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Mn-Mediated Radical-Ionic Annulations of Chiral *N*-Acylhydrazones

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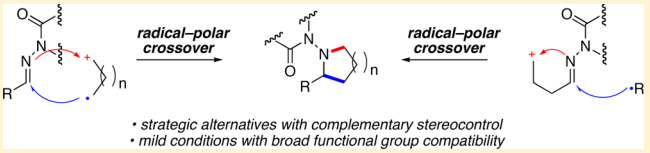
Supporting Information

ABSTRACT: Sequencing a free radical addition and nucleophilic substitution enables [3 + 2] and [4 + 2] annulations of *N*-acylhydrazones to afford substituted pyrrolidines and piperidines. Photolysis of alkyl iodides in the presence of $Mn_2(CO)_{10}$ leads to chemoselective iodine atom abstraction and radical addition to *N*-acylhydrazones without affecting alkyl chloride functionality. Using radical precursors or acceptors bearing a suitably positioned alkyl chloride, the radical addition is followed by further bond construction enabled by radical−polar crossover. After the alkyl radical adds to the imine bond, the resulting *N*-nucleophile displaces the alkyl chloride leaving group via 5-*exo*-*tet* or 6-*exo*-*tet* cyclizations, furnishing either pyrrolidine or piperidine, respectively. When both 5-*exo*-*tet* and 6-*exo*-*tet* pathways are available, the 5-*exo*-*tet* cyclization is preferred. Isolation of the intermediate radical adduct, still bearing the alkyl chloride functionality, confirms the order of events in this radical−polar crossover annulation. A chiral oxazolidinone stereocontrol element in the *N*-acylhydrazones provides excellent stereocontrol in these reactions.



INTRODUCTION

Radical-polar crossover (RPC) reactions are attractive in synthesis as they allow for rapid increase of complexity through multiple bond constructions, carbon−carbon and/or carbon−heteroatom, in a single pot.[1] Combining both radical and ionic reactivity in sequential bond constructions offers new opportunities to rapidly build molecular complexity through annulation reactions. Among the structural outcomes of such reactions are highly functionalized cyclohexanes, γ-lactones, tetrahydrofurans, lactams, and pyrrolidines.[2] Thus, it is hardly surprising that RPC reactions have begun to appear in synthetic routes to polycyclic ring systems of natural products, such as aspidospermidine,[3] penitrems,[4] and acutumine.[5]

In considering the fundamental chemical behavior of the imine functional group class, including oximes and hydrazones, there is not only the well-recognized basic and nucleophilic behavior at the C═N nitrogen but also the radical acceptor behavior of the C═N carbon (Figure 1a). The latter has emerged in recent years as a powerful alternative for C−C bond construction approaches to chiral amines.[6,7] Combining these two concepts for bond construction allows for a novel annulation approach to be conceived, in which both radical and polar bond constructions would be incorporated into one ring-forming reaction.

From a retrosynthetic standpoint, the radical−ionic annulation disconnection could be envisioned in two modes that differ by which component carries the electrophilic reactivity (Figure 1b): Type I annulation places the nucleofuge and radical in the same component, while Type II annulation entails linking the nucleofuge to the imino compound.[8] A key chemoselectivity challenge in executing either of these approaches would be to ensure that the two bond constructions occur with orthogonal reactivity. Initiating the annulation with a carbon-centered radical rather than an organometallic nucleophile (e.g., organolithium) would avoid unproductive base-induced elimination, metal−halogen exchange, or other side reactions.

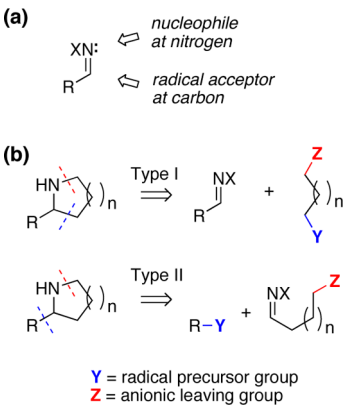


Figure 1. Conception of radical−polar crossover approach to imine annulation. (a) Two distinct chemical behaviors at carbon and nitrogen of the C═N bond. (b) Type I and Type II retrosynthetic disconnection of *N*-heterocycles via radical−ionic annulation.

Carbon−carbon bond construction approaches to asymmetric amine synthesis have seen numerous advances in recent years.[9,10] Our laboratories have disclosed a number of methods for synthesis of chiral amines via additions to *N*-acylhydrazones built from chiral *N*-aminooxazolidinones.[11] With these substrates, a Lewis acid participates in two-point binding of the imino nitrogen and the oxazolidinone carbonyl for electrophilic activation and rotamer control, leading to excellent stereoselectivity in most addition reactions.[12]

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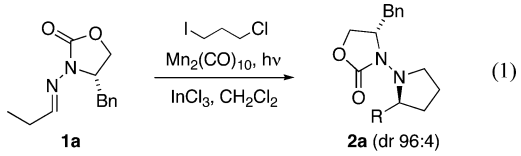
In our prior work on radical addition reactions of chiral *N*-acylhydrazones, we found that Mn-mediated additions of alkyl iodides to these C═N acceptors proceed via addition of free carbon-centered radicals rather than organomanganese species.[13] The alkyl radicals are generated via a well-precedented halogen atom transfer from alkyl iodide to pentacarbonylmanganese radicals formed on photolysis of $Mn_2(CO)_{10}$.[14] The synthetic utility of these reactions is enhanced by their functional group tolerance; numerous examples illustrate compatibility with free hydroxyls, esters, silyl ethers, and alkyl chlorides.[15] The Mn-mediated radical additions are therefore well-suited to applications to complex targets, as we have documented in synthetic studies of tubulysins[16] and in a formal synthesis of quinine.[17] Of special relevance to the present study, the compatibility of these conditions with an alkyl chloride prevents interference between radical and polar phases of a radical−polar crossover process, ensuring two orthogonal bond constructions can be accomplished during the annulation envisioned in Figure 1b.

RESULTS AND DISCUSSION

During prior studies, we had occasion to attempt the addition of various ω-chloroalkyl iodides mediated by photolysis of dimanganese decacarbonyl ($Mn_2(CO)_{10}$).[18] Most of these reactions preserved the chloride in the product (a useful chemoselectivity feature), but the addition of 3-chloropropyl iodide (**3a**) to propionaldehyde hydrazone **1a** resulted in pyrrolidine **2a** (eq 1, R = Et). Also, while exploring the Mn-



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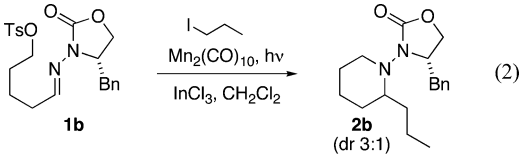
mediated radical addition in the presence of *p*-toluenesulfonate ester functionality (eq 2), the sulfonate was displaced to form

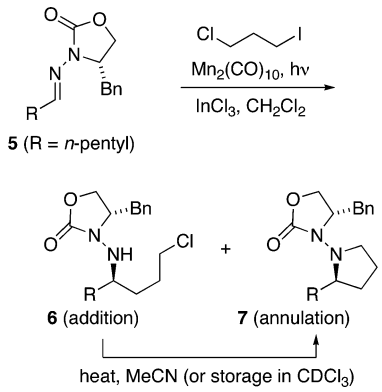


(2)

piperidine **2b**. However, anomalously poor stereoselectivity (dr 3:1) suggested polar cyclization preceded radical addition, disrupting Lewis acid binding and stereocontrol.[13] On the other hand, in a reaction similar to eq 1, carboxylate ester functionality was unaffected (**2a**, R = $CH_2CH_2CO_2Me$).[19] These initial examples suggested that *N*-alkylation by tosylate was too rapid, and *N*-acylation by an ester was too slow, at least within the typical conditions of the Mn-mediated radical addition. Between these extremes, the alkyl halide offered sufficient reactivity, without interfering with the radical addition. Thus, it was selected for development of a new radical−polar crossover approach to annulation of C═N bonds.

The reaction development effort began with an effort to rigorously determine the order of events in the radical−ionic annulation of eq 1. Although we suspected that the radical addition occurred prior to a nucleophilic substitution of the alkyl chloride, evidence was lacking. To address this, we carried out additions of 3-chloropropyl iodide to hydrazone **5** (Scheme 1) in the presence of $Mn_2(CO)_{10}$ and $InCl_3$ using shorter photolysis times, with careful analysis of minor products. These

Scheme 1



experiments revealed that chloropropyl adduct **6** appeared in variable amounts. After chromatographic separation, a solution of pure **6** in acetonitrile was heated, cleanly converting it to annulation product **7**. The same cyclization was also observed in $CDCl_3$ solutions prepared for NMR experiments. This clearly suggests **6** is an intermediate en route to **7**, indicating that radical addition happens first in this annulation.

By examining the diastereomer ratio of **7**, further evidence was obtained regarding the potential for a competing process involving an initial *N*-alkylation. As noted above, the erosion of stereocontrol in the Type II cyclization of **4** (dr 3:1) was attributed to premature cyclization, forming an iminium ion prior to radical addition; this would disrupt two-point binding of the Lewis acid by the *N*-acylhydrazone, leading to poor control of rotamer populations.[20] Similarly, if some of the annulation product **7** had been produced via *N*-alkylation preceding radical addition, the stereocontrol would be eroded. This hypothesis could be easily addressed, because we had in hand two separate samples of **7**, one produced by the cyclization of purified chloroalkyl adduct **6**, and one isolated from the one-pot annulation. The ^{13}C NMR spectra of both samples showed no evidence of the minor diastereomer, sharply contrasting with the result in eq 2.[21] This offers further evidence that radical addition precedes polar cyclization in the events leading to most (if not all) of **7**. Thus, the cyclization component involves a 5-*exo-tet* polar cyclization rather than 5-*endo-trig* radical cyclization, consistent with intramolecular reactivity tendencies outlined by Baldwin.[22]

The mechanistic picture was further sharpened upon identifying varying amounts of dichloromethyl adduct **8** among the minor components of product mixtures. This indicates that a hydrogen atom abstraction event produces ·$CHCl_2$, which then competes for the radical acceptor. Thus, it appears that hydrogen atom abstraction by the adduct, a *N*-centered aminyl radical, intervenes between radical addition and cyclization.[23] While a hypothetical *N*-metalated species cannot be rigorously excluded, there is no apparent requirement for it, nor evidence for it.

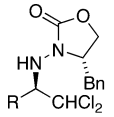


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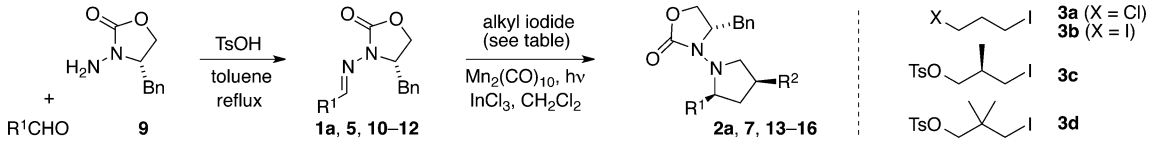
Table 1. Scope of Type I [3 + 2] Radical–Ionic Annulations of Chiral *N*-Acylhydrazones[a]



entry	R^1	hydrazone, yield[b]	alkyl iodide	annulation product, yield[b]	*dr*[c]
1	CH_3CH_2	**1a**[d]	**3a**	**2a**, 52%	96:4[d]
2	$CH_3(CH_2)_3CH_2$	**5**[d]	**3a**	**7**, 70%	>95:5
3[e]	$CH_3(CH_2)_3CH_2$	**5**[d]	**3a**	**7** (10%)[e]	83:17[e]
4	$CH_3(CH_2)_8CH_2$	**10**, 74%	**3a**	**13**, 54%	>95:5
5	$PhCH_2CH_2$	**11**, 70%	**3a**	**14**, 60%	>95:5
6	$(CH_3)_2CHCH_2$	**12**[d]	**3a**	**15**, 86%	>95:5
7	CH_3CH_2	**1a**[d]	**3b**	**2a**, 18%[f]	–
8	CH_3CH_2	**1a**[d]	**3c**	**16**, 42%	>95:5
9	CH_3CH_2	**1a**[d]	**3d**	–[g]	–[g]

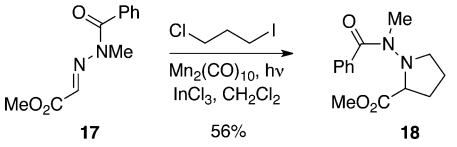
[a]Conditions: 1. R^1CHO (5 equiv), TsOH, 4Å molecular sieves, toluene, reflux; 2. alkyl iodide (10 equiv), $Mn_2(CO)_{10}$ (2 equiv), $InCl_3$ (2 equiv), CH_2Cl_2, hν (300 nm, Rayonet), 40 h; then workup with Et_3N and flash chromatography on silica gel. [b]Isolated yield. [c]Ratio determined by NMR. [d]Previously reported compound.[13] [e]$InCl_3$ was omitted from this run. [f]Reductive dehalogenation to afford an acyclic *n*-propyl adduct (**2b**) was also observed, in 13% yield. [g]No reaction.

After gathering this evidence, our attention turned toward the optimization and scope of the [3 + 2] radical–ionic annulation reaction. Known chiral *N*-acyl hydrazones **1a**, **5**, **12** and new hydrazones **10** and **11** (Table 1) were prepared according to the established methods[11] and subjected to annulations using some modifications to the conditions of Scheme 1. The first modification was to run the reaction at a higher concentration, which minimized the dichloromethyl adduct **8** to negligible quantities. A longer reaction time was employed to facilitate the completion of the cyclization stage of the annulation. Using these modified conditions, three hydrazones of varying aliphatic chain lengths gave annulation products in yields ranging from 52% to 70% (Table 1, entries 1, 2, and 4). The phenyl group in hydrocinnamaldehyde hydrazone **11** was well tolerated, giving an annulation product yield of 60% (entry 5). Isovaleraldehyde hydrazone **12**, bearing branching at the β-position, worked especially well, yielding 86% of the annulation product (entry 6). Mass balances in these annulations were quite good; when corrected for conversion (on the basis of recovered starting material), the combined yields of chloroalkyl adducts and annulation products range from 63% to 100%.

Diastereoselectivity in the annulation reactions is consistent with Mn-mediated radical additions reported previously. All cases exhibited diastereomer ratios >95:5 with minor diastereomer peaks undetected in ^1H NMR (500 MHz), ^{13}C NMR, or HPLC. An authentic diastereomer mixture (**7**, dr 83:17), produced in the absence of $InCl_3$ (entry 3), exhibited clearly resolved minor diastereomer peaks in ^1H NMR and ^{13}C NMR spectra (see Supporting Information).

Variations to the halide leaving group in the 3-position of the alkyl iodide component were examined. Exchanging iodide for chloride (1,3-diiodopropane, **3b**) led to complications from reductive dehalogenation; a 13% yield of the acyclic *n*-propyl adduct accompanied the low-yielding radical–ionic annulation (entry 7). Using (*R*)-3-iodo-2-methylpropyl *p*-toluenesulfonate (**3c**), with one neighboring methyl substituent, the annulation was moderately successful, furnishing disubstituted pyrrolidine **16** in 42% yield. This was somewhat unexpected, given the previously described behavior of the tosylate shown in eq 2. Annulation with iodide **3d**, bearing *gem*-dimethyl substitution, was unsuccessful.

Hydrazones prepared from chloroacetaldehyde and *O*-*tert*-butyldimethylsilylglycolaldehyde did not perform well in these annulations, despite their success in earlier Mn-mediated radical additions.[24] In both cases, crude mixtures showed evidence of the expected annulation product, but it apparently decomposed during chromatographic purification. On the other hand, ester functionality at the α-position was compatible with the conditions; annulation of *N*-benzoylhydrazone **17** with 3-chloropropyl iodide (eq 3) afforded a 56% yield of **18**, a



(3)

hydrazine analog of proline. Thus, the scope of other iodides for [3 + 2]-annulations of Type I may have broader potential for further application to multifunctional compounds.

The Type II annulation approach to pyrrolidines was next explored. Additions of ethyl, isopropyl, isobutyl, pentyl, and 4-chlorobutyl iodides to hydrazone **19** resulted in pyrrolidines **20**–**24** (Table 2). Unsurprisingly, isopropyl iodide gives the highest yield (**21**, 85%), consistent with its ease of conversion to the secondary radical. Data from X-ray crystallography confirmed the assigned structure of isopropyl-substituted pyrrolidine **21** (see Supporting Information). It is noteworthy that the simple primary alkyl iodides are also successful (59–67% yield); primary radicals perform inefficiently in most intermolecular additions, but are handled smoothly by the Mn-mediated conditions.

Addition of 4-chlorobutyl iodide to hydrazone **19** would be expected to give intermediate **25** (Scheme 2), setting up a direct internal competition between cyclization of two ω-chloroalkyl groups of different length, either 5-*exo*-*tet* or 6-*exo*-*tet*. Although some compounds closely related to **25** have been reported, mainly in the literature of indolizidine alkaloid synthesis,[25] these were employed for bis-cyclizations without discussion of group selectivity. Therefore, the annulation affording **24** was of some further interest. In the event,

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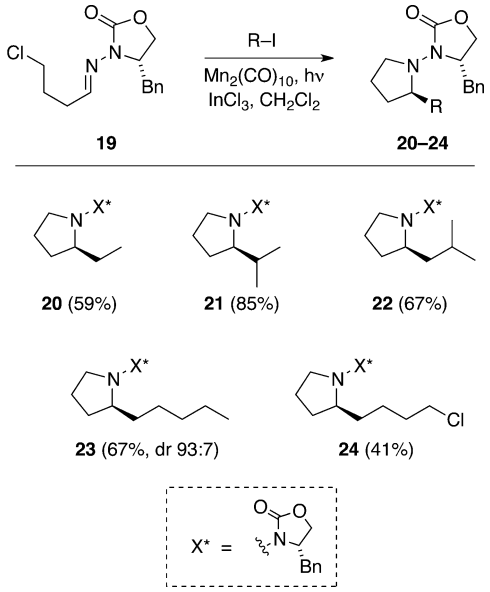
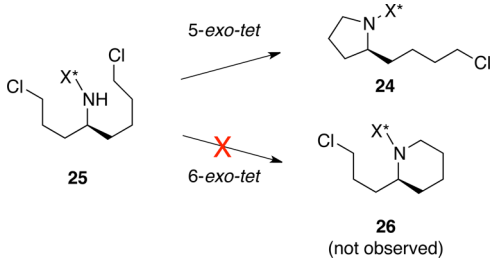
Table 2. Type II Annulations Leading to Pyrrolidines[a]



[a]Diastereomer ratios were >95:5, unless otherwise noted, as judged by ^{1}H and ^{13}C NMR spectra.

Scheme 2



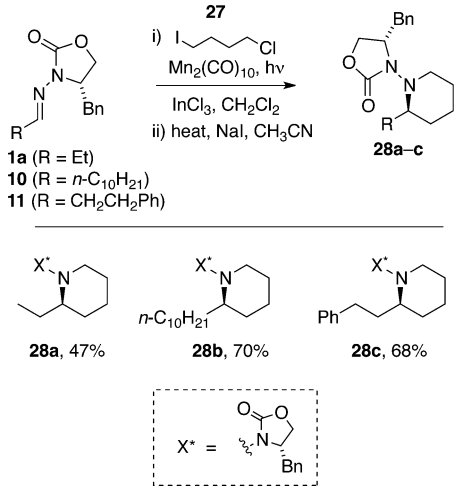
group-selective cyclization occurred, providing only the pyrrolidine **24**. This selectivity was consistent with reports of related 5-*exo-tet* cyclizations to afford bis-pyrrolidines wherein no products of 6-*exo-tet* cyclization were observed.[26]

In comparison with the products in Table 1, pyrrolidines **20**–**24** in Table 2 are formed with opposite configuration at the new stereogenic center. This outcome follows from the fact that the roles of the reactant partners are interchanged in Type I vs Type II annulations. Considering that the enantiomeric stereocontrol element is also available, there are four complementary routes to access the two pyrrolidine C2 epimers, highlighting the synthetic design flexibility of radical addition to *N*-acylhydrazones.

The first attempt at piperidine synthesis according to this strategy involved a Type II annulation resulting in poor diastereoselectivity (eq 2). As noted above, we attributed this anomalously poor selectivity to a change in mechanism; premature cyclization to form an iminium ion would disrupt the stereocontrol of radical addition. From this we hypothesized that moderating the reactivity of the leaving group would potentially delay cyclization until after the radical addition, avoiding stereocontrol problems. We previously encountered a 4-chlorobutyl adduct which did not readily cyclize; this adduct was stable during isolation, storage, and transport for combustion analysis.[18] The fact that the 6-*exo-tet* cyclization required to complete the annulation of the 4-chlorobutyl adducts is relatively slow was also noted above in the Type II group-selective annulation **19** → **24** (Table 2).

Supported by the above reasoning, 4-chlorobutyl iodide (**27**) was chosen for further examination for a Type I [4 + 2] annulation of a series of hydrazones (Table 3). By adjustments

Table 3. Type I Annulations Leading to Piperidines[a]

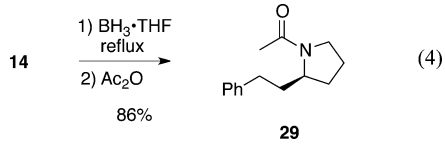


[a]Diastereomer ratios were >95:5 in all cases, as judged by ^{1}H and ^{13}C NMR spectra.

to the conditions, using a solvent change to accelerate the polar cyclization, efficient and general Type I annulations indeed provided the desired piperidines **28a**–**c**. The improved method entailed addition of **27** under routine Mn-mediated radical addition conditions, followed by separation of Mn-containing byproducts (filtration through silica gel), then heating with NaI in refluxing acetonitrile. Presumably, the more polar medium and higher reflux temperature both contributed to the improvement in the polar component of this annulation.

From a mechanistic standpoint, a working model (Scheme 3) consistent with the available data involves radical generation via I atom abstraction from the corresponding iodide by pentacarbonylmanganese radical (from photolysis of $Mn_2(CO)_{10}$), followed by a radical addition via the nonchain Mn-mediated process described previously.[13] The resulting aminyl radical undergoes H atom abstraction from the solvent (dichloromethane), and finally S_N2 cyclization. The Lewis acid ($InCl_3$) assists in the radical addition step by coordinating to the imino nitrogen,[19] lowering the LUMO energy of the radical acceptor, but its involvement during the H atom abstraction is unclear.

Lastly, to establish synthetic utility, the chiral auxiliary was removed without alteration of the pyrrolidine ring. Borane reduction of **14** with a 1 M solution of BH_3·THF resulted in clean and complete reductive cleavage of the N–N bond to afford the free amine. The product was worked up with acetic anhydride for ease of isolation, furnishing **29** in 86% yield (eq 4).



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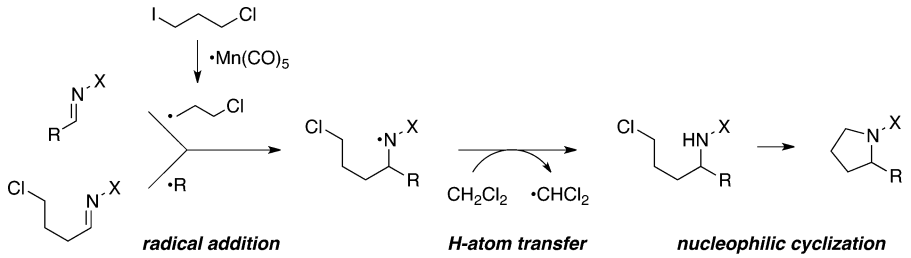
Scheme 3



CONCLUSION

The radical−ionic annulation offers a nonbasic C−C bond construction approach with excellent stereocontrol in order to make pyrrolidines and piperidines, which are ubiquitous substructures in compounds of importance to medicinal and biological chemistry. The radical conditions permit the presence of additional electrophilic functionality, avoiding a limitation that often plagues carbanion-based bond constructions. Either configuration of the heterocyclic product may be synthesized by switching the roles of the precursors (Type I or Type II annulations) or by using the enantiomeric chiral auxiliary. Compared with previously reported radical−polar crossover annulations of imino compounds, these conditions provide three additional elements of versatility, enabling (a) use of a variety of primary alkyl radicals, (b) generation of both five- and six-membered heterocycles, and (c) availability of two alternate routes with placement of the polar cyclization functionality in either precursor. Further studies of radical−polar crossover reactions will be reported in due course.

EXPERIMENTAL SECTION

General Information. Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. Toluene and CH_2Cl_2 were purchased inhibitor-free, sparged with argon, and passed through columns of activated alumina under an argon atmosphere prior to use. Nitrogen was passed successively through columns of anhydrous $CaSO_4$ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with a UV indicator. Flash chromatography columns were packed with 230−400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient as indicated. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed using commercially supplied rotors. Nuclear magnetic resonance (NMR) data were obtained at operating frequencies indicated in the text and are reported in units of ppm. Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission method. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low and high resolution mass spectra (TOF) were obtained from local instrumentation facilities services.

(*R*)-3-Iodo-2-methylpropyl 4-Methylbenzenesulfonate (3c). To (*R*)-(−)-3-bromo-2-methyl-1-propanol (0.34 mL, 3.25 mmol) in acetone (0.42 M) was added sodium iodide (1.22 g, 8.12 mmol) portionwise. The mixture was heated at reflux for 16 h, then concentrated, and partitioned between H_2O with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated to afford (*R*)-3-iodo-2-methyl-1-propanol (479.7 mg, 74%) as a colorless oil which was used without further purification. To a solution of (*R*)-3-iodo-2-methyl-1-propanol (28 mg, 0.14 mmol) in CH_2Cl_2 (0.08 M) were added 4-(dimethylamino)pyridine (<1 mg), *p*-toluenesulfonyl chloride (29 mg, 0.15 mmol), and triethylamine (0.02 mL, 0.15 mmol). The mixture was stirred at rt for 20 h. Flash chromatography (1:1 hexane/CH_2Cl_2, Et_2O) furnished **3c** (35.9 mg, 72%) as a yellow oil. $[\alpha]_D^{25}$ −8.0 (*c* 1.80, $CHCl_3$); IR (film from $CDCl_3$) 2970, 2917, 1593, 1454, 1262; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 8.5 Hz, 2H), 7.37 (d, 8.4 Hz, 2H), 3.96 (dd, *J* = 5.1, 9.8 Hz, 1H), 3.86 (dd, *J* = 6.9, 9.7 Hz, 1H), 3.17 (d, *J* = 5.1 Hz, 2H), 2.45 (s, 3H), 1.92−1.78 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 132.6, 129.9, 128.0, 73.2, 34.4, 21.6, 17.1, 10.5; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}O_3SNaI$ 376.9684 ([M + Na^+]), found 376.9707.

Preparation of *N*-Acylhydrazones. *N*-Acylhydrazones **10**, **11**, and **17** were prepared as described below. Preparation and characterization of *N*-acylhydrazones **1a**,[11] **5**,[18] **12**,[18] and **19**[18] have been previously reported.

(*S*)-*E*-4-Benzyl-3-(undecylideneamino)oxazolidin-2-one (10). To a mixture of (*S*)-3-amino-4-phenylmethyl-2-oxazolidinone (**9**,[11] 246 mg, 1.28 mmol) in toluene (1 M), 4 Å molecular sieves (ca. 30 mg) and *p*-TsOH (ca. 0.1 mg) were added to a solution of undecanal (1.30 mL, 6.30 mmol) in toluene (1.3 M) over 25−40 min. The reaction was heated at reflux for 2 h and then filtered through Celite, washing the cake with EtOAc. Concentration and flash chromatography (hexane/EtOAc) furnished *N*-acylhydrazone **10** (324 mg, 74%) as a colorless oil. $[\alpha]_D^{26}$ −1.2 (*c* 0.505, $CHCl_3$); IR (film from CH_2Cl_2) 3026, 2928, 1763, 1207, 1087 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (t, *J* = 5.6 Hz, 1H), 7.36−7.15 (m, 5H), 4.38−4.30 (m, 1H), 4.23 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.07 (dd, *J* = 5.7, 8.7 Hz, 1H), 3.21 (dd, *J* = 3.6, 13.8 Hz, 1H), 2.79 (dd, *J* = 8.8, 13.8 Hz, 1H), 2.41−2.34 (m, 2H), 1.62−1.52 (m, 2H), 1.40−1.26 (m, 14H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 154.5, 135.3, 129.2, 128.9, 127.2, 65.7, 57.9, 37.3, 33.3, 31.9, 29.5, 29.4, 29.3, 29.2, 29.1, 26.4, 22.6, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{32}N_2O_2Na$ 367.2361 ([M + $Na]^+$), found 367.2362.

(*S*)-*E*-4-Benzyl-3-((3-phenylpropylidene)amino)oxazolidin-2-one (11). A solution of **9** (512 mg, 2.66 mmol) in toluene (1 M) was added over 30 min to a mixture of 4 Å molecular sieves (ca. 30 mg), *p*-TsOH (ca. 0.1 mg), and hydrocinnamaldehyde (1.75 mL, 13.3 mmol) in toluene (1.3 M). The reaction mixture was heated at reflux for 100 min and then filtered through Celite, washing the cake with EtOAc. Concentration and flash chromatography (hexane/EtOAc) furnished **11** (571 mg, 70%) as a yellow oil. $[\alpha]_D^{26}$ +0.99 (*c* 0.505, $CHCl_3$); IR (film from CH_2Cl_2) 3023, 2925, 1757, 1205, 1082 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (t, *J* = 5.3 Hz, 1H), 7.34−7.08 (m, 10H), 4.36−4.27 (m, 1H), 4.23 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.07 (dd, *J* = 5.2, 8.6 Hz, 1H), 3.15 (dd, *J* = 3.4, 13.8 Hz, 1H), 2.95−2.90 (m, 2H), 2.77−2.72 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 154.4, 140.6, 135.2, 129.3, 128.9, 128.5, 128.4, 127.2, 126.2, 65.7, 57.6, 37.0, 34.8, 32.6; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{20}N_2O_2Na$ 331.1422 ([M + $Na]^+$), found 331.1426; calcd for $C_{19}H_{21}N_2O_2$ 309.1603 ([M + $H]^+$), found 309.1613.

Methyl *E*-2-(2-Benzoyl-2-methylhydrazono)acetate (17). To methyl glyoxylate (1.24 g, 14.1 mmol) in toluene (30 mL) was added *N*-benzoyl-*N*-methyl hydrazine (1.90 g, 13.0 mmol), and the mixture was heated at reflux for 1 h under a Dean−Stark trap. Concentration and cooling afforded crystalline **17** as colorless plates, mp 127−129 °C. Concentration of the mother liquor and recrystallization afforded two additional crops, first from $CHCl_3/Et_2O$, second from $CHCl_3/Et_2O$/hexane, for a total of 2.5 g (87%). IR (film from $CDCl_3$) 3064,

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2958, 1712, 1675, 1569, 1446; ^{1}H (300 MHz, $CDCl_3$) δ 7.79−7.75 (m, 2H), 7.51−7.39 (m, 3H), 7.11 (s, 1H), 3.80 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 163.6, 133.0, 131.3, 130.6, 128.6, 127.6, 52.4, 29.5; HRMS (ESI) m/z calcd for $C_{11}H_{12}N_2O_3Na$ 243.0746 ([M + Na]$^+$), found 243.0749; calcd for $C_{11}H_{13}N_2O_3$ 221.0927 ([M + H]$^+$), found 221.0928.

Radical−Ionic Annulation of *N*-Acylhydrazones (General Procedure A). To the *N*-acylhydrazone (0.1−0.3 mmol) in CH_2Cl_2 (0.17 M) in a Pyrex reaction tube was added $InCl_3$ (2.2−2.3 equiv), and this mixture was stirred for 3 h. To this mixture were added 1-chloro-3-iodopropane (or other iodide as specified in Table 1, 10.0 equiv) and $Mn_2(CO)_{10}$ (2.0 equiv). After briefly heating the flask to reflux, the N_2 inlet was quickly replaced with a Teflon-coated glass stopper. The reaction mixture was irradiated (300 nm, Rayonet photoreactor) for 40−45 h, during which time the temperature was ca. 35 °C. The reaction was diluted with an equal volume of hexane, and NEt_3 (10 equiv) was added. After stirring for 1 h, the mixture was filtered through a pad of silica gel, eluting sequentially with 13:1 hexane/Et_2O, 5.5:1 hexane/Et_2O, and a more polar eluent (either 0.8:1 hexane/Et_2O or EtOAc). Concentration of the fraction eluted with the more polar eluent, followed by gradient flash chromatography (20:1 hexane/EtOAc to EtOAc) furnished adducts **2a**, **7**, **13**, **14**, **15**, **16**, and **18** as indicated in Table 1 and eq 1.

(*S*)-4-Benzyl-3-((*R*)-2-ethylpyrrolidin-1-yl)oxazolidin-2-one (2a). From **1a** (79.8 mg, 0.344 mmol) by General Procedure A (2.3 equiv of $InCl_3$) was obtained **2a**[18] (49.7 mg, 52%) as a colorless oil.

(*S*)-3-(1-Chlorononan-4-ylamino)-4-benzyloxazolidin-2-one (6). From **5** (52.5 mg, 0.19 mmol) by a modification of General Procedure A (shorter reaction time of 16 h) was obtained **6** (24.7 mg, 37%) as a yellow oil which gradually transformed to a mixture of **6** and **7**. Data for **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (dd, J = 3.4, 13.3 Hz, 1H), 3.17−3.12 (ddd, J = 4.4, 8.0, 8.0, Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 135.9, 129.04, 128.9, 127.1, 65.9, 59.6, 58.5, 45.3, 37.1, 32.2, 32.1, 29.3, 28.4, 24.8, 22.6, several resonances of **6** were unresolved from those of **7**; MS (ESI) m/z (relative intensity) 377 ([M + Na]$^+$, ^{37}Cl, 26%), 375 ([M + Na]$^+$, ^{35}Cl, 70%), 355 ([M + H]$^+$, ^{37}Cl, 22%), 353 ([M + H]$^+$, ^{35}Cl, 63%), 317 ([M − Cl]$^+$, 100%). Optical rotation and high resolution mass spectra were not obtained because samples of **6** transformed into **7**.

(*S*)-4-Benzyl-3-((*R*)-2-pentylpyrrolidin-1-yl)oxazolidin-2-one (7). From **5** (49.4 mg, 0.180 mmol) by General Procedure A (2.3 equiv of $InCl_3$) was obtained **7** (39.6 mg, 70%) as a colorless oil. $[\alpha]_D^{26}$ +7.1 (c 0.525, $CHCl_3$); IR (film from $CDCl_3$) 2958, 2925, 2864, 1752, 1242, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H), 4.14 (dd, J = 8.5, 8.5 Hz, 1H), 3.99 (dd, J = 5.6, 8.8 Hz, 1H), 3.95−3.89 (m, 1H), 3.62−3.57 (m, 1H), 3.53 (ddd, J = 8.3, 8.3, 8.3 Hz, 1H), 3.41 (dd, J = 3.5, 13.3 Hz, 1H), 3.12 (ddd, J = 8.2, 8.2, 4.3 Hz, 1H), 2.60 (dd, J = 10.6, 13.3 Hz, 1H), 2.04−1.96 (m, 1H), 1.92−1.84 (m, 1H), 1.82−1.72 (m, 1H), 1.62−1.57 (m, 1H), 1.46−1.38 (m, 1H), 1.36−1.25 (m, 7H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 154.7, 136.1, 129.0, 128.8, 126.9, 66.3, 61.3, 60.3, 51.9, 38.9, 34.6, 32.3, 29.0, 25.9, 22.7, 21.7, 14.0; HRMS (ESI) m/z calcd for $C_{19}H_{28}N_2O_2Na$ 339.2048 ([M + Na]$^+$), found 339.2064; calcd for $C_{19}H_{29}N_2O_2$ 317.2229 ([M + H]$^+$), found 317.2225. Minor diastereomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (ddd, J = 8.2, 8.2, 8.2 Hz, 1H), 2.52 (dd, J = 10.3, 13.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.3, 129.6, 128.77, 128.3, 67.4, 60.4, 57.9, 48.5, 39.5, 34.5, 29.7, 28.99, 26.1, 21.5; several minor diastereomer resonances were unresolved from those of **7**.

Chemical Correlation of 6 and 7. A solution of chloropropyl adduct **6** (24.7 mg, 0.07 mmol) in CH_3CN (0.023 M) was heated at reflux for 19 h and then concentrated to afford **7** (24.7 mg, 100%). Spectroscopic data (^{1}H and ^{13}C NMR) matched data for the sample of **7** obtained from the radical−ionic annulation using General Procedure A, as described above.

(*S*)-4-Benzyl-3-((*R*)-2-decylpyrrolidin-1-yl)oxazolidin-2-one (13). From **10** (42.5 mg, 0.123 mmol) by General Procedure A (2.2 equiv of $InCl_3$) was obtained **13** (25.6 mg, 54%) as a yellow oil. $[\alpha]_D^{23}$ 1.3 (c 0.08, $CHCl_3$); IR (film from CH_2Cl_2) 3019, 2921, 1753, 1234, 1095, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H), 4.15 (dd, J = 8.6, 8.6 Hz, 1H), 4.00 (dd, J = 5.6, 8.9 Hz, 1H), 3.96−3.90 (m, 1H), 3.60−3.56 (m, 1H), 3.53 (ddd, J = 8.4, 8.4, 8.4 Hz, 1H), 3.42 (dd, J = 3.6, 13.4 Hz, 1H), 3.12 (ddd, J = 4.3, 8.2, 8.2 Hz, 1H), 2.61 (dd, J = 10.7, 13.3 Hz, 1H), 2.04−1.97 (m, 1H), 1.94−1.85 (m, 1H), 1.81−1.73 (m, 1H), 1.59−1.56 (m, 2H), 1.45−1.38 (m, 1H), 1.30−1.25 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 136.2, 129.0, 128.8, 126.9, 66.3, 61.3, 60.3, 51.9, 38.9, 34.7, 31.9, 30.1, 29.73, 29.69, 29.63, 29.3, 29.0, 26.2, 22.7, 21.7, 14.1; HRMS (ESI) m/z calcd for $C_{24}H_{38}N_2O_2Na$ ([M + Na]$^+$) 409.2831, found 409.2823; calcd for $C_{24}H_{39}N_2O_2$ ([M + H]$^+$) 387.3012, found 387.3036.

(*S*)-4-Benzyl-3-((*R*)-2-phenethylpyrrolidin-1-yl)oxazolidin-2-one (14). From **11** (31.0 mg, 0.101 mmol) by General Procedure A (2.2 equiv of $InCl_3$) was obtained **14** (21.2 mg, 60%) as off-white crystals. $[\alpha]_D^{25}$ −2.4 (c 0.805, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2932, 1757, 1599, 1245, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.20 (m, 10H), 4.19 (dd, J = 8.6, 8.6 Hz, 1H), 4.06 (dd, J = 5.5, 8.9 Hz, 1H), 4.02−3.97 (m, 1H), 3.80−3.74 (m, 1H), 3.62 (ddd, J = 8.4, 8.4, 8.4 Hz, 1H), 3.46 (dd, J = 3.6, 13.3 Hz, 1H), 3.23 (ddd, J = 4.3, 8.2, 8.2 Hz, 1H), 2.76−2.64 (m, 3H), 2.18−2.10 (m, 1H), 2.05−1.96 (m, 2H), 1.93−1.85 (m, 1H), 1.76−1.68 (m, 1H), 1.61−1.54 (m, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 154.8, 142.3, 136.0, 129.0, 128.8, 128.4, 128.3, 127.0, 125.9, 66.2, 61.3, 60.1, 51.9, 38.9, 36.7, 32.6, 29.1, 21.8; HRMS (ESI) m/z calcd for $C_{22}H_{27}N_2O_2$ 351.2073 ([M + H]$^+$), found 351.2101; calcd for $C_{22}H_{26}N_2O_2Na$ 373.1892 ([M + Na]$^+$), found 373.1895.

(*S*)-4-Benzyl-3-((*S*)-2-isobutylpyrrolidin-1-yl)oxazolidin-2-one (15). From **12** (26.3 mg, 0.101 mmol) by General Procedure A (2.2 equiv of $InCl_3$) was obtained **15** (26.4 mg, 86%) as yellow oil. $[\alpha]_D^{26}$ +2.9 (c 0.735, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2950, 1748, 1233, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.17 (m, 5H), 4.15 (dd, J = 8.6, 8.6 Hz, 1H), 3.99 (dd, J = 5.4, 8.9 Hz, 1H), 3.96−3.90 (m, 1H), 3.70−3.64 (m, 1H), 3.50 (ddd, J = 8.5, 8.5, 8.5 Hz, 1H), 3.40 (dd, J = 3.5, 13.3 Hz, 1H), 3.11 (ddd, J = 4.3, 8.2, 8.2 Hz, 1H), 2.59 (dd, J = 10.6, 13.2 Hz, 1H), 2.07−2.00 (m, 1H), 1.94−1.86 (m, 1H), 1.82−1.74 (m, 1H), 1.67−1.57 (m, 1H), 1.46−1.35 (m, 2H), 1.29−1.24 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 154.7, 136.1, 129.0, 128.8, 126.9, 66.2, 60.3, 59.8, 51.7, 44.2, 38.8, 29.5, 26.0, 23.9, 22.4, 21.7; HRMS (ESI) m/z calcd for $C_{18}H_{27}N_2O_2$ 303.2073 ([M + H$^+$]), found 303.2085.

(*S*)-4-Benzyl-3-((2*R*,4*S*)-2-ethyl-4-methylpyrrolidin-1-yl)-oxazolidin-2-one (16). From **1a** (23.2 mg, 0.10 mmol) and **3c** by General Procedure A (2.2 equiv of $InCl_3$) was obtained **16** (12 mg, 42%) as a yellow oil. $[\alpha]_D^{23}$ +0.4 (c 0.26, $CHCl_3$); IR (film from $CDCl_3$) 2958, 2868, 1757, 1454, 1233, 1099; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.16 (m, 5H), 4.14 (dd, J = 8.6, 8.6 Hz, 1H), 3.99 (dd, J = 5.3, 8.9 Hz, 1H), 3.94−3.90 (m, 1H), 3.66−3.65 (m, 1H), 3.62 (dd, J = 9.0, 9.0 Hz, 1H), 3.41 (dd, J = 3.6, 13.9 Hz, 1H), 2.81 (dd, J = 6.6, 8.7 Hz, 1H), 2.59 (dd, J = 10.7, 13.3 Hz, 1H), 2.46−2.41 (m, 1H), 2.13−2.08 (m, 1H), 1.70−1.65 (m, 1H), 1.37−1.32 (m, 1H), 1.07−1.02 (m, 1H), 1.04 (d, J = 7.3 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 154.8, 136.2, 129.0, 128.8, 126.9, 66.1, 64.0, 60.4, 60.2, 38.8, 38.2, 30.2, 26.9, 20.3, 10.2; HRMS (ESI) m/z calcd for $C_{17}H_{25}N_2O_2$ 289.1916 ([M + H$^+$]), found 289.1915; calcd for $C_{17}H_{24}N_2O_2Na$ 311.1735 ([M + Na$^+$]), found 311.1732.

Methyl 1-(*N*-Methylbenzamido)pyrrolidine-2-carboxylate (*rac*-18). From **17** (22.0 mg, 0.100 mmol) by General Procedure A (2.2 equiv of $InCl_3$) was obtained racemic **18** (14.7 mg, 56%) as a yellow oil. IR (film from $CDCl_3$) 2929, 1736, 1638, 1442, 1262 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 7.44−7.42 (m, 2H), 7.36−7.30 (m, 3H), 3.76−3.72 (m, 1H), 3.11−3.07 (m, 2H), 3.42 (s, 3H), 3.00 (s, 3H), 2.03−1.94 (m, 1H), 1.83−1.76 (m, 2H), 1.73−1.65 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 171.3, 171.0, 136.4, 128.5, 126.8, 126.7, 60.3, 50.8, 50.2, 28.4, 26.5, 21.5; HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2O_3Na$ 285.1215 ([M + Na$^+$]), found 285.1221; calcd for $C_{14}H_{19}N_2O_3$ 263.1400 ([M + H$^+$]), found 263.1405.

(*S*)-4-Benzyl-3-((*S*)-2-ethylpyrrolidin-1-yl)oxazolidin-2-one (20). From hydrazone **19** (32.9 mg, 0.12 mmol) and iodoethane (0.09

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mL, 1.17 mmol) by General Procedure A (2.3 equiv on $InCl_3$) was obtained **20**[18] (19.0 mg, 59%) as a colorless oil.

(*S*)-4-Benzyl-3-((*R*)-2-isopropylpyrrolidin-1-yl)oxazolidin-2-one (21). From hydrazone **19** (31.8 mg, 0.11 mmol) and 2-iodopropane (0.11 mL, 1.13 mmol) by General Procedure A (2.2 equiv of $InCl_3$) was obtained **21** (27.7 mg, 85%) as colorless crystals. Mp 59−62 °C; $[\alpha]_D^{23}$ +79.3 (*c* 0.595, $CHCl_3$); IR (film from $CDCl_3$) 3032, 2950, 2872, 1753, 1213, 1103, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.15 (m, 5H), 4.12−4.06 (m, 1H), 4.00−3.92 (m, 2H), 3.67 (ddd, *J* = 3.3, 6.9, 9.2 Hz, 1H), 3.45 (dd, *J* = 2.7, 13.0 Hz, 1H), 3.27 (ddd, *J* = 8.1, 8.1, 8.1 Hz, 1H), 3.18 (ddd, *J* = 3.3, 7.5, 10.9 Hz, 1H), 2.53 (dd, *J* = 10.3, 13.2 Hz, 1H), 1.96−1.81 (m, 3H), 1.75−1.66 (m, 1H), 1.58−1.52 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 136.2, 128.9, 128.7, 127.0, 67.4, 65.1, 58.1, 49.3, 39.3, 28.8, 23.0, 22.8, 20.2, 15.2; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{25}N_2O_2$ ($[M + H]^+$) 289.1916, found 289.1916. The structural assignment was confirmed by X-ray crystallography.

(*S*)-4-Benzyl-3-((*R*)-2-isobutylpyrrolidin-1-yl)oxazolidin-2-one (22). From hydrazone **19** (26.4 mg, 0.094 mmol) and 1-iodo-2-methylpropane (0.11 mL, 0.94 mmol) by General Procedure A (2.3 equiv of $InCl_3$) was obtained **22** (19.0 mg, 67%) as a white solid. $[\alpha]_D^{25}$ +80.3 (*c* 0.63, $CHCl_3$); IR (film from $CDCl_3$) 3023, 2957, 2863, 1752, 1392, 1225, 1102, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H), 4.13 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.98 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.94−3.88 (m, 1H), 3.73−3.67 (m, 1H), 3.45 (dd, *J* = 3.3, 13.4 Hz, 1H), 3.27 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1H), 3.17 (ddd, *J* = 4.1, 8.4, 8.4 Hz, 1H), 2.53 (dd, *J* = 10.8, 13.2 Hz, 1H), 2.08−2.02 (m, 1H), 1.95−1.87 (m, 1H), 1.84−1.77 (m, 1H), 1.64−1.58 (m, 1H), 1.53−1.50 (m, 1H), 1.41−1.33 (m, 1H), 1.24−1.18 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 136.5, 129.0, 129.0, 127.1, 67.6, 58.9, 58.1, 48.4, 44.1, 39.7, 29.5, 26.2, 24.5, 22.2, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{26}N_2O_2Na$ ($[M + Na]^+$) 325.1892, found 325.1887; calcd for $C_{18}H_{27}N_2O_2$ ($[M + H]^+$) 303.2073, found 303.2065.

(*S*)-4-Benzyl-3-((*S*)-2-pentylpyrrolidin-1-yl)oxazolidin-2-one (23). From hydrazone **19** (30.9 mg, 0.11 mmol) and iodopentane (0.14 mL, 1.07 mmol) by General Procedure A (2.2 equiv of $InCl_3$) was obtained **23** (19.0 mg, 67%) as a colorless oil. $[\alpha]_D^{23}$ +79.0 (*c* 0.765, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2954, 2925, 2856, 1753, 1397, 1217, 1099, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26−7.09 (m, 5H), 4.08 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.93 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.88−3.82 (m, 1H), 3.58−3.52 (m, 1H), 3.36 (dd, *J* = 3.5, 13.5 Hz, 1H), 3.22 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1H), 3.08 (ddd, *J* = 4.1, 8.0, 8.0 Hz, 1H), 2.46 (dd, *J* = 10.5, 13.3 Hz, 1H), 2.00−1.94 (m, 1H), 1.88−1.80 (m, 1H), 1.76−1.67 (m, 1H), 1.66−1.61 (m, 1H), 1.36−1.30 (m, 1H), 1.28−1.13 (m, 7H), 0.82 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.3, 128.8, 128.77, 126.9, 67.4, 60.4, 57.9, 48.5, 39.5, 34.5, 32.3, 28.98, 26.1, 22.7, 21.5, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{28}N_2O_2Na$ ($[M + Na]^+$) 339.2048, found 339.2039; calcd for $C_{19}H_{29}N_2O_2$ ($[M + H]^+$) 317.2229, found 317.2224.

(*S*)-4-Benzyl-3-((*S*)-2-(4-chlorobutyl)pyrrolidin-1-yl)-oxazolidin-2-one (24). From hydrazone **19** (39.7 mg, 0.14 mmol) and 1-chloro-4-iodobutane (0.17 mL, 1.41 mmol) by General Procedure A (2.2 equiv of $InCl_3$) was obtained **24** (19.5 mg, 41%) as a yellow oil. $[\alpha]_D^{24}$ +70.2 (*c* 0.50, $CHCl_3$); IR (film from $CDCl_3$) 3021, 2938, 2868, 1757, 1221, 1086, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H), 4.13 (dd, *J* = 8.1, 8.1 Hz, 1H), 3.98 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.95−3.89 (m, 1H), 3.69−3.63 (m, 1H), 3.55 (m, apparent t, *J* = 6.6 Hz, 2H), 3.44 (dd, *J* = 3.5, 13.4 Hz, 1H), 3.24 (ddd, *J* = 8.2, 8.2, 8.2 Hz, 1H), 3.18 (ddd, *J* = 4.1, 8.1, 8.1 Hz, 1H), 2.53 (dd, *J* = 10.5, 13.3 Hz, 1H), 2.09−2.02 (m, 1H), 1.96−1.88 (m, 1H), 1.85−1.70 (m, 4H), 1.56−1.37 (m, 3H), 1.31−1.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 136.1, 128.9, 128.8, 127.0, 67.4, 60.1, 57.9, 48.5, 45.0, 39.4, 33.7, 32.8, 28.9, 23.7, 21.5; HRMS (ESI) *m*/*z* (relative intensity) calcd for $C_{18}H_{25}N_2O_2ClNa$ ($[M + Na]^+$, ^{37}Cl) 361.1473, found 361.1477 (5%); calcd for $C_{18}H_{25}N_2O_2ClNa$ ($[M + Na]^+$, ^{35}Cl) 359.1502, found 359.1500 (17%); calcd for $C_{18}H_{26}N_2O_2Cl$ ($[M + H]^+$, ^{37}Cl) 339.1654, found 339.1646 (33%); calcd for $C_{18}H_{26}N_2O_2Cl$ ($[M + H]^+$, ^{35}Cl) 337.1683, found 337.1685 (100%).

Modified Radical−Ionic Annulation of *N*-Acylhydrazones (General Procedure B). General Procedure A was employed, with the following modification: The reaction mixture was irradiated for 23−24 h. After filtration of the crude product through silica gel, the fraction eluting with 0.8:1 hexane/Et_2O was concentrated in vacuo and then heated with NaI (2.5 equiv) in refluxing CH_3CN (0.3 M) for 1−2 d. After concentration, the residue was partitioned between Et_2O and H_2O. The organic phase was dried (Na_2SO_4), concentrated, and purified by radial chromatography (hexane/Et_2O).

(*S*)-4-Benzyl-3-((*R*)-2-ethylpiperidin-1-yl)oxazolidin-2-one (28a). From hydrazone **1a** (28.0 mg, 0.12 mmol) and 1-chloro-4-iodobutane (0.15 mL, 1.23 mmol) by General Procedure B (2.3 equiv of $InCl_3$, omitting the NEt_3 step from the workup) was obtained **28a** (16.4 mg, 47%) as a yellow oil. $[\alpha]_D^{24}$ +13.3 (*c* 0.77, $CHCl_3$); IR (film from $CDCl_3$) 3032, 2938, 2848, 1757, 1397, 1230, 1082, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.15 (m, 5H), 4.16 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.00 (dd, *J* = 6.7, 8.9 Hz, 1H), 3.92−3.86 (m, 1H), 3.58−3.54 (m, apparent t, *J* = 11.5 Hz, 1H), 3.45 (dd, *J* = 3.7, 13.3 Hz, 1H), 3.35−3.31 (m, 1H), 2.98−2.95 (m, 1H), 2.58 (dd, *J* = 10.8, 13.2 Hz, 1H), 1.84−1.81 (m, 1H), 1.70−1.63 (m, 3H), 1.60−1.52 (m, 1H), 1.34−1.25 (m, 2H), 1.22−1.08 (m, apparent qd, *J* = 3.2, 13.2 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 136.2, 128.9, 128.8, 126.9, 66.8, 61.5, 60.5, 54.6, 38.7, 30.8, 26.5, 25.6, 23.8, 9.5; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{24}N_2O_2Na$ ($[M + Na]^+$) 311.1735, found 311.1728; calcd for $C_{17}H_{25}N_2O_2$ ($[M + H]^+$) 289.1916, found 289.1912.

(*S*)-4-benzyl-3-((*R*)-2-decylpiperidin-1-yl)oxazolidin-2-one (28b). From hydrazone **10** (30.5 mg, 0.089 mmol) and 1-chloro-4-iodobutane (0.11 mL, 0.89 mmol) by General Procedure B (2.3 equiv of $InCl_3$, omitting the NEt_3 step from the workup) was obtained **28b** (24.9 mg, 70%) as a colorless oil. $[\alpha]_D^{23.9}$ +4.02 (*c* 0.82, $CHCl_3$); IR (film from $CDCl_3$) 3026, 2925, 2852, 1755, 1396, 1225, 1084, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H), 4.17 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.00 (dd, *J* = 6.6, 9.0 Hz, 1H), 3.89−3.83 (m, 1H), 3.58−3.54 (m, apparent t, 11.1 Hz, 1H), 3.44 (dd, *J* = 3.6, 13.2 Hz, 1H), 3.41−3.35 (m, 1H), 2.97−2.95 (m, apparent d, *J* = 10.7 Hz, 1H), 2.57 (dd, *J* = 10.8, 13.2 Hz, 1H), 1.84−1.80 (m, 1H), 1.69−1.65 (m, 2H), 1.61−1.55 (m, 2H), 1.36−1.13 (m, 19H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.4, 129.1, 129.0, 127.1, 67.0, 60.8, 60.7, 54.8, 38.9, 33.3, 32.0, 31.7, 30.3, 29.9, 29.76, 29.75, 29.5, 26.7, 25.4, 24.0, 22.8, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{40}N_2O_2Na$ ($[M + Na]^+$) 423.2987, found 423.2988; calcd for $C_{25}H_{41}N_2O_2$ ($[M + H]^+$) 401.3168, found 401.3176.

(*S*)-4-Benzyl-3-((*R*)-2-phenethylpiperidin-1-yl)oxazolidin-2-one (28c). From hydrazone **11** (32.0 mg, 0.10 mmol) and 1-chloro-4-iodobutane (0.13 mL, 1.04 mmol) by modified general procedure C and workup C (2.3 equiv of $InCl_3$) was obtained **28c** (25.9 mg, 68%) as a yellow solid. Mp 78−81 °C; $[\alpha]_D^{23}$ +15.0 (*c* 1.19, $CHCl_3$); IR (film from $CDCl_3$) 3027, 2938, 2856, 1757, 1397, 1225, 1078, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.12 (m, 10H), 4.10 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.97 (dd, *J* = 6.4, 9.0 Hz, 1H), 3.88−3.82 (m, 1H), 3.60−3.56 (m, 1H), 3.52−3.48 (m, 1H), 3.42 (dd, *J* = 3.6, 13.2 Hz, 1H), 2.99−2.97 (m, 1H), 2.71 (ddd, *J* = 5.0, 12.2, 13.5 Hz, 1H), 2.59−2.54 (m, 2H), 1.97−1.90 (m, 2H), 1.71−1.66 (m, 2H), 1.63−1.56 (m, 2H), 1.37−1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 142.2, 136.0, 128.9, 128.8, 128.4, 128.2, 126.9, 125.8, 66.7, 60.5 (2C), 54.6, 38.7, 35.0, 31.7, 31.6, 26.4, 23.8; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{28}N_2O_2Na$ ($[M + Na]^+$) 387.2048, found 387.2046; calcd for $C_{23}H_{29}N_2O_2$ ($[M + H]^+$) 365.2229, found 365.2221.

(*R*)-1-(2-Phenethylpyrrolidin-1-yl)ethanone (29). A mixture of **14** (110.9 mg, 0.316 mmol) and BH_3·THF (1 M solution in THF, 9.49 mL, 9.49 mmol) was heated to reflux and sealed under a coldfinger condenser. After heating at reflux for 48 h, additional BH_3·THF (6.3 mL, 6.3 mmol) was added and heating was continued for 72 h. After cooling to rt, 2 M HCl was cautiously added until gas evolution ceased. The mixture was then made basic by addition of aqueous 1.25 M KOH and concentrated, and the aqueous residue was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated. After azeotropic removal of moisture by concentration from benzene solution, CH_2Cl_2 (1.46 mL) and acetic anhydride (1.86

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mL, 19.65 mmol) were added, and the mixture was heated at reflux. After 24 h, the reaction mixture was partitioned between water and CH_2Cl_2, and the organic phase was dried (Na_2SO_4), filtered, and concentrated. Filtration through a plug of silica gel, eluting first with an 85:15 mixture of hexane/(5:1 CH_2Cl_2/MeOH), and then with 60:40 hexane/(5:1 CH_2Cl_2/MeOH), afforded crude **29** in the more polar fraction. Radial chromatography (1 mm plate, eluted with EtOAc) provided **29** (56 mg, 86%) as a yellow oil. $[\alpha]_D^{24}$ −71.75 (*c* 2.21, $CHCl_3$); IR (film from $CDCl_3$) 3023, 2954, 1646, 1450, 1197 cm^{-1}; ^1H NMR (400 MHz, DMSO, 115 °C) δ 7.28−7.14 (m, 5H), 4.00−3.90 (br s, 1H), 3.49−3.42 (m, 1H), 3.42−3.30 (br s, 1H), 2.64−2.58 (m, 2H), 1.92 (s, 3H), 1.87−1.80 (m, 2H), 1.78−1.75 (m, 2H), 1.71−1.66 (m, 2H); ^{13}C NMR (100 MHz, DMSO, 115 °C) δ 167.2, 141.2, 129.61, 129.59 (detected by DEPT), 124.9, 56.0, 46.0, 34.4, 31.3, 28.9, 22.4, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}NO$ 218.1545 ([M + H^+]), found 218.1548.

(*S*)-4-Benzyl-3-((*R*)-hexan-3-ylamino)oxazolidin-2-one (2b). From **1a** (31.2 mg, 0.13 mmol) and **3b** (0.15 mL, 1.34 mmol) by the General Procedure A (2.2 equiv of $InCl_3$) was obtained **2a** (6.6 mg, 18%) and **2b**[18] (4.9 mg, 13%) as a yellow oil.

(*S*)-4-Benzyl-3-(((*R*)-1,1-dichlorobutan-2-yl)amino)-oxazolidin-2-one (8, R = ethyl). From **1a** (76 mg, 0.33 mmol) by the General Procedure A (except operating at a lower concentration of 0.057 M in CH_2Cl_2) were obtained **2a** (39.4 mg, 44%) and **8** (R = ethyl)[18] (18.6 mg, 14%) as a yellow oil.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR and ^{13}C NMR spectra for new compounds, and crystallographic data for **21**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00863.

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Notes

The authors declare no competing financial interest.

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(24) Both substrates have previously been found to be compatible with the Mn-mediated radical addition (e.g., refs 17 and 18), albeit with shorter reaction times.
(25) Reports of related acyclic amines with the potential for both 5-*exo*-tet and 6-*exo*-tet cyclizations via displacement of halides did not discuss the group selectivity reported herein. For examples, see (a) Prelog, V.; Balenovic, K. *Ber. Dtsch. Chem. Ges. A* **1941**, *74B*, 1510−1512. (b) Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett.* **2011**, *13*, 3988−3991.
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