Chiral *N*-Acylhydrazones: Versatile Imino Acceptors for Asymmetric Amine Synthesis

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Keywords: Hydrazones / Amines / Radical reactions / Nucleophilic addition / Asymmetric synthesis

Addition to C=N bonds with acyclic stereocontrol offers excellent potential for development of new carbon–carbon bond construction approaches to chiral amines. This review features the design and implementation of novel chiral *N*-acylhydrazones as versatile imino acceptors for addition of radicals and nucleophiles. The initial design was inspired by the goal of asymmetric radical addition to chiral C=N radical acceptors. The chiral *N*-acylhydrazones are prepared from commercially available materials by amination of 4-alkyl-2-oxazolidinones with NH_2^+ equivalents to afford *N*-(amino) oxazolidinones, followed by condensation with aldehydes or ketones. These chiral *N*-acylhydrazones undergo addition reactions with various partners, including radicals, allylsilanes, allylindiums, silyl enol ethers, and hydride donors. The adducts can be converted to chiral amines by N–N bond cleavage. Reliably high stereoselectivity was observed for addition reactions in the presence of Lewis acids. For the prototype case, *N*-acylhydrazones derived from (*S*)-4-benzyl-2-oxazolidinone, two alternative stereocontrol models are consistent with the results. Lewis acids capable of chelate formation activate through two-point binding of the imino nitrogen and the carbonyl oxygen, exposing the *si*-face for addition. On the other hand, boron trifluoride activates through a monodentate interaction, favoring a rotamer which exposes the *re*-face. Applications from the author's research program are reviewed together with results from other groups.

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Gregory K. Friestad was born in 1968 in Alexandria, Minnesota, USA. Following undergraduate studies at Bradley University in Peoria, Illinois (BS Chemistry, 1990), he moved west to the University of Oregon and earned a PhD in Organic Chemistry in 1995 working with Professor Bruce P. Branchaud on a new synthetic approach to Amaryllidaceae phenanthridone alkaloids. A National Institutes of Health postdoctoral fellowship with Professor Amos B. Smith, III at the University of Pennsylvania followed, during which he completed the total syntheses of calyculins A and B. Dr. Friestad began his independent career as Assistant Professor in the Department of Chemistry of University of Vermont, and was promoted to Associate Professor there in 2004. He moved in 2005 to his current position as Associate Professor in the Department of Chemistry at the University of Iowa. He has also held temporary appointments as visiting professor at the University of Wisconsin-Madison, and Kobe Pharmaceutical University, Japan. Professor Friestad's research interests include development of new synthetic methodology, radical addition reactions, applications of organosilicon compounds in synthesis, natural product synthesis, and asymmetric catalysis.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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Introduction

1. 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 (Figure 1a) holds promise for improved efficiency by introducing the stereogenic center and carbon–carbon bond in one step under mild, non-basic conditions. Stereocontrolled addition to imines[1] is underdeveloped, and consequently, the more common approach involves stepwise introduction of carbon–carbon bonds, stereogenic centers, and nitrogen (e.g., alkene synthesis followed by epoxide opening with *N*-nucleophiles). New stereocontrolled carbon–carbon bond construction methods would broaden the scope of the direct asymmetric amine synthesis strategy for access to chiral amines.

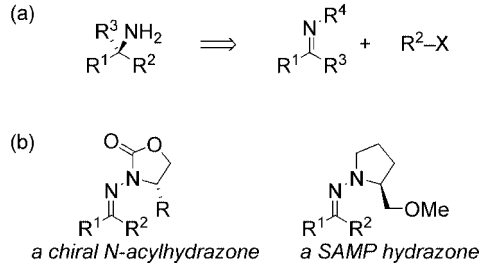


Figure 1. (a) The C–C bond disconnection approach to asymmetric amine synthesis. (b) Examples of a chiral *N*-acylhydrazone and an Enders SAMP hydrazone.

Nucleophilic additions to C=N bonds according to Figure 1a may be compromised by functional group incompatibilities or competing aza-enolization[2] due to the basicity of the reagents. The high basicity associated with these organometallic nucleophiles is complemented by the milder conditions inherent to Strecker[3] and Mannich[4] addition reactions, although these place some significant structural limitations on the incoming nucleophile. In pursuit of more versatile methods for highly stereocontrolled addition to C=N bonds, we have introduced novel chiral *N*-acylhydrazones (Figure 1b), the design, preparation, and application of which are the main focus of this review.

2. Design and Synthesis of Chiral *N*-Acylhydrazones

Chiral *N*,*N*-dialkylhydrazones have served prominent roles in the early development of asymmetric synthesis. Most notable among these achievements are Enders' SAMP (Figure 1b) and RAMP chiral auxiliaries for enantioselective α-alkylation of carbonyl compounds,[5] which have also been used for addition of organometallic reagents to the C=N bond.[6,7] Related chiral hydrazones were exploited by Corey for asymmetric amine synthesis by reductive amination.[8] Applications of chiral hydrazones have broadened in recent years; new developments include allene anion additions to SAMP hydrazones,[9] chiral umpolung reactivity[10] and [2+2] cycloadditions[11] employing formaldehyde hydrazones, and asymmetric catalysis with hydrazone chelate complexes.[12]

2.1. Design

The design of chiral *N*-acylhydrazones was initially conceived in the context of radical addition to C=N bonds as an entry to asymmetric amine synthesis.[13] When implemented, the *N*-acylhydrazone motif proved to be generally useful beyond radical addition, but for the purposes of this review, the design aspects will be discussed from the perspective of radical addition reactions.

Radical acceptors for intermolecular additions to C=N bonds are rare.[14] Activation of the C=N bond toward radical addition has been achieved by use of oxime ethers or hydrazones, where the substituent on nitrogen can stabilize the intermediate adduct (*N*-centered aminyl radical). Previous work, by Naito and Bertrand respectively, had identified the ability to impart either activation or stereocontrol through the influence of the C=N nitrogen substituent.[15] 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 2). Successful addition would then be independent of the identity of the aldehyde precursor to the imine, offering a potentially broader reaction scope.

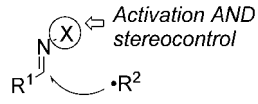


Figure 2. Previous approaches to stereocontrol for radical addition to C=N bonds required both *C*- and *N*-substituents of the C=N bond to play separate roles for activation and stereocontrol. Here the goal is to combine both roles within the *N*-substituent, making the process independent of R^1.

Toward this end, we conceived a nitrogen-linked chiral auxiliary approach incorporating Lewis acid activation[16] and restriction of rotamer populations as key design elements. Thus the hydrazone functional group emerged as a desirable starting point for a new imino 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 stable than imines toward hydrolysis, and are more effective than imines as radical acceptors.[14] Early transition states were assumed for the addition steps, which is well-established for radical addition.[14] 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. 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 reagents, including nucleophilic radicals, by lowering the LUMO energy of the C=N bond.[16] 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.

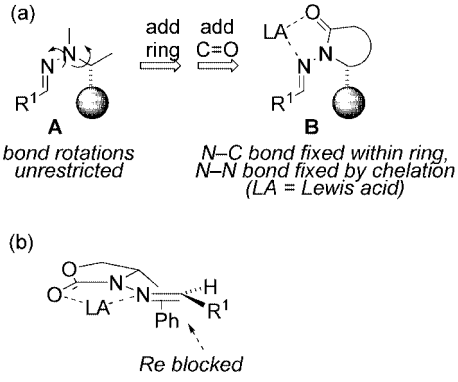
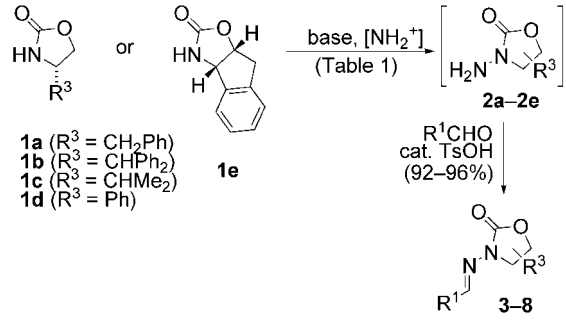


Figure 3. (a) Design of a hypothetical *N*-linked auxiliary approach for stereocontrolled addition to C=N bonds, with Lewis acid (LA) chelation inducing a rigid, electron-deficient imino acceptor. (b) Implementation with *N*-acylhydrazones derived from 4-benzyl-2-oxazolidinone.

Oxazolidinones[19,20] such as **1a**–**1e** (Scheme 1) emerged as obvious initial candidates to test our hypothesis. Prior to our work, *N*-amino derivatives of oxazolidinones had appeared in the literature only rarely,[21] and to the best of our knowledge had never been used for asymmetric synthesis. Upon condensation with aldehydes and ketones, the *N*-(amino)oxazolidinones (e.g. **2a**–**2e**) would lead to chiral *N*-acylhydrazones.

The proposed *N*-acylhydrazones were attractive for the reasons outlined above, but also duly noted were the extensive studies by Kobayashi's group, which emphasized the value of *N*-acylhydrazones as stable, isolable imine equivalents for various stoichiometric and asymmetric catalytic addition reactions.[22,23] Those studies, which focused mainly on *N*-benzoylhydrazones, also included examples of 1,2-diastereocontrol, where the stereogenic α-carbon of the hydrazone serves as the stereocontrol element.[24]



Scheme 1.

2.2. *N*-Amination of Oxazolidinones

For our initial test of the design hypothesis outlined above, we employed commercially available (*S*)-4-benzyl-2-oxazolidinone (**1a**, Scheme 1). With modifications of White's amination procedure for related oxazolidinones,[21a] using either *O*-(mesitylenesulfonyl)hydroxylamine ($MtsONH_2$) or *O*-(*p*-nitrobenzoyl)hydroxylamine ($NbzONH_2$) as NH_2^+ equivalents, *N*-(amino)oxazolidinone **2a** was obtained in good yield. 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.[25,26]

2.3. Preparation of *N*-Acylhydrazones from Aldehydes and Ketones

After *N*-amination, condensation with aldehydes proceeds reliably, with or without isolation of the intermediate *N*-(amino)oxazolidinone, to afford a wide range of chiral hydrazones **3**–**8** in good overall yields (Table 1). A series of other chiral *N*-acylhydrazones bearing different substituents on the oxazolidinone were prepared starting from commercially available chiral oxazolidinones **1b**–**1e** (Scheme 1). Amination and condensation with propionaldehyde provided the hydrazones **3b**–**3e**.

Additional practical notes are worth mentioning. 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. The condensation may be conducted without added acid, although trace amounts of *p*TsOH, or use of unpurified CH_2Cl_2 (presumably containing traces of HCl) may be beneficial. If desired, the *N*-(amino)oxazolidinone **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. With purified **2a**, yields over 90% are routine for the condensation step.

The method described above affords good yields of chiral *N*-acylhydrazones from aldehydes on small to multigram scale. For example, benzaldehyde hydrazone **7** (9.4 g) was obtained in 74% yield from **1a** employing crystallization

Table 1. Amination of oxazolidinones and condensation with aldehydes (Scheme 1).

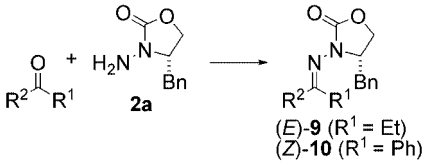
Entry	Oxazolidinone	R^1	Method[a]	Product[b]
1	**1a**	Et	A	**3a**, 81%
2	**1a**	*i*Pr	A	**4**, 70%
3	**1a**	*t*Bu	A	**5**, 72%
4	**1a**	*c*-C_6H_{11}	A	**6**, 65%
5	**1a**	Ph	A	**7**, 67%
6[c]	**1a**	Ph	B[d]	**7**, 80% (74%)[e]
7	**1a**	CO_2Me	A	**8a**, 71%
8	**1b**	Et	B	**3b**, 75%
10	**1c**	Et	B	**3c**, 49%
12	**1d**	Et	B[c]	**3d**, 65%
14	**1e**	Et	B	**3e**, 87%

[a] Method A: i. *n*BuLi, THF, –78 °C, 40 min; ii. $MtsONH_2$, –78 °C → room temp.; iii. R^1CHO, room temp. Method B: (1) i. KH, dioxane, 60 °C, 1 h; ii. $NBzONH_2$, room temp. (2) R^1CHO, cat. *p*TsOH, toluene, room temp. [b] Isolated yield except where noted. [c] Ref.[21] [d] NaH was used place of KH. [e] Yield on 10 g scale, employing crystallization.

from ethanol to recover most of the pure hydrazone before chromatography of the mother liquors. One can prepare a large quantity of a crystalline, indefinitely stable hydrazone for long-term storage, then exchange the carbonyl component as desired.[25]

Prochiral ketimine derivatives may be prepared in similar fashion, although the yields are not as high.[27] Condensation of various ketones with *N*-(amino)oxazolidinone **2a** in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene afforded ketone *N*-acylhydrazones **9** and **10** (Table 2). Mixtures of *E*/*Z* isomers were usually obtained, although ketone *N*-acylhydrazones **9d** and **10d**, with highly branched tertiary butyl (*t*Bu) substituents, were formed as single isomers.

Table 2. Preparation of ketone hydrazones.



Entry	R^1	R^2	Hydrazone (yield)	*E*/*Z* Ratio
1	Et	*i*Pr	**9a** (84%)	77:23
2	Et	*c*-C_5H_9	**9b** (49%)	79:21
3	Et	*c*-C_6H_{11}	**9c** (64%)	85:15
4	Et	*t*Bu	**9d** (67%)	>98:2
5	Ph	*i*Pr	**10a** (55%)	19:81
6	Ph	*c*-C_5H_9	**10b** (59%)	26:74
7	Ph	*c*-C_6H_{11}	**10c** (55%)	13:87
8	Ph	*t*Bu	**10d** (73%)	<2:98

2.4. Geometry of the C=N Bond in *N*-Acylhydrazones

Assignment of C=N bond geometry in the ketone hydrazone derivatives was achieved through comparison of ^{13}C NMR chemical shifts of the α-carbon of the *E* and *Z* isomers.[27] Steric compression shifts in ^{13}C NMR spectroscopy,[28,29] which arise from steric perturbations of carbon nuclei, can distinguish carbons which have *cis* and *trans* relationships to the *N*-substituent of a C=N bond. Specifically, the α-carbon with a *cis* relationship to the *N*-substituent is found upfield from the same α-carbon having a *trans* relationship to the *N*-substituent, usually by several ppm.

For ketone *N*-acylhydrazones obtained as mixtures of *E*/*Z* isomers, steric compression shifts ($\Delta\delta$) could be observed clearly for one or both of the α-carbon atoms. The key data used for assignment of C=N bond geometries of the hydrazones are found in Table 3.

The ^1H chemical shifts of the α-hydrogen within R^2 were also found to be reliable indicators of a *cis* or *trans* relationship of R^2 with the *N*-substituent on the C=N bond (i.e., the oxazolidinone). The *trans* methine (relative to the oxazolidinone) was found upfield of the *cis* methine in all compounds, with the differences in chemical shifts ranging from 0.45 to 0.84 ppm.

3. Radical Additions: Proof of Principle

The radical addition approach to chiral amines, where R^2–X of Figure 1a is used to generate a free radical, offers the potential for practical advantages in chemoselectivity and versatility typical of radical reactions.[30] Several methodologies which illustrate this point have been developed.

3.1. Tin-Mediated Addition of Secondary and Tertiary Radicals

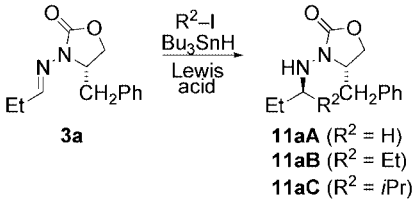
The first synthetic application of the chiral *N*-acylhydrazones was in tin-mediated radical addition.[13] To examine

Table 3. Key NMR spectroscopic data for (*E*)- and (*Z*)-hydrazones in $CDCl_3$ at 500 MHz (^1H) or 125 MHz (^{13}C).

Hydrazone	α-Carbon of R^2 [δ, ppm] R^2-*trans*[a]	R^2-*cis*[a]	$\Delta\delta$ [ppm]	α-Hydrogen of R^2 [δ, ppm] R^2-*trans*[a]	R^2-*cis*[a]
9a	34.18 (*E*)	30.86 (*Z*)	3.32	2.68[b] (*E*)	3.24 (*Z*)
9b	45.35 (*E*)	42.16 (*Z*)	3.19	2.85 (*E*)	3.30 (*Z*)
9c	44.34 (*E*)	41.91 (*Z*)	2.43	2.36[c] (*E*)	3.13 (*Z*)
10a	37.33 (*Z*)	31.33 (*E*)	6.00	2.99[b] (*Z*)	3.52 (*E*)
10b	48.53 (*Z*)	42.48 (*E*)	6.05	3.12 (*Z*)	3.54 (*E*)
10c	47.51 (*Z*)	42.91 (*E*)	4.60	2.62[c] (*Z*)	3.46 (*E*)

[a] The designations *trans* and *cis* refers to the relationship between R^2 and the *N*-substituent. Therefore (*E*)-**9a**–**9c** and (*Z*)-**10a**–**10c** are designated here as *trans*. [b] cf. corresponding aldehyde hydrazone (*E*): δ = 2.60 ppm. [c] cf. corresponding aldehyde hydrazone (*E*): δ = 2.34 ppm.

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 (Scheme 2). Using the tin hydride method with triethylborane initiation[31] (Bu_3SnH, Et_3B/O_2), the effects of Lewis acids were assessed. In particular, $InCl_3$ and $ZnCl_2$ afforded clean (albeit incomplete) conversion to desired adduct **11aC** with high diastereoselectivity. In contrast, **11aC** was produced with poor selectivity (*dr* 2:1) in the absence of Lewis acid.



Scheme 2.

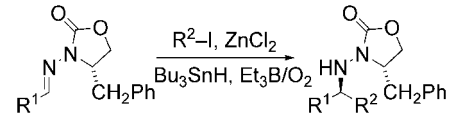
The scope of the reaction was evaluated by variations to both the radical and the radical acceptor. In the presence of $ZnCl_2$, the propionaldehyde *N*-acylhydrazone **3a** was subjected to radical additions of various organic iodides (Table 4, Entries 1–6). Ethyl radical (from the triethylborane) can compete for the radical acceptor, and as a result, the separable ethyl radical adduct **11aB** (Scheme 2) was observed (<10% yield) in all cases. With simple secondary and tertiary alkyl iodides as radical precursors (Entries 1–4), additions to **3a** occurred with moderate yields to afford *N*-acylhydrazines. Radical reactivity is important in predicting the success of the addition reactions: primary, aromatic, allylic, and electrophilic radicals were ineffective under these conditions.[13b]

A variety of aldehyde hydrazones were screened (Table 4, Entries 7–15).[13b] Branching at a saturated α-carbon was detrimental (Entries 7–10), but aromatic benzaldehyde hydrazone **7** offered successful additions, with yields ranging from 30–83% (Entries 11–14). With the exception of **8a**, which decomposed under the reaction conditions, 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.

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.[13]

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. Without optimizing for yield, isopropyl radical additions to several *N*-acylhydrazones **3a**–**3e** (see Scheme 1 for structures) were compared for stereoselectivity (Table 5). Although the measurement was not available for **3c**, all of the auxiliaries gave very high diastereoselectivity in addition of isopropyl radical to propionaldehyde hydrazone.[13b]

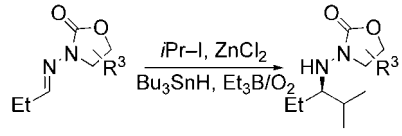
Table 4. Reactivity scope of tin-mediated radical addition to *N*-acylhydrazones (R^3 = Bn) in the presence of $ZnCl_2$.



Entry	R^1	R^2	Recovery[a]	Yield[b] (*dr*)
1	Et (**3a**)	*i*Pr	29%	60% (99:1)
2	Et (**3a**)	*c*-C_5H_9	–[c]	59% (96:4)
3	Et (**3a**)	*c*-C_6H_{11}	60%	28% (97:5)
4	Et (**3a**)	*t*Bu	14%	54% (95:5)
5	Et (**3a**)	*i*Bu	50%	6%
6	Et (**3a**)	allyl	73%	7%
7	*i*Pr (**4**)	Et	88%	6%
8	*i*Pr (**4**)	*c*-C_6H_{11}	77%	9%
9[b]	*c*-C_6H_{11} (**6**)	Et	61%	15%
10	*c*-C_6H_{11} (**6**)	*i*Pr	79%	9%
11	Ph (**7**)	*i*Pr	33%	42% (99:1)
12	Ph (**7**)	*c*-C_5H_9	23%	59% (96:4)
13	Ph (**7**)	*c*-C_6H_{11}	64%	30% (99:1)
14	Ph (**7**)	*t*Bu	–[c]	83% (93:7)
15	CO_2Me (**8a**)	*i*Pr	0%	0%

[a] Recovered hydrazone,%; Reaction conditions: Bu_3SnH (5 equiv.) and O_2 (7 mL/mmol) by syringe pump, *i*PrI (10 equiv.), Et_3B (10 equiv.), and Lewis acid (2 equiv.), 2:1 CH_2Cl_2/ether, –78 °C → room temp. [b] Isolated yield, %. [c] Not determined.

Table 5. Effect of different stereocontrol elements on diastereoselectivity in isopropyl radical addition.[a]



Entry	Hydrazone	R^3	*dr*[b]
1	**3a**	CH_2Ph	99:1
2	**3b**	$CHPh_2$	>98:2
3	**3c**	*i*Pr	–[c]
4	**3d**	Ph	94:6
5	**3e**	bicyclic[d]	95:5

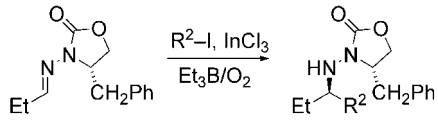
[a] Reaction conditions and isolated yield: Table 2. [b] Diastereomer ratios by HPLC, GCMS, or ^1H NMR integration vs. authentic mixtures. [c] Ratio not available. [d] See Scheme 1 for structure.

3.2. Tin-Free Radical Addition

Triethylborane or diethylzinc have been proposed to have multiple roles, including both initiation and chain transfer,[15a,15b] in radical additions to C=N bonds. This offers the potential for a radical chain process without tin hydride. Accordingly, we attempted triethylborane-mediated tin-free additions of various halides, using $InCl_3$ as the Lewis acid (Table 6).[13b] As in the case of tin-mediated additions, the secondary iodides worked quite well in additions to the pro-

pionaldehyde hydrazone (Entries 2–4). Although other primary radicals were ineffective, chloroiodomethane did lead to successful addition of the $\cdot CH_2Cl$ group, retaining the chloride for subsequent functional group manipulations.

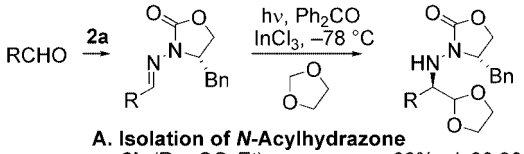
Table 6. Scope of halide in tin-free radical addition to **3a** in the presence of $InCl_3$.



Entry	R^2	Yield[a]
1	Et	33%
2	*i*Pr	75%[b]
3	*c*-C_5H_9	47%
4	*c*-C_6H_{11}	56%
5	CH_2Cl	33%

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

Alonso et al. reported a tin-free method for addition of formyl radical equivalents to these chiral *N*-acylhydrazones.[15d] Photolysis in 1,3-dioxolane in the presence of 1 equiv. benzophenone led to H-atom abstraction from the dioxolane followed by intermolecular radical addition to chiral *N*-acylhydrazones (Scheme 3). Consistent with our results, stereocontrol here was low in the absence of Lewis acid, but rose to excellent levels in the presence of $InCl_3$. After N–N bond cleavage and oxidation at the formyl carbon, preparation of α-amino acids was achieved with high stereoselectivity. The preferred diastereomer was that suggested by the Lewis acid chelate model, as we had observed in the results described above. In contrast to our findings, the reactions of glyoxylate hydrazone **8b** could be achieved under these conditions, although the stereoselectivity was limited to 4.1:1 diastereomer ratio. Interestingly, the addition of Lewis acid did not improve the selectivity in this case. A one-pot protocol was introduced which begins with the aldehyde; the *N*-acylhydrazone need not be isolated. For a series of aldehydes, the corresponding adducts were obtained with yields ranging from 75–99%. Stereocontrol was variable, with the synthetically useful levels restricted to aliphatic aldehyde precursors. Alonso's impressive method provides an independent validation of our stereocontrol hypothesis, and renders the radical additions applicable to a broader range of functionalized targets.



A. Isolation of *N*-Acylhydrazone

8b (R = CO_2Et)	68%, *dr* 80:20
3a (R = Et)	87%, *dr* 91:9

B. One-Pot Protocol

R = Et	96%, *dr* 98:2
R = cyclopropyl	85%, *dr* 97:3
R = dimethoxymethyl	75%, *dr* 95:5
R = *p*-methoxyphenyl	88%, *dr* 50:50
R = 2-furyl	93%, *dr* 80:20

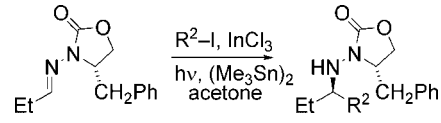
Scheme 3.

3.3. Tin-Mediated Addition of Primary Radicals

The synthetic potential of the intermolecular radical additions would be dramatically enhanced by development of conditions compatible with primary radicals. Less stable 1° radicals (vs. 2° or 3°) often suffer premature reduction by hydrogen atom abstraction processes, and are impractical under Et_3B/O_2 initiation conditions due to the competition with ethyl radicals. These considerations led us to seek alternatives to triethylborane.

Applying Kim's photolysis conditions[32] in the presence of $InCl_3$, we found that ethyl and isopropyl addition to hydrazone **3a** occurred in reasonable yield (Table 7, Entries 1 and 2).[13b] These conditions enable both primary and secondary radical additions to be achieved readily, although *tert*-butyl addition (Entry 3) failed. This method has good potential. Unfortunately, further increase in efficiency was prevented by a carbonyl exchange side reaction[33] with the acetone sensitizer to give the acetone hydrazone. Alternative Mn-mediated photolytic conditions proved to be even more effective (vide infra).

Table 7. Photolytic tin-mediated radical addition to *N*-acylhydrazone **3a** in the presence of $InCl_3$.



Entry	R^2 of halide	Recovered **3a**[a]	Yield[a]
1[b]	Et	8%	56%
2	*i*Pr	(33%)	50%[c]
3	*t*Bu	(63%)	–[d]
4	allyl	–[d]	25%
5	CH_2Cl	30%	32%
6	Me	25%	9%

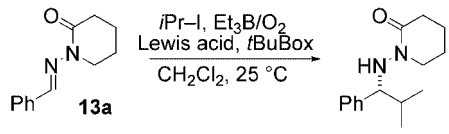
[a] Isolated yield (or recovery). Numbers in parentheses are for the corresponding acetone hydrazone derivative. Reaction conditions: R^2-I (10 equiv.), $Me_3SnSnMe_3$ (1.2 equiv.), $InCl_3$ (2.3 equiv.), acetone (5 equiv.), CH_2Cl_2, hν (300 nm, Rayonet), ca. 30–35 °C. [b] EtI: 2 equiv. [c] *dr* >95:5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

3.4. Asymmetric Catalysis of Radical Addition

Asymmetric catalysis of radical addition to C=N bonds[34] remains a challenge for further synthetic methodology development. Our effort toward this goal began with the hypothesis that the two-point binding of Lewis acids by *N*-acylhydrazones (Figure 4) would facilitate development of a versatile means of stereocontrol.

The first successes exploited the tin-free conditions described above, with radical initiation by triethylborane and

Table 8. Studies of Lewis acids, reaction medium, and chiral ligand structure in isopropyl addition to 13a.[a]



Entry	Chiral ligand, Lewis acid	Solvent	Yield[b]	*ee*,%[c]
1	(*t*Bu)Box, $InCl_3$	CH_2Cl_2	33	57 (*R*)
2	(*t*Bu)Box, $Mg(ClO_4)_2$	CH_2Cl_2	41	66 (*R*)
3	(*t*Bu)Box, $Cu(OTf)_2$	CH_2Cl_2	41	59 (*R*)
4[d][e][f]	(*t*Bu)Box, $Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	66	95 (*R*)
5[d][e][f][g]	(*t*Bu)Box, $Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1)	94	86 (*R*)

[a] Reaction conditions: Lewis acid (1 equiv.), chiral ligand (1 equiv.), 2-iodopropane (6 equiv.), Et_3B/O_2 (6 equiv.), 25 °C. [b] Isolated yield,%. [c] Enantiomeric excess by HPLC (95:5 hexane/2-propanol, Chiralcel OD or AD). [d] Et_3N was added after the reaction to facilitate product isolation. [e] In the presence of powdered 4A molecular sieves. [f] Preformed aquo complex $Cu(t\text{Bu-Box})(H_2O)_2(OTf)_2$ was used. [g] Larger amounts (10 equiv.) of 2-iodopropane and Et_3B were used.

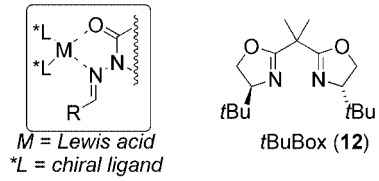


Figure 4. Two-point binding of *N*-acylhydrazones involving Lewis acid and chiral ligand(s).

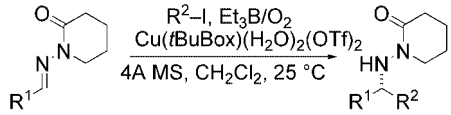
oxygen. Using valerolactam-derived achiral *N*-acylhydrazone acceptor **13a** (Table 8), we discovered highly enantioselective radical additions promoted by 1 equivalent each of Lewis acid and bisoxazoline ligand **12** (Figure 4). $InCl_3$, $Mg(ClO_4)_2$, and $Cu(OTf)_2$ offered only modest yields (Entries 1–3), but we were gratified to find *higher enantioselectivities than previously reported for any radical addition to a C=N bond*.[35] Upon changing to benzene/CH_2Cl_2 (Entry 4) the selectivity increased to 95% *ee* (66% yield). A less polar medium was assumed to facilitate the assembly of a ternary complex of ligand, Lewis acid, and substrate. The yield improved to 94% with larger amounts of 2-iodopropane and Et_3B (Entry 5), but this came at the expense of some selectivity.

Various radical precursors and acceptors may be employed with high enantioselectivity (Table 9). Isopropyl additions to electron-rich and electron-deficient aromatic hydrazones **13b**,**c** were all highly enantioselective, as were additions of various radicals, including chloromethyl, to **13a** (Entries 1–6). To test the potential for development of asymmetric catalysis, we checked for turnover by lowering the catalyst loading (Table 9, Entries 7–10). The yield remained high, while enantioselection decreased. With 46% *ee* and 74% yield at 10 mol-% catalyst loading, a catalytic cycle involving **12** is implied – the first evidence of asymmetric catalysis in radical addition to C=N bonds.

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. For this general transformation, reduction has been typically employed, using hydrogenolysis[36] [H_2 with Pd-C,

Table 9. Scope of radical addition to **13a**–**13c** promoted by $Cu(t\text{Bu-Box})(H_2O)_2(OTf)_2$ and effects of Cu^{II} catalyst loading.[a]



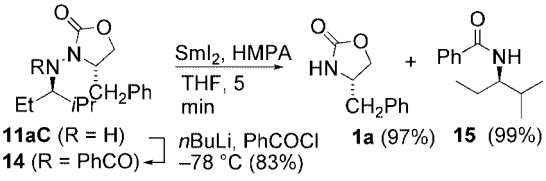
Entry	Halide	Hydrazone (R^1)	Catalyst load	% Yield[b](% *ee*[c])
1	*i*PrI	**13b** (*p*-$MeOC_6H_4$)	1 equiv.	46 (90)
2	*i*PrI	**13c** (*p*-ClC_6H_4)	1 equiv.	53 (81)
3	EtI[d]	**13a** (Ph)	1 equiv.	88 (83)
4	*c*-C_5H_9I[d]	**13a** (Ph)	1 equiv.	86 (84)
5	*c*-$C_6H_{11}I$[d]	**13a** (Ph)	1 equiv.	84 (89)
6	$ClCH_2I$[d]	**13a** (Ph)	1 equiv.	44[e] (95)
7	*i*PrI	**13a** (Ph)	1 equiv.	66 (95)
8	*i*PrI	**13a** (Ph)	0.5 equiv.	71 (81)
9	*i*PrI	**13a** (Ph)	0.2 equiv.	83 (58)
10	*i*PrI	**13a** (Ph)	0.1 equiv.	74 (46)

[a] Reaction conditions: see Table 8, Entry 7. [b] Isolated yield,%. [c] Enantiomeric excess,% (hexane/2-propanol, Chiralcel OD or AD). [d] 10 equiv. of alkyl halide was used. [e] 56% recovery of unreacted hydrazone.

$Pd(OH)_2$, PtO_2, Pt, or Raney nickel catalysts], dissolving metal reduction,[37] or other methods.[38] Recently, cleavage of the N–N bond in hydrazines has been achieved by oxidation with magnesium monoperoxyphthalate.[39] Reductive cleavage with samarium(II) iodide[40] (SmI_2), with various additives, has gained prominence in many recent studies.[41]

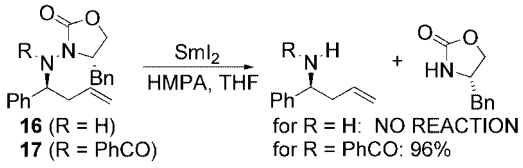
4.1. Exploratory Studies

Our experimental studies of N–N bond cleavage became focused on the use of samarium(II) iodide because of its compatibility with alkene functionality and the operational simplicity of the experimental procedures (e.g., rapid reaction at ambient temperature and pressure). Unfortunately, there was no reaction upon direct treatment of hydrazide radical adducts (e.g., **11aC**, Scheme 4) with SmI_2. Considering the strong precedent for cleavage of benzoic hydrazides with SmI_2,[41] we resorted to benzoylation of the basic nitrogen of hydrazide **11aC**. This was readily achieved by sequential treatment with *n*BuLi and benzoyl chloride, affording benzamide derivative **14** in 83% yield (Scheme 4). Exposure of **14** to SmI_2 cleanly afforded **15** (99% yield) and **1a** (97% yield) within 5 minutes.[13]



Scheme 4.

Similarly, the hydrazine **16** gave no reaction with SmI_2 and HMPA in THF [Equation (1)], but the corresponding *N*-benzoyl derivative **17** underwent rapid, quantitative N–N bond cleavage under these conditions.[42] Unfortunately, hydrolysis of the resulting benzamide required harsh conditions which ultimately caused decomposition. From this it was concluded that general applications in multifunctional synthetic schemes would require a more readily removable acyl activating group.

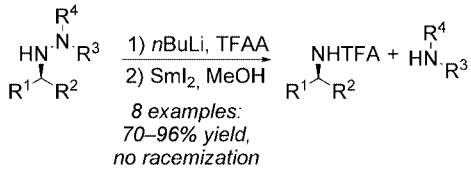


(1)

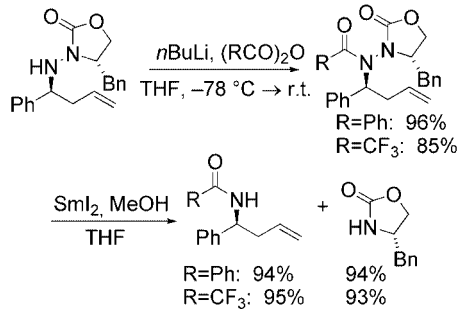
4.2. Trifluoroacetyl Activation for N–N Cleavage

Although reductive removal of the auxiliary was achieved easily from the benzamide **17** as shown in Equation (1), this operation left behind an unwieldy benzoyl group. Inspired by Flowers' suggestion that chelation by neighboring fluoride substituents can enhance the reducing power of SmI_2,[43] we came to believe that a trifluoroacetyl (TFA) group might facilitate the N–N bond cleavage process. Importantly, TFA is a popular amine-protecting group, easily removed by hydrolysis.

Indeed, we found that *N*-trifluoroacetylation activates the SmI_2-mediated N–N bond cleavage process, enabling smooth conversion of a variety of trisubstituted hydrazines to TFA-protected amines [Equation (2)].[44] Optimal conditions of the TFA-activated N–N cleavage entailed sequential lithiation (*n*BuLi), reaction with trifluoroacetic anhydride (TFAA) and treatment with samarium(II) iodide at room temperature in the presence of MeOH as additive. Good yields of trifluoroacetamides are routinely obtained without racemization by this procedure, which also enables quantitative recovery of the oxazolidinone **1a**. A specific example is illustrated in Scheme 5.



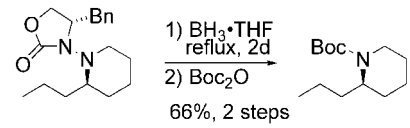
(2)



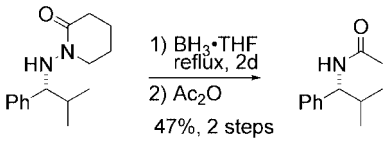
Scheme 5.

4.3. N–N Cleavage with Borane

Borane reacts with hydrazines to accomplish reductive N–N bond cleavage.[45] This method has been reliable in application to our *N*-acylhydrazine (hydrazide) radical adducts, but it requires a large excess of borane and long reaction times in refluxing THF. For those targets which do not present functional group incompatibility with these conditions, borane reduction is effective. For example, the cleavage of a piperidine hydrazide was accomplished in this manner, with isolation of the product as the *N*-Boc derivative [Equation (3)].[46] Similarly, a valerolactam-containing hydrazide was cleaved with trapping of the free amine as the acetyl derivative [Equation (4)].[35] The oxazolidinone is not recoverable under these conditions. Optimization of the isolation procedure is recommended for this method; the reactions are quite clean but exhibit poor mass balance.



(3)



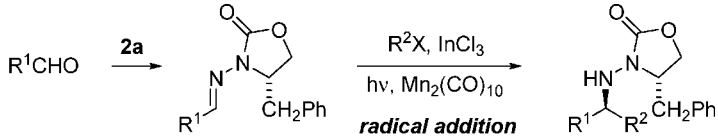
(4)

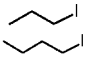
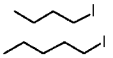
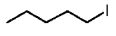
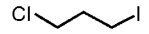
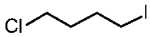
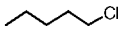
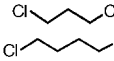
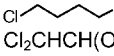
5. Manganese-Mediated Radical Addition

Photolytic radical generation with hexamethylditin has shown promise for addition of primary radicals to *N*-acylhydrazones (Section 3.3), but yield optimization was complicated by a side reaction with the acetone used as a photosensitizer. We became interested in manganese carbonyl [$Mn_2(CO)_{10}$],[47] which requires no sensitizer (λ_{max} 340 nm, $\sigma_{Mn-Mn} \rightarrow \sigma^*_{Mn-Mn}$) for homolytic metal–metal bond cleavage. This process had apparently been scarcely recognized by synthetic organic chemists prior to a series of papers by Parsons.[48]

In fact, for ethyl iodide addition to **3a** (Table 10), irradiation (300 nm) with [$Mn_2(CO)_{10}$] using $InCl_3$ as a Lewis acid furnished the ethyl adduct in 85% yield,[46] a dramatic improvement over use of triethylborane or hexamethylditin. Control experiments revealed a requirement for both irradiation and [$Mn_2(CO)_{10}$]. Without $InCl_3$, the reaction was slow (21% yield after 2 d). Several other halides, including methyl iodide and difunctional halides, were also effective (Table 10), with the exception of 2-chloroethyl addition, which gave low yield presumably due to radical fragmentation. Ethyl radical addition to nine additional hydrazones **18**–**26** occurred in good yields. These adducts are epimeric to those derived from hydrazone **3a** with respect to the new stereogenic center, as a result of simply changing the roles of the aldehyde and iodide precursors. Synthetically useful yields and reliably high diastereomer ratios were obtained

Table 10. Results of metal-mediated radical addition to propionaldehyde hydrazone **3a**. Reaction conditions: (1) Aldehyde or acetal (5–10 equiv.), **2a**, *p*-toluenesulfonic acid, CH_2Cl_2, room temp. (2) Hydrazone in deoxygenated CH_2Cl_2 (0.1 M), $InCl_3$ (2.2 equiv.), $Mn_2(CO)_{10}$ (1–2 equiv.), R^2X (10 equiv.), *hν* (300 nm, pyrex), 1–2 d, ca. 35 °C.



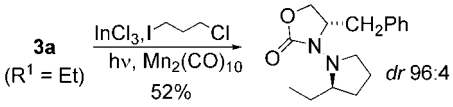
Aldehyde (or acetal)	Hydrazone[a]	Halide R^2X	Yield, config[b]	*dr*
CH_3CH_2CHO	**3a**, 81%	CH_3CH_2I	85%	–
		CH_3I	48%[c,d], *S*	95:5[e]
			66%, *R*	94:6[e]
			78%, *R*	95:5[e]
			79%, *R*	96:4[e]
			54%[c], *R*	95:5[f]
			75%, *R*	95:5[f]
		$ClCH_2I$	63%, *R*	93:7[e]
			52%, *R*	96:4[f]
			55%, *R*	96:4[e]
		Cl_2CHBr	38%[c,d], *R*	98:2[f]
CH_3CHO	**18**, 66%	CH_3CH_2I	66%, *R*	95:5[e]
	**19**, 87%		63%, *S*	95:5[e]
	**20**, 89%		72%, *S*	97:3[e]
	**21**, 88%		77%, *S*	97:3[e]
	**22**, 85%		65%, *S*	95:5[f]
$ClCH_2CH(OMe)_2$	**23**, 85%		57%, *S*	93:7[e]
	**24**, 95%		60%, *S*	93:7[f]
	**25**, 89%		62%, *S*	97:3[e]
$Cl_2CHCH(OEt)_2$	**26**, 54%		34%[c], *S*	89:11[f]

[a] Isolated yield. [b] Isolated yields of purified diastereomer mixtures. *R* or *S* denotes the configuration of the new stereogenic center. Addition of methyl iodide gives opposite configurations due to the lower priority of the methyl ligand. [c] 20 equiv. of R^2X was used. [d] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used in removal of Mn byproducts. [e] Ratio by HPLC (Chiralcel OD, 2-PrOH/hexane). [f] Ratio by ^1H NMR spectroscopy.

from these reactions, with some adducts bearing additional functionality for further elaboration.

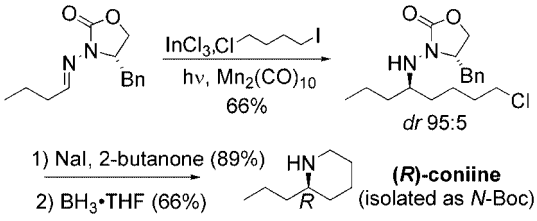
5.2. Hybrid Radical–Ionic Annulation

Interestingly, the 3-chloro-1-iodopropane addition in Table 10 led exclusively to a pyrrolidine [Equation (5)]; there was none of the acyclic adduct found.[46] Presumably radical addition was followed by in situ S_N2-type cyclization. The same cyclization (giving the epimeric pyrrolidine) occurs upon ethyl addition to the 3-chlorobutyraldehyde hydrazone **24**. These reactions are hybrid radical–ionic annulations of the C=N bond, a new class of radical–polar crossover reactions.[49]



(5)

The hybrid radical–ionic annulation was envisioned to be useful for piperidine alkaloid synthesis. The alkaloid coniine[50] (Scheme 6) offers a simple test case. Starting with the butyraldehyde hydrazone, Mn-mediated photolysis with 4-chloro-iodobutane afforded the acyclic adduct in 66% yield with a diastereomer ratio of 95:5.[46] In this case, Finkelstein conditions were needed for cyclization, and reductive removal of the auxiliary afforded coniine in 34% overall yield for 4 steps. An interesting aspect of this reaction sequence is the direct comparison of the efficiency of radical- and carbanion-based syntheses. Using the same retrosynthetic disconnection, a carbanion approach requires 9–10 steps.[50b,50f] This illustrates the potential for improved efficiency through novel radical addition strategies.



Scheme 6.

5.2. Application to γ-Amino Acid Synthesis

Synthesis of γ-amino acids is of interest because they are building blocks for bioorganic and medicinal chemistry.[51,52] Recently, we have exploited the Mn-mediated photolysis for a novel synthesis of γ-amino acids **27** and **28** (Figure 5).[53] The C–C bond disconnections shown would require oxygen-containing iodides or hydrazones, and therefore constitute an important test of the synthetic versatility of the Mn-mediated coupling reactions.

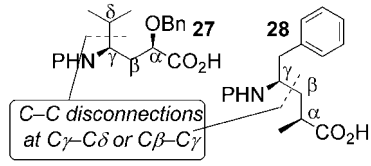
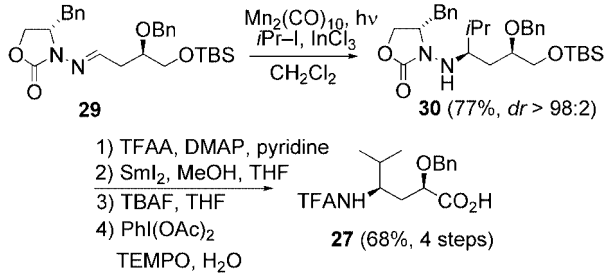


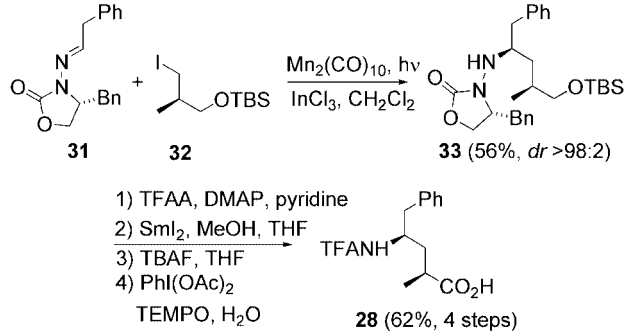
Figure 5. Alternative C–C bond disconnections of the tubulysin γ-amino acids at the γ–δ and β–γ bonds.

For synthesis of α-alkoxy-γ-amino acid **27** (Scheme 7), nonbasic conditions would be a necessity, considering the potential for β-elimination of the alkoxy group from the hydrazone precursor **29**. Here, the addition of isopropyl iodide under the Mn-mediated photolysis conditions afforded **30** as a single diastereomer in 77% yield, without any evidence of β-elimination. Cleavage of the N–N bond and oxidation to the carboxylic acid gave **27** in good overall yield.[53]



Scheme 7.

For the γ-amino acid **28** (Scheme 8), the preparation began with phenylacetaldehyde *N*-acylhydrazone **31**. Mn-mediated addition of difunctional iodide **32** (5 equiv.) proceeded in 56% yield, affording **33** as a single diastereomer.[53] The yield was 45% using 2 equiv. of iodide, a remarkable result considering that typical intermolecular radical additions require 10–20 equiv. (or more) of the radical precursor.

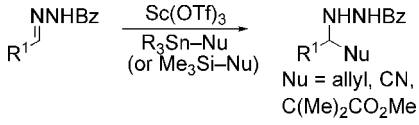


Scheme 8.

6. Allyl Addition

The allyl group enables a wide range of synthetic manipulations, so extensive efforts have been directed toward stereoselective allyl addition to chiral imines, iminium ions, and

related C=N electrophiles.[54] With *N*-acylhydrazones, some early examples of allyl additions were achieved by Kobayashi et al. using allylstannanes[55] [Equation (6)] and allylsilanes[56] [Equation (7)]. More recently, Leighton has explored chiral strain-activated allylsilane reagents[57] [Equation (8)], and Kobayashi has reported nucleophilic catalysis of allyltrichlorosilane addition [Equation (7)] using chiral sulfoxides;[58] both afford highly enantioselective addition to *N*-acylhydrazones.



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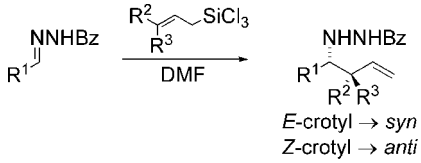

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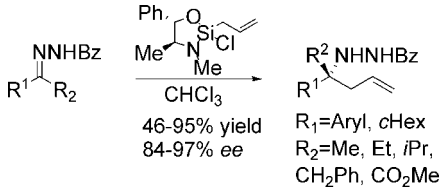


(8)

In the additions of allylchlorosilanes to *N*-acylhydrazones, coordination of the *N*-acyl oxygen atom to the silicon may play an important role, as illustrated in two similar transition states proposed by Kobayashi and Leighton (Figure 6).

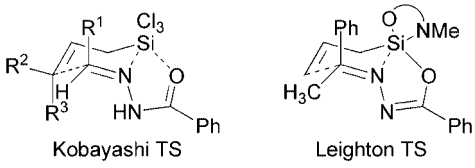


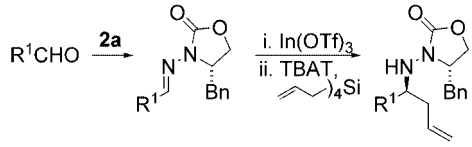
Figure 6. Proposed allyl addition transition states emphasizing the role of the *N*-acylhydrazone.

6.1. Allylsilane Addition to Chiral *N*-Acylhydrazones

In 2001 we reported highly stereoselective allylsilane additions to chiral *N*-acylhydrazones using a novel dual activation concept.[59,60] In this approach, both allylsilane and allyl acceptor were activated by fluoride and indium(III) trifluoromethanesulfonate [$In(OTf)_3$], repectively, to promote C–C bond construction under relatively mild conditions. Combining a fluoride ion source in the same reaction flask with Lewis acids necessitated careful consideration of experimental protocols to avoid potential incompatibilities.

Tetrabutylammonium triphenyldifluorosilicate (TBAT)[61] effectively promoted tetraallylsilane (or allyltrimethylsilane) addition to the complex formed by mixing benzaldehyde hydrazone **7** with $In(OTf)_3$, providing **16** with good stereoselectivity (Table 11). With most other Lewis acids, the hydrazone was not consumed at all, an observation which may be attributable to mutual incompatibility of the Lewis acid and fluoride which would interfere with dual activation. A preliminary survey of the scope of the reaction revealed that *N*-acylhydrazones **34**–**38**, derived from aromatic or α,β-unsaturated aldehydes, gave homoallylic amines in good yield with excellent stereoselectivity. Propionaldehyde hydrazone **3a** also participated in the reaction, but stereoselectivity was modest.

Table 11. Preparation of various aldehyde hydrazones and TBAT/$In(OTf)_3$-promoted addition of tetraallylsilane.

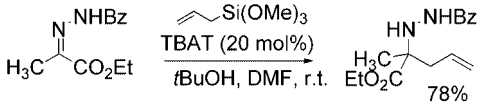


R^1	Hydrazone[a]	Allyl adduct[b]	*dr*[c]
phenyl	**7**	78%	>99:1
p-tolyl	**34**, 94%	94%	98:2
m-nitrophenyl	**35**, 91%	71%	>99:1
2-naphthyl	**36**, 92%	82%	98:2
2-furyl	**37**, 92%	58%	96:4
–CH=CHPh	(*E*)-**38**, 97%	60%	95:5
$–CH_2CH_3$	**3a**	51%	82:18

[a] Isolated yield. [b] Isolated yields of purified diastereomer mixtures. [c] Diastereomer ratio by HPLC.

Control experiments with **7** gave some mechanistic insight to better understand the roles of the reactants. Both $In(OTf)_3$ and TBAT are required for good reactivity, while $In(OTf)_3$ also is important for stereocontrol. Transmetallation to an allylindium species is slow, and if allowed to occur leads to a species which does not duplicate the results of Table 11.[62] Furthermore, variation of reactivity and selectivity upon changing the silicon ligands suggests the presence of silicon at the transition state. Together these results show that the transmetallation is not mechanistically relevant, and addition of a hypervalent allylsilicate to the Lewis acid complexed hydrazone appears to best explain the observations. Stereochemical results are consistent with the chelate structure in Figure 3, wherein restriction of rotamer populations facilitates steric blocking of the re face.

We are also building toward an asymmetric catalytic version of this reaction. Addition of allyltrimethoxysilane to *N*-benzoylhydrazones is catalyzed by a combination of fluoride ion and Cu^{I} in the presence of phosphanes, but the use of chiral ligands gave poor selectivity in this reaction. Interestingly, substoichiometric amounts of fluoride lead to an efficient catalytic reaction, even in the absence of Cu, and this reaction permits the formation of highly functionalized quaternary nitrogen-bearing stereocenters [tertiary carbinamines, Equation (9)].[63]

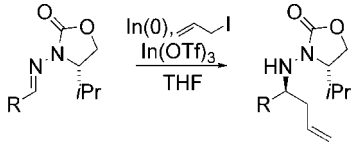


(9)

6.2. Allylindium Addition to Chiral *N*-Acylhydrazones

Allyl additions to chiral *N*-acylhydrazones are also effective using a reagent generated in situ from allyl iodide and indium metal (Table 12).[64] Cook and co-workers examined hydrazones derived from chiral *N*-(amino)oxazolidinones **1a** and **1c**–**1e** (Scheme 1) under these conditions, and except for the phenylglycinol-derived auxiliary (from **1c**) virtually complete diastereoselectivity was observed in the additions. A range of hydrazones derived from various aldehydes, including aliphatic ones, were successfully converted into the corresponding allyl adducts in the presence of indium triflate. Diastereoselectivities were outstanding in these reactions. Stereoselectivity decreased in the absence of $In(OTf)_3$, additional support for a stereocontrol model based on the chelated structure in Figure 3.

Table 12. Cook's allylindium additions.



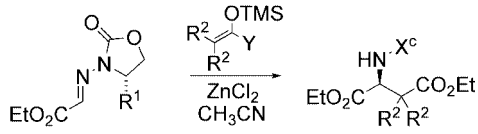
R	Yield[b]	*dr*[c]
phenyl[a]	99%	>99:1
2-furyl	95%	>99:1
2-naphthyl[a]	95%	>99:1
o-fluorophenyl	90%	97:3
o-bromophenyl	96%	92:8
p-nitrophenyl	95%	>99:1
p-methoxyphenyl	95%	>99:1
–CH=CHPh	90%	97:3
cyclohexyl	92%	>95:5
cyclohexyl[a]	99%	66:33
isopropyl	90%	>95:5
ethyl	90%	>95:5

[a] Reaction in the absence of $In(OTf)_3$. [b] Isolated yield. [c] Diastereomer ratio by ^1H NMR spectroscopy.

7. Mannich-Type Reactions of *N*-Acylhydrazones

The *N*-acylhydrazone chiral auxiliary system has proved to be useful in Mannich-type reactions to afford β-amino acid derivatives. Skrydstrup has reported the highly stereoselective addition of silyl ketene acetals to chiral *N*-acylhydrazones derived from ethyl glyoxylate and **2a**, **2c**, or **2d** (Table 13).[65] Yields in the 60% range were achieved with different ketene acetals. Among several Lewis acids, zinc chloride was the most effective, providing diastereomer ratios generally >95:5. As observed by Cook et al., the phenylglycinol-derived compound **2c** gave lower selectivity.[64]

Table 13. Skrydstrup's Mannich reactions.



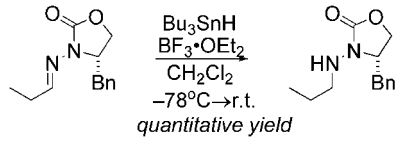
R^1	R^2, Y	Yield[a]	*dr*[b]
benzyl	Me, OEt	64%	97:3
isopropyl	Me, OEt	64%	98:2
phenyl	Me, OEt	35%	80:20
benzyl	H, OEt	61%	98:2
benzyl	H, O*t*Bu	56%	97:3
benzyl	H, SPh	62%	96:4
benzyl	H, SEt	30%	95:5

[a] Isolated yields of purified diastereomer mixtures. [b] Diastereomer ratio by ^1H NMR spectroscopy.

8. Hydride Addition to Ketone *N*-Acylhydrazones

Reductive amination of ketones is a useful and practical method for access to some valuable chiral amines.[66] High selectivity may be obtained for reduction of imino compounds derived from aryl alkyl ketones, where the two alkyl branches of the carbonyl compound are easily distinguished.[67] When both substituents of a ketimine have similar steric properties, low *E*/*Z* isomer ratios with respect to the C=N bond geometry and/or poor discrimination of enantiotopic faces of the imine can present difficult problems. Chiral auxiliaries offer a practical advantage under these circumstances, because in principle *E*/*Z* mixtures of the starting imine could be separated prior to use, or mixtures of diastereomeric products could be resolved before removal of the auxiliary.

We found that extremely rapid and quantitative reduction of chiral *N*-acylhydrazones can be achieved using tributyltin hydride in the presence of $BF_3{\cdot}OEt_2$.[13a] Thus, *N*-acylhydrazone **3a** was reduced by Bu_3SnH to afford the corresponding amine in quantitative yield within 5 min [Equation (10)].

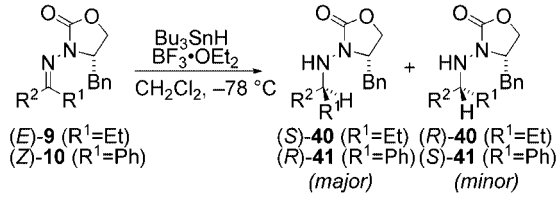


(10)

Reductions of ketone *N*-acylhydrazones **9** and **10** under the same conditions afforded hydrazides **40** and **41** as diastereomer mixtures in good-to-excellent yield (Table 14).[27] In each case, the major isomer is that arising from addition of hydride from the α-face (as drawn in Table 14). The hydride additions appear to be highly stereospecific, as the diastereomeric ratios of products were dependent on the *E*/*Z* isomer ratios of the hydrazones. Both the chiral auxiliary and the configuration of the C=N bond participate to define the configuration of the newly formed stereocenter. For example, reduction of **9c** as 85:15 *E*/*Z* mixture afforded hy-

drazine **40c** with a diastereomer ratio (*S*/*R*) 85:15. This suggests a stereospecific process in which both *E* and *Z* isomers are reduced with good stereocontrol. The stereospecificity is not complete, however: The reductions of hydrazones **9d** and **10d**, employed as single isomers, gave 89:11 and 88:12 diastereomeric ratios, respectively.[27]

Table 14. Stereoselectivity and yield in reduction of *N*-acylhydrazones.



N-Acylhydrazone (*E*/*Z* ratio)	Hydrazide (yield)	*dr*[a]
(*E*)-**9a** (77:23)	(*S*)-**40a** (89%)	80:20
(*E*)-**9b** (79:21)	(*S*)-**40b** (82%)	76:24
(*E*)-**9c** (85:15)	(*S*)-**40c** (76%)	85:15
(*E*)-**9d** (>98:2)	(*S*)-**40d** (94%)	89:11
(*Z*)-**10a** (19:81)	(*R*)-**41a** (92%)	19:81
(*Z*)-**10b** (26:74)	(*R*)-**41b** (78%)	26:74
(*Z*)-**10c** (13:87)	(*R*)-**41c** (94%)	18:82
(*Z*)-**10d** (<2:98)	(*R*)-**41d** (94%)	12:88

[a] Ratio of diastereomers *S*:*R* (configurations of new stereogenic center).

The diastereoface selectivity observed in these hydride additions to ketone *N*-acylhydrazones is opposite that of radical or allylsilane additions using Zn^{II} or In^{III} salts as Lewis acids. The stereochemical outcome is consistent with a non-chelated model involving a tetracoordinate BF_3 complex with boron bound only to the imino nitrogen (Figure 7). This would lack rotational restriction of the N–N bond, and a combination of steric and dipole repulsions would be expected to destabilize conformer **A**, in which the benzyl group blocks the α-face. Hydride addition to the more exposed α-face of preferred conformer **B** is consistent with the stereochemical outcome of these reactions. Further support for this model is offered by the lower stereoselectivity in comparison to the radical additions; this is consistent with conformer **B** because the stereocontrol element is farther away from the C=N carbon in the non-chelated N–N bond rotamer.

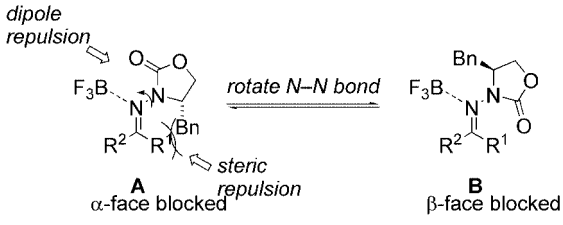


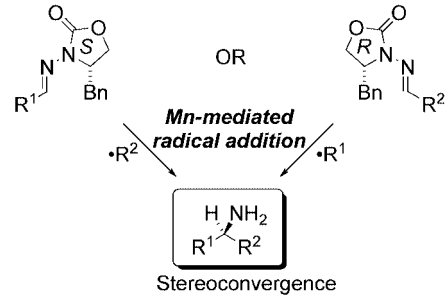
Figure 7. Non-chelated stereocontrol model for reduction in the presence of boron trifluoride.

9. Practical Considerations for Synthetic Application

The *N*-acylhydrazones derived from *N*-(amino)oxazolidinones **2a**–**2e** according to Scheme 1 represent a novel and potentially versatile chiral hydrazone moiety. The *N*-acylhydrazones are efficiently and reliably obtained in good-to-excellent yields from the oxazolidinones. There are numerous variations on this design which remain to be explored, since numerous chiral 2-oxazolidinones bearing varied substitution patterns are commercially available.[68] Furthermore, a wide range of related oxazolidinones may be easily accessed from well-established methods.[69]

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 6 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).

The Mn-mediated radical additions offer an inherently flexible carbon–carbon bond construction approach to amine synthesis. Because of the broad functional group compatibility in both the radical precursor and acceptor, the roles of these precursors can be switched to result in construction of either of two C–C bonds at the chiral amine (Scheme 9). The epimeric configuration can be selected by either (A) employing the enantiomeric auxiliary, or (B) interchanging the roles of R^1 and R^2 in the alkyl halide and aldehyde precursors of Scheme 1.[70] Combining these two tactics, the optimal roles of R^1 and R^2 with respect to yield and selectivity can be chosen. Such strategic flexibility contributes to the synthetic potential of these radical addition reactions.



Scheme 9.

Numerous applications of these chiral *N*-acylhydrazones and the hydrazide products of their addition reactions[71] may be envisioned, and indeed, some are coming to fruition. Following our preliminary communication in 2000, several new applications of these chiral *N*-acylhydrazones have been reported by other groups,[15d,64,65] suggesting the general utility of this novel chiral auxiliary system for asymmetric amine synthesis. As only a small surface of the potential has been scratched so far, broader and deeper explorations of these chiral *N*-acylhydrazones promise to offer many more methods of utility to practitioners of organic synthesis.

Acknowledgments

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