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Mn-Mediated Coupling of Alkyl Iodides and Chiral *N*-Acylhydrazones: Optimization, Scope, and Evidence for a Radical Mechanism

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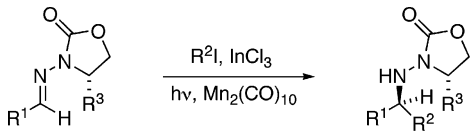

- *method development and stereoselectivity*
- *carbometallation vs. radical mechanism*
- *evidence concerning the role of* R^2–$Mn(CO)_5$

Stereoselective radical additions have excellent potential as mild, nonbasic carbon−carbon bond constructions for direct asymmetric amine synthesis. Efficient intermolecular radical addition to C═N bonds with acyclic stereocontrol has previously been limited mainly to secondary and tertiary radicals, a serious limitation from the perspective of synthetic applications. Here, we provide full details of the use of photolysis with manganese carbonyl to mediate stereoselective intermolecular radical addition to *N*-acylhydrazones. Photolysis (300 nm) of alkyl halides and hydrazones in the presence of $Mn_2(CO)_{10}$ and $InCl_3$ as a Lewis acid led to reductive radical addition; diastereomer ratios ranged from 93:7 to 98:2 at ca. 35 °C. The reaction tolerates additional functionality in either reactant, enabling subsequent transformations as shown in an efficient asymmetric synthesis of coniine. A series of hydrazones bearing different substituents on the oxazolidinone auxiliary were compared; consistently high diastereocontrol revealed that the identity of the substituent had little practical effect on the diastereoselectivity. Further mechanistic control experiments confirmed the intermediacy of radicals and showed that independently prepared alkyl- or acylmanganese pentacarbonyl compounds do not undergo efficient addition to the *N*-acylhydrazones under thermal or photolytic (300 nm) conditions. These Mn-mediated conditions avoid toxic tin reagents and enable stereoselective intermolecular radical additions to C═N bonds with the broadest range of alkyl halides yet reported, including previously ineffective primary alkyl halides.

Introduction

Chiral α-branched amines are common substructures of bioactive synthetic targets such as alkaloids and amino acids. Direct asymmetric amine synthesis by 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. Furthermore, the most versatile methods to achieve this objective would enable disconnection of either C−C bond at the amine stereogenic center (Scheme 1); the choice could be made depending on issues of synthetic expediency, such as the availability of precursors and the presence of complicating structural features. In this context, development of general methods for acyclic stereocontrol remains a significant challenge, especially within the constraints of mild reaction conditions compatible with complex multifunctional precursors.

Stereocontrolled intermolecular radical addition[2] to imino compounds is an attractive approach to asymmetric amine

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(1) Reviews: Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315−1392. Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. Alvaro, G.; Savoia, D. *Synlett* **2002**, 651−673. Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999−1004.

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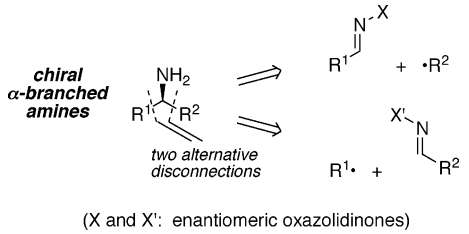
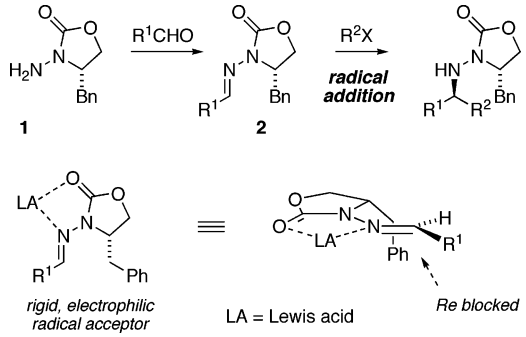
SCHEME 1



synthesis.[3] Additions of basic organometallic reagents often suffer from competing aza-enolization[4] or lack of generality and functional group tolerance. In contrast, carbon-centered radicals are nonbasic, avoiding aza-enolization, and can be generated under mild conditions. Their intermolecular addition reactions to π systems can accommodate the presence of additional functionality in both precursors because they exhibit good chemoselectivity for addition to C═C and C═N bonds. The reaction conditions are quite flexible; although neutral conditions are typical, nonpolar radical intermediates are usually compatible with Lewis acids or bases. Many of these attributes offer significant advantages relative to reactions of traditional organometallic nucleophiles. Seminal work by Naito[5] and Bertrand[6] to develop intermolecular radical additions to imino compounds has inspired increasing effort toward this goal.[7,8]

We envisioned that new radical addition conditions enabling the use of primary iodides would dramatically expand the range of potential synthetic applications of radical additions to C═N bonds. We were indeed successful in developing suitable conditions to achieve this goal: photolysis of manganese carbonyl mediates highly stereoselective intermolecular radical addition of primary alkyl halides to *N*-acylhydrazones.[9] Here, we disclose optimization and expansion of the scope of these novel Mn-mediated reactions, along with studies of stereoselectivity and new experimental evidence regarding the mechanism; a complete discussion of the development of the methodology is also provided.

SCHEME 2



Background

We have designed novel chiral *N*-acylhydrazones as chiral imino acceptors incorporating Lewis acid activation[10] and restriction of rotamer populations (Scheme 2). Versatile and reliable methods for their efficient preparation from *N*-amino-2-oxazolidinones (e.g., **1**) have been developed,[11] such that the hydrazones exemplified by **2** have been prepared successfully from every aldehyde attempted (greater than 60 to date). Our initial studies of radical[12] and allylsilane[13] additions uncovered the excellent synthetic potential of these novel chiral hydrazones, and several other related addition reactions have since been reported.[14] Despite the effectiveness of this stereocontrol design for radical additions to *N*-acylhydrazones, the earlier reactions

(2) General reviews of radical reactions and their stereocontrol: (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: New York, 2001. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: New York, 1995. (c) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171. (d) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2563−2579. (e) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856. (f) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286. (g) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. (h) Hart, D. J. *Science* **1984**, *223*, 883−887.

(3) Reviews of radical additions to imines and related acceptors: (a) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594.

(4) (a) Aza-enolization of imines with Grignard reagents: Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178−2180. Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 683−684. Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7−14. (b) Even organocerium reagents, considered relatively nonbasic nucleophiles, can promote aza-enolization of hydrazones. Enders, D.; Diez, E.; Fernandez, R.; Martin-Zamora, E.; Munoz, J. M.; Pappalardo, R. R.; Lassaletta, J. M. *J. Org. Chem.* **1999**, *64*, 6329−6336.

(5) (a) Miyabe, H.; Ushiro, C.; Naito, T. *J. Chem. Soc., Chem. Commun.* **1997**, 1789−1790. (b) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176−185. (c) For a review of the Naito group's work in this area, see: Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140−1157. (d) For more recent examples, see: Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227−4235. (e) McNabb, S. B.; Ueda, M.; Naito, T. *Org. Lett.* **2004**, *6*, 1911−1914. (f) Ueda, M.; Miyabe, H.; Sugino, H.; Naito, T. *Org. Biomol. Chem.* **2005**, *3*, 1124−1128. (g) Ueda, M.; Miyabe, H.; Teramachi, M.; Miyata, O.; Naito, T. *J. Org. Chem.* **2005**, *70*, 6653−6660. (h) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190−6193.

(6) Radical additions to chiral glyoxylate imines: Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780−782. Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148−1150. Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951−3961. Bertrand, M.; Feray, L.; Gastaldi, S. *Comptes Rend. Acad. Sci. Paris, Chimie* **2002**, *5*, 623−638.

(7) (a) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87−89. (b) Yamamoto, Y.; Maekawa, M.; Akindele, T.; Yamada, K.; Tomioka, K. *Tetrahedron* **2005**, *61*, 379−384. (c) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. *J. Org. Chem.* **2004**, *69*, 1531−1534. (d) Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797−1799. (e) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509−3511. (f) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985−1987. Also see ref 14a. (g) Masson, G.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772−1775. (h) Alves, M. J.; Fortes, G.; Guimarães, E.; Lemos, A. *Synlett* **2003**, 1403−1406. (i) Liu, X.; Zhu, S.; Wang, S. *Synthesis* **2004**, 683−691. (j) Singh, N.; Anand, R. D.; Trehan, S. *Tetrahedron Lett.* **2004**, *45*, 2911−2913. (k) Halland, N.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290−1295. (l) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324−3327. (m) Cannella, R.; Clerici, A.; Pastori, N.; Regolini, E.; Porta, O. *Org. Lett.* **2005**, *7*, 645−648. (n) Clerici, A.; Cannella, R.; Panzeri, W.; Pastori, N.; Regolini, E.; Porta, O. *Tetrahedron Lett.* **2005**, *46*, 8351−8354. (o) Risberg, E.; Fischer, A.; Somfai, P. *Tetrahedron* **2005**, *61*, 8443.

(8) Friestad, G. K.; Shen, Y.; Ruggles, E. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5061−5063.

(9) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922−9923.

(10) 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*, 373−375.

(11) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236−6239.

(12) (a) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329−8330. (b) Friestad, G. K.; Draghici, C.; Soukri, M.; Qin, J. *J. Org. Chem.* **2005**, *70*, 6330−6338.

(13) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491−4493.

(14) (a) Radical addition: Fernández, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461−2464. (b) Allylindium addition: Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1749−1752. (c) Mannich-type reaction: Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792−4796.

were limited to secondary and tertiary radicals.[12] In fact, this is a routine limitation to intermolecular radical addition reactions.

In the previous studies, we typically recovered unchanged hydrazones when attempting the addition of primary iodides in the presence of Bu_3SnH, whereas $Et^\bullet$ addition (from Et_3B/O_2 initiation[15]) was the major product in the absence of Bu_3SnH. The latter is a common problem associated with the use of triethylborane or diethylzinc as radical initiators. These observations can be attributed to some significant problems which have plagued most efforts to apply intermolecular additions of primary alkyl radicals using existing methods: First, less-stable 1° radicals (vs 2° or 3°) might not be sufficiently long lived to avoid premature reduction by hydrogen-atom abstraction from solvent (H−S, eq 1). Second, in most cases, the iodine atom transfer between the primary $Et^\bullet$ and a primary alkyl iodide (eq 2) is thermoneutral and disfavored relative to side reactions of $Et^\bullet$ (e.g., undesired addition reactions of $Et^\bullet$ or quenching by H-atom transfer from solvent according to eq 1).

$$R^\bullet + H{-}S \rightarrow R{-}H + {}^\bullet S \quad (1)$$

$$Et^\bullet + I{-}R \rightarrow Et{-}I + {}^\bullet R \quad (2)$$

These considerations led us to examine photolytic initiation. Kim has employed nonreductive radical conditions using photochemical initiation and hexamethylditin to mediate addition−elimination reactions of *C*-sulfonyl oxime ethers, a rare example of the successful intermolecular addition of various functionalized primary alkyl halides.[16] Though Kim's addition−elimination reactions were mechanistically distinct from our desired process, and did not result in a new stereogenic center, the precedent was encouraging, and we in fact attempted the use of Kim's conditions in our earlier study of tin- and boron-mediated radical additions.[12] Although ethyl iodide addition to acylhydrazone **2** provided a promising 56% yield, unfortunately, the reaction was not general and was complicated by exchange of the carbonyl component with the acetone sensitizer. This previous study suggested a possible improvement of these photochemical nonreductive conditions through the use of a reagent which could react in a fashion similar to $Me_3SnSnMe_3$ but which would not require a sensitizer.

It became interesting to consider whether dimanganese decacarbonyl [$Mn_2(CO)_{10}$] might offer a solution to the problem of primary alkyl radical addition to *N*-acylhydrazones. This commercially available yellow solid has a molecular structure consisting of two $Mn(CO)_5$ units, each with octahedral coordination, linked by a weak manganese−manganese single bond (38 kcal mol^{-1}).[17] $Mn_2(CO)_{10}$ is UV active; its λ_{max} is 324 nm (cyclohexane), associated with the $\sigma \rightarrow \sigma^*$ transition of the Mn−Mn bond, which may be homolyzed by thermal or photochemical conditions (eq 3).[18,19] The resulting $^\bullet Mn(CO)_5$ has been detected using EPR spectroscopy and spin-trapping techniques.[20]

$$(CO)_5Mn{-}Mn(CO)_5 \xrightarrow{h\nu} 2(CO)_5Mn^\bullet \quad (3)$$

$$(CO)_5Mn^\bullet + I{-}R \rightarrow (CO)_5Mn{-}I + {}^\bullet R \quad (4)$$

The reactivity profile of $^\bullet Mn(CO)_5$ includes hydrogen-[21] or halogen-atom[22] abstraction reactions (eq 4); the latter behavior is quite similar to that of $^\bullet SnR_3$. Halogen-atom abstraction from alkyl halides by $^\bullet Mn(CO)_5$ generates alkyl radicals along with products of the type $X{-}Mn(CO)_5$[17b] at rates (C−I > C−Br > C−Cl) which are inversely proportional to the strength of the C−X bond. Brown has shown that the rates are also decreased by steric hindrance: when bulky phosphines replace carbonyl ligands on the Mn, the halogen-atom abstraction is inhibited.[22b]

Unlike the more well-established oxidative radical reactions using $Mn(OAc)_3$,[23] applications of $Mn_2(CO)_{10}$ in organic synthesis are just beginning to emerge. Recent explorations by Parsons and others with Wurtz-type homocoupling,[24] radical cyclizations,[25] TEMPO trapping,[25b] and polymerization[26] have shown some interesting attributes of this reagent. In the case of the homocoupling, success was ascribed in part to high concentrations of the carbon-centered radicals produced in the photolysis with $Mn_2(CO)_{10}$. Interestingly, Parsons noted that reaction of $^\bullet Mn(CO)_5$ with 1° halides was much more facile than with 2° or 3° halides. This is contrary to the usual order of reactivity for generation of alkyl radicals, yet in agreement with Brown's

(15) Under Et_3B or Et_2Zn conditions, the action of O_2 on these initiators results in formation of $Et^\bullet$; iodine atom transfer to $Et^\bullet$ from an alkyl iodide (R−I) generates the desired radical $R^\bullet$. Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403−409.

(16) (a) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138−5139. Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982−5983. Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190−12191. Jeon, G.-H.; Yoon, J.-Y.; Kim, S.; Kim, S. S. *Synlett* **2000**, 128−130. Kim, S.; Kim, N.; Yoon, J.-Y.; Oh, D. H. *Synlett* **2000**, 1148−1150. Kim, S.; Kavali, R. *Tetrahedron Lett.* **2002**, *43*, 7189−7191. (b) For a related method using primary alkyl tellurides, see: Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524−2526.

(17) (a) The experimental measurements of *D*(Mn−Mn) by a variety of methods range from 19 to 42 kcal mol^{-1} and have been reviewed critically: Martinho Simões, J. A.; Beauchamp, J. A. *Chem. Rev.* **1990**, *90*, 629−688. In that review, the value of choice was 38 ± 5 kcal mol^{-1}, determined by photoacoustic calorimetry: Goodman, J. L.; Peters, K. S.; Vaida, V. *Organometallics* **1986**, *5*, 815−816. (b) Bond strengths *D*(Mn−X) for $I{-}Mn(CO)_5$, $Br{-}Mn(CO)_5$, and $Cl{-}Mn(CO)_5$ are 54, 66, and 78 kcal mol^{-1}, respectively. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, California, 1987; p 368.

(18) Geoffroy, G. L.; Wrighton, M. S. *Organometallic Photochemistry*; Academic Press: New York, 1979.

(19) Reviews: (a) Pauson, P. L. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 2, pp 1471−1474. (b) Meyer, T. J.; Caspar, J. V. *Chem. Rev.* **1985**, *85*, 187. Gilbert, B. C.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 2* **2002**, 367−387.

(20) (a) Hudson, A.; Lappert, M. F.; Lednor, P. W.; Nicholson, B. K. *J. Chem. Soc., Chem. Commun.* **1974**, 966−967. (b) Hudson, A.; Lappert, M. F.; Nicholson, B. K. *J. Chem. Soc., Dalton Trans.* **1977**, 551−554.

(21) (a) McCullen, S. B.; Brown, T. L. *J. Am. Chem. Soc.* **1982**, *104*, 7496−7500. (b) Freidlina, R. K.; Terent'ev, A. B.; Petrova, R. G.; Churkina, T. D.; Moskalenko, M. A. *Dokl. Akad. Nauk SSSR* **1986**, *288*, 1436−1439. (c) Chukovskaya, E. T.; Kuz'mina, N. A.; Blinova, N. V.; Friedlina, R. K. *Izv. Akad. Nauk SSR, Ser. Khim.* **1984**, 2061−2064.

(22) (a) Connor, J. A.; Zafarani-Moattar, M. T.; Bickerton, J.; Saied, N. I. E.; Suradi, S.; Carson, R.; Takhin, G. A.; Skinner, H. A. *Organometallics* **1982**, *1*, 1166−1174. (b) Herrick, R. S.; Herrinton, T. R.; Walker, H. W.; Brown, T. L. *Organometallics* **1985**, *4*, 42−45. (c) Biddulph, M. A.; Davis, R.; Wilson, F. I. C. *J. Organomet. Chem.* **1990**, *387*, 277−293. For selected studies by Friedlina et al. of the reactions of polychlorinated compounds with $Mn_2(CO)_{10}$, see: (d) Chukovskaya, E. T.; Rozhkova, M. A.; Kuz'mina, N. A.; Freidlina, R. K. *Izv. Akad. Nauk SSR, Ser. Khim.* **1982**, 354−359. (e) Gasanov, R. G.; Friedlina, R. K. *Dokl. Akad. Nauk SSSR* **1979**, *246*, 111−114.

(23) (a) For a review, see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363. (b) Nonreductive additions of 1,3-cyclohexanediones to imines using $Mn(OAc)_3$ as an oxidant have recently been reported. Zhang, Z.; Wang, G.-W.; Miao, C.-B.; Dang, Y.-W.; Shen, Y.-B. *Chem. Commun.* **2004**, 1832−1833.

(24) (a) Gilbert, B. C.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *Synth. Commun.* **1999**, *29*, 2711−2718. (b) Masters, A. P.; Sorensen, T. S. *Can. J. Chem.* **1990**, *68*, 492−501.

assessment of the importance of steric hindrance in the halogen-atom transfer reactions of Mn(0)-centered radicals.[22b]

Some practical considerations also warrant mention. Unlike the organotin reagents, $Mn_2(CO)_{10}$ is a solid; it may be easily handled for short periods in an ambient laboratory atmosphere (e.g., for measurement and transfer) and stored for long periods under an inert atmosphere in the freezer without decomposition. In contrast to tin halides such as Bu_3SnBr, the manganese(I) halide byproducts obtained from atom abstraction reactions with alkyl halides are relatively easy to remove.

On the basis of the above considerations, dimanganese decacarbonyl emerged as a promising candidate for improving the synthetic potential of radical additions to imino compounds. Despite the interesting features of Mn-mediated radical reactions, their applications in synthesis have been sporadic to date, and their use in addition to C=N bonds had not been reported prior to this study. In particular, we were intrigued by the notion that the photolytic Mn−Mn homolysis of manganese carbonyl [$Mn_2(CO)_{10}$], which requires no sensitizer, could be exploited for intermolecular addition to C=N bonds. This hypothesis was addressed experimentally, resulting in dramatically broadened scope of this important class of reactions to include primary alkyl iodides and α,ω-dihaloalkanes as radical precursors with enhanced synthetic potential.

Results and Discussion

Manganese-Mediated Addition of Primary and Secondary Radicals. As an initial test case for the Mn-mediated addition, ethyl iodide addition to **2a**[12] (Table 1) was chosen. This would generate no new stereogenic centers but would offer an important challenge to the hypothesis that this reagent could allow primary radical addition. Irradiation (300 nm, Rayonet) of **2a**, EtI (10 equiv), and $Mn_2(CO)_{10}$ (1 equiv) with $InCl_3$ (2.3 equiv) as a Lewis acid[27] in CH_2Cl_2 afforded **3**[12] in 85% yield, a dramatic improvement over the use of triethylborane or hexamethylditin.

Several other halides were also effective, furnishing radical addition products **4S** and **5R**−**13R**[28] with high diastereomer ratios (Table 1). Methyl iodide underwent the reaction in 48% yield despite its volatility. Consistent positive results were obtained from a range of *n*-alkyl iodides. On the other hand, allyl bromide gave low yield, whereas benzyl and *tert*-butyl bromides gave no addition products.[29] However, the versatility of the method extends to functionalized radical precursors, specifically α,ω-dihaloalkanes bearing iodine along with less-reactive chlorine. These transferred synthetically attractive ω-chloroalkyl groups. Products **10R**−**13R** retain functionality originating in the difunctional radical precursor, offering opportunities for further elaboration.

The addition of ω-haloalkyl radicals deserves further comment. Although the 1,1-, 1,3-, and 1,4-dihaloalkanes all gave reasonable yields of adducts (Table 1), the additions of 1,2-dihaloethanes were unsuccessful. These anomalies may be attributable to β-elimination of the halogen atom from intermediate radicals, which bear an exceptionally weak C−X bond. For example, 1,2-diiodoethane gave none of the 2-iodoethyl adduct, and the yield of 2-chloroethyl adduct **14** from 1-chloro-2-iodoethane was only 14% (eq 5). The difference between the efficiencies of the latter two reactions may reflect C−X bond dissociation energies (BDE) in the corresponding radical intermediates, which have been examined theoretically by Zewail et al.[30] For $ICH_2CH_2^{\bullet}$, the BDE(C−I) was calculated (B3LYP)

TABLE 1. Results of Metal-Mediated Radical Addition to Propionaldehyde Hydrazone 2a*

2a **3**, **4S**, **5R**−**13R**

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

* 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 days at ca. 35 °C under N_2. [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 the removal of Mn byproducts. [e] Ratio by HPLC (Chiralcel OD, 2-PrOH/hexane). [f] Ratio by ^1H NMR. [g] $InCl_3$ and hydrazone were stored under vacuum (ca. 1 mmHg) overnight prior to use, and a smaller amount of *i*-PrI (3 equiv) was used.

(25) (a) Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *Tetrahedron Lett.* **1999**, *40*, 6095−6098. (b) Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1187−1194. (c) Huther, N.; McGrail, P. T.; Parsons, A. F. *Tetrahedron Lett.* **2002**, *43*, 2535−2538. (d) Huther, N.; McGrail, P. T.; Parsons, A. F. *Eur. J. Org. Chem.* **2004**, 1740−1749.

(26) (a) Jenkins, D. W.; Hudson, S. M. *Macromolecules* **2002**, *35*, 3413−3419. (b) Gilbert, B. C.; Harrison, R. J.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Southward, R.; Irvine, D. J. *Macromolecules* **2003**, *36*, 9020−9023. For selected earlier studies of related telomerization reactions, see: (c) Terent'ev, A. B.; Moskalenko, M. A.; Friedlina, R. K. *Izv. Akad. Nauk SSR, Ser. Khim.* **1981**, 374−379. (d) Grigor'ev, N. A.; Tumanskaya, A. L.; Friedlina, R. K. *Izv. Akad. Nauk SSR, Ser. Khim.* **1983**, 1122−1125. (e) Terent'ev, A. B.; Moskalenko, M. A.; Friedlina, R. K. *Izv. Akad. Nauk SSR, Ser. Khim.* **1984**, 2825−2827.

(27) Use of $ZnCl_2$ as the Lewis acid was precluded due to limited solubility. A brief screen of In(III) Lewis acids ($InCl_3$, InF_3, InI_3, $In(OAc)_3$) in hexamethylditin-mediated photolysis indicated $InCl_3$ to be superior (see ref 12b). $InCl_3$ is also only slightly soluble in CH_2Cl_2. Significant dissolution of the $InCl_3$ occurs when all reaction components are present, although the reaction mixture is still not homogeneous. Lower stoichiometries of $InCl_3$ result in lower conversion.

(28) Configurations are assigned by analogy with **9R** and **15**, which were unambiguously determined through chemical correlation with valine and coniine, respectively.

(29) Allyl bromide gave 12% of the allyl adduct. Benzyl bromide led to recovery of the starting hydrazone, and *tert*-butyl bromide resulted in decomposition.

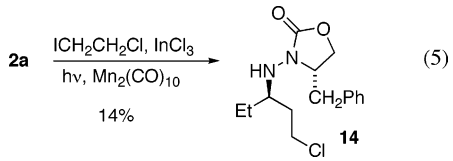
(30) Ihee, H.; Zewail, A. H.; Goddard, W. A., III. *J. Phys. Chem. A* **1999**, *103*, 6638−6649.

TABLE 2. Preparation and $Mn_2(CO)_{10}$-Mediated Iodoethane Addition to Aldehyde Hydrazones According to Scheme 1*

entry	aldehyde R^1CHO (or acetal)	hydrazone, yield[a]	$Et^\bullet$ adduct, yield[b]	dr
1	CH_3CHO	**2b**, 66%	**4R**, 66%	95:5[d]
2		**2c**, 87%	**5S**, 63%	95:5[d]
3		**2d**, 89%	**6S**, 72%	97:3[d]
4		**2e**, 88%	**7S**, 77%	97:3[d]
5		**2f**, 85%	**8S**, 65%; 83%[f]	95:5[e]
6	$ClCH_2CH(OMe)_2$	**2g**, 85%	**10S**, 57%	93:7[d]
7		**2h**, 95%	**11S**, 60%	93:7[e]
8		**2i**, 89%	**12S**, 62%	97:3[d]
9	$Cl_2CHCH(OEt)_2$	**2j**, 54%	**13S**, 34%[c]	89:11[e]

* Reaction conditions for hydrazone formation: Aldehyde (5−10 equiv), **1**, *p*-toluenesulfonic acid, CH_2Cl_2, rt. For radical addition conditions, see Table 1. [a] Isolated yield. [b] Isolated yield of the diastereomer mixture. [c] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used in the removal of Mn byproducts. [d] Ratio by HPLC. [e] Ratio by ^1H NMR. [f] $InCl_3$ and hydrazone were stored under vacuum (ca. 1 mmHg) overnight prior to use, and a smaller amount of EtI (3 equiv) was used.

at 5 kcal/mol, whereas for $ClCH_2CH_2^\bullet$, the same calculation yields BDE(C−X) of 12 kcal/mol. Experimental data indicate an even greater difference.[31]



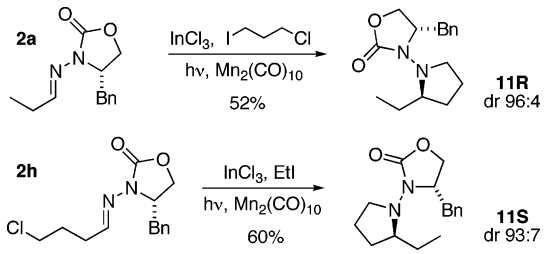
(5)

To examine the generality of the reaction with respect to the radical acceptor, additional hydrazones **2b**−**2j** were prepared in excellent yield by condensation of *N*-aminooxazolidinone **1a** with the corresponding aldehyde or acetal (Table 2). Iodoethane addition to these hydrazones occurred in good yields (57−77%) with the exception of **2j** (34%). The adducts **4R** and **5S**−**13S** (Table 2) are epimeric to **4S** and **5R**−**13R** (Table 1) with respect to the new stereogenic center, demonstrating the flexibility inherent in this carbon−carbon bond construction approach to amine synthesis.

Remarkably, these intermolecular additions appear to be amenable to the use of only small excesses of alkyl iodide, a very unusual finding among intermolecular radical addition reactions. Our current practice, based on an empirically discovered improvement in yields, is to (a) reduce the stoichiometry of the alkyl iodide to 3 equiv and (b) store the $InCl_3$ and hydrazone separately under an oil-pump vacuum overnight prior to use. The effectiveness of this modified method can be seen from the data in Table 1, entry 9, and Table 2, entry 5, where the yield is increased by about 20% relative to the control experiments. Although reaction times of 1−2 days were used in most of these experiments, we have since discovered that the reaction is complete after ca. 8 h (or after overnight irradiation). In cases when the reaction is incomplete, addition of another portion of $Mn_2(CO)_{10}$ does not lead to further conversion, a point which is not yet understood.

(31) Comparison of the estimated experimental values reported by Zewail et al. (ref 30) shows that C−X bond dissociation of $Cl-CH_2CH_2^\bullet$ is 28 kcal/mol higher than that of $I-CH_2CH_2^\bullet$.

SCHEME 3



Numerous synthetic applications of this new Mn-mediated addition methodology may be envisioned; its appealing features include accommodation of primary alkyl radicals and tolerance of multifunctional precursors.[32] Furthermore, the epimeric configuration in the adducts can be selected by either (A) employing the enantiomeric auxiliary or (B) interchanging the roles of R^1 and R^2 in Scheme 1 (i.e., the alkyl halide and aldehyde precursors of Scheme 2).[33] 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.

Hybrid Radical−Ionic Annulation. Interestingly, addition of 3-chloro-1-iodopropane to propionaldehyde hydrazone **2a** led exclusively to pyrrolidine **11R** (Scheme 3), presumably via 3-chloropropyl radical addition and in situ nonradical cyclization. When the 3-chloropropyl group was linked to the C=N moiety in hydrazone **2h**, the epimeric pyrrolidine **11S** was obtained upon ethyl addition. These are two examples of a potentially useful hybrid radical−ionic annulation, a novel entry to a class of reactions known as radical−polar crossover reactions.[34]

To illustrate its potential in asymmetric amine synthesis, we applied Mn-mediated radical addition to prepare the simple piperidine alkaloid coniine (Scheme 4).[35] We envisioned a radical addition followed by cyclization, as suggested by the previous experiments of Scheme 3. Two alternative disconnections can be considered. The exocyclic propyl group may be introduced as part of the radical acceptor (path A) or may originate in the radical precursor (path B).

Propyl radical addition to a difunctional hydrazone was attempted first (path B). However, it was noted previously that

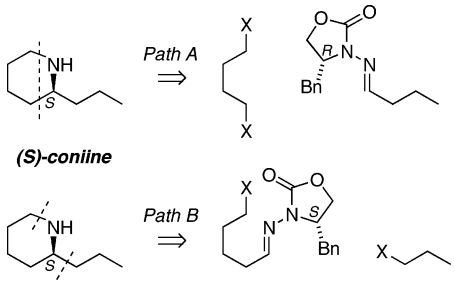
(32) During preparation of this manuscript, Tomioka et al. have very recently reported some impressive intermolecular radical additions to *N*-tosylimines using alkyl iodide stoichiometries from 1.5 to 5 equiv. See ref 7a.

(33) 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*, 383−394.

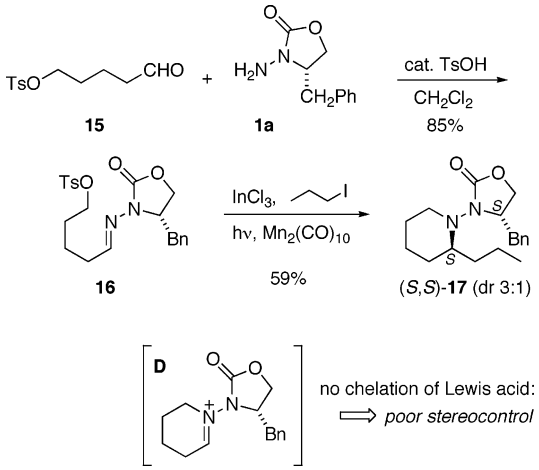
(34) (a) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995−1001. (b) Jahn, U.; Muller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212−5213. (c) Rivkin, A.; Nagashima, T.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419−422. (d) Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4043−4046. (e) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261−4274. (f) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190−6193.

(35) Coniine is a common target for testing the 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*, 7754−7755. (b) Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173−177. (c) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623−4636. (d) Reding, M. T.; Buchwald, S. R. *J. Org. Chem.* **1998**, *63*, 6344−6347. (e) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155−158. (f) For reviews of asymmetric syntheses of piperidine alkaloids, see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781−1813. O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446.

SCHEME 4



SCHEME 5

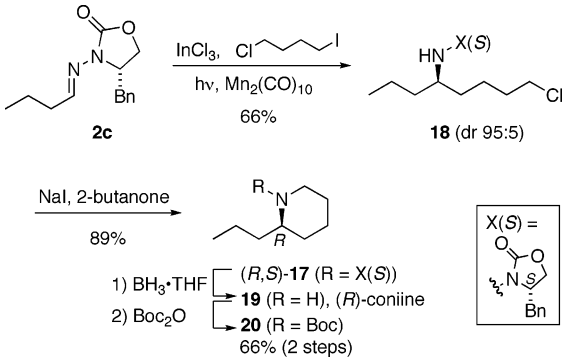


addition of an ethyl radical to difunctional 5-chloropentanal hydrazone **2i** (Table 2) did not result in cyclization in situ. It was expected that replacing the chloride substituent with a tosylate nucleofuge would facilitate the polar cyclization after radical addition. The requisite *N*-acylhydrazone **16** (Scheme 5) was obtained in 85% yield by condensing *N*-aminooxazolidinone **1a** with 5-(*p*-toluenesulfonyl)oxypentanal[36] (**15**) in the presence of *p*-toluenesulfonic acid in CH_2Cl_2. The Mn-mediated addition of iodopropane to *N*-acylhydrazone **16** indeed provided the expected annulation product **17** in 59% yield. Unfortunately, anomalously poor stereocontrol was observed (dr 3:1). The major diastereomer was assigned the indicated configuration by analogy to previous additions to *N*-acylhydrazones and was confirmed later upon preparation of the minor diastereomer by a different route (vide infra).

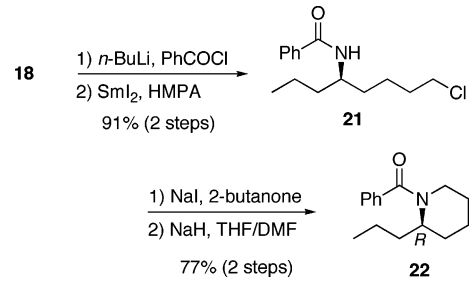
The lack of high selectivity in the addition to 5-tosyloxypentanal hydrazone **16** is unique among all the examples of Mn-mediated addition to C═N seen to this point. Of most relevance is the contrasting highly diastereoselective ethyl addition to the related chloropentanal hydrazone **2i** (dr 97:3, 63% yield, Table 2). Upon ethyl addition, **2i** does not undergo the polar cyclization; the product retains the chloride. Together, these comparisons of **2i** and **16** suggest a mechanistic difference. For **16**, the cyclization could occur either before or after radical addition. The lower stereoselectivity provides evidence for a polar cyclization to form iminium ion **D** (Scheme 5) prior to radical addition; such a cyclization would be detrimental to stereoselectivity due to the loss of two-point binding of the Lewis acid. The mass balance in the Mn-mediated additions is routinely 80−100%, so yields in the range of 60% are often accompanied by easily detected amounts of the unchanged hydrazone. In contrast, no reactant hydrazone was found after reaction of tosylate **16**, suggesting decomposition which would be consistent with the intermediacy of iminium ion **D**.

(36) Börjeson, L.; Welch, C. J. *Tetrahedron* **1992**, *48*, 6325−6334.

SCHEME 6



SCHEME 7



Interchanging the alkyl groups in the coupling partners (i.e., R^1 and R^2 of Scheme 2) gave superior results. Accordingly, Mn-mediated radical addition of 4-chlorobutyl iodide to **2c** furnished **18** with high diastereoselectivity (Scheme 6).[37] Cyclization occurred under Finkelstein conditions, affording piperidine derivative (*R*,*S*)-**17**, identical to the minor diastereomer obtained by the previous route. Reduction with BH_3·THF[38] afforded (*R*)-coniine (**19**). After conversion to the *tert*-butyl carbamate (*N*-Boc) derivative **20** for ease of isolation (coniine is volatile), the yield was 66%. The absolute configuration of **20** was determined by comparison of its optical rotation, $[\alpha]_D^{26} = -28.1$ ($c = 1.0$, $CHCl_3$), with the literature value.[39] The correlation of (*R*,*S*)-**17** to (*R*)-coniine also establishes the configurations of the minor (*R*,*S*) and major (*S*,*S*) diastereomers obtained by propyl addition to tosyloxypentanal hydrazone **16**.

Additional information establishing the configuration of **17** was obtained by an alternative route leading to *N*-benzoyl (*R*)-coniine (Scheme 7). Benzoylation of hydrazine **18** (94% yield) and N−N bond cleavage by SmI_2 (97% yield) afforded **21**, along with 94% recovery of (*S*)-4-benzyl-2-oxazolidinone. Finkelstein reaction and base treatment of the resulting iodide provided *N*-benzoyl (*R*)-coniine (**22**) in 77% yield for two steps. The absolute configuration was confirmed by comparison of the optical rotation, $[\alpha]_D^{27} = -37.5$ ($c = 0.80$, $CHCl_3$), with the literature data.[40]

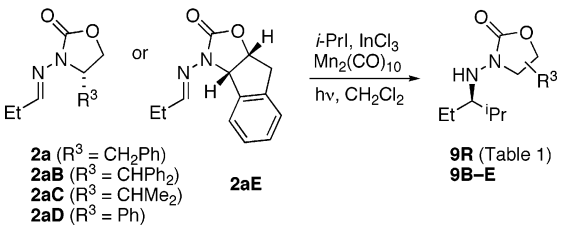
(37) Identical results were observed on ca. a 200 mg or 1 g scale.

(38) N−N cleavage with BH_3·THF: Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970**, *35*, 1468−1471. For recent examples, see: Enders, D.; Lochtman, R.; Meiers, M.; Muller, S.; Lazny, R. *Synlett* **1998**, 1182−1184.

(39) For (*R*)-*N*-Boc-coniine, $[\alpha]_D^{23} = -31.6$ ($c = 0.86$, $CHCl_3$). Ref 35b.

(40) For *N*-benzoyl-D-coniine, $[\alpha]_D^{26} = +37.7$. Ladenburg, A. *Chem. Ber.* **1893**, *26*, 854−865.

TABLE 3. Comparison of Chiral Auxiliaries*



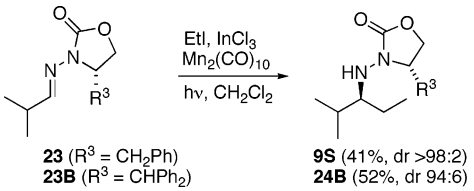
entry	hydrazone	product (yield[a,b]), dr[c]
1	**2a**	**9R** (94%), 95:5 (Table 1)
2	**2aB**	**9B** (90%), 98:2
3	**2aC**	**9C** (88%), 98:2[d]
4	**2aD**	**9D** (95%), 95:5
5	**2aE**	**9E** (81%), 95:5[e]

* Reaction conditions: Table 1. [a] Isolated yield. [b] $InCl_3$ and hydrazone were stored under vacuum (ca. 1 mmHg) overnight prior to use. [c] dr = diastereomer ratio, measured by ^1H NMR spectrometry vs authentic mixtures. [d] Estimated ratio. The minor diastereomer was not detected in ^{13}C NMR or ^1H NMR spectra, although ^1H resonances were poorly resolved. [e] By HPLC (Chirex 3014, 9:1 hexane−$CHCl_3$), the dr measurement was 96.7:3.3.

Attempts to cleave the N−N bond of **17** by other methods were disappointing. Hydrogenation with pressures up to 160 psi, using a variety of catalysts (Raney Ni,[41] Pd/C, PtO_2,[42] Pt/C, or $Pd(OH)_2$[43]), resulted in the saturation of the benzyl group of the auxiliary but did not cleave the N−N bond. Raney nickel reduction with ultrasonic irradiation[41c] gave no reaction. Oxidative cleavage of the N−N bond with magnesium monoperoxyphthalate hexahydrate (MMPP)[44] was achieved, as judged by recovery of (*S*)-4-benzyl-2-oxazolidinone in 92% yield, but the basic amine component (coniine) was not isolated under these conditions, presumably due to oxidative decomposition.

Stereocontrol. The conversion of **18** to (*R*)-coniine by two alternative routes (Schemes 5 and 6), as well as the configuration established in sequence **18** → **22** (Scheme 7), provided further support for the general stereocontrol model previously proposed for reactions of these *N*-acylhydrazones in the presence of chelate-forming Lewis acids. All available evidence along these lines suggests the hydrazone acceptor adopts the chelate structure illustrated in Scheme 2; the benzyl substituent blocks the *re* face such that bond formation occurs on the opposite face.

A series of related *N*-acylhydrazones were prepared, as described previously,[12b] to assess the importance of variations to the stereocontrol element in the chiral auxiliary. Hydrazones **2aB**−**2aE** were submitted to isopropyl addition via the Mn-mediated photolysis conditions (Table 3), and without exception, all diastereomer ratios of the products **9B**−**9E**[12b] were quite high. This observation is consistent with earlier findings regarding the stereocontrol of tin- and boron-mediated radical additions to the *N*-acylhydrazone radical acceptors.[12b] A second series of reactions involving ethyl addition to isobutyraldehyde hydrazones **23** and **23B** (eq 6) afforded **9S** and **24B** in very high diastereoselectivity (as judged by ^1H NMR and ^{13}C NMR spectra).[45] These products established the viability of additions



(6)

to α-branched imino compounds for the first time and also served as standards to prepare authentic mixtures for the HPLC analysis reported in Table 3. The additions with all different oxazolidinone auxiliaries proceeded with high diastereoselection, indicating that there is little practical importance of the identity of the stereocontrol element among those examined here.

TABLE 4. Mechanistic Control Experiments with Hydrazone 2a*

entry	RI	reaction conditions	hydrazone recovery[a]	R• adduct, yield[b]
1	EtI	$Mn_2(CO)_{10}$, hν,[b] $InCl_3$	−	**3**, 85%
2	EtI	hν,[b] $InCl_3$	nr[d]	−
3	EtI	$Mn_2(CO)_{10}$, dark,[c] $InCl_3$	nr[d]	−
4	EtI	$Mn_2(CO)_{10}$, hν[b]	18%	**3**, 21%
5	EtI	$Mn_2(CO)_{10}$, indoor ambient light, $InCl_3$	45%	**3**, 24%
6	*n*-$C_5H_{11}I$	$Mn_2(CO)_{10}$, hν,[b] $InCl_3$, galvinoxyl (0.5 equiv)	75%	**7R**, 12%
7	*n*-$C_5H_{11}I$	$Mn_2(CO)_{10}$, hν,[b] $InCl_3$, galvinoxyl (2.5 equiv)	80%	**7R**, 0%

* Reaction conditions: see Table 1; reaction time 18−24 h. [a] Isolated yield. [b] Rayonet, 300 nm. [c] Al foil was wrapped around the reaction flask. [d] nr = no reaction; amount of **2a** was not quantified, but **2a** was unchanged (as judged by TLC).

Qualitative Mechanistic Data. With some documented utility of this Mn-mediated addition process, we began to look more carefully at mechanistic questions. Control experiments revealed some basic information about the roles of the reaction components (Table 4). In the absence of $Mn_2(CO)_{10}$, there was no reaction after irradiation for 24 h (entry 2). Similarly, without irradiation, no reaction occurred (entry 3). In contrast, some **3** was obtained (21% yield) in the absence of $InCl_3$ (entry 4), although the reaction was slow. This shows that the indium chloride is not a mechanistic requirement; rather, it appears to only facilitate the reaction as a Lewis acid activator. In ambient light, the addition proceeded but was much less efficient than the reaction employing UV irradiation (compare entries 1 and 5). The presence of galvinoxyl inhibited the reaction, but large quantities of this radical scavenger were required to completely shut down the reaction (entries 6 and 7). This suggests a non-chain radical process[46] or a very short chain length.

The mass balance of an addition involving 4-(*tert*-butyldimethylsilyloxy)butyl iodide (Scheme 8) gave further insights about the nature of the addition reaction. In addition to expected adduct **25**, an interesting side product, dichloromethyl adduct **13R**, was detected in 19% yield; the dichloromethyl group clearly originated from the solvent. This product has also been detected in small amounts in other additions. Considering the

(41) (a) Enders, D.; Schubert, H.; Nübling, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1109−1110. (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395−6397. (c) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625−626.

(42) Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265−8266.

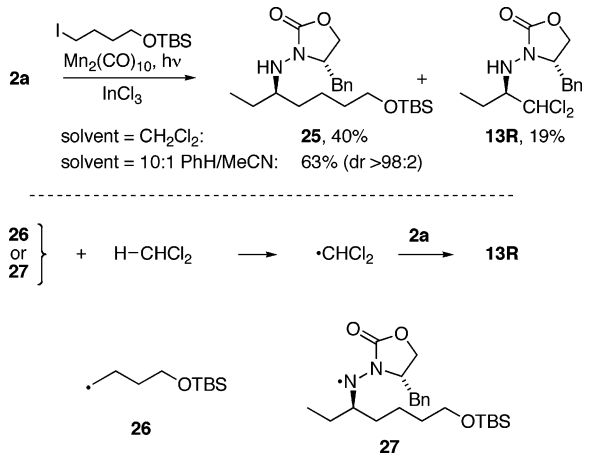
(43) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543−5546.

(44) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2893−2897. Fernández, R.; Ferrete, A.; Llera, J. M.; Magriz, A.; Martín-Zamora, E.; Díez, E.; Lassaletta, J. M. *Chem.−Eur. J.* **2004**, *10*, 737−745.

(45) The compound **24B** was shown by GC to have dr = 94:6.

(46) A nonchain radical character was also identified in studies of photo- and electrochemical carbonylation of alkyl iodides in the presence of CO, MeOH, and Mn_2CO_{10}. Kondo, T.; Sone, Y.; Tsuji, Y.; Watanabe, Y. *J. Organomet. Chem.* **1994**, *473*, 163−173.

SCHEME 8

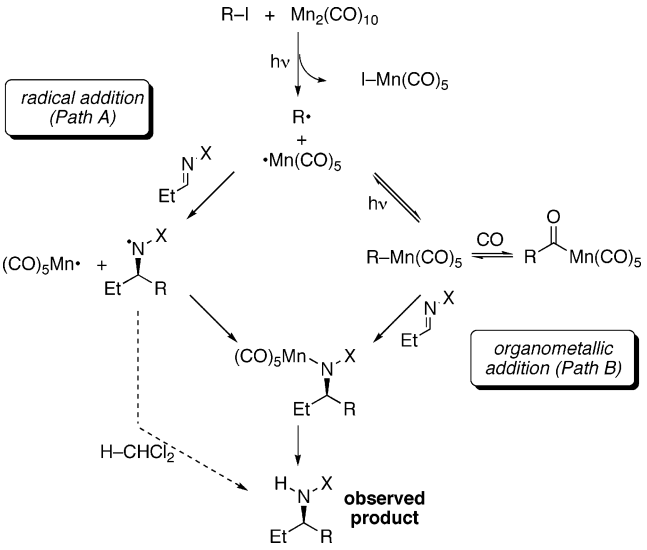


nonbasic conditions of the reaction, the most reasonable explanation for this result is H-atom transfer from CH_2Cl_2, followed by competitive additions of the resulting $^{\bullet}CHCl_2$ and $^{\bullet}CH_2(CH_2)_3$-OTBS (**26**). Either this latter alkyl radical or the N-centered radical **27** may be responsible for the H-atom abstraction; in the presence of a Lewis acid, the aminyl radical should be quite reactive.[47]

The scenario above predicts that switching to a solvent less prone to H-atom abstraction might lead to minimized consumption of alkyl iodide. In fact, when the reaction of Scheme 8 was conducted in a mixture of 10:1 benzene/acetonitrile, *using only 1.5 equiv of the iodide*, compound **25** was isolated in 63% yield. The generality of reactions with low iodide stoichiometry is under further investigation.

The photolysis of dimanganese decacarbonyl in the presence of alkyl iodides is well-known to generate alkyl radicals which can be used for various reactions,[17−26] so the more interesting mechanistic questions are found in subsequent steps proposed in Scheme 9. One alternative is of course a one-electron free-radical process, consisting of alkyl radical addition followed by recombination of the resulting aminyl radical with a pentacarbonylmanganese radical (the manganese amide has been neither observed nor ruled out) or H-atom abstraction from solvent (path A). This photolysis chemistry also produces alkylmanganese species from iodides by radical−radical coupling. So, one must consider the alternative possibility that such a species could undergo a two-electron carbometalation-type reaction leading to the same adduct (path B). Further, photolysis of $R-Mn(CO)_5$ is known to generate $R^{\bullet}$ species.[20,48] If the photolysis conditions employed in our additions to *N*-acylhydrazones could permit a reversible homolysis and recombination of $R-Mn(CO)_5$, these alkylmanganese species could modulate the reactivity of radicals via the persistent radical effect (PRE).[49] Specifically, the buildup of a small excess of persistent metal-centered radicals could suppress the destructive homocoupling of transient alkyl radicals. This could serve to focus

SCHEME 9



the conversion of alkyl radicals along the desired reaction pathway, addition to the *N*-acylhydrazone acceptor. On the other hand, it is also known that photolysis of $R-Mn(CO)_5$ does result in formation of $Mn_2(CO)_{10}$, a point which clearly differentiates this system from ideal examples of PRE wherein the homocoupling of the persistent radical is not observed to any significant extent.[50] To clarify these issues, it was clearly desirable to probe for the presence of alkylmanganese species.

The first approach to evaluate the importance of alkylmanganese intermediates was to prepare the $R-Mn(CO)_5$ compounds by an alternative method and examine their reactivity with *N*-acylhydrazones. Acyl- and alkylmanganese pentacarbonyls are well-known compounds, easily prepared by simple methods.[51] For example, $(C_5H_{11})Mn(CO)_5$ (**26a**) and its corresponding migratory insertion product, $(C_5H_{11}CO)Mn(CO)_5$ (**26b**), were prepared from $NaMn(CO)_5$ by alkylation with 1-iodopentane or acylation with hexanoyl chloride, respectively. Tridecyl analogues $(C_{13}H_{27})Mn(CO)_5$ (**28a**) and $(C_{13}H_{27}CO)$-$Mn(CO)_5$ (**28b**) were prepared in the same fashion. The expected types of reactivity were observed; these pairs of compounds interconverted thermally and photochemically, with the latter conditions leading to decomposition to alkane. Photolysis in CH_2Cl_2 in the absence of *N*-acylhydrazone gave tridecane in 46% yield from **28a** and in 25% yield from **28b**, and the alkyl dimer ($C_{26}H_{54}$) was not detected. Apparently, H-atom abstraction from CH_2Cl_2 predominates under these conditions.

Next, we systematically examined the reactivity of **26a** and **26b** in combination with the propionaldehyde-derived *N*-acylhydrazone **2a** (Scheme 10). No reaction took place in the

(47) (a) A deuterium incorporation experiment is complicated by the potential for NH exchange on processing the reaction product. (b) Horner, J. H.; Martinez, F. N.; Musa, O. M.; Newcomb, M.; Shahin, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 11124−11133. Ha, C.; Musa, O. M.; Martinez, F. N.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 2704−2710. Newcomb, M.; Musa, O. M.; Martinez, F. N.; Horner, J. H. *J. Am. Chem. Soc.* **1997**, *119*, 4569−4577. Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738−7748.

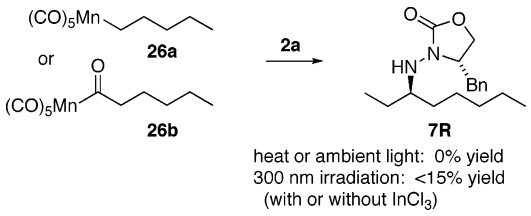
(48) Young, K. M.; Wrighton, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 157−166.

(49) (a) Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925−3927. (b) Daikh, B. E.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 2938−2943. (c) For reviews of the persistent radical effect, see: Fischer, H. *Chem. Rev.* **2001**, *101*, 3581−3610. Studer, A. *Chem.−Eur. J.* **2001**, *7*, 1159−1164. Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267−273. (d) For selected examples of applications in synthesis, see: Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631−1633. Branchaud, B. P.; Yu, G.-X. *Organometallics* **1993**, *12*, 4262−4264. Studer, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1108−1111. Wetter, C.; Studer, A. *J. Chem. Soc., Chem. Commun.* **2004**, 174−175.

(50) Although the homocoupling of the persistent radical $^{\bullet}Mn(CO)_5$ does occur, its reversibility under the photolysis conditions may maintain a slight excess of $^{\bullet}Mn(CO)_5$ (a necessary condition for the PRE).

(51) Coffield, T. H.; Kozikowski, J.; Closson, R. D. *J. Org. Chem.* **1957**, *22*, 598. Anderson, J. M.; Moss, J. R. *Organometallics* **1994**, *13*, 5013−5020.

SCHEME 10



dark or in ambient light, with or without Lewis acid; the results of Tables 1 and 2 were not reproduced by these experiments. It is clear from these negative results that the organomanganese compounds do not react directly with the *N*-acylhydrazones (e.g., via a two-electron carbometalation or migratory insertion of the C═N bond). Upon photolysis of **26a** with **2a** at 300 nm in the presence of $InCl_3$, the *n*-pentyl radical adduct **7R** was found in small amounts (<15% yield), along with small amounts of dimanganese decacarbonyl. Upon employing **26b** in the latter experiment, no addition took place, although formation of **26a** by decarbonylation of **26b** was observed.

We wondered if some interaction between the possible Mn-containing components could be important to provide some reactivity which would not be duplicated by the isolated alkylmanganese compound. For example, mixtures containing R−Mn(CO)$_5$ and I−Mn(CO$_5$ are generated in situ during photolysis, and the reversible migratory insertion can also provide RC(O)−Mn(CO)$_5$. Mixtures of (a) R−Mn(CO)$_5$ and I−Mn(CO$_5$ or (b) R−Mn(CO)$_5$, RC(O)−Mn(CO)$_5$, I−Mn(CO)$_5$, and $Mn_2(CO)_{10}$ were prepared separately, then mixed with the *N*-acylhydrazone **2a** and submitted to the standard photolysis conditions in the presence of $InCl_3$. Still, the results typical in Tables 1 and 2 were not duplicated; no significant amount of addition product was found.

Finally, a crossover experiment was employed to examine the role of the alkyl iodide. When $C_{13}H_{27}COMn(CO)_5$ (**28b**) was used in the photolysis, irradiation for several hours produced no observable addition reaction (TLC). Consistent with the observations noted above, a significant amount of $Mn_2(CO)_{10}$ formed during this period, detected qualitatively by TLC and visual inspection (yellow solid on the upper walls of the reaction vessel). At this point, iodopentane was added to the flask, and upon further irradiation, the addition reaction appeared to take its normal course (as observed in Tables 1 and 2). The only addition product detected contained the pentyl group (**7R**, 44% yield); the tridecyl group from **28b** was not incorporated to any detectable extent.[52] This clearly identified the origin of the alkyl group; it must have come from pentyl iodide *without the intervention of an alkylmanganese species*.

To summarize the results of these experiments, we can conclude that nonradical reactions of alkyl- or acylmanganese species do not play a significant role under the conditions of Tables 1 and 2. The free-radical addition appears to either be nonchain or have a short chain length, and it requires generation of radicals from the alkyl iodide. Together, all these results suggest that the effectiveness of the Mn-mediated additions may derive from relatively high radical concentrations, as Parsons has noted previously in the context of Wurtz-type dimerization of alkyl halides. It is curious that the alkyl- and acylmanganese compounds can result in photolytic reduction to alkane (presumably a radical process) yet do not undergo addition to any great extent. One possible explanation involves a solvent cage effect. The alkyl- or acylmanganese homolysis produces a caged radical pair, kinetically distinguishing its alkyl radical component from the free alkyl radical produced by bimolecular halogen-atom abstraction. In the latter case, intermolecular addition to the *N*-acylhydrazone is facilitated; in-cage recombination is obviated because the Mn-containing component in the solvent cage is I−Mn(CO)$_5$, not $^{\bullet}$Mn(CO)$_5$.

Conclusion

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. The stoichiometry of alkyl iodide can be limited to three equivalents without any decrease in yield. Qualitative mechanistic studies confirm the importance of free radicals, imply that this is a nonchain (or short chain length) free-radical process, and reveal that organomanganese compounds are not a viable source of alkyl radicals for the addition reaction under the conditions examined here.[53]

Experimental Section

Preparation of *N*-Acylhydrazones (General Procedure A). To a solution of (*S*)-3-amino-4-phenylmethyl-2-oxazolidinone (**1**) in CH_2Cl_2 (0.2 M) was added TsOH·H_2O (cat.) and aldehyde (5−10 equiv) at room temperature.[54] When the reaction was complete (TLC), the mixture was concentrated and purified by gradient flash chromatography (hexane → 1:1 hexane/EtOAc) to afford the hydrazone as a single C═N isomer (>98:2). In some cases, small amounts (<5%) of another component (tentatively identified as an enamine derived from 4-phenylmethyl-2-oxazolidinone) were detected by ^{1}H NMR and were not removed prior to subsequent radical addition reactions. For specific data concerning preparation and characterization data of *N*-acylhydrazones, see Supporting Information.

Radical Addition to *N*-Acylhydrazones (General Procedure B). To a deoxygenated (N_2) solution of the hydrazone (e.g., **2a**) in CH_2Cl_2 (ca. 0.1 M) was added $InCl_3$ (2.2 equiv) at room temperature. After 40 min, the appropriate alkyl iodide (3−20 equiv, see Tables 1 and 2) and $Mn_2(CO)_{10}$ (1−2 equiv) were added and the mixture was irradiated for 8−24 h before product isolation according to workup A or workup B. Longer irradiation times have been used in some cases (as reported in the preliminary communication), but there is no evidence of any advantage. **Workup A:** 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 5 equiv) was added, and the mixture was stirred for 40 min and concentrated. Gradient flash chromatography, with care to avoid enrichment of the diastereomer ratio, afforded *N*-acylhydrazines **4S** and **5R**−**13R** as diastereomer mixtures. Diastereomer ratios were determined by comparison with authentic diastereomer mixtures prepared by an admixture of **4R** and **5S**−**13S** prepared by a similar route (see Supporting Information). **Workup B:** Same as workup A except treatment with DBU was omitted.

(*S*)-3-(3′-Pentanamino)-4-phenylmethyl-2-oxazolidinone (3). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (54 mg, 0.233 mmol) and iodoethane (0.186 mL, 2.33 mmol) by general procedure B and workup B was obtained **3**[12] (52 mg, 85%) as a colorless oil.

(52) Unreacted *N*-acylhydrazone **2a** was recovered (48%), giving mass balance of 92% for this experiment. Traces of side products among the remaining 8% of mass were examined carefully by ^{1}H NMR spectrometry, but there was no evidence of a tridecyl adduct.

(53) Although this study is focused on intermolecular addition, precedent suggests applicability to cyclizations (ref 25).

(54) A statement of general experimental procedures is provided in the Supporting Information.

(4*S*,2′*S*)-3-(2′-Butanamino)-4-phenylmethyl-2-oxazolidinone (4S). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (76 mg, 0.33 mmol) and iodomethane (0.41 mL, 6.54 mmol) by general procedure B and workup A was obtained **4S** (39 mg, 48%; *S*,*S*/*S*,*R* = 95:5, HPLC analysis) as a colorless oil: $[\alpha]_D^{26}$ +49.2 (*c* 0.65, $CHCl_3$); IR (film) 3288, 3028, 2966, 2877, 1758, 1498, 1454, 1399, 1218, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.25 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 4.15 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.03 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.93−3.88 (m, 1H), 4.30−3.70 (brs, 1H), 3.33 (dd, *J* = 13.5, 3.6 Hz, 1H), 3.19−3.10 (m, 1H), 2.62 (dd, *J* = 13.4, 9.9 Hz, 1H), 1.60−1.57 (m, 1H), 1.41−1.32 (m, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.95 (dd, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 136.0, 129.1, 128.8, 127.0, 66.0, 59.7, 56.0, 37.3, 27.5, 18.0, 9.7; MS (CI) *m*/*z* (relative intensity) 249 ([M + H]$^+$, 100%). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.79; H, 8.09; N, 11.22.

(4*S*,3′*R*)-3-(3′-Hexanamino)-4-phenylmethyl-2-oxazolidinone (5R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (50 mg, 0.22 mmol) and 1-iodopropane (0.21 mL, 2.16 mmol) by general procedure B and workup B was obtained **5R** (39 mg, 66%; *S*,*R*/*S*,*S* = 94:6, HPLC analysis) as a colorless oil: $[\alpha]_D^{26}$ +31.6 (*c* 1.5, $CHCl_3$); IR (film) 3292, 3063, 3028, 2960, 2873, 1758, 1454, 1399, 1238, 1090, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 6.8, 6.8 Hz, 2H), 7.25 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 4.14 (dd, *J* = 8.2, 8.2 Hz, 1H), 4.03 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.93−3.88 (m, 1H), 3.95 (br s, 1H), 3.34 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.05−2.97 (m, 1H), 2.61 (dd, *J* = 13.4, 10 Hz, 1H), 1.54−1.38 (m, 6H), 0.96 (dd, *J* = 7.4, 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 136.0, 129.1, 128.9, 127.0, 65.7, 60.1, 59.9, 36.9, 33.7, 24.8, 18.8, 14.3, 9.0; MS (CI) *m*/*z* (relative intensity) 277 ([M + H]$^+$, 100%), 193 (30%). Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.46; H, 8.85; N, 10.01.

(4*S*,3′*R*)-3-(3′-Heptanamino)-4-phenylmethyl-2-oxazolidinone (6R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (100 mg, 0.43 mmol) and 1-iodobutane (0.49 mL, 4.31 mmol) by general procedure B and workup B was obtained **6R** (98 mg, 78%; *S*,*R*/*S*,*S* = 95:5, HPLC analysis) as a colorless oil: $[\alpha]_D^{26}$ +28.3 (*c* 2.8, $CHCl_3$); IR (film) 3292, 3028, 2960, 2873, 1758, 1498, 1455, 1399, 1217, 1198, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 4.13 (dd, *J* = 8.8, 7.7 Hz, 1H), 4.03 (dd, *J* = 8.9, 4.6 Hz, 1H), 3.92−3.88 (m, 1H), 4.18−3.85 (br s, 1H), 3.33 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.01 (dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 2.61 (dd, *J* = 13.4, 10.0 Hz, 1H), 1.55−1.31 (m, 8H), 0.97−0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 136.1, 129.1, 128.9, 127.0, 65.7, 60.3, 59.9, 37.0, 31.2, 27.8, 24.7, 22.9, 14.0, 9.0; MS (EI) *m*/*z* (relative intensity) 91 (100%), 117 (80%), 233 (60%), 290 (M$^+$, 8%). Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.29; H, 9.08; N, 9.72.

(4*S*,3′*R*)-3-(3′-Octanamino)-4-phenylmethyl-2-oxazolidinone (7R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (91 mg, 0.39 mmol) and 1-iodopentane (0.51 mL, 3.92 mmol) by general procedure B and workup B was obtained **7R** (94 mg, 79%; *S*,*R*/*S*,*S* = 95:5, HPLC analysis) as a colorless oil: $[\alpha]_D^{25}$ +23.3 (*c* 2.2, $CHCl_3$); IR (film) 3293, 3063, 2958, 2931, 1760, 1498, 1455 cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.25 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 4.13 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.03 (dd, *J* = 8.8, 4.3 Hz, 1H), 3.94−3.85 (m, 1H), 4.30−3.75 (br s, 1H), 3.33 (dd, *J* = 13.3, 2.5 Hz, 1H), 3.08−2.95 (m, 1H), 2.61 (dd, *J* = 13.2, 9.9 Hz, 1H), 1.55−1.25 (m, 10H), 0.95 (dd, *J* = 7.2, 7.2 Hz, 3H), 0.90 (dd, *J* = 6.8, 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 136.1, 129.1, 128.9, 127.0, 65.7, 60.3, 59.9, 37.0, 32.1, 31.5, 25.2, 24.7, 22.6, 14.0, 9.0; MS (EI) *m*/*z* (relative intensity) 91 (100%), 117 (77%), 304 (M$^+$, 9%). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.12; H, 9.34; N, 9.04.

(4*S*,3′*R*)-3-(5′-Methyl-3′-hexanamino)-4-phenylmethyl-2-oxazolidinone (8R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (74 mg, 0.32 mmol) and isobutyl iodide (0.74 mL, 6.4 mmol) by general procedure B and workup B was obtained **8R** (50 mg, 54%; *S*,*R*/*S*,*S* = 95:5, NMR analysis) as a colorless oil: $[\alpha]_D^{25}$ +19.5 (*c* 0.85, $CHCl_3$); IR (film) 3299, 3028, 2958, 2872, 1758, 1497, 1454, 1399, 1238, 1091, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.25 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 4.14 (dd, *J* = 8.2, 8.2 Hz, 1H), 4.03 (dd, *J* = 8.9, 4.4 Hz, 1H), 3.92−3.87 (m, 1H), 3.97 (br s, 1H), 3.35 (dd, *J* = 13.5, 3.4 Hz, 1H), 3.12−3.03 (m, 1H), 2.60 (dd, *J* = 13.4, 10.1 Hz, 1H), 1.82−1.73 (m, 1H), 1.58−1.42 (m, 2H), 1.29 (dd, *J* = 6.9, 6.9 Hz, 2H), 0.99−0.94 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 136.1, 129.1, 128.9, 127.0, 65.6, 60.1, 58.4, 41.1, 36.8, 25.4, 24.9, 23.1, 22.7, 8.9; MS (CI) *m*/*z* (relative intensity) 291 ([M + H]$^+$, 100%). Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.21; H, 8.97; N, 9.55.

(4*S*,3′*R*)-3-(2′-Methyl-3′-pentanamino)-4-phenylmethyl-2-oxazolidinone (9R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (54 mg, 0.23 mmol) and 2-iodopropane (0.24 mL, 2.3 mmol) by general procedure B and workup B was obtained **9R**[12] (48 mg, 75%; *S*,*R*/*S*,*S* = 95:5, NMR analysis) as a colorless solid.

(4*S*,2′*R*)-3-(1′-Chloro-2′-butanamino)-4-phenylmethyl-2-oxazolidinone (10R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (50 mg, 0.22 mmol) and chloroiodomethane (0.16 mL, 2.16 mmol) by general procedure B and workup B was obtained **10R** (38 mg, 63%; *S*,*R*/*S*,*S* = 93:7, HPLC analysis) as a colorless oil: $[\alpha]_D^{27}$ +44.9 (*c* 3.4, $CHCl_3$); IR (film) 3286, 3028, 2966, 2878, 1758, 1497, 1400, 1240, 1217, 1091, 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.25 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 4.13 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.03 (dd, *J* = 8.9, 5.8 Hz, 1H), 3.93−3.88 (m, 1H), 4.25−3.85 (br s, 1H), 3.65 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.59 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.41 (dd, *J* = 13.4, 3.6 Hz, 1H), 3.24 (dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 2.63 (dd, *J* = 13.3, 10.1 Hz, 1H), 1.70−1.56 (m, 2H), 1.01 (dd, *J* = 7.4, 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 135.8, 129.0, 128.9, 127.1, 66.2, 61.3, 59.7, 45.5, 37.1, 23.4, 9.8; MS (CI) *m*/*z* (relative intensity) 283 ([M + H]$^+$, 100%). Anal. Calcd for $C_{14}H_{19}N_2O_2Cl$: C, 59.47; H, 6.77; N, 9.91. Found: C, 59.69; H, 6.82; N, 9.80.

(4*S*,2′*R*)-3-(2′-Ethyl-pyrrolidin-1-yl)-4-phenylmethyl-2-oxazolidinone (11R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (50 mg, 0.22 mmol) and 1-chloro-3-iodopropane (0.23 mL, 2.16 mmol) by general procedure B and workup B was obtained **11R** (31 mg, 52%; *S*,*R*/*S*,*S* = 96:4, NMR analysis) as a colorless oil: $[\alpha]_D^{26}$ +34.6 (*c* 0.85, $CHCl_3$); IR (film) 3054, 3004, 2968, 2875, 1731, 1494, 1415, 1237, 1118, 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.1, 7.1 Hz, 2H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 4.14 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.01−3.92 (m, 2H), 3.60−3.52 (m, 2H), 3.42 (dd, *J* = 13.3, 3.6 Hz, 1H), 3.16−3.12 (m, 1H), 2.61 (dd, *J* = 13.3, 10.4 Hz, 1H), 2.05−1.98 (m, 1H), 1.95−1.86 (m, 1H), 1.82−1.74 (m, 1H), 1.70−1.62 (m, 1H), 1.47−1.31 (m, 2H), 0.93 (dd, *J* = 7.4, 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 136.1, 129.0, 128.8, 126.9, 66.3, 62.5, 60.2, 52.1, 38.8, 28.5, 27.1, 21.7, 10.1; MS (CI) *m*/*z* (relative intensity) 275 ([M + H]$^+$, 100%). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.10; H, 8.11; N, 10.01.

(4*S*,3′*R*)-3-(7′-Chloro-3′-heptanamino)-4-phenylmethyl-2-oxazolidinone (12R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (75 mg, 0.32 mmol) and 1-chloro-4-iodobutane (0.40 mL, 3.23 mmol) by general procedure B and workup B was obtained **12R** (58 mg, 55%; *S*,*R*/*S*,*S* = 96:4, HPLC analysis) as a colorless oil: $[\alpha]_D^{26}$ +34.0 (*c* 0.6, $CHCl_3$); IR (film) 3291, 3063, 3028, 2960, 2873, 1757, 1454, 1400, 1238, 1090, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.26 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.16 (d, *J* = 6.9 Hz, 2H), 4.14 (dd, *J* = 8.8, 7.7 Hz, 1H), 4.03 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.94−3.87

(m, 2H), 3.56 (dd, J = 6.6, 6.6 Hz, 2H), 3.32 (dd, J = 13.5, 3.6 Hz, 1H), 3.07−2.95 (m, 1H), 2.62 (dd, J = 13.4, 9.9 Hz, 1H), 1.85−1.77 (m, 2H), 1.60−1.44 (m, 6H), 0.96 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 135.9, 129.0, 128.9, 127.0, 65.7, 60.1, 59.7, 44.8, 37.0, 32.7, 30.7, 24.7, 22.8, 9.1; MS (CI) m/z (relative intensity) 325 ([M + H]$^+$, 100%). Anal. Calcd for $C_{17}H_{25}N_2O_2Cl$: C, 62.86; H, 7.76; N, 8.62. Found: C, 63.07; H, 7.77; N, 8.45.

(4*S*,2′*R*)-3-(1′,1′-Dichloro-2′-butanamino)-4-phenylmethyl-2-oxazolidinone (13R). From (*S*)-3-(propylidene)amino-4-phenylmethyl-2-oxazolidinone (50 mg, 0.22 mmol) and bromodichloromethane (0.36 mL, 2.16 mmol) by general procedure B and workup A was obtained **13R** (26 mg, 38%; *S*,*R*/*S*,*S* = 98:2, NMR analysis) as a colorless oil: $[\alpha]_D^{26}$ +59.2 (*c* 0.9, $CHCl_3$); IR (film) 3293, 3028, 2971, 1759, 1497, 1455, 1402, 1220, 1091, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.1, 7.1 Hz, 2H), 7.27 (dd, J = 7.2, 7.2 Hz, 1H), 7.16 (d, J = 7.1 Hz, 2H), 6.06 (d, J = 2.6 Hz, 1H), 4.44−4.30 (br s, 1H), 4.16 (dd, J = 8.9, 8.9 Hz, 1H), 4.07 (dd, J = 8.9, 5.0 Hz, 1H), 3.93−3.88 (m, 1H), 3.43 (dd, J = 13.4, 3.4 Hz, 1H), 3.28−3.23 (m, 1H), 2.63 (dd, J = 13.3, 10.2 Hz, 1H), 1.99−1.91 (m, 1H), 1.69−1.59 (m, 1H), 1.15 (dd, J = 7.4, 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 135.6, 129.0 (2C), 127.2, 74.3, 68.9, 66.1, 59.4, 36.7, 20.7, 10.7; MS (CI) m/z (relative intensity) 317 ([M + H]$^+$, 100%). Anal. Calcd for $C_{14}H_{18}N_2O_2Cl_2$: C, 53.01; H, 5.72; N, 8.83. Found: C, 53.18; H, 5.82; N, 8.65.

(4*S*,3′*R*)-3-(1′-Chloro-3′-pentanamino)-4-phenylmethyl-2-oxazolidinone (14). From **2a** (53 mg, 0.23 mmol) and 1-chloro-2-iodoethane (104 μL, 1.14 mmol) by general procedure B and workup B was obtained **14** as an inseparable mixture with the starting material (44 mg, 14% yield and 65% **2a** by ^{1}H NMR). For characterization, a pure sample was obtained by an alternative method[55] as a colorless oil: $[\alpha]_D^{25}$ +26.5 (*c* 0.8, $CHCl_3$); IR (film) 3289, 2964, 2931, 2876, 1755, 1497, 1454, 1400, 1363, 1239, 1091, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.25 (m, 3H), 7.18 (dd, J = 6.6, 1.6 Hz, 2H), 4.16 (dd, J = 8.6, 7.6 Hz, 1H), 4.04 (dd, J = 8.8, 5.7 Hz, 1H), 3.99−3.91 (m, 2H), 3.81−3.62 (m, 2H), 3.37 (dd, J = 13.4, 3.6 Hz, 1H), 3.13 (m, 1H), 2.67 (dd, J = 13.4, 9.8 Hz, 1H), 1.97−1.90 (m, 2H), 1.64−1.45 (m, 2H), 0.99 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 135.7, 128.9 (2C), 127.0, 66.0, 59.8, 58.4, 41.7, 37.2, 34.8, 25.0, 9.5; MS (EI) m/z (relative intensity) 296 (M$^+$, 6%), 267 (19%), 233 (42%), 205 (57%). Anal. Calcd for $C_{15}H_{21}ClN_2O_2$: C, 60.70; H, 7.13; N, 9.44. Found: C, 60.99; H, 7.17; N, 9.40.

(4*S*,2′*S*)-3-(2′-Propyl-piperidin-1-yl)-4-phenylmethyl-2-oxazolidinone [(*S*,*S*)-17]. From **16** (50 mg, 0.12 mmol) and 1-iodopropane (0.23 mL, 2.3 mmol) by general procedure B was obtained (*S*,*S*)-**17** (16 mg, 45%, *S*,*S*/*S*,*R* = 3.2:1, NMR analysis) as a colorless oil: IR (film) 3028, 2936, 2860, 1758, 1495, 1454, 1398, 1365, 1231, 1186, 1084 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.6, 7.6 Hz, 2H), 7.24 (dd, J = 7.5, 7.5 Hz, 1H), 7.16 (d, J = 7.1 Hz, 2H), 4.14 (dd, J = 8.3, 8.3 Hz, 1H), 4.00 (dd, J = 8.8, 8.8 Hz, 1H), 3.95−3.84 (m, 1H), 3.45−3.28 (m, 2H), 2.96 (br d, J = 10.9 Hz, 1H), 2.53 (dd, J = 13.6, 10.7 Hz, 1H), 1.93−1.04 (m, 10H), 0.94 (dd, J = 7.3, 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.5, 128.8, 128.7, 126.9, 67.5, 59.6, 56.6, 49.9, 39.1, 35.5, 32.0, 26.4, 24.0, 18.9, 14.4; MS (CI) m/z (relative intensity) 303 ([M]$^+$, 96%), 259 (100%). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.41; H, 8.68; N, 9.21.

(4*S*,4′*R*)-3-(8′-Chloro-4′-octanamino)-4-phenylmethyl-2-oxazolidinone (18). To a deoxygenated (N_2) solution of **2c** (1.01 g, 4.10 mmol) in CH_2Cl_2 (40 mL) was added $InCl_3$ (2.00 g, 9.03 mmol). After 40 min, $Mn_2(CO)_{10}$ (3.20 g, 8.20 mmol) and 1-chloro-4-iodobutane (5.03 mL, 41.0 mmol) were added and the mixture was irradiated for 2 days. DBU (2.49 mL, 16.4 mmol) was added, and after 1 h, the mixture was concentrated and purified by gradient flash chromatography (hexane → 1:1 hexane/EtOAc) to afford **18** as a pale yellow oil (910 mg, 66% yield). From a separate smaller-scale reaction, 225 mg of **2c** gave **18** in 65% yield (*S*,*R*/*S*,*S* = 95:5, HPLC analysis) as a colorless oil: $[\alpha]_D^{26}$ +28.2 (*c* 2.0, $CHCl_3$); IR (film) 3292, 3028, 2956, 2933, 1757, 1497, 1455, 1399, 1238, 1089, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 7.2, 7.2 Hz, 2H), 7.26 (dd, J = 7.2, 7.2 Hz, 1H), 7.16 (d, J = 7.1 Hz, 2H), 4.15 (dd, J = 8.7, 7.7 Hz, 1H), 4.03 (dd, J = 8.9, 4.7 Hz, 1H), 3.92−3.86 (m, 1H), 4.20−3.80 (br s, 1H), 3.56 (dd, J = 6.5, 6.5 Hz, 2H), 3.32 (dd, J = 13.4, 3.6 Hz, 1H), 3.04 (dddd, J = 5.3, 5.3, 5.3, 5.3 Hz, 1H), 2.62 (dd, J = 13.4, 9.9 Hz, 1H), 1.87−1.74 (m, 2H), 1.63−1.34 (m, 8H), 0.95 (dd, J = 6.8, 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 135.9, 129.0, 128.9, 127.0, 65.8, 59.7, 58.8, 44.8, 37.0, 34.5, 32.7, 31.4, 22.8, 18.4, 14.3; MS (CI) m/z (relative intensity) 339 ([M + H]$^+$, 100%). Anal. Calcd for $C_{18}H_{27}N_2O_2Cl$: C, 63.80; H, 8.03; N, 8.27. Found: C, 64.02; H, 7.99; N, 8.19.

(4*S*,3′*S*)-3-(2′-Methyl-3′-pentanamino)-4-phenylmethyl-2-oxazolidinone (9S). From **23** (60 mg, 0.24 mmol) and ethyl iodide (0.12 mL, 1.46 mmol) by general procedure B and workup B was obtained unreacted **23** (29 mg, 49%) and **9S** (28 mg, 41% yield) as a colorless oil: $[\alpha]_D^{25}$ +17.4 (*c* 0.17, $CHCl_3$); IR (film) 3304, 2960, 2929, 2873, 1759, 1498, 1453, 1397, 1365, 1259, 1238, 1216, 1090, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 7.2, 7.2 Hz, 2H), 7.25 (dd, J = 7.4, 7.4 Hz, 1H), 7.15 (d, J = 7.1 Hz, 2H), 4.13 (dd, J = 7.7, 7.7 Hz, 1H), 4.04 (dd, J = 8.9, 4.2 Hz, 1H), 4.02 (br s, 1H), 3.92−3.87 (m, 1H), 3.35 (dd, J = 13.4, 2.7 Hz, 1H), 2.80 (m, 1H), 2.61 (dd, J = 13.4, 10.1 Hz, 1H), 1.92−1.85 (m, 1H), 1.53−1.47 (m, 1H), 1.39−1.29 (m, 1H), 1.04 (dd, J = 7.5, 7.5 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 136.1, 129.1, 128.9, 127.0, 66.2, 65.5, 59.6, 36.8, 28.6, 20.8, 18.4, 16.9, 10.9; MS (EI) m/z (relative intensity) 276 (M$^+$, 2%), 247 (3%), 233 (100%). Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.76; H, 8.85; N, 10.14.

(4*S*,3′*S*)-3-(2′-Methyl-3′-pentanamino)-4-diphenylmethyl-2-oxazolidinone (24B). From **23B** (80 mg, 0.25 mmol) and ethyl iodide (0.20 mL, 2.48 mmol) by general procedure B and workup B was obtained unreacted **23B** (25 mg, 31%) and **24B** (46 mg, 52% yield) as colorless needles: mp 132−134 °C; $[\alpha]_D^{25}$ +66.0 (*c* 0.5, $CHCl_3$); IR (film) 3301, 2961, 2929, 1755, 1494, 1451, 1406, 1221, 1090, 1031, 1009 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.35−7.29 (m, 4H), 7.27−7.24 (m, 2H), 7.19 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 7.1 Hz, 2H), 4.66 (d, J = 5.2 Hz, 1H), 4.56−4.52 (m, 1H), 4.37 (dd, J = 8.8, 8.8 Hz, 1H), 4.27 (dd, J = 9.1, 3.4 Hz, 1H), 2.71 (ddd, J = 7.8, 4.3, 4.3 Hz, 1H), 1.78−1.72 (m, 1H), 1.46−1.38 (m, 1H), 1.32−1.24 (m, 2H), 0.95 (dd, J = 7.5, 7.5 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 140.7, 139.0, 128.8 (2C), 128.7, 128.3, 127.4, 127.0, 65.1, 64.1, 59.5, 50.9, 28.6, 20.7, 18.4, 17.1, 10.7; MS (EI) m/z (relative intensity) 352 (M$^+$, 2%), 309 (52%), 185 (100%). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.70; H, 7.97; N, 7.91.

(4*S*,3′*S*)-3-(7′-(*tert*-Butyldimethylsilyloxy)-3′-heptanamino)-4-phenylmethyl-2-oxazolidinone (25). A mixture of hydrazone **2a** (75 mg, 0.32 mmol) and $InCl_3$ (143 mg, 0.64 mmol) in benzene/CH_3CN (10:1 v/v, 2.2 mL) was stirred at room temperature under N_2 for 30 min. Then $Mn_2(CO)_{10}$ (250 mg, 0.64 mmol) and TBSO-$(CH_2)_4$I (151 mg, 0.48 mmol) were added, and the mixture was irradiated for 16 h. Gradient flash chromatography (hexane/EtOAc 7:1 to 1:1) afforded hydrazine **25** (82 mg, 0.195 mmol, 63% yield, >98:2 dr, ^{1}H NMR analysis) as a colorless oil: $[\alpha]_D^{29}$ +6.6° (*c* 2.4, $CHCl_3$); IR (film) 3292, 3028, 2930, 2858, 1761, 1498, 1462, 1472, 1395, 1361, 1252, 1095, 1030, 1006 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.9, 7.9 Hz, 2H), 7.25 (dd, J = 6.8, 6.8 Hz, 1H), 7.15 (d, J = 7.9 Hz, 2H), 4.13 (dd, J = 7.9, 7.9 Hz, 1H), 4.03 (dd, J = 9.1, 4.1 Hz, 1H), 3.93−3.85 (m, 1H), 4.22−

(55) Addition of iodoethanol to **2a** according to general procedure B, followed by conversion of the alcohol to chloride (PPh_3, CCl_4, DMF, 75% yield) gave **14** which matched the NMR data of **14** as observed in the mixture of **14** and **2a**. Details will be reported elsewhere.

3.72 (br s, 1H), 3.63 (dd, $J = 6.4$, 6.4 Hz, 2H), 3.33 (dd, $J = 13.6$, 3.4 Hz, 1H), 3.06−2.94 (m, 1H), 2.61 (dd, $J = 13.9$, 9.8 Hz, 1H), 1.64−1.37 (m, 8H), 0.95 (dd, $J = 7.5$, 7.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 136.0, 129.0, 128.8, 127.0, 65.7, 62.9, 60.3, 59.9, 37.0, 33.0, 31.3, 25.9, 24.6, 21.8, 18.3, 9.0, −5.4; MS (CI) *m*/*z* (relative intensity) 421.1 ([M + H]$^+$, 100%); HRMS (EI) calcd for $C_{23}H_{40}N_2O_3Si$: 420.2808. Found: 420.2811.

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

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