns toward achieving enantioselectivity in these processes have achieved some remarkable success, particularly in additions to C=C bonds.[2,3] Reductive radical addition to C=N bonds of imino radical acceptors generates chiral α-branched amines,[4] a class of compounds ubiquitous in biochemistry, medicinal chemistry, and natural product synthesis. The nonbasic character of alkyl radicals takes on particular importance in this case because the use of strongly basic nucleophiles may be compromised by the presence of acidic or electrophilic functionalities. Despite the very recent development of the reaction methodology, intermolecular radical addition to C=N bonds can already be carried out with acyclic stereocontrol through 1,2-asymmetric induction[5] or by using chiral auxiliaries covalently attached to either the carbon branch[6] or the nitrogen substituent.[7,8] We now report the first highly enantioselective radical additions to imino acceptors mediated by chiral Lewis acids, and also present the first evidence for chiral catalyst turnover in radical additions to C=N bonds.

Recently, asymmetric induction with chiral Lewis acids has been documented for radical addition to glyoxylate imines,[6b,9] but no catalytic cycle was evident judging from the low yield and/or high catalyst loading.[10] In these reactions, the two-point-binding glyoxylate moiety places an undesirable restriction on structural variations to the radical acceptor. We envisioned that incorporating the potential of chelation within the nitrogen substituent of the imine radical acceptor might be the foundation for a more versatile approach; the two-point-binding motif of the imine substrate (i.e. **A**, Scheme 1) would then be completely independent of its aldehyde precursor. With this in mind, we chose *N*-acyl hydrazones as a class of substrates for the development of the first asymmetric catalytic radical addition to C=N bonds.

Chiral oxazolidinone-derived *N*-acyl hydrazones are effective radical acceptors, but only upon activation with Lewis acids.[8,11] This fact gave rise to the expectation that achiral oxazolidinone **1** (Scheme 1) would not compete as a radical acceptor in the presence of its corresponding chelate **A** activated by a chiral Lewis acid. Our initial experiments, involving a screening of several chiral ligands (1 equiv) and Lewis acids (1 equiv) in the addition of isopropyl iodide to **1** using Et_3B/O_2 initiation at room temperature, met with disappointment. Although $ZnCl_2$ and $InCl_3$ had previously proved effective in activating the related chiral oxazolidinone-derived hydrazones,[8] significant enantioselectivity was never observed with **1**, and yields of the reductive isopropyl addition product were modest at best.



Scheme 1. *N*-Acyl hydrazones, selected bisoxazoline ligands, and their predicted binding mode (**A**) with Lewis acids.

Surprisingly, though, with valerolactam-derived *N*-acyl hydrazone acceptor **2a**,[12] we found a dramatic improvement in the selectivity of isopropyl addition (Scheme 2).[13] With 1 equivalent each of $ZnCl_2$ and bisoxazoline ligand **3**, a reasonable yield of reductive addition product **8a** was obtained (64%), but there was still no stereocontrol (Table 1, entry 1).[14] $InCl_3$ and $Mg(ClO_4)_2$ offered only modest yields (Table 1, entries 2 and 3), but we were gratified to find 57 and 66% *ee*, respectively, with these Lewis acids. Before any optimization, these results offered higher enantioselectivity than previously reported for any radical addition to a C=N bond.

Interestingly, in further variations of the Lewis acid, we found that copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) gave promising results (41% yield, 59% *ee*). In optimization studies, we tested the effect of a less polar medium, which we assumed would facilitate the assembly of a ternary complex of ligand, Lewis acid, and substrate. In contrast to $Mg(ClO_4)_2$[15] $Cu(OTf)_2$ did not exhibit a reversal of selectivity upon

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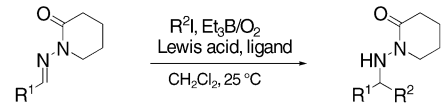

2a R^1 = Ph
2b R^1 = *p*-C_6H_4OMe
2c R^1 = *p*-C_6H_4Cl

8a–c (R^2=*i*Pr)
9 (R^2=Et)
10 (R^2=*c*-C_5H_9)
11 (R^2=*c*-C_6H_{11})
12 (R^2=CH_2Cl)

Scheme 2. Enantioselective radical addition to *N*-acyl hydrazones.

Table 1: Studies of Lewis acids, reaction medium, and chiral ligand structure in the addition of the isopropyl radical to **2a** (Scheme 2).[a]

Entry	Chiral Ligand	Lewis acid	Solvent	Yield[b] (**8a**) [%]	*ee*[c] [%]
1	**3**	$ZnCl_2$	CH_2Cl_2	64	< 5 (*R*)
2	**3**	$InCl_3$	CH_2Cl_2	33	57 (*R*)
3	**3**	$Mg(ClO_4)_2$	CH_2Cl_2	41	66 (*R*)
4	**3**	$Mg(ClO_4)_2$	PhH/CH_2Cl_2 (2:1)	21	30 (*S*)
5	**3**	$Cu(OTf)_2$	CH_2Cl_2	41	59 (*R*)
6[d,e]	**3**	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	67	84 (*R*)
7[d–f]	**3**	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	66	**95** (*R*)
8[d–g]	**3**	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	**94**	86 (*R*)
9[d,e]	**4**	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	47	5 (*S*)
10[d,e]	**5**	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	74	72 (*S*)
11[d,e]	**6**	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	73	94 (*S*)
12[d,e]	**7**	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	38	< 1

[a] Reaction conditions: Lewis acid (1 equiv), chiral ligand (1 equiv), 2-iodopropane (6 equiv), Et_3B/O_2 (6 equiv), 25 °C. For details see Experimental Section. [b] Yield of isolated product. [c] Enantiomeric excess by HPLC (95:5 hexane/2-propanol, Chiralcel OD or AD). Configuration of major product indicated in parentheses. [d] Et_3N was added after the reaction to facilitate isolation of the product. [e] In the presence of powdered molecular sieves (4 Å). [f] Preformed aquo complex [Cu(**3**)$(H_2O)_2(OTf)_2$] was used. [g] Larger amounts (10 equiv) of 2-iodopropane and Et_3B were used.

changing to benzene/CH_2Cl_2, and in this less polar medium, very good (*R*) enantioselectivity[16] was observed (Table 1, entries 3–6). Powdered molecular sieves (4 Å) had little effect on selectivity or yield. This facilitated the use of the preformed aquo complex [Cu(**3**)$(H_2O)_2(OTf)_2$], which can be activated by molecular sieves in situ as reported by Evans et al.[17] This latter modification (Table 1, entry 7) gave enhanced operational simplicity and raised the selectivity to 95% *ee* (66% yield). The yield improved with the use of larger amounts of 2-iodopropane and Et_3B (Table 1, entry 8), but this came at the expense of some selectivity.

Other bisoxazoline ligands were next examined.[18] Neither **4** nor **7** afforded enantioselectivity (Table 1, entries 9 and 12), but ligand **5** gave fairly good stereocontrol (Table 1, entry 10). The more highly substituted bisoxazoline **6** gave very high enantioselectivity with an improved yield relative to ligand **3** (compare Table 1, entries 7 and 11).

High enantioselectivity was maintained with variations to both radical precursor and acceptor (Table 2). Without further ligand optimization, additions of isopropyl to hydrazones **2b,c**[12] and additions of various radicals to **2a** were all highly enantioselective (Table 2, entries 1–6).[19] Importantly, the chloromethyl group of **12** (Table 2, entry 6) offers additional functionality for further synthetic transformations.

Table 2: Scope of radical addition to hydrazones **2a–2c** promoted by [Cu(**3**)$(H_2O)_2(OTf)_2$] and effects of Cu^{II} catalyst loading.[a]

Entry	Halide	**2**	Catalyst [equiv]	Product	Yield [%][b]	*ee* [%][c]
1	*i*PrI	**b**	1	(+)-**8b**	46	90
2	*i*PrI	**c**	1	(+)-**8c**	53	81
3	EtI[d]	**a**	1	(+)-**9**	88	83
4	*c*-C_5H_9I[d]	**a**	1	(+)-**10**	86	84
5	*c*-$C_6H_{11}I$[d]	**a**	1	(+)-**11**	84	89
6	$ClCH_2I$[d]	**a**	1	(+)-**12**	44[e]	95
7	*i*PrI	**a**	1	(*R*)-(+)-**8a**	66	95
8	*i*PrI	**a**	0.5	(*R*)-(+)-**8a**	71	81
9	*i*PrI	**a**	0.2	(*R*)-(+)-**8a**	83	58
10	*i*PrI	**a**	0.1	(*R*)-(+)-**8a**	74	46

[a] Reaction conditions: see Table 1, entry 7. [b] Yield of isolated product. [c] Enantiomeric excess (hexane/2-propanol, Chiralcel OD or AD). Enantiomer resolution by HPLC was confirmed by comparison with racemic control samples in all cases. [d] Alkyl halide: 10 equiv. [e] Unreacted **2a** recovered: 56%.

Finally, to test the potential for development of asymmetric catalysis, we checked for turnover by lowering the catalyst loading (Table 2, entries 7–10). The yield remained high, while enantioselectivity decreased. With 46% *ee* and 74% yield at 10 mol% catalyst loading, a catalytic cycle involving **3** is implied.[20] This is the first evidence of asymmetric catalysis in radical additions to C=N bonds.

In comparison with other carbon–carbon bond constructions for amine synthesis, such as the Strecker and the Mannich reactions, methodology for intermolecular radical addition to C=N bonds has only emerged recently. Levels of induction reported herein establish the viability of asymmetric catalysis in radical addition approaches to asymmetric synthesis of amines, and warrant continued development of these intriguing reactions.

Experimental Section

General procedure: A mixture of [Cu((*S,S*)-*t*Bu-box)$(H_2O)_2$-(OTf)](OTf)[17] and the hydrazone in CH_2Cl_2 (ca. 0.1 M) was stirred with powdered molecular sieves (4 Å; 4 g per mmol of catalyst) at room temperature for 30 min. Benzene was added to achieve a 2:1 ratio with CH_2Cl_2, followed by the iodide (3–10 equiv), and triethylborane (6 equiv, 1 M in hexane). A syringe pump was used to add oxygen (40 mL mmol^{-1} hydrazone) over approximately 2 h through a syringe needle in the headspace above the reaction mixture. If necessary (TLC), additional aliquots of oxygen were added to achieve higher conversion. After 10–38 h, the reaction mixture was diluted with EtOAc/Et_3N (5:1) and adsorbed onto silica gel by concentration to a dry, free-flowing powder. Flash chromatography (hexane/EtOAc) afforded the radical addition products with yields and enantiomeric purities indicated in Tables 1 and 2.

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[14] Under the conditions of Table 1 without chiral Lewis acid, the racemic adduct **8a** was obtained in 75% yield, suggesting that Et_3B could promote addition to **2a**.
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[18] Because ligands **4**–**7** are pseudoenantiomeric to **3**, compound **8a** obtained from these ligands has the opposite configuration.
[19] Small amounts (0–4%) of ethyl adducts (from Et_3B) were detected in some cases, and were separable by flash chromatography.
[20] The detailed mechanism is under investigation. Preliminary infrared spectroscopy shows increased intensity of N–H absorbance after workup. Because turnover of the chiral Lewis acid catalyst has been demonstrated, we speculate that the product before workup contains an N-BEt_2 moiety, which may suppress binding of product to catalyst. For related mechanistic proposals, see references [7] and [6c].

