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Radical Addition Approach to Asymmetric Amine Synthesis: Design, Implementation, and Comparison of Chiral *N*-Acylhydrazones

Gregory K. Friestad,*,† Cristian Draghici,‡ Mustapha Soukri,‡ and Jun Qin‡

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, and Department of Chemistry, University of Vermont, Burlington, Vermont 05405

gregory-friestad@uiowa.edu

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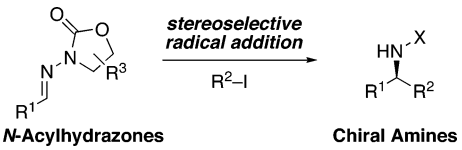

Intermolecular radical addition to C=N bonds with acyclic stereocontrol offers excellent potential as a mild, nonbasic carbon−carbon bond construction approach to chiral amines. Here, complete details of the first radical additions to chiral *N*-acylhydrazones as an approach to asymmetric amine synthesis are disclosed. Novel *N*-acylhydrazones were designed as chiral C=N radical acceptors with Lewis acid activation, restriction of conformational mobility, and commercial availability of precursors. Amination of 4-alkyl-2-oxazolidinones with *O*-(mesitylenesulfonyl)hydroxylamine or *O*-(*p*-nitrobenzoyl)hydroxylamine afforded *N*-aminooxazolidinones which were condensed with aldehydes to afford *N*-acylhydrazones **3**−**8**. Three synthetic methods were developed, implementing these *N*-acylhydrazones in Lewis acid-promoted intermolecular radical additions to C=N bonds. First, additions of various secondary and tertiary alkyl iodides to propionaldehyde and benzaldehyde hydrazones (**3** and **7**) under tin hydride radical chain conditions in the presence of $ZnCl_2$ gave *N*-acylhydrazine adducts with diastereomeric ratios ranging from 93:7 to 99:1. Radical additions to a series of *N*-acylhydrazones with different substituents on the oxazolidinone revealed that benzyl and diphenylmethyl were more effective stereocontrol elements than those with the aromatic ring directly attached to the oxazolidinone. Second, a tin-free method, exploiting dual functions of triethylborane for both initiation and chain propagation, enabled improved yields in addition of secondary alkyl iodides. Third, under photolytic conditions with hexamethylditin, primary radical addition could be achieved with ethyl iodide in the presence of diethyl ether as cosolvent; the 1-ethoxyethyl adduct was observed as a minor product. Chloromethyl addition was achieved under both the tin-free and photolytic conditions; in this case, the adduct bears alkyl chloride functionality with potential for further elaboration.

Background and Introduction

Chiral α-branched amines are common substructures of bioactive synthetic targets. 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 under mild, nonbasic conditions. New stereocontrolled carbon−carbon bond construction methods would broaden the scope of the direct asymmetric amine synthesis strategy for access to chiral amines. An ongoing search for more versatile methods for addition to C=N bonds under mild conditions has led to several promising developments, including intermolecular radical addition to imino compounds.[2−5]

The radical addition approach to chiral amines (Figure 1) offers the potential for practical advantages in chemoselectivity and versatility typical of radical reactions.[6,7] One illustration is seen by comparison with related additions of basic organometallic reagents.[1] These often suffer from competing aza-enolization[8] or lack of generality and functional group tolerance. For example, a complication

† University of Iowa.
‡ University of Vermont.

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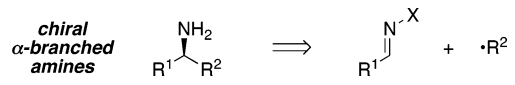

FIGURE 1. Radical carbon−carbon bond disconnection of chiral amines.

can be observed with branched organometallic reagents such as *i*-PrMgBr, which can competitively reduce the C=N bond via hydride transfer.[9] Hindered reagents such as *t*-BuMgBr or *t*-BuLi often fail to give addition products,[10] whereas *tert*-butyl radical addition is quite capable of constructing hindered C−C bonds. The high basicity associated with these organometallic nucleophiles is complemented by the milder conditions inherent to Strecker,[11] Mannich,[12] and allylsilane additions,[13] along with other recently developed addition reactions.[14] Still, these place significant restrictions on the identity of the incoming nucleophile destined to become R^2 of the chiral amine (Figure 1). On the other hand, radical reactions can accommodate a broad range of functionality within the radical itelf. This suggests great potential scope in their future application in asymmetric amine synthesis, pending development of versatile imino acceptors capable of effective stereocontrol.

Previous intermolecular radical additions by Naito[3] and Bertrand[4] showed that imino acceptors could be effectively employed in additions of secondary and tertiary alkyl iodides. These reactions exploited triethylborane or diethylzinc as initiators, with or without tributyltin hydride. In some cases, the additions have been rendered stereoselective by employing a chiral auxiliary attached either to the carbon or nitrogen of the C=N bond.[3a,f,i,p,4b,d] These seminal precedents established that stereochemical information can be transferred through the carbon branch or nitrogen substituent of the imine (Figure 2a). However, in each case, a second independent activating substituent was employed, and thus, the imino acceptors required modifications to both nitrogen and carbon substituents of the imine.

A potentially more versatile approach to stereocontrolled radical addition to imines would achieve both activation and stereocontrol from a single modification to the nitrogen substituent of the imino acceptor (Figure

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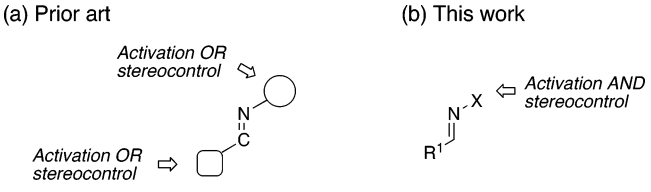

FIGURE 2. Approaches to stereocontrol for radical addition to C=N bonds. (a) Previous approaches showing the requirement for both C- and N-substituents of the C=N bond to play separate roles for activation and stereocontrol. (b) In the approach developed here, the C-substituent serves no role in the reaction, enabling improved versatility.

2b). Successful addition would then be independent of the identity of the aldehyde precursor to the imine, which would potentially broaden the scope of the reaction. Toward this end, we conceived a nitrogen-linked chiral auxiliary approach incorporating Lewis acid activation[15] and restriction of rotamer populations as key design elements. We now disclose complete details of the design and preparation of novel chiral *N*-acylhydrazones from 2-oxazolidinones and their implementation for highly stereoselective intermolecular radical addition reactions.[16]

Results and Discussion

Design and Synthesis of Chiral *N*-Acylhydrazones. Early in the design phase, the hydrazone functional group emerged as a desirable starting point for a new chiral radical acceptor; some basic aspects of hydrazone structure and reactivity supported this notion. Although formation of *E*/*Z* mixtures frequently complicates the use of oxime ethers, aldehyde hydrazones generally adopt C=N *E*-geometry. In hydrazones, the nitrogen external to the C=N offers two valences from which to build a stereocontrol element, a further advantage over oxime ethers. Spectroscopic methods have shown *N*,*N*-dialkylhydrazones to have a predominant conformer with the *N*-alkyl bond nearly coplanar with C=N bond.[17] Hydrazones are more effective than imines as radical acceptors for nucleophilic alkyl radicals. Rate constants for 6-aza-5-hexenyl radical cyclizations (eq 1) of *N*-benzylimine, *O*-benzyloxime, and *N*,*N*-diphenylhydrazone are 6.0×10^6 s^{-1}, 2.4×10^7 s^{-1}, and 1.6×10^8 s^{-1} (80 °C), respectively.[2a] This trend may be attributed to beneficial effects of the heteroatom substituent X of the C=N-X system, combining inductive activation of the acceptor toward nucleophilic radicals and stabilization of the adduct aminyl radical by the adjacent nonbonding electrons.

(1)

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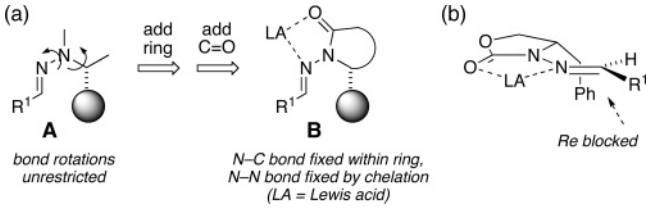

FIGURE 3. (a) Design of a hypothetical *N*-linked auxiliary approach for stereocontrolled radical addition to C=N bonds, with Lewis acid (LA) chelation inducing a rigid, electronically activated radical acceptor. (b) Implementation with *N*-acylhydrazones derived from 4-benzyl-2-oxazolidinone.

The exothermicity of 6-aza-5-hexenyl cyclization of a dimethylhydrazone (eq 1, X = NMe_2; $\Delta H = -11.6$ kcal/mol) suggests an early transition state for the addition step.[2a] This assumption simplifies the design of a stereocontrol model because it enables the ground-state structure to serve as a reasonable approximation of the transition-state geometry for radical addition to the hydrazones. Together, these factors prompted our choice of hydrazones as a platform for auxiliary design. We hypothesized that steric blocking of one of the enantiotopic approach trajectories by a substituent above or below the plane of the hydrazone should lead to an enantioselective process.

The design process next focused on incorporating specific features desirable for stereocontrol, namely *restricted rotamer populations* and *Lewis acid activation*, beginning with a hydrazone bearing a proximal stereogenic center (**A**, Figure 3). Constraining the C−N bond within a ring and including a carbonyl group would enable two-point binding of a Lewis acid to afford a rigid chelate structure (**B**) with the stereocontrol element localized over one face of the hydrazone. The Lewis acid would also increase reactivity toward nucleophilic radicals by lowering the LUMO energy of the C=N bond.[6,15] Finally, we noted the facility of reductive cleavage of N−N bonds,[18] whereby an *N*-linked auxiliary could be released for reuse after stereoisomer purification. Oxazolidinones[19,20] emerged as obvious initial candidates to test our hypothesis.

Experimental evaluation of our design hypothesis began with preparation of the requisite hydrazones. Prior to our work, *N*-amino derivatives of oxazolidinones had appeared in the literature only rarely[21] and to our knowledge had never been used for asymmetric synthesis. Initially, we employed commercially available (*S*)-4-benzyl-2-oxazolidinone (**1a**, Scheme 1), using White's amination procedure for related oxazolidinones.[21a] This entailed sequential treatment of **1a** with *n*-butyllithium

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SCHEME 1

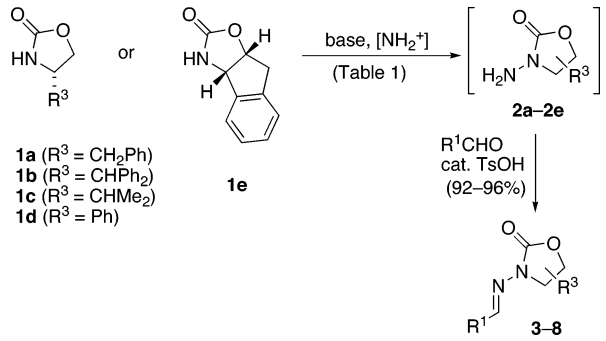


TABLE 1. Amination of Oxazolidinones and Condensation with Aldehydes (Scheme 1)

entry	oxazolidinone	R^1	method[a]	product, yield[b] (%)
1	**1a**	Et	A	**3a**, 81
2	**1a**	*i*-Pr	A	**4**, 70
3	**1a**	*t*-Bu	A	**5**, 72
4	**1a**	*c*-C_6H_{11}	A	**6**, 65
5	**1a**	Ph	A	**7**, 67
6[c]	**1a**	Ph	B[d]	**7**, 80 (74)[e]
7	**1a**	CO_2Me	A	**8**, 71
8	**1b**	Et	B	**3b**, 99
9	**1c**	Et	B	**3c**, 84
10	**1d**	Et	B[d]	**3d**, 76
11	**1e**	Et	B	**3e**, 83

[a] Method A: (i) *n*-BuLi, THF, −78 °C, 40 min; (ii) $MtsONH_2$, −78 °C → rt; (iii) R^1CHO, rt. Method B: (1) (i) KH, dioxane, 60 °C, 1 h; (ii) $NBzONH_2$, rt; (2) R^1CHO, cat. *p*-TsOH, toluene, rt. [b] Isolated yield from **1**. [c] Reference 22. [d] NaH was used place of KH. [e] Yield on 10 g scale, employing crystallization.

and *O*-(mesitylenesulfonyl)hydroxylamine ($MtsONH_2$) and furnished novel *N*-aminooxazolidinone **2a** in 75% yield. Condensation with various aldehydes (toluene, cat. *p*-toluenesulfonic acid) afforded chiral *N*-acylhydrazones **3a**−**8** as single isomers in very good overall yields from **2a** (Table 1). Alternatively, introduction of aldehydes directly to the amination reaction mixture gave hydrazones via a convenient one-pot protocol.

After the preliminary communication of this work, *O*-(*p*-nitrobenzoyl)hydroxylamine ($NBzONH_2$) was adopted as the reagent of choice for the amination reaction.[22,23] This electrophilic ammonia equivalent is more easily prepared, handled, and stored than $MtsONH_2$; the latter has a tendency toward exothermic decomposition. Our optimized procedure for *N*-amination using $NBzONH_2$ involved heating the oxazolidinones with NaH (or KH) in dioxane, followed by introduction of $NBzONH_2$ as a solid at ambient temperature. The condensation with aldehydes may be conducted without added acid, although trace amounts of *p*-TsOH can be beneficial. Employing this optimized procedure, a series of other chiral *N*-acylhydrazones bearing different substituents on the oxazolidinone were prepared starting from commercially available chiral oxazolidinones **1b**−**e** (Scheme 1). Amination and condensation with propionaldehyde provided hydrazones **3b**−**e**.

Additional practical notes are worth mentioning. The method described above affords good yields of chiral *N*-acylhydrazones from small to multigram scale. For example, benzaldehyde hydrazone **7** (9.4 g) was obtained in 74% yield from **1a** employing crystallization (ethanol) to recover most of the pure hydrazone before chromatography of the mother liquors.[22] Small amounts of **1a** which may remain after amination do not interfere with the condensation of **2a** with aldehydes. Therefore, it is generally convenient to use unpurified **2a** directly in the condensation step. If desired, the *N*-aminooxazolidinone **2a** may be purified via its hydrochloride salt; addition of dry HCl to a diethyl ether solution of **2a** causes precipitation of the hygroscopic salt, which can be separated by filtration and converted back to the free base.

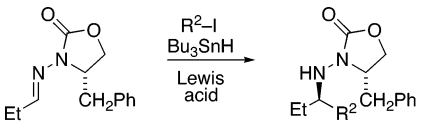
The *N*-acylhydrazones **3**−**8** represent a novel and potentially versatile chiral hydrazone moiety. Following the preliminary communication of this work, several related applications of these chiral *N*-acylhydrazones have been reported,[24,25] suggesting the general utility of this novel chiral auxiliary system for asymmetric amine synthesis. It is worthwhile to compare the preparations of the *N*-amino-oxazolidinones **2** with those of the well-known Enders chiral hydrazines SAMP and RAMP. The latter are prepared in six steps from proline or can be purchased for about $100/g. Our *N*-amino-oxazolidinone **2a** can be prepared in one step from commercial **1a** (or three steps from phenylalanine). With the exception of **1c**,[26] the oxazolidinones we have examined are efficiently and reliably transformed into good-to-excellent yields of the *N*-acylhydrazones. Both enantiomers of **1a**−**e** and various other chiral 2-oxazolidinones bearing numerous substitution patterns are commercially available.[27] Furthermore, a wide range of related oxazolidinones may be easily accessed from well-established methods.[28] Numerous applications of these chiral *N*-acylhydrazones may be envisioned.

Tin-Mediated Addition of Secondary and Tertiary Radicals. To examine the potential of oxazolidinone-derived chiral *N*-acylhydrazones in radical addition reactions, the addition of isopropyl iodide to propionaldehyde hydrazone **3a** was chosen for initial screening. Using the tin hydride method with triethylborane initiation[29] (Bu_3SnH, Et_3B/O_2), the effects of Lewis acids were assessed (Scheme 2, Table 2). A blank control revealed that inefficient reaction occurred in the absence of Lewis acid (entry 1). Next, a survey of a variety of simple Lewis

(22) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236−6239.
(23) Hynes et al. have recently reported a simple, scalable method for *N*-amination of heterocyclic amines with monochloramine: Hynes, J., Jr.; Doubleday: W. W.; Dyckman, A. J.; Godfrey, J. D., Jr.; Grosso, J. A.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368−1371.

(24) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491−4493. Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922−9923.
(25) (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*, 1741−1743. (c) Mannich-type reaction: Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792−4796.
(26) Lower yields with **1c** sometimes occur as a result of poor conversion in the amination step.
(27) For example, 4-(benzoyloxy)methyl-, 4-benzyl-5,5-dimethyl-, 4-*tert*-butyl-, 5,5-dimethyl-4-phenyl-, *cis*-4,5-diphenyl-, 5,5-diphenyl-4-benzyl-, 4-isopropyl-5,5-dimethyl, 4-isopropyl-5,5-diphenyl-, *cis*-4-methyl-5-phenyl-, and 4,5,5-triphenyl-2-oxazolidinone are also commercially available.
(28) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875.
(29) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403−409. Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692−700.

SCHEME 2



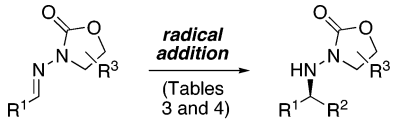
3a **9aA** (R^2 = H) **9aB** (R^2 = Et) **9aC** (R^2 = *i*-Pr)

TABLE 2. Survey of Lewis Acids for Promotion of Radical Addition to Propionaldehyde Hydrazone 3a (Scheme 2)[a]

entry	Lewis acid	yield of **9aC**[b] (%)	recovery of **3a**[b] (%)	product ratio (**9aC/9aB/9aA**)[c]
1	none	13	70	
2	$BF_3{\cdot}Et_2O$	0		0:0:100
3	$MgBr_2$	NR		
4	$InCl_3$	55		92:8:0
5	$ZnCl_2$	60	29	91:9:0
6	$Zn(OTf)_2$	53	24	93:7:0
7	$Sc(OTf)_3$	15[d]		
8	$La(OTf)_3$	20[d]	80[d]	
9	$Yb(OTf)_3$	32		96:4:0

[a] NR = no reaction. Reaction conditions: Bu_3SnH (5 equiv) and O_2 (7 mL/mmol **3a**) by syringe pump, *i*-PrI (10 equiv), Et_3B (10 equiv), and Lewis acid (2 equiv), 2:1 CH_2Cl_2/ether, −78 °C → rt. [b] Isolated yield except where noted. [c] Ratios by ^1H NMR spectra after removal of tin residues. [d] Yield estimated from ^1H NMR spectrum.

SCHEME 3



3–8 **9–12**

acids was conducted. With $BF_3{\cdot}OEt_2$, undesired C=N reduction occurred to afford **9aA** in quantitative yield within 5 min (entry 2), indicating that **3a** was remarkably prone to Lewis acid activation. Magnesium bromide did not promote radical addition (entry 3). On the other hand, $InCl_3$ and Zn(II) salts afforded clean (albeit incomplete) conversion to desired adduct **9aC** (entries 4−6). Scandium triflate and lanthanide triflates (entries 7−9) gave modest yields. Gratifyingly, initial examination by ^1H NMR spectroscopy showed a single diastereomer (dr >98:2). In contrast, **9aC** was produced with poor selectivity (dr 2:1) in the absence of Lewis acid.

The scope of the reaction was evaluated by variations to both the radical and the radical acceptor. In the presence of $ZnCl_2$, the propionaldehyde *N*-acylhydrazone **3a** was subjected to radical additions of various organic iodides (Scheme 3, Table 3, entries 1−6). Ethyl radical (from the triethylborane) can compete for the radical acceptor, and as a result, the separable ethyl radical adduct **9aB** was observed (<10% yield) in all cases. Radical reactivity is important in predicting the success of the addition reactions. With simple secondary and tertiary alkyl iodides as radical precursors (entries 1−4), additions to **3a** occurred with moderate yields to afford *N*-acylhydrazines **9aC**−**9aF**. A primary radical precursor, 1-iodo-2-methylpropane, gave a low yield of isobutyl adduct **9aG** (entry 5). Not unexpectedly, iodobenzene gave no phenyl adduct (not shown). The more reactive radicals formed in these cases likely suffer hydrogen atom abstraction from solvent, although that fate was not confirmed by experiment. On the other hand, allylic radical intermediates may not be sufficiently reactive for the addition step: allyl iodide gave a 7% yield with 73% recovery of the reactant hydrazone (entry 6). As may be expected for an electrophilic radical, electronically mismatched with an electrophilic acceptor, ethyl iodoacetate gave none of the desired adduct. This negative result is consistent with the description of Lewis acid-chelated *N*-acylhydrazones as electrophilic radical acceptors.

TABLE 3. Scope of Tin-Mediated Radical Addition to *N*-Acylhydrazones (R^3 = Bn) in the Presence of $ZnCl_2$[a]

entry	R^1 of hydrazone	R^2 of halide	recovered hydrazone[b] (%)	product, yield[b] (%)
1	Et (**3a**)	*i*-Pr	29	**9aC**, 60
2	Et (**3a**)	*c*-C_5H_9	*c*	**9aD**, 59
3	Et (**3a**)	*c*-C_6H_{11}	60	**9aE**, 28
4	Et (**3a**)	*t*-Bu	14	**9aF,** 54
5	Et (**3a**)	*i*-Bu	50	**9aG**, 6
6	Et (**3a**)	allyl	73	**9aH**, 7
7	*i*-Pr (**4**)	Et	88	**10aB**, 6
8	*i*-Pr (**4**)	*c*-C_6H_{11}	77	**10aE**, 9
9[c]	*c*-C_6H_{11} (**6**)	Et	61	**11aB**, 15
10	*c*-C_6H_{11} (**6**)	*i*-Pr	79	**11aC**, 9
11	Ph (**7**)	*i*-Pr	33	**12aC**, 42
12	Ph (**7**)	*c*-C_5H_9	23	**12aD**, 59
13	Ph (**7**)	*c*-C_6H_{11}	64	**12aE**, 30
14	Ph (**7**)	*t*-Bu	*c*	**12aF**, 83
15	CO_2Me (**8**)	*i*-Pr	0	**1a**, 57

[a] Reaction conditions: see Table 2. [b] Isolated yield (or recovery). [c] Not determined.

A variety of aldehyde hydrazones were screened (Table 3, entries 7−15). Branching at a saturated α-carbon was detrimental (entries 7−10); in the extreme case of the pivalaldehyde hydrazone **5** (R^1 = *t*-Bu), no ethyl adduct could be detected (not shown). On the other hand, the aromatic benzaldehyde hydrazone **7** offered successful additions, with yields ranging from 30 to 83% (entries 11−14). In one experiment with highly electrophilic glyoxylate derivative **8** as the radical acceptor, **1a** was obtained as the major product (57% yield, entry 15). The formation of **1a** from **8** involves cleavage of the N−N bond, which may be explained by Skrydstrup's mechanistic rationale in a related process.[30] With the exception of **8**, however, the reactions were quite clean. Even in the examples with lower yields, the mass balance after recovery of the hydrazone precursor was generally 80−90%, demonstrating the excellent chemoselectivity of the reactions of radicals with *N*-acylhydrazones.

Diastereoselectivity. For analysis of the diastereoselectivity in these radical additions, the synthetically useful secondary and tertiary radical additions to hydrazones **3** and **7** were selected (Table 4). We were delighted to find that the radical additions had occurred with *excellent stereocontrol in all cases*, with diastereomer ratios ranging from 93:7 to 99:1. Authentic diastereomeric mixtures, prepared by reduction of ketone hydrazones,[31] were used as standards for spectroscopic and chromatographic analysis by HPLC and GCMS.

(30) Reduction or radical addition of **8** could be followed by proton transfer from the α-carbon of the amine and β-elimination of **1a**. The adjacent carbomethoxy substituent would be expected to facilitate the proton transfer. See ref 25c.

TABLE 4. Diastereoselectivity in Tin-Mediated Radical Additions of Various Alkyl Iodides with Hydrazones

entry	hydrazone	R^2	product, diastereomer ratio[c]
1	**3a**	*i*-Pr	**9aC**, 99:1
2	**3a**	*c*-C_5H_9	**9aD**, 96:4
3	**3a**	*c*-C_6H_{11}	**9aE**, 97:3
4	**3a**	*t*-Bu	**9aF,** 95:5
5	**7**	*i*-Pr	**12aC**, 99:1
6	**7**	*c*-C_5H_9	**12aD**, 96:4
7	**7**	*c*-C_6H_{11}	**12aE**, 99:1
8	**7**	*t*-Bu	**12aF**, 93:7
9	**3b**	*i*-Pr	**9bC** (15%),[b] >98:2
10	**3c**	*i*-Pr	**9cC** (16%),[b] –[d]
11	**3d**	*i*-Pr	**9dC** (35%),[b] 94:6
12	**3e**	*i*-Pr	**9eC** (50%),[b] 95:5

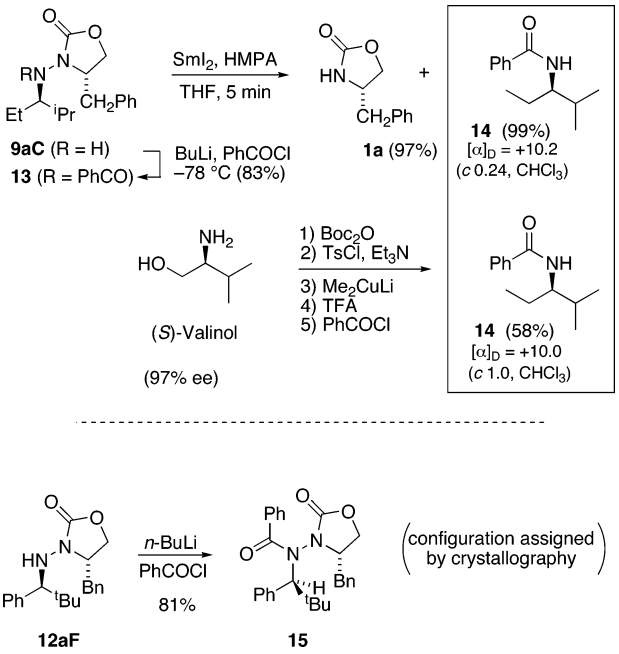
[a] Reaction conditions: Table 2. [b] Isolated yield. [c] Ratios by HPLC (**9aC**–**9aF**, **9eC**), GCMS (**12aC**–**12aF**), or ^{1}H NMR integration (**9bC**, **9dC**) versus authentic mixtures. In separate reactions, diastereomer ratios of **9aE** and **9aF** were reproduced within 0.5%. Yields for entries 1–8 are found in Table 3. [d] Ratio not available; no method was found to resolve the diastereomers **9cC**.

The two lowest selectivities are those involving *tert*-butyl addition, which is surprising considering the later transition state expected for addition of this more stable radical. Later diastereomeric transition states might be expected to be more effectively differentiated by the steric control. However, the design of the chiral *N*-acylhydrazone motif was built around the assumption of reactant-like planar geometry at the C=N bond. The decreased stereoselectivity with *tert*-butyl addition may be rationalized by considering the limitations of this assumption; later transition states may be deformed from the simple ground-state geometry of Figure 3 by further rehybridization (i.e., from sp^2 to sp^3 at the imine carbon). Thus, the addition of more stable radicals such as *tert*-butyl may require refining of the model.

Next, the effects of varying the stereocontrol element substituents on the oxazolidinone moiety were assessed, with the main goal to examine the change in diastereoselectivity. Isopropyl radical additions to several *N*-acylhydrazones **3a**–**e** are compared in Table 4. Although the yields given for reactions of **3b**–**e** (entries 9–12) were inferior to the previous addition to **3a** (entry 1, see Table 3), they were not optimized for yield and there was no attempt to achieve complete conversion. All of the auxiliaries gave very high diastereoselectivity in the addition reactions, using the specific case of addition of isopropyl radical to propionaldehyde hydrazone. Comparing entry 1 with entries 9–12, the benzyl (dr 99:1 by HPLC) and diphenylmethyl (dr >98:2 by ^{1}H NMR) blocking groups gave the most effective stereocontrol. With diphenylmethyl, none of the minor diastereomer could be detected by ^{1}H NMR. The reason for decreased stereoselectivity in additions to **3d** and **3e** is unclear, but it might be speculated that increased rigidity of the blocking group on the oxazolidinone prevents the aromatic π-system from effectively blocking the face of the C=N bond.

In contrast to related additions to α,β-unsaturated amides which require a larger blocking group,[20,32] in these additions the simple benzyl control element affords the highest selectivity. This distinction can be attributed to the closer proximity of the control element and acceptor carbon in hydrazones **3a** and **7** relative to *N*-enoyloxazolidinones, resulting in more effective steric blocking while limiting rotational freedom.

SCHEME 4



Reductive N–N Bond Cleavage. For synthetic access to chiral α-branched amines, cleavage of the N–N bond of the adduct hydrazines is required (Scheme 4). Because reported conditions for such N–N bond cleavage reactions appeared to be highly substrate dependent, we screened a variety of conditions. The results were initially discouraging. Treatment of **9aC** with SmI_2 in THF/HMPA gave no reaction at all, and other one-electron reductants (Na/NH_3 or sodium naphthalenide) resulted in complex reaction mixtures. Neither Zn/HOAc[33] nor Raney nickel[34] was effective; the starting material was recovered. Likewise, hydrogenation with $Pd(OH)_2$[35] ($HCOONH_4$ or 1 atm H_2) in neutral or acidic conditions produced no cleavage of the auxiliary. Considering the strong precedent for cleavage of benzoic hydrazides with SmI_2, we finally resorted to benzoylation of the basic nitrogen of hydrazide **9aC**. This was readily achieved by sequential treatment with *n*-BuLi and benzoyl chloride, affording benzamide derivative **13** in 83% yield (Scheme 4). Exposure of **13** to SmI_2 cleanly afforded **14** (99% yield) and **1a** (97% yield) within 5 min.[36]

Stereochemical Assignment. Chemical correlation and X-ray crystallographic analysis were employed for

(31) Reduction (Bu_3SnH, $BF_3{\cdot}OEt_2$) of *N*-acylhydrazones proved to be generally efficient. For details regarding this stereospecific reduction reaction, see: Qin, J.; Friestad, G. K. *Tetrahedron* **2003**, *59*, 6393–6402.

(32) Sibi et al. found that 4-(diphenylmethyl)-2-oxazolidinone was needed for good stereocontrol (dr = 45: 1) in isopropyl radical addition to *N*-cinnamoyl derivatives (4-benzyl-2-oxazolidinone gave dr = 2:1). See ref 20b.

(33) Evans, D. A.; Johnson, D. S. *Org. Lett*. **1999**, *1*, 595–598.

(34) (a) Enders, D.; Schubert, H.; Nubling, 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*, 6395–6396. (c) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625–626.

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

(36) When hydrazide **9aC** was acylated by *n*-BuLi/MeOCOCl (81% yield) or *n*-BuLi/CbzCl (89% yield), the products did not react with SmI_2.

TABLE 5. Scope of Radical Precursor in Tin-Free Radical Addition to 3a in the Presence of $InCl_3$[a]

entry	R^2 of halide	product, yield[b] (%)
1	Et	**9aB**, 33
2	*i*-Pr	**9aC**, 75[c]
3	*c*-C_5H_9	**9aD**, 47
4	*c*-C_6H_{11}	**9aE**, 56
5	CH_2Cl	**9aI**, 33

[a] Reaction conditions: as in entry 4 of Table 2, minus Bu_3SnH. [b] Isolated yield. [c] dr > 95:5 (^1H NMR).

assignment of the absolute configurations of **9aC** and **12aF**. Starting from (*S*)-valinol (Scheme 4), Boc-protection, *O*-tosylation, homologation with Me_2CuLi, and exchange of the carbamate for benzamide afforded **14**, $[\alpha] = +10.0$ (*c* 1.0, $CHCl_3$). The same compound, when obtained by N−N bond cleavage of **13** as described above, had virtually identical specific rotation: $[\alpha] = +10.2$ (*c* 0.24, $CHCl_3$). The (*R*) configuration can thus be assigned to benzamide **14** and isopropyl radical addition product **9aC**. Configurations of the other adducts **9**−**11** were assigned by analogy with **9aC**. Extension of this assignment to benzaldehyde-derived adducts **12** was bolstered by X-ray crystallographic analysis of **15**, obtained by benzoylation of **12aF**. Here the (*S*) configuration was observed (see the Supporting Information), enabling unambiguous assignment of the same configuration to **12aC**−**12aE**. It should be noted that the configurational designations in this case imply the same transition state topology for formation of **9aC** and **12aF**; they differ only due to different substituent priorities in the products. All the available stereochemical evidence is consistent with radical addition to the *si* face of the chelated model **B** (Figure 3).

Tin-Free Radical Addition. An attractive attribute of the use of triethylborane or diethylzinc as initiators in radical additions to C=N bonds is the potential for a radical chain process without tin hydride. In the absence of tin hydride, the Et_3B and Et_2Zn were proposed to have multiple roles, including both initiation and chain transfer.[3e,4b] Chain propagation in this scenario has been proposed to involve a homolytic substitution at the boron center by the adduct aminyl radical, releasing another ethyl radical. Thus, because the triethylborane serves as both initiator and chain transfer agent, stoichiometric quantities are consumed.

In search of improvement of the radical additions to *N*-acylhydrazones, triethylborane-mediated tin-free additions of various halides were attempted, using $InCl_3$ as the Lewis acid (Table 5). As in the case of tin-mediated additions, the secondary iodides worked quite well in additions to the propionaldehyde hydrazone (entries 2−4). Toward more synthetic versatility, additions of a series of functionalized radicals of general formula $^{\bullet}CH_2X$ were attempted using *N*-acylhydrazone **3a**. These were chosen on the basis of the expectation of favorable reactivity in the crucial iodine atom-transfer step. Using triethylborane initiation, ethyl radical from triethylborane must abstract iodine atom from the alkyl iodide, a process which is favored by formation of a more stable radical. Unfortunately, despite numerous attempts, the functionalized radical additions were mostly unsuccessful.[37] However, chloroiodomethane did lead to successful addition of the $^{\bullet}CH_2Cl$ group to afford **9aI**, albeit in modest 33% yield (entry 5). The adduct, which retains the chloride, offers the potential for subsequent functional group manipulations of the radical-derived alkyl group.

TABLE 6. PhotolyticTin-Mediated Radical Addition to *N*-Acylhydrazone 3a in the Presence of $InCl_3$[a]

entry	R^2 of halide	recovered **3a**[b] (%)	product, yield[b] (%)
1[c]	Et	8	**9aB**, 56
2	*i*-Pr	(33)	**9aC**, 50[d]
3	*t*-Bu	(63)	*e*
4	allyl	*e*	**9aH**, 25
5	CH_2Cl	30	**9aI**, 32
6	Me	25	**9aJ**, 9

[a] Reaction conditions: R^2-I (10 equiv), $Me_3SnSnMe_3$ (1.2 equiv), $InCl_3$ (2.3 equiv), acetone (5 equiv), CH_2Cl_2, $h\nu$ (300 nm, Rayonet), ca. 30−35 °C. [a] Isolated yield (or recovery). Numbers in parentheses are for acetone hydrazone **16**. [b] EtI: 2 equiv. [c] dr > 95:5 (^1H NMR). [d] Not detected.

Tin-Mediated Addition of Primary Radicals. Despite the success in addition of chloromethyl and simple alkyl radicals in both tin-mediated and tin-free methods, the synthetic potential of these intermolecular radical additions could be dramatically enhanced by development of conditions compatible with primary radicals. We recognized two significant problems interfering with primary radical addition using existing methods: Less stable primary radicals (versus secondary or tertiary) might not be sufficiently long-lived to avoid premature reduction by hydrogen atom abstraction processes, and generation of the desired radical from a primary alkyl iodide under tin-free conditions requires an unfavorable iodine atom transfer to the $Et^{\bullet}$ produced from the Et_3B/O_2 initiator. Thus, we typically recovered hydrazones unchanged when attempting the use of primary iodides in the presence of Bu_3SnH, while $Et^{\bullet}$ addition was the major product in the absence of Bu_3SnH. These observations led us to consider alternatives to Et_3B/O_2 initiation.

Kim has extensively developed the use of nonreductive radical addition−elimination reactions to *C*-sulfonyl oxime ethers.[38,39] In these reactions, photochemical initiation with acetone as a sensitizer enables hexamethylditin to mediate addition of various simple and functionalized primary alkyl halides. We wondered if these conditions might also offer a solution to the problem of reductive radical addition of primary alkyl iodides to our *N*-acylhydrazones.

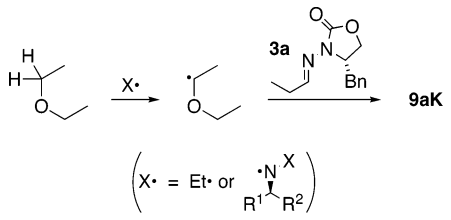
Applying the Kim conditions in the presence of $InCl_3$, iodoethane underwent addition to hydrazone **3a** in 56% yield (entry 1, Table 6). Use of related In(III) salts offered

(37) (a) Other functionalized halide precursors attempted without success (<5% yield) include ethyl iodoacetate, iodomethyl methyl ether, bromomethyl acetate, iodomethyltrimethylsilane, and allyl iodide. (b) The tin-free conditions did not solve the problem of branched hydrazones: only 6% yield was obtained in ethyl iodide addition to cyclohexanecarboxaldehyde hydrazone **6** (48% recovery of **6**).

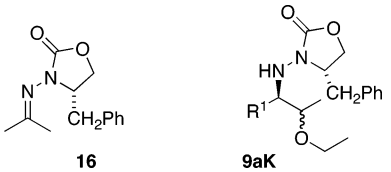
(38) (a) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138−5139. Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982−5983. Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190−12191. Jeon, G.-H.; 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.

(39) 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.

SCHEME 5



no improvement.[40] Isopropyl iodide addition proceeded in 50% yield (entry 2), although *tert*-butyl addition (entry 3) failed. Chloromethyl and allyl additions under these conditions gave low yields (entries 4 and 5), and other attempts to use functionalized primary radicals ($^{\bullet}CH_2OMe$, $^{\bullet}CH_2SiMe_3$, $^{\bullet}CH_2CO_2Me$, $^{\bullet}CH_2CH_2OH$) resulted in no observed adduct. Methyl addition afforded only a very low yield of **9aJ** (entry 6). A further increase in efficiency was never achieved, in part due to complications from the use of acetone as a sensitizer. Acetone replaced the aldehyde component of the hydrazone through a carbonyl exchange side reaction[41] to provide variable amounts of hydrazone **16**. For example, the isopropyl adduct was accompanied by 33% yield of **16** (entry 2), while a 63% yield of this byproduct was the only material recovered in an attempted *tert*-butyl addition (Entry 3).



Further insight was gleaned from the exploratory studies of the photolytic conditions. Interestingly, when trials of ethyl radical addition were carried out in the presence of diethyl ether as a cosolvent, adduct **9aK** was obtained as a minor product (14% yield) along with the expected **9aB** (25% yield). This product can be attributed to a hydrogen atom abstraction process by ethyl radicals or aminyl radicals (i.e., hydrazone adduct radicals) in which diethyl ether serves as the H-atom donor (Scheme 5).[42] This provides a 1-ethoxyethyl radical which can compete for the *N*-acylhydrazone acceptor. Importantly, evidence of slight stereocontrol was seen at the ethoxyethyl stereocenter (dr 2:1), suggesting that it may be possible to design an approach to stereocontrol in addition of related prochiral radicals.

Conclusion

In conclusion, a novel *N*-acylhydrazone auxiliary approach gives excellent stereocontrol in radical addition to C=N bonds. Notably, this is the first intermolecular radical addition to C=N bonds which does not require adjacent carbonyl functionality for auxiliary linkage or acceptor activation. The tin-mediated reaction is mainly useful for addition of secondary and tertiary radicals, although chloromethyl and allyl have been added using two complementary methods. New insights and elements of expanded scope are highlighted in this full paper: (1) Comparison of several other control elements on the oxazolidinone showed that all were effective. Although the benzyl substituent gives slightly higher diastereomer ratios, only slight differences were noted which are insignificant from a synthetic standpoint. (2) Tin-free reactions were developed exploiting dual functions of triethylborane for both initiation and chain propagation. (3) Photolytic reactions with hexamethylditin enabled addition of primary radicals in modest yields.

Experimental Section[43]

(*S*)-3-Amino-4-phenylmethyl-2-oxazolidinone (2a). To a solution of (*S*)-(−)-4-benzyl-2-oxazolidinone (**1a**) (3.50 g, 19.77 mmol) in THF (350 mL) was added *n*-BuLi (12.35 mL, 2.0 M in hexane, 24.7 mmol) at −78 °C. After 1 h, *O*-(mesitylenesulfonyl)hydroxylamine [$MtsONH_2$, **CAUTION**[44]] (5.53 g, 25.7 mmol) was added, and the reaction mixture was allowed to warm to room temperature. Concentration and gradient flash chromatography (hexane → 1:5 hexane/EtOAc) afforded **2a** as a pale yellow oil (2.85 g, 75% yield): $[\alpha]^{22}_D$ +72.8 (*c* 3.7, $CHCl_3$); IR (film) 3339, 3215, 3061, 2921, 1762, 1625, 1454, 1230, 1091, 1025, 921 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, J = 7.3, 7.3 Hz, 2H), 7.23 (dd, J = 7.3, 7.3 Hz, 1H), 7.14 (d, J = 7.3 Hz, 2H), 4.14 (dd, J = 7.5, 7.5 Hz, 1H), 3.98−3.90 (m, 4H), 3.27 (dd, J = 13.8, 3.6 Hz, 1H), 2.70 (dd, J = 13.6, 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 135.5, 129.0, 128.7, 126.9, 66.0, 59.5, 37.3; MS (CI) *m/z* (relative intensity) 193 ([M + H]$^+$, 100), 178 (100). Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.05; H, 6.34; N, 14.27.

Preparation of Hydrazones (Table 1): General Procedures. Compounds **3**−**8** were prepared by general procedures A and B as indicated in Table 1, with details provided in the Supporting Information. Although this general procedure A was used to obtain **4**−**8** for our initial studies, we now recommend the alternative general procedure B. Representative preparations of **3a** and **3b** are described below.

General Procedure A. To a solution of **1** in THF (0.06 M) was added *n*-BuLi (2.5 M in hexane, 1.1 equiv) at −78 °C. After 40 min, $MtsONH_2$[1] (1.2 equiv) was added, the reaction mixture was allowed to warm to room temperature, and the appropriate aldehyde (5 equiv) was introduced. When the reaction was complete (TLC), the mixture was diluted with twice its volume of ether and partitioned between ether and water. The organic phase was dried over Na_2SO_4 and concentrated. Gradient flash chromatography (hexane → 3:1 hexane/EtOAc) furnished pure hydrazones as single C=N isomers (>98:2, ^1H NMR).

(*S*)-3-(Propylidene)amino-4-phenylmethyl-2-oxazolidinone (3a). From **1a** (400 mg, 2.26 mmol) and propionaldehyde by general procedure A was obtained **3a** (425 mg, 81% yield) as a pale yellow oil: $[\alpha]^{25}_D$ +7.5 (*c* 3.8, $CHCl_3$); IR (film) 3062, 2935, 2877, 1762, 1632, 1478, 1405, 1208, 1093, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (t, J = 5.2 Hz, 1H), 7.27−7.11 (m, 5H), 4.31 (dddd, J = 8.2, 8.2, 4.0, 4.0 Hz, 1H), 4.17 (dd, J = 8.8, 8.8 Hz, 1H), 4.02 (dd, J = 8.8, 5.6 Hz, 1H), 3.16 (dd, J = 13.9, 3,7 Hz, 1H), 2.76 (dd, J = 13.9, 8.6 Hz, 1H), 2.37−2.34 (m, 2H), 1.10 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

(40) Use of other In(III) Lewis acids led to the following yields of **9aB**: InF_3 (16%), InI_3 (54%), $In(OAc)_3$ (12%), and $In(OTf)_3$ (30%).

(41) We have previously described preparative exchange reactions between certain *N*-acylhydrazones and carbonyl compounds. See ref 22.

(42) The presence of several other potential H-atom donors, including EtOH, Et_3SiH, Ph_3SiH, $(Me_3Si)_3SiH$, resulted in a decreased yield of **9aB**.

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

(44) **CAUTION:** *O*-(Mesitylenesulfonyl)hydroxylamine ($MtsONH_2$) shows a tendency toward exothermic spontaneous decomposition during its preparation and storage. Although most of the work described here was conducted using $MtsONH_2$, we have discontinued use of this compound in favor of the alternative amination reagent *O*-(*p*-nitrobenzoyl)hydroxylamine ($NbzONH_2$), which gives similar results in the amination of oxazolidinones. Another viable alternative is *O*-(diphenylphosphinoyl)hydroxylamine ($DppONH_2$).

δ 157.3, 154.3, 135.2, 129.1, 128.7, 127.0, 65.6, 57.6, 37.1, 26.5, 10.5; MS (CI) *m/z* (relative intensity) 233 ([M + H]$^+$, 100), 232 (M, 7). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.98; H, 6.83; N, 12.06.

General Procedure B. As described in detail elsewhere,[22] hydrazones **3b**−**e** were prepared by the following sequence: (i) NaH (or KH; 1.05 equiv), dioxane, reflux; (ii) *O*-(*p*-nitrobenzoyl)hydroxylamine ($NbzONH_2$; 1.05 equiv); (iii) aldehyde, *p*-TsOH, toluene.)

(*S*)-3-(Propylidene)amino-4-diphenylmethyl-2-oxazolidinone (3b). From **1b** (160 mg, 1.03 mmol) and propionaldehyde by general procedure B was obtained **3b** (192 mg, 99% yield) as a pale yellow oil: [α]$^{28}_D$ +32.3 (*c* 0.65, $CHCl_3$); IR (film) 3493, 2982, 2913, 1753, 1495, 1410, 1222, 1091, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (t, *J* = 4.35 Hz, 1H), 7.21−7.04 (m, 10H), 4.81 (ddd, *J* = 8.5, 6.1, 6.1 Hz, 1H), 4.38 (d, *J* = 6.4 Hz, 1H), 4.33 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.06 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.14−2.08 (m, 2H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.2, 154.7, 140.2, 139.1, 128.8 (2C), 128.7, 128.6, 127.4, 126.9, 64.9, 59.9, 53.1, 26.5, 10.2; MS (CI) *m/z* (relative intensity) 309.5 ([M + H]$^+$, 100%). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.82; H, 6.60; N, 8.85.

Tin-Mediated Radical Addition to Hydrazones (Tables 2−4): General Procedure C. To a solution of the hydrazone in CH_2Cl_2 (ca. 0.25 M) was added $ZnCl_2$ (1 M in Et_2O, 2 equiv). After 1 h at room temperature, the mixture was cooled to −78 °C, followed by addition of Et_3B (10 equiv) and the appropriate alkyl iodide (10 equiv). Bu_3SnH (0.25 M in CH_2Cl_2, 5 equiv) and O_2 (ca. 7 mL/mmol hydrazone) were introduced by syringe pump over ca. 5 h. The reaction mixture was allowed to warm slowly to room temperature. After 2 d, stannanes were removed by dilution with EtOAc, stirring overnight with excess KF, and filtration through a short pad of silica gel. Concentration and radial chromatography (hexane/EtOAc) afforded *N*-acylhydrazines **9**−**12**. Side products **9aA** and **9aB** were obtained in varying amounts in some experiments. For those *N*-acylhydrazines for which diastereomer ratios are reported, control experiments established that no change in the diastereomer ratios occurred prior to analysis. Diastereomer ratios were determined by comparison with authentic diastereomer mixtures prepared by an alternative route.[5] Diastereomer ratios of **9aC**−**9aF** and **9eC** were determined by HPLC. Diastereomer ratios of *N*-acylhydrazines **12aC**−**12aF** were determined by GCMS. Diastereomer ratios of **9bC** and **9cC** were determined by integration of ^{1}H NMR data obtained in the presence of the NMR shift reagent tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium(III) (Sievers reagent).

(4*S*,3′*R*)-3-(2′-Methyl-3′-pentylamino)-4-phenylmethyl-2-oxazolidinone (9aC). From **3a** (32 mg, 0.138 mmol) and 2-iodopropane by general procedure C was obtained **9aC** (23 mg, 60% yield, *S*,*R*/*S*,*S* = 99:1) as a colorless solid: HPLC retention time 11.3 min; mp 75−76 °C; [α]$^{26}_D$ + 38.3 (*c* 0.65, $CHCl_3$); IR (film) 3296, 3089, 3026, 2960, 2927, 1779, 1604, 1491, 1392, 1368, 1252, 1082, 953, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.23 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 2H), 4.09 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.00 (dd, *J* = 8.8, 4.9 Hz, 2H), 3.89−3.84 (m, 1H), 3.32 (dd, *J* = 13.4, 3.5 Hz, 1H), 2.75 (m, apparent quartet, *J* = 6.1 Hz, 1H), 2.59 (dd, *J* = 13.4, 10.0 Hz, 1H), 1.83 (m, apparent octet, *J* = 4.8 Hz, 1H), 1.52−1.44 (m, 1H), 1.43−1.35 (m, 1H), 0.98−0.92 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 136.1, 129.1, 128.9, 127.0, 65.8, 59.7, 37.0, 28.2, 21.5, 18.4, 17.9, 10.2; MS (CI) *m/z* (relative intensity) 277 ([M + H]$^+$, 100), 276 (M, 8); HRMS (FAB+) calcd for $C_{16}H_{24}N_2O_2Li$ 283.1998, found 283.1993.

Tin-Free Radical Addition Using $InCl_3$ with Triethylborane Initiation (Table 5): General Procedure D. The standard method for tin-mediated radical addition (general procedure C) was employed, with the following modifications: $InCl_3$ was substituted for $ZnCl_2$, and Bu_3SnH was omitted.

(4*S*,2′*R*)-3-(1′-Chloro-2′-butanamino)-4-phenylmethyl-2-oxazolidinone (9aI). From **3a** (48 mg, 0.21 mmol) and chloroiodomethane (0.15 ml, 2.07 mmol) by general procedure D was obtained **9aI** (19 mg, 33% yield) as a colorless oil: [α]$^{27}_D$ +44.9 (*c* 3.4, $CHCl_3$); IR (film) 3286, 3028, 2966, 2878, 1758, 1497, 1400, 1240, 1217, 1091, 1207, 745, 702 cm^{-1}; ^{1}H 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), 3.62 (ABX, $\Delta\nu_{AB}$ = 28 Hz, J_{AB} = 11.4 Hz, J_{AX} = 4.6 Hz, J_{BX} = 4.9 Hz, 2H), 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 (t, *J* = 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.

Photolytic Tin-Mediated Radical Addition (Table 6): Hydrazines 9aB and 9aK (General Procedure E). To a solution of hydrazone **3a** (60 mg, 0.26 mmol) and $InCl_3$ (132 mg, 0.60 mmol) in CH_2Cl_2/Et_2O (2 mL/2 mL) were added EtI (41 μL, 0.52 mmol), $(CH_3)_3SnSn(CH_3)_3$ (102 mg, 0.31 mmol), and acetone (95 μL, 1.30 mmol), and the mixture was irradiated for 18 h under N_2. Stannanes were removed by dilution with EtOAc, stirring overnight with excess KF, and filtration through a short pad of silica gel. Concentration and gradient flash chromatography (hexane to hexane/EtOAc 3:1) afforded **9aK**[45] (7 mg of major isomer, 4 mg of minor isomer, 14% yield) and **9aB** (17 mg, 25% yield) as a colorless oil: [α]$^{23}_D$ +33.5 (*c* 0.21, $CHCl_3$); IR (film) 3291, 3028, 2963, 1758, 1604, 1454, 1239, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dddd, *J* = 7.0, 7.0, 1.6, 1.6 Hz, 2H), 7.25 (dddd, *J* = 7.3, 7.3, 1.3, 1.3 Hz, 1H), 7.16 (ddd, *J* = 7.1, 1.5, 1.5 Hz, 2H), 4.14 (dd, *J* = 8.8, 7.6 Hz, 1H), 4.03 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.95 (d, *J* = 3.8 Hz, 1H), 3.92−3.87 (m, 1H), 3.34 (dd, *J* = 13.5, 3,6 Hz, 1H), 2.98−2.92 (m, 1H), 2.62 (dd, *J* = 13.5, 10.0 Hz, 1H), 1.53−1.45 (m, 4H), 1.00−0.94 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 136.1, 129.1, 128.9, 127.0, 65.7, 61.5, 59.8, 37.0, 24.2, 24.1, 9.7, 9.1; MS (CI) *m/z* (relative intensity) 263 ([M + H]$^+$, 100). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.44; H, 8.42; N, 10.54.

A similar experiment in the absence of Et_2O afforded **9aB** in 56% yield; **9aK** was not observed. The rest of the results in Table 6 were also obtained in the absence of Et_2O.

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Supporting Information Available: Characterization data for **2**−**16** with selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(45) For characterization data, see the Supporting Information.