Intermolecular Alkyl Radical Addition to Chiral *N*-Acylhydrazones Mediated by Manganese Carbonyl

Gregory K. Friestad* and Jun Qin

Department of Chemistry
University of Vermont
Burlington, Vermont, 05405

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Chiral α-branched amines are common substructures of bioactive synthetic targets. Direct asymmetric amine synthesis by radical addition to the C=N bond of carbonyl imino derivatives[1] holds promise for improved efficiency by introducing the stereogenic center and carbon−carbon bond in one step under mild, nonbasic conditions. Because related additions of basic organometallic reagents[2] often suffer from competing aza-enolization[3] or lack of generality and functional group tolerance, an ongoing search for new stereocontrolled carbon−carbon bond-construction methods has led to several promising developments,[4] including stereocontrolled intermolecular radical addition.[5]

We have designed and implemented chiral *N*-acylhydrazones from *N*-amino-4-benzyl-2-oxazolidinone (**1**) for stereoselective radical addition incorporating Lewis acid activation[6] and restriction of rotamer populations as key design elements.[7] In this approach (Scheme 1), as well as in radical additions by Naito[8] and Bertrand,[9] secondary and tertiary alkyl iodides were effective, but additions of primary alkyl radicals have been undermined by competing ethyl radical addition. We envisioned that new conditions enabling the use of primary iodides would dramatically expand the range of potential synthetic applications. We now disclose such conditions: photolysis of manganese carbonyl mediates highly stereoselective intermolecular radical addition of primary alkyl halides to *N*-acylhydrazones.

Scheme 1

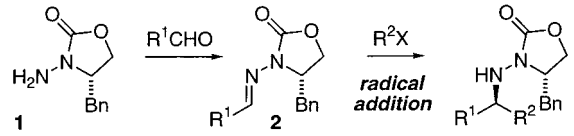
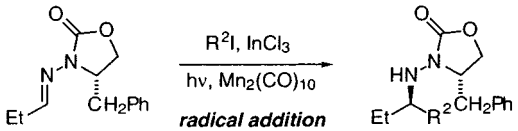
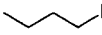
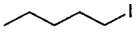
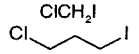
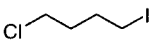


Table 1. Results of Metal-Mediated Radical Addition to Propionaldehyde Hydrazone **2a**[g]



mediator (equiv)	alkyl halide R^2X	adduct, yield[b]	dr
Et_3B (5)[a]	CH_3CH_2I	**3**, 33%	-
Me_6Sn_2 (1.2)	CH_3CH_2I	**3**, 56%	-
$Mn_2(CO)_{10}$ (1.0)	CH_3CH_2I	**3**, 85%	-
$Mn_2(CO)_{10}$ (2.0)	CH_3I	**4S**, 48%[c,d]	95:5[e]
$Mn_2(CO)_{10}$ (2.0)		**5R**, 66%	94:6[e]
$Mn_2(CO)_{10}$ (2.0)		**6R**, 78%	95:5[e]
$Mn_2(CO)_{10}$ (2.0)		**7R**, 79%	96:4[e]
$Mn_2(CO)_{10}$ (2.0)		**8R**, 54%[c]	95:5[f]
$Mn_2(CO)_{10}$ (1.0)		**9R**, 75%	95:5[f]
$Mn_2(CO)_{10}$ (2.0)	$ClCH_2I$	**10R**, 63%	93:7[e]
$Mn_2(CO)_{10}$ (2.0)		**11R**, 52%	96:4[f]
$Mn_2(CO)_{10}$ (2.0)		**12R**, 55%	96:4[e]
$Mn_2(CO)_{10}$ (2.0)	Cl_2CHBr	**13R**, 38%[c,d]	98:2[f]

[a] Irradiation was omitted. [b] Isolated yields of purified diastereomer mixtures. R or S denotes the configuration of the new stereogenic center. Addition of methyl iodide gives S configuration due to the lower priority of the methyl ligand. [c] 20 equiv of R^2X was used. [d] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used in removal of Mn byproducts. [e] Ratio by HPLC (Chiralcel OD, 2-PrOH/hexane). [f] Ratio by ^1H NMR. [g] Reaction conditions: To a deoxygenated solution of $InCl_3$ (2.2 equiv) and hydrazone **2a** in CH_2Cl_2 (0.1 M) was added the mediator and R^2X (10 equiv) followed by irradiation (300 nm, Pyrex) for 1−2 d at ca. 35 °C under N_2.

We recognized two significant problems interfering with primary radical addition using existing methods: Less stable 1° radicals (versus 2° or 3°) might not be sufficiently long-lived to avoid premature reduction by Bu_3SnH, and generation of the desired radical from a 1° alkyl iodide requires an unfavorable iodine atom transfer to Et• when using Et_3B or Et_2Zn as the initiator without Bu_3SnH. Thus, we typically recovered hydrazones unchanged when attempting the use of primary iodides in the presence of Bu_3SnH, while Et• addition was the major product in the absence of Bu_3SnH. These observations led us to consider photolytic initiation in the presence of hexamethylditin.[10] Unfortunately, these conditions never reached desirable efficiencies for Et• additions to hydrazone **2a** (Table 1) in part due to complications from the use of acetone as a sensitizer.

(1) (a) Reviews of radical addition to C=N bonds: Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.

(2) 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.

(3) (a) Aza-enolization of imines with Grignard reagents: Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178. Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 683. (b) Deprotonation of iminium ions can be competitive with addition: Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (c) 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.

(4) For selected recent examples, see: (a) Review of Strecker reactions: Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875. (b) Mannich reactions: Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (c) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (d) Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891. (e) Miura, K.; Tamaki, K.; Nakagawa, T.; Hosomi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1958.

(5) 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.

(6) 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.

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(8) Radical additions to camphorsultam-modified glyoxylate and malonate oxime ether derivatives: (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.

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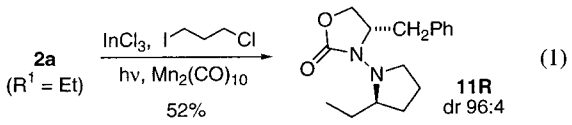
We were intrigued by the notion that the photolytic Mn−Mn homolysis of manganese carbonyl [$Mn_2(CO)_{10}$],[11] which requires no sensitizer (λ_{max} 340 nm, $\sigma_{Mn-Mn} \rightarrow \sigma^*_{Mn-Mn}$), could be exploited for intermolecular addition of primary alkyl radicals to C=N bonds. Interestingly, Parsons noted that reaction of •Mn(CO)$_5$ with 1° halides was much more facile than with 2° or 3° halides.[12] Furthermore, avoiding the difficult removal of toxic tin byproducts was attractive.

In a test case of ethyl iodide addition to **2a**[7] (Table 1), irradiation (300 nm) of **2a**, EtI (10 equiv), and $Mn_2(CO)_{10}$ (1 equiv) with $InCl_3$ (2.3 equiv) as a Lewis acid[13] in CH_2Cl_2 afforded **3**[7] in 85% yield,[14] a dramatic improvement over use of triethylborane or hexamethylditin. Several other halides, including methyl iodide and difunctional halides,[15] were also effective, furnishing radical addition products **4S**, **5R**−**13R**[16] with high diastereomer ratios (Table 1). Products **10R**, **12R,** and **13R** bear undisturbed chloride substituents, offering opportunities for further elaboration. Interestingly, 3-chloro-1-iodopropane led exclusively to pyrrolidine **11R** (eq 1), presumably via radical addition and in situ nonradical cyclization; this constitutes a potentially useful hybrid radical−ionic annulation.



(1)

Ethyl radical addition to nine additional hydrazones **2b**−**2j** (Table 2) occurred in good yields (with the exception of **2j**). These adducts **4R, 5S**−**13S** are epimeric to **4S, 5R**−**13R** (Table 1) with respect to the new stereogenic center, demonstrating a useful feature inherent in this carbon−carbon bond-construction approach to amine synthesis. The epimeric configuration can be selected by either (A) employing the enantiomeric auxiliary or (B) interchanging the roles of R^1 and R^2 in the alkyl halide and aldehyde precursors of Scheme 1.[17] By combining these two tactics, the optimal roles of R^1 and R^2 with respect to yield and selectivity can be chosen. Such strategic flexibility is not readily achieved through Strecker, Mannich, or organometallic addition strategies.

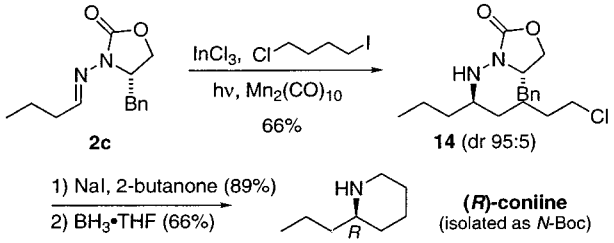
To illustrate its potential in asymmetric amine synthesis, we applied Mn-mediated radical addition to prepare the piperidine alkaloid coniine (Scheme 2).[18] Although propyl radical addition to a difunctional hydrazone could be used, interchanging the alkyl groups in the coupling partners (i.e., R^1 and R^2 of Scheme 1) gave superior results. Accordingly, Mn-mediated radical addition of 4-chlorobutyl iodide to **2c** furnished **14** with high diastereoselectivity.[19] Cyclization and reductive N−N cleavage[20] afforded *R*-coniine (four steps from butyraldehyde).[21]

Table 2. Preparation and $Mn_2(CO)_{10}$-Mediated Ethyl Radical Addition to Aldehyde Hydrazones According to Scheme 1[f]

aldehyde R^1CHO (or acetal)	hydrazone, yield[a]	Et• adduct, yield[b]	dr
CH_3CHO	**2b**, 66%	**4R**, 66%	95:5[d]
CHO	**2c**, 87%	**5S**, 63%	95:5[d]
CHO	**2d**, 89%	**6S**, 72%	97:3[d]
CHO	**2e**, 88%	**7S**, 77%	97:3[d]
CHO	**2f**, 85%	**8S**, 65%	95:5[e]
$ClCH_2CH(OMe)_2$	**2g**, 85%	**10S**, 57%	93:7[d]
Cl CHO	**2h**, 95%	**11S**, 60%	93:7[e]
Cl CHO	**2i**, 89%	**12S**, 62%	97:3[d]
$Cl_2CHCH(OEt)_2$	**2j**, 54%	**13S**, 34%[c]	89:11[e]

[a] Isolated yield. [b] Isolated yield of diastereomer mixture. [c] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used in removal of Mn byproducts. [d] Ratio by HPLC. [e] Ratio by ^{1}H NMR. [f] Reaction conditions for hydrazone formation: Aldehyde (5−10 equiv), **1**, *p*-toluenesulfonic acid, CH_2Cl_2, rt. For radical addition conditions see Table 1.

Scheme 2



In summary, manganese carbonyl mediates stereoselective photolytic radical addition of alkyl iodides to chiral *N*-acylhydrazones with tolerance of additional functionality in both coupling partners and excellent flexibility for synthetic planning.

Acknowledgment. We thank the NSF (CHE-0096803), Research Corporation, Petroleum Research Fund, Vermont EPSCoR, and the University of Vermont for generous support.

Supporting Information Available: Characterization data for **2**−**14** with selected experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Reviews: Pauson, P. L. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995, Vol. 2, pp 1471−1474. Meyer, T. J.; Caspar, J. V. *Chem. Rev.* **1985**, *85*, 187. (b) Halogen atom transfer to •Mn(CO)$_5$: Herrick, R. S.; Herrinton, T. R.; Walker, H. W.; Brown, T. L. *Organometallics* **1985**, *4*, 42.

(12) Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *Tetrahedron Lett.* **1999**, *40*, 6095. Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *J. Chem. Soc., Perkin 1* **2000**, 1187.

(13) Use of $ZnCl_2$ as the Lewis acid was precluded due to limited solubility.

(14) Control experiments revealed a requirement for both irradiation and $Mn_2(CO)_{10}$. Without $InCl_3$, the reaction was slow (21% yield after 2 d).

(15) Addition of 1,2-dihaloethanes occurred in rather low yield (0−14%), probably due to radical fragmentation.

(16) Configurations are assigned by analogy with **9R** and **14**, which were unambiguously determined through chemical correlation with valine and coniine, respectively. See ref 7.

(17) For related examples of this tactic, see: (a) Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; pp 275−339. (b) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

(18) Coniine is a common target for testing asymmetric amine synthesis methodology. For selected asymmetric syntheses, see: (a) Guerrier, L. Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (b) Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173. (c) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623. (d) Reding, M. T.; Buchwald, S. R. *J. Org. Chem.* **1998**, *63*, 6344. (e) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155. (f) For reviews of asymmetric syntheses of piperidine alkaloids, see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.

(19) Identical results were observed on ca. 200-mg or 1-g scale.

(20) N−N cleavage with BH_3•THF: Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970**, *35*, 1468. For recent examples, see: Enders, D.; Lochtman, R.; Meiers, M.; Muller, S.; Lazny, R. *Synlett* **1998**, 1182.

(21) Conversion of volatile *R*-coniine to its *N*-*tert*-butoxycarbonyl derivative facilitated isolation and characterization.