# Highly Stereoselective Intermolecular Radical Addition to Aldehyde Hydrazones from a Chiral 3-Amino-2-oxazolidinone

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Asymmetric synthesis of chiral α-branched amines, ubiquitous substructures within natural products and other biologically active synthetic targets, is underdeveloped relative to that of other functional groups. Consequently, commonly used indirect synthetic methods exploit stepwise introduction of carbon−carbon bonds, stereogenic centers, and nitrogen (e.g., epoxide opening with *N*-nucleophiles). Direct asymmetric amine synthesis by addition of carbon nucleophiles to the C═N bond of carbonyl imino derivatives holds promise for improved efficiency by introducing the stereogenic center and carbon−carbon bond in one step. However, employing basic organometallic reagents for this purpose[1] often results in competing aza-enolization[2] and can lack generality or functional group tolerance, while Strecker[3a] and Mannich[3b] reactions restrict the incoming nucleophile to cyanide and enolizable carbonyl compounds, respectively. Versatile new stereocontrolled carbon−carbon bond construction methods for direct asymmetric amine synthesis under mild conditions are therefore in high demand.[3]

To address the general problem of asymmetric amine synthesis, nonpolar radical additions to C═N bonds[4,5] (Figure 1) would (a) circumvent imine enolization problems, (b) efficiently construct crowded C−C bonds, and (c) avoid some functional group restrictions associated with ionic transformations. Stereocontrolled intermolecular radical addition[6] to C═N bonds was unknown until Naito[7] and Bertrand[8] independently reported additions to chiral glyoxylate and malonate imino derivatives. In these cases the nearby carbonyl groups were required to activate the radical acceptor or attach a chiral auxiliary. Obviating these requirements would considerably enhance the versatility of radical additions for asymmetric amine synthesis. Toward this end, we envisioned a nitrogen-linked auxiliary approach incorporating Lewis acid activation and restriction of rotamer populations as key design elements. We now disclose preparation of novel *N*-acylhydrazones from *N*-amino-4-benzyl-2-oxazolidinone and their implementation for highly enantioselective intermolecular radical addition reactions.

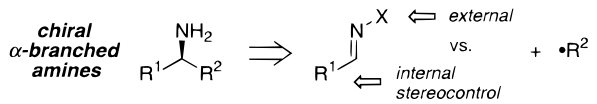


**Figure 1.** Retrosynthetic analysis of chiral α-branched amines according to a radical addition strategy and potential origins of stereocontrol.

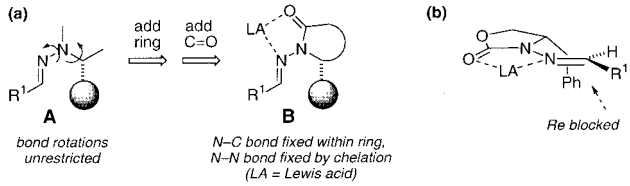


**Figure 2.** (a) Design of a hypothetical *N*-linked auxiliary approach for stereocontrolled radical addition to C═N bonds, with Lewis acid (LA) chelation inducing a rigid, electronically activated radical acceptor. (b) Implementation with *N*-acylhydrazones derived from 4-benzyl-2-oxazolidinone.

We first focused on incorporating features desirable for stereocontrol, namely *restricted rotamer populations* and *Lewis acid activation*, beginning with a hydrazone with a proximal stereogenic center (**A**, Figure 2). Constraining the C−N bond within a ring and including a carbonyl group would enable two-point binding of a Lewis acid to afford a rigid structure (**B**) with the stereocontrol element localized over one face of the hydrazone. The Lewis acid would also increase reactivity toward nucleophilic radicals[9] by lowering the LUMO energy of the C═N bond. Finally, we noted the facility of reductive cleavage of N−N bonds,[1d,10] whereby the *N*-linked auxiliary would be released for reuse after stereoisomer purification. Oxazolidinones[11,12] emerged as obvious initial candidates to test our hypothesis. Surprisingly, *N*-amino derivatives of oxazolidinones have appeared in the literature only rarely,[13] and to our knowledge have never been used for asymmetric synthesis.

(1) Reviews: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Enders, D.; Reinhold: U. *Tetrahedron Asymmetry* **1997**, *8*, 1895. (e) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999.

(2) Aza-enolization of imines with Grignard reagents: Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178. Less basic organocerium reagents also exhibit aza-enolization: Enders, D.; Diez, E.; Fernandez, R.; Martin-Zamora, E.; Munoz, J. M.; Pappalardo, R. R.; Lassaleta, J. M. *J. Org. Chem.* **1999**, *64*, 6329.

(3) For selected recent examples, see: (a) Strecker reactions: Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657. Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (b) Mannich reactions: Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168. (c) Allylation: Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942. (d) Imino-ene reaction: Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159.

(4) (a) Review of radical cyclizations involving nitrogen: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) General reviews of radical reactions in organic synthesis: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.

(5) For representative nonstereoselective intermolecular radical additions to C═N, see: Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* **1991**, *32*, 525. Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1991**, *32*, 3555. Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982. Miyabe, H.; Shibata, R.; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631. Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431. Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413.

(6) For reviews of acyclic stereocontrol in radical addition to C═C bonds, see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163 and references therein. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions; Concepts, Guidelines, and Synthetic Applications*; VCH: New York; 1995.

(7) (a) Miyabe, H.; Ushiro, C.; Naito, T. *J. Chem. Soc., Chem. Commun.* **1997**, 1789. (b) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569. (c) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (d) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443.

(8) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780. Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951.

(9) Protonation of imines leads to improved yields in radical addition. Russell, G. A.; Yao, C.-F.; Rajaratnam, R.; Kim, B. H. *J. Am. Chem. Soc.* **1991**, *113*, 373. For a review of Lewis acid effects in radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(10) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447.

(11) Evans, D. A.; Kim, A. S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 1, pp 345−356.

(12) Oxazolidinones have been used previously for stereocontrolled radical addition to alkenes. (a) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (b) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517.

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**Scheme 1**

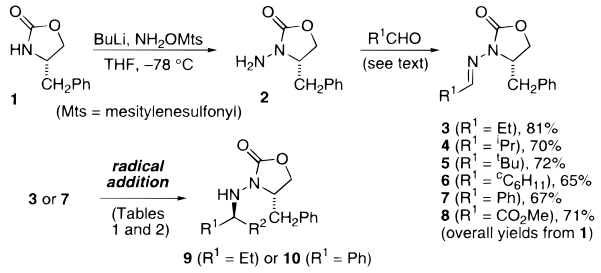



**Table 1.** Survey of Lewis Acids for Promotion of Radical Addition to Propionaldehyde Hydrazone **3** (Scheme 1)

| entry | Lewis acid | yield of **9c**, %[a] | recovery of **3**, % | product ratio (**9c**:**9b**:**9a**)[b] |
|---|---|---|---|---|
| 1 | none | NR | | |
| 2 | $BF_3{\cdot}Et_2O$ | 0 | | 0:0:100 |
| 3 | $MgBr_2$ | NR | | |
| 4 | $Yb(OTf)_3$ | 32 | | 96:4:0 |
| 5 | $InCl_3$ | 55 | | 92:8:0 |
| 6 | $ZnCl_2$ | 60 | 29 | 91:9:0 |
| 7 | $Zn(OTf)_2$ | 53 | 24 | 93:7:0 |

[a] Isolated yield of pure **9c** ($R^2$ = $^i$Pr). NR = no reaction. Reaction conditions: $Bu_3SnH$ (5 equiv) and $O_2$ (7 mL/mmol **3**) by syringe pump, $^i$PrI (10 equiv), $Et_3B$ (10 equiv), and Lewis acid (2 equiv), 2:1 $CH_2Cl_2$/ether, −78 °C → room temperature. [b] **9a**: $R^2$ = H. **9b**: $R^2$ = Et. Ratios by $^1$H NMR spectra after removal of tin residues.

Experimental evaluation of our design hypothesis began with preparation of the requisite hydrazones. Amination of commercially available (*S*)-4-benzyl-2-oxazolidinone (**1**, Scheme 1) with *n*-butyllithium and *O*-(mesitylenesulfonyl)hydroxylamine[13a,d] gave *N*-aminooxazolidinone **2** (75% yield). Condensation with various aldehydes (toluene; *p*-toluenesulfonic acid catalyst) afforded chiral *N*-acylhydrazones **3**−**8** as single isomers in 92−96% yield from **2**. Alternatively, introduction of aldehydes directly to the amination reaction mixture gave hydrazones via a convenient one-pot protocol.

A survey of a variety of simple Lewis acids in isopropyl radical addition ($Bu_3SnH$, $Et_3B/O_2$[14]) to hydrazone **3** (Scheme 1, Table 1) revealed initially that Lewis acid was required for the reaction (entry 1). With $BF_3{\cdot}OEt_2$, undesired C=N reduction occurred to afford **9a** in quantitative yield within 5 min, indicating that **3** was remarkably prone to Lewis acid activation.[15] Magnesium salts did not promote radical addition (entry 3), while ytterbium triflate (entry 4) gave modest yields. On the other hand, $InCl_3$ and Zn(II) salts afforded clean (albeit incomplete) conversion to desired adduct **9c** (entries 5−7).[16] Gratifyingly, initial examination by $^1$H NMR spectroscopy showed a single diastereomer (dr >98:2).

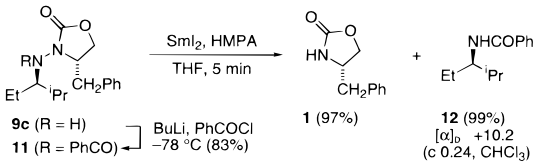
For diastereoselectivity analysis in radical additions, we selected hydrazones **3** and **7** with $ZnCl_2$ as the Lewis acid promoter (Table 2). With various secondary and tertiary alkyl iodide radical precursors, we were delighted to find that additions to both **3** and **7** occurred with *excellent stereocontrol in all cases* to afford *N*-acylhydrazines **9c**−**f** and **10c**−**f**.[16] Chemical correlation and X-ray crystallographic analysis confirmed the absolute configurations of **9c** and **10f**.[17] After *N*-benzoylation of **9c** (Scheme 2), exposure of **11** to $SmI_2$[10] cleanly afforded **12** (99% yield) and **1** (97% yield) within 5 min.

**Table 2.** Radical Addition Reactions of Various Alkyl Iodides with Hydrazones **3** and **7** in the Presence of $ZnCl_2$[c]

| entry | $R^1$ | $R^2$ | product, yield (%)[a] | diastereomer ratio[b] |
|---|---|---|---|---|
| 1 | Et | $^i$Pr | **9c**, 60 | 99:1 |
| 2 | Et | $^c$C$_5$H$_9$ | **9d**, 59 | 96:4 |
| 3 | Et | $^c$C$_6$H$_{11}$ | **9e**, 28 | 97:3 |
| 4 | Et | $^t$Bu | **9f**, 54 | 95:5 |
| 5 | Ph | $^i$Pr | **10c**, 42 | 99:1 |
| 6 | Ph | $^c$C$_5$H$_9$ | **10d**, 59 | 96:4 |
| 7 | Ph | $^c$C$_6$H$_{11}$ | **10e**, 30 | 99:1 |
| 8 | Ph | $^t$Bu | **10f**, 83 | 93:7 |

[a] Isolated yield. [b] Ratios by HPLC (**9c**−**f**) or GCMS (**10c**−**f**) versus authentic mixtures. In separate reactions, diastereomer ratios of **9e** and **9f** were reproduced within 0.5%. [c] Reaction conditions: see Table 1.

**Scheme 2**




In conclusion, a novel *N*-acylhydrazone auxiliary approach gives excellent stereocontrol in radical addition to C=N bonds. Notably, this is the first such radical addition that does not require adjacent carbonyl functionality for auxiliary linkage or acceptor activation. In contrast to related additions to α,β-unsaturated amides which require a larger blocking group,[12,18] the simple benzyl control element affords high selectivity in all cases examined. This distinction can be attributed to the closer proximity of the control element and acceptor carbon in hydrazones **3** and **7** relative to *N*-enoyloxazolidinones, resulting in more effective steric blocking while limiting rotational freedom. With excellent stereocontrol now at hand, evaluation of additional hydrazones, reaction optimization, and modifications to facilitate direct auxiliary removal are underway, as are efforts toward chiral Lewis acid catalysis.

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**Supporting Information Available:** Characterization data for **2**−**12** and selected experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Kim, M.; White, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 1172. (b) Ciufolini, M. A.; Shimizu, T.; Swaminathan, S.; Xi, N. *Tetrahedron Lett.* **1997**, *38*, 4947. (c) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. (d) The more convenient *N*-electrophile *O*-(diphenylphosphinyl)hydroxylamine also gives reliable results in the amination of **1** (73−79%). Details will be reported elsewhere.

(14) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403. Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692.

(15) Reduction ($Bu_3SnH$, $BF_3{\cdot}OEt_2$) of *N*-acylhydrazones proved to be generally efficient; from appropriate ketone *N*-acylhydrazones, both diastereomers of **9c**−**f** and **10c**−**f** were acquired for characterization purposes (see Supporting Information).

(16) Separable ethyl radical adduct **9b** (or **10b**) was observed (<10% yield) in all cases. The remaining mass balance was unreacted hydrazone **3** (or **7**). Primary halides have thus far given low yields in these reactions, presumably due to ineffective chain transfer.[7] Preliminary experiments with **8** gave **1** as the major product (57% yield).

(17) Configurations of **9d**−**f** and **10c**−**e** are assigned by analogy with **9c** and **10f**. These are consistent with model **B** (Figure 2), although the available data do not permit rigorous exclusion of alternative substrate−Lewis acid binding modes. (a) (*S*)-Valinol was converted to **12** with $[\alpha]_D$ +10.0 (*c* 1.0, $CHCl_3$) by treatment of its *N*-Boc-*O*-tosylate derivative with $Me_2CuLi$ followed by interchange of the carbamate to benzamide. (b) Benzoylation of **10f** (81% yield) as indicated in Scheme 2 gave material suitable for X-ray crystallography (see Supporting Information).

(18) Sibi et al. found that 4-(diphenylmethyl)-2-oxazolidinone was needed for good stereocontrol (dr = 45:1) in isopropyl radical addition to *N*-cinnamoyl derivatives (4-benzyl-2-oxazolidinone gave dr = 2:1).[12b]