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Control of Asymmetry in the Radical Addition Approach to Chiral Amine Synthesis

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Abstract

The state-of-the-science in asymmetric free radical additions to imino compounds is presented, beginning with an overview of methods involving stereocontrol by various chiral auxiliary approaches. Chiral *N*-acylhydrazones are discussed with respect to their use as radical acceptors for Mn-mediated intermolecular additions, from design to scope surveys to applications to biologically active targets. A variety of aldehydes and ketones serve as viable precursors for the chiral hydrazones, and a variety of alkyl iodides may be employed as radical precursors, as discussed in a critical review of the functional group compatibility of the reaction. Applications to amino acid and alkaloid synthesis are presented to illustrate the synthetic potential of these versatile stereocontrolled carbon–carbon bond construction reactions. Asymmetric catalysis is discussed, from seminal work on the stereocontrol of radical addition to imino compounds by non-covalent interactions with stoichiometric amounts of catalysts, to more recent examples demonstrating catalyst turnover.

1. Background and Introduction

Chiral α-branched amine functionalities are present in a wide range of bioactive synthetic targets, both natural and unnatural. Accordingly, a variety of methods for asymmetric amine synthesis have been developed over recent years, many of which involve carbon–carbon bond constructions by addition to the C=N bond of carbonyl imino derivatives, represented in the retrosynthetic direction in Figure 1 [1].

As is typical in most of synthetic chemistry, methods in this area accrue higher impact if they offer configurational control under mild conditions compatible with a range of spectator functional groups. Unfortunately, many methods involving nucleophilic additions of carbanion-type reagents to C=N bonds have limited compatibility with electrophilic or acidic functionality, or may result in competing deprotonation at the imine α-carbon due to the basicity of the organometallic reagent.[2] These limitations have spurred the development of free radical additions [3] to imino compounds (Figure 2) as a C–C bond construction approach to chiral amines under mild conditions, offering a valuable complement to organometallic additions and expanding the scope of this α-C–C retrosynthetic disconnection.[4]

Seeking to probe the improved versatility which might be associated with the radical addition approach, we initiated a program to develop a variety of radical additions to imino

compounds.[5] In the process, we introduced several new modes of stereocontrol using hydrazones as the C=N radical acceptor functionality. Imino compounds have been extensively used for cyclizations [6], and initially we built upon this foundation by introducing a temporary tethering approach [7,8] which has been effective in establishing relative configuration in a predictable diastereoselective fashion via reactions of α-hydroxyaldehyde hydrazones [9]. In this review, we will focus on the intermolecular variant of the reaction, for which we have introduced methodology to build chiral amines from achiral precursors using chiral auxiliaries or chiral catalysts for stereocontrol;[10] the design and experimental evaluation of these strategies will be described along with synthetic applications.

2. Intermolecular Radical Addition to Chiral *N*-Acylhydrazones

2.1. Use of Chiral Auxiliaries in Radical Additions to Imino Compounds

In many areas of synthetic methods development, the reaction methodology has progressed to a point where it is quite well-understood, and the exciting new advances are mostly focused on extension to asymmetric catalysis. In contrast, in the area of radical additions to C=N bonds, only rare examples of intermolecular coupling reactions were available prior to the initial work on asymmetric methods [11] Thus, the development of asymmetric induction for radical addition to imino compounds has been slow, pending important advances that are still needed in the fundamental reaction chemistry. As this chemistry emerges, the challenges of adapting the new chemistry to all types of stereocontrol modes, including auxiliary, reagent and catalyst, continue to attract active investigation. An overview of some of the main approaches to chiral auxiliary-mediated stereocontrol is provided below.

Naito and coworkers reported the first general method for achieving reductive addition of carbon-centered radicals to imino compounds; by using Et_3B/oxygen initiation in the presence of BF_3•OEt_2, neutral radicals were added successfully to prochiral aldoximes.[12] Although unhindered formaldoximes and activated glyoxylic oxime ethers did not require Lewis acid activation, the beneficial effect of BF_3•OEt_2 allowed general application to various oxime ethers. This enabled the use of **1** bearing a chiral auxiliary for asymmetric induction (Table 1).[13] The proposed stereocontrol model invokes steric blocking by one of the sultam oxygens (Figure 3). Although difunctional alkyl iodides afforded lower yields, subsequent work has successfully employed more complex radicals.[14]

Bertrand and coworkers reported the radical addition of various alkyl iodides to cyclic and acyclic chiral glyoxylate imines using either tin-mediated conditions initiated by AIBN, or triethylborane conditions initiated by oxygen.[15] Building on these initial studies, Bertrand discovered the combination of diethylzinc and air was useful to promote radical addition to chiral imines (Scheme 1).[16] Stereoselectivity was modest in additions to 1-phenylethylimines. However, two-point binding imines capable of chelating Zn(II), such as norephedrine-derived imine **3**, led to improved diastereomer ratios. [17]

Chiral *N*-sulfinylimines, pioneered by Davis and Ellman for stereocontrolled additions of carbanion reagents,[18] have also been employed successfully in radical additions. Tomioka

and coworkers have used the dimethylzinc/air method to generate radicals by H-atom abstraction from ethers and acetals which then add to the C=N bond of the *N*-sulfinylimines **6**.[19] Although tetrahydrofuran and *tert*-butyl methyl ether gave modest stereocontrol, formaldehyde acetals were more promising, with the best results observed for addition of dioxolane **7** (Scheme 2) to substituted benzaldehyde imines (70–83% ee, measured after oxidation to sulfonamide). Subsequently, increasing the steric demand of the arenesulfinyl stereocontrol element led to improved enantioselectivities.[20] Recently the reaction has been extended to include triethylborane-mediated addition of an iodomethyl ester to *N*-alkoxycarbonylimines.[21]

2.2. Design of Chiral *N*-Acylhydrazones

In the late 1990s we began our work in developing hydrazones as promising radical acceptors for asymmetric tranformations. At that time, oxime ethers were the most commonly explored C=N radical acceptors.[22,23,24] We considered that linking an amino or amido substituent to the C=N nitrogen atom could afford the same reactivity enhancement seen in oxime ethers, and would also provide opportunities for superior rotamer control needed for stereoselectivity. Both activation and stereocontrol would be achieved through one removable *N*-substituent on the imine, and the substituents on the carbon of the C=N bond would then be freed from those roles, offering potential for broader scope.

Our new type of chiral hydrazone, tailored for use in free radical addition reactions, incorporates Lewis acid activation and restriction of rotamer populations as key design elements. We hypothesized that the restricted rotation achieved through two-point binding would fix a substituent relative to the plane of the C=N bond to differentiate the enantiotopic approach trajectories (Figure 3). The Lewis acid would also lower the LUMO energy of the C=N π bond, increasing its reactivity toward nucleophilic alkyl radicals.[25] This would ensure selective reactivity via the chelated structure, suppressing the non-selective background reaction. After radical addition, H-atom abstraction would occur to afford an *N*-acylhydrazine product; reductive cleavage of the N–N bond [26] would provide an enantiomerically pure amine and release the chiral auxiliary for reuse. For the first test of our design, *N*-acylhydrazones derived from *N*-aminooxazolidinones [27] were chosen to satisfy all these design criteria (Figure 3).

2.3. Preparation and Initial Reactivity Studies of Chiral *N*-Acylhydrazones

Although *N*-amino derivatives of oxazolidinones such as **9** (Scheme 3) were sporadically reported in the literature,[28] the installation of the *N*-amino group was not well-developed. Therefore we began with a study of electrophilic amination of commercial oxazolidinones. A variety of electrophilic amination reagents were employed for this purpose, and the preferred reagents were *O*-(*p*-nitrobenzoyl)hydroxylamine ($NbzONH_2$), O-(diphenylphosphinyl)hydroxylamine ($Ph_2P(=O)ONH_2$) and NH_2Cl.[29,30] The optimized procedure for *N*-amination with $NbzONH_2$ entailed deprotonation with NaH (or KH) in hot dioxane, followed by introduction of $NbzONH_2$ as a solid at ambient temperature.[31] With NH_2Cl the same procedure may be followed, but the stoichiometry of base and chloramine should be carefully controlled to nearly one equivalent in order to obtain reproducible yields in the amination. A survey of representative condensations of *N*-aminooxazolidinone **9** with

aldehydes and ketones (Scheme 3) shows that the sequence is robust and general, affording a wide range of chiral *N*-acylhydrazones **10**.[32] The reaction is readily scaled to multigram quantities, and the carbonyl component of these *N*-acylhydrazones may be exchanged with other carbonyl compounds.[31]

Ketone-derived chiral *N*-acylhydrazones may also be prepared by direct condensation with *N*-aminooxazolidinones (Scheme 3).[30,33] Mixtures of *E/Z* isomers were usually obtained, although ketone *N*-acylhydrazones with highly branched tertiary butyl (*t*-Bu) substituents, were formed as single isomers. A pyruvate-derived hydrazone was formed with high selectivity, and the major isomer was readily separated from its minor (*Z*)-isomer by flash chromatography.[30] Others have recently used these amination and condensation procedures to prepare very similar chiral *N*-acylhydrazones from ketones with excellent results.[34]

2.3.1. Additions of Secondary and Tertiary Radicals—The first test of the chiral *N*-acylhydrazones was in tin-mediated radical addition of various secondary and tertiary iodides.[32] Using the tin hydride method with triethylborane initiation [35] (Bu_3SnH, Et_3B/O_2), with $ZnCl_2$ as a Lewis acid additive, addition of isopropyl iodide to N-acylhydrazone **10a** afforded adduct **11a** with a diastereomer ratio of 99:1 (Table 2). In contrast, **11a** was produced with poor selectivity (*dr* 2:1) in the absence of Lewis acid, which validated the two-point binding stereocontrol model (Figure 3). Cyclopentyl, cyclohexyl, and *tert*-butyl iodides successfully added both to propionaldehyde *N*-acylhydrazone **10a** and to benzaldehyde *N*-acylhydrazone **10b** (Table 2). Ethyl radical generated from triethylborane can compete for the radical acceptor, and as a result, the ethyl radical adduct was observed (<10% yield) in all cases.

In search of optimal stereocontrol, substituents on the oxazolidinone moiety were varied. Thus, isopropyl radical additions to several propionaldehyde *N*-acylhydrazones were compared for stereoselectivity (Scheme 4). High diastereoselectivities were observed in all adducts **12a**–**12e**, although a rigorous measurement was not obtained on **12c** (R = *i*-Pr). All of the auxiliaries impart stereocontrol suitable for practical synthetic application.[32b]

2.3.2. Triethylborane-Mediated Radical Additions Without Tin—Triethylborane and diethylzinc may serve both as initiator and chain transfer agents in radical additions to C=N bonds.[17,22] This raised the question of whether similar additions to chiral *N*-acylhydrazones may occur in the absence of tin hydride. Accordingly, we attempted tin-free additions of various halides to the propionaldehyde hydrazone **10a** in the presence of triethylborane, using $InCl_3$ as the Lewis acid.[32b] These reactions were indeed successful with various secondary iodides (Table 3, Entries 2–4). Chloroiodomethane also gave successful addition, and the chloromethyl adduct bears functionality suitable for subsequent manipulations.

The use of photolysis also enabled a tin-free method devised by Fernández and Alonso for addition of the 1,3-dioxolan-2-yl radical to these chiral *N*-acylhydrazones.[36] Irradiation in the presence of 1 equiv benzophenone led to H-atom abstraction from the solvent, 1,3-dioxolane, followed by intermolecular radical addition to chiral *N*-acylhydrazones (Scheme

5). The Lewis acid ($InCl_3$) facilitated excellent diastereoselectivity in addition of this formyl radical equivalent. The preferred diastereomer was that suggested by the Lewis acid chelate model, consistent with the model supported by our own observations (see Figure 3). After N–N bond cleavage and oxidation at the formyl carbon, preparation of α-amino acids was achieved with high stereoselectivity. A one-pot protocol was also introduced for this reaction, preparing the *N*-acylhydrazone in situ for the radical addition; thus, for a series of aldehydes, the corresponding adducts **13a**–**13f** were obtained with yields ranging from 75–99%.

A limitation of the aforementioned methods is that they are unsuitable for the use of primary alkyl iodides. Under Et_3B/O_2 initiation conditions, the desired radical is generated by I-atom transfer from the alkyl iodide to ethyl radicals; this is not favorable in the case of primary iodides. Thus ethyl radical (from Et_3B) competes with the desired addition of a primary radical in these circumstances. Also, generating radicals by H-atom transfer from ethers or acetals has limited applicability because the radical precursor is generally also a solvent. Because of the expanded synthetic potential of primary alkyl iodides as radical precursors, there is great import in finding alternatives to accomplish I-atom transfers of broader utility for radical additions.

2.4. Manganese-Mediated Radical Addition: Discovery and Method Development

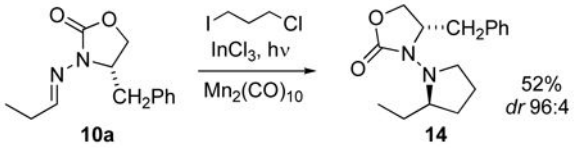
Our attention was drawn to photolytic radical generation with hexamethylditin because it showed promise in Kim's prior work with C=N radical acceptors, which included additions of primary radicals.[37] We noted, however, that manganese carbonyl [38] [$Mn_2(CO)_{10}$] (λ_{max} 340 nm, $\sigma_{Mn–Mn} \rightarrow \sigma^*_{Mn–Mn}$) may be photolyzed without any sensitizer, leading to homolytic metal–metal bond cleavage. This produces two $\bullet Mn(CO)_5$ radicals, which are well-known to abstract halogen atoms from alkyl halides.[39] Despite its longtime familiarity in organometallic chemistry, the first studies of the synthetic scope of this reactivity mode appeared in a series of papers by Parsons.[40,41]

Armed with these precedents, we applied these manganese-mediated photolytic conditions to the addition of ethyl iodide to *N*-acylhydrazone **10a** (Table 4).[42] Irradiation (300 nm) with $Mn_2(CO)_{10}$ using $InCl_3$ as a Lewis acid furnished the ethyl adduct in 85% yield (entry 1), 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 proceeded sluggishly (21% yield, 2 d).

A variety of other halides, including methyl iodide and dihaloalkanes, were also effective (Table 4, entries 2–11). An exception was a low-yielding addition of 2-chloroethyl iodide, which presumably was compromised by fragmentation of the 2-chloroethyl radical. Similar versatility was displayed with respect to the hydrazone component; ethyl radical addition to various *N*-acylhydrazones occurred in good yields (entries 12–20). These adducts are epimeric to those derived from hydrazone **10a** with respect to the new stereogenic center, as a result of simply changing the roles of the aldehyde and iodide precursors. From the strategy standpoint, this combination of stereocontrol flexibility and functional group compatibility is advantageous for total synthesis applications.

2.5. Hybrid Radical–Ionic Annulation

2.5.1. Pyrrolidine Synthesis—Applying radical addition reactions in the presence of electrophilic spectator functionalities was attractive, as such demonstrations of compatibility would illustrate the complementarity of radical conditions and strongly nucleophilic conditions. In this regard, it should be noted that dihalopropanes had been used as radical precursors (Table 4, entries 8–11), preserving halide functionality in most cases. However, in one case, addition of 3-chloro-1-iodopropane (eq. 1), characterization of the adduct indicated there was no chlorine present; this reaction had afforded pyrrolidine **14**.[42] This outcome may be explained by sequential radical addition and S_N2-type cyclization *in situ*. Support for such a process also was found upon addition of ethyl iodide to the 3-chlorobutyraldehyde hydrazone (Table 4, entry 18), which gave the epimeric pyrrolidine (*epi*-**14**). These radical–polar crossover reactions,[43] which also may be termed hybrid radical–ionic annulations, offer a novel way to achieve 1,2-bis-functionalization of the C=N bond.



Equation 1

Control of the steps, interrupting the pyrrolidine annulation after the radical addition step, has been observed upon slight modifications to the conditions using hydrazone **15** (Scheme 6).[44] After a 15-hour reaction time, the initial radical adduct **16** was isolated in 45% yield, and on extending the reaction time to 65 hours, the radical adduct had mostly cyclized to the pyrrolidine **17**. When the reaction was carried out in the absence of Lewis acid, the only observed product was pyrrolidine **17**. Further studies of the scope of these pyrrolidine constructions are ongoing.

2.5.2. Stepwise Annulation in Piperidine Synthesis—The simple piperidine alkaloid coniine[45] (Scheme 7) offered a preliminary test case for hybrid radical–ionic annulation in alkaloid synthesis. We envisioned a radical addition followed by cyclization, and two alternative bond constructions can be considered. The exocyclic propyl group may be introduced as part of the radical acceptor (path A), or may originate in the radical precursor (path B).

In contrast to the pyrrolidine constructions, the addition of ethyl radical to a difunctional 5-chloropentanal hydrazone (Table 4, entry 19) did not result in cyclization *in situ*. Therefore, the chloride substituent was replaced with a tosylate to facilitate the polar cyclization. The Mn-mediated addition of 1-iodopropane to 5-tosyloxypentanal *N*-acylhydrazone **18** (Scheme 8) indeed provided the expected annulation product **19** in 59% yield. Unfortunately, unusually poor stereocontrol was observed (dr 3:1).[42b] The lack of high selectivity in the addition to hydrazone **18** is very unusual among all the examples of Mn-mediated radical

addition observed to date. This, together with anomalously poor mass balance (no reactant hydrazone was recovered), provides evidence for a polar cyclization to form iminium ion **20** (Scheme 8) prior to radical addition; such a cyclization would be detrimental to stereoselectivity due to the loss of two-point binding of the Lewis acid.

Because of the problems with the premature ionic cyclization noted above, a stepwise approach was adopted for piperidine construction. From butyraldehyde hydrazone **21** (Scheme 9) and 4-chloro-iodobutane (**22**), Mn-mediated photolysis afforded the acyclic adduct **23** in 66% yield (dr 95:5); the cyclization did not occur *in situ*.[42] Nevertheless, Finkelstein conditions afforded the piperidine, and reductive removal of the auxiliary afforded coniine in 34% overall yield for 4 steps. This reaction sequence offers a favorable comparison between radical- and carbanion-based syntheses using the same retrosynthetic disconnection.[45b,f]

2.5.3. Application to Formal Synthesis of Quinine—Our approach to the antimalarial alkaloid quinine focuses on strategic application of the Mn-mediated hybrid radical–ionic annulation.[46] Retrosynthetic disconnection of the azabicyclic ring system to a piperidine **A** (Scheme 10) suggests isoquinolizidine **B** as a potential precursor, where functionality of C6 and C7 would eventually be exploited for ring cleavage. The radical–ionic annulation is then applied via disconnection of either of two C–C bonds in structure **B**, involving either ***Path a*** or ***Path b***. With enantiomeric chiral auxiliaries, these paths converge to structures **B** and **B′**, which differ only in the configuration of the removable chiral auxiliary. A pseudo-C2-symmetric precursor **C** would facilitate efficient access to the coupling components needed to test either of these strategies.

The ultimately successful radical–ionic annulation was carried out in the presence of protected 1,2-diol functionality at C6 and C7, specifically the coupling of **24** with **25** (Scheme 11). Stoichiometry was a concern, because iodide **25** had been prepared through several synthetic steps, making it impractical to rely on large excesses of radical precursor, as is commonly required for many intermolecular radical additions. Fortunately, the Mn-mediated coupling of **24** and **25** with only 1.25-fold excess of **25** proceeded in 93% yield in 1 mmol scale, giving **26** as a single diastereomer. Although completion of the hybrid radical–ionic annulation *in situ* during the Mn-mediated coupling has not yet been achieved, a stepwise process provided decahydroisoquinoline **27** in a quite satisfactory overall yield (85% for 3 steps).[46a] The low stoichiometric requirement in the coupling of the multifunctional iodide **25** to an imino compound is attractive and should enable broader applications of this Mn-mediated coupling process in complex target synthesis.

To complete a formal synthesis of quinine, quinolizidine **28** was converted in three steps to the piperidine **29** (Scheme 12). Unfortunately the cyclization to form an azabicyclic ring system was not regioselective; both hydroxyethyl groups cyclized, and the preferred product contained the azabicyclo[3.2.1]octane rather than the desired azabicyclo[2.2.2]octane. This necessitated a 6-step sequence to differentiate the hydroxyethyl groups of **13**. This eventually furnished quincorine, which has previously been converted in two steps to quinine.[46b]

2.6. Applications in Amino Acid Synthesis

2.6.1. Synthesis of γ-amino acids—Although α- and β-amino acids have drawn more attention in synthetic chemistry, γ-amino acids such as **30** and **31** (Figure 4) are also important targets from the perspective of bioorganic and medicinal chemistry.[47,48,49,50] Disconnections of C–C bonds as shown calls for iodides and hydrazones bearing oxygen-containing functional groups, an important challenge to the synthetic versatility of the Mn-mediated coupling reactions. With this in mind, we employed Mn-mediated radical addition for a novel synthesis of γ-amino acids **30** and **31**.[51]

Because disconnection of α-alkoxy-γ-amino acid **30** calls for a base-sensitive β-alkoxyhydrazone **32** (Scheme 13), there is a potential for β-elimination of the alkoxy group from the hydrazone precursor **32** which makes non-basic conditions critical. In fact, treatment of **32** with TBAF in THF led to just such a β-elimination.[52] However, the Mn-mediated radical addition of isopropyl iodide proceeded in 77% yield, without any evidence of β-elimination, to afford **33** as a single diastereomer. Reductive removal of the chiral auxiliary and oxidation to the carboxylic acid gave **30** in good overall yield.[51]

Phenylacetaldehyde *N*-acylhydrazone **34** served as the radical acceptor for assembly of γ-amino acid **31** (Scheme 14), employing difunctional iodide **35** in the Mn-mediated radical addition (56% yield, single diastereomer).[51] As with **33** (shown above), this radical adduct **36** was converted through the same 4-step sequence to γ-amino acid **31**.

Although the aforementioned routes provided the desired γ-amino acids, it was desirable to develop a synthesis which incorporates the carboxylic acid oxidation state *prior to coupling*. We hypothesized that Mn-mediated radical addition would accomplish this objective, and therefore initiated a study of Mn-mediated coupling of alkyl iodides with γ-hydrazonoesters (Figure 5).[44] We had already shown that the Mn-mediated radical addition conditions offer excellent chemoselectivity, but it remained to be seen whether the stereocontrol model would be disrupted; would an additional Lewis basic ester function in the hydrazone interfere with the role of In(III) in two-point binding and rotamer control?

Prototypical radical additions were examined under Mn-mediated photolysis conditions with $InCl_3$ as the Lewis acid, coupling isopropyl iodide with a variety of γ-hydrazonoesters **37a**–**37d** (Table 5) bearing varied substitution at the position α to the ester. The α-methyl, αα, -dimethyl, and α-benzyloxy substituents appeared to have little effect on reaction efficiency and selectivity, as all provided the isopropyl adducts with consistently high diastereoselectivities and excellent yields (91–98%). Surprisingly, the selectivity was only slightly diminished in the absence of $InCl_3$ (entries 5 and 6); the yield in the absence of Lewis acid activation was modest but synthetically useful.

For the γ-hydrazonoesters, NMR experiments substantiated the typical two-point chelation model. A mixture of **37a** with $InCl_3$ in CD_2Cl_2 exhibited the H–C=N absorbance of the γ-hydrazonoester at 7.74 ppm, 0.30 ppm upfield from **37a** alone, consistent with precedent regarding Lewis acid coordination to imino compounds.[53] Also, the carbons of the oxazolidinone C=O and the hydrazone C=N were shifted downfield by 8 and 5 ppm on mixing with $InCl_3$. In contrast, the C=O carbon of the ester showed minimal change (<1

ppm). This suggests that the $InCl_3$ is chelated by the imino nitrogen and the oxazolidinone carbonyl in the usual way, without significant interference by the ester function.

A range of iodides were next examined in reactions with and without $InCl_3$, starting with a comparison of secondary and primary iodides (Table 5). When secondary iodides were subjected to coupling with γ-hydrazonoester **37a** the yields were excellent (entries 1 and 5), while primary iodides gave the desired adducts in moderate yields (33–66%, entries 6–10). All of these reactions occurred with good-to-excellent diastereoselectivities, and it was worth noting that both silyl ether and alcohol functionality were compatible with the coupling.

To document the synthetic applicability of these reactions, N–N bond cleavage was needed. After trifluoroacetylation of **38a** (Scheme 15) under microwave irradiation,[54] exposure to SmI_2 smoothly furnished known γ-aminoester **45** and offered proof of absolute configuration.[55]

2.6.2. Synthesis of α,α-Disubstituted α-Amino Acids—Although radical additions to aldimine-type acceptors have now become well-established, intermolecular additions to ketimine radical acceptors are rare by comparison.[56,57] We envisioned that the versatility of the Mn-mediated radical additions might offer potential access to a diverse range of *tert*-alkyl amines which are difficult to prepare by other means.[58] In planning a study of such reactions we were cognizant of the importance of ensuring the reaction takes place exclusively through a single C=N pi-bond geometry. Aldehyde *N*-acylhydrazone derivatives are exclusively obtained in *E* geometry, making this issue of little relevance, but ketone hydrazones are generally formed as mixtures of *E* and *Z* isomers. Therefore we sought a ketone hydrazone which could be obtained predominantly as one isomer.

The *N*-amino-2-oxazolidinone **9a** was condensed with methyl pyruvate (**46**) to give hydrazone **47** (Scheme 16) as an *E*/*Z* mixture (dr 92:8), from which the minor (*Z*)-isomer was removed via flash chromatography to give pure (*E*)-**47** in 75% yield. Addition of ethyl iodide under Mn-mediated photolysis conditions in the presence of $InCl_3$ gave a moderate yield of **48a** (66% yield, dr 70:30), while the corresponding isopropyl adduct **48b** was very effectively produced (85% yield, dr 92:8). The N–N bond was cleaved upon conversion of isopropyl adduct **48b** to the benzoyl derivative and treatment with SmI_2/MeOH (Scheme 10) to afford known benzamide (*S*)-(+)-**49**[59] and confirm the assigned configuration.

In the additions to **47** it was noted, through variations of the stoichiometric loading of Lewis acid, that amounts of $InCl_3$ less than 2 equiv resulted in lower diastereoselectivity. From this it may be inferred that the Lewis acid, aside from its usual chelation by the *N*-acylhydrazone, may interact with another Lewis basic site (e.g., the ester).

2.7. Considerations for Synthesis Design Using Mn-Mediated Radical Addition

2.7.1. Functional Group Compatibility—In the forgoing sections, there are numerous examples illustrating the use of Mn-mediated radical additions to couple compounds containing more than one functional group. Although there are still combinations left to be

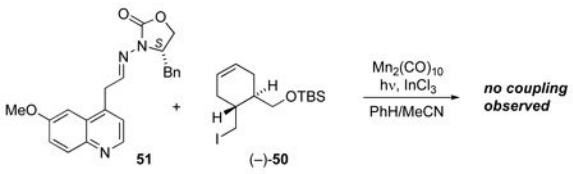
explored, the examples published to date already illustrate that various useful functionalities may be tolerated within either of the precursors.

In the radical precursor, the alkyl iodide may be accompanied by alkyl chloride, alcohol, benzylic ether, or silyl ether functionalities. The alkyl chlorides have certain limitations on the location relative to the radical; 2-chloroethyl radical may eliminate chloride prior to radical addition, and the adduct from 3-chloropropyl radical may cyclize after radical addition.

In the *N*-acylhydrazone radical acceptor, the functionalities tolerated include alkyl chloride, benzylic ether, silyl ether, and ester. An alkoxy leaving group may be accomodated at the β-carbon of an N-acylhydrazone without β-elimination, which complements the functional group tolerance of basic organometallic reagents. Depending on the chain length, a subsequent cyclization may occur in radical adducts containing alkyl chloride.

What types of functionalities are not compatible? Applications to total synthesis are rigorous proving grounds, often revealing that potentially useful methodologies are in fact limited to simple monofunctional precursors. Despite the tolerances for functional groups noted above, application of Mn-mediated radical additions to total synthesis objectives uncovered some cases of incompatibility which deserve further mention.

In the early stages of developing a synthetic route to quinine, the $Mn_2(CO)_{10}$-mediated coupling of iodide **50** and *N*-acylhydrazone **51** was attempted in 10:1 PhH/MeCN (eq. 2). Unfortunately no coupling product could be found, so each of the spectator functionalities had to be examined in control experiments in order to find the structural features which might be interfering with the reaction. Mn-mediated radical additions of iodides containing the silyl ether moiety had previously been successful in various contexts,[42,44,46,51] so interference by the silyl ether was ruled out. However, it was noted that a precipitate formed on mixing hydrazone **51** with $InCl_3$ in 10:1 PhH/MeCN, and the precipitate remained insoluble even at higher ratios of CH_3CN. This suggested closer examination of the *N*-acylhydrazone to determine whether complexation of the *N*-acylhydrazone with $InCl_3$, normally required to facilitate radical addition, had been disrupted by the basic methoxyquinoline. A second concern was that the compatibility of an electron-rich methoxyaryl group with the Mn-mediated radical additions had not previously been established.



Equation 2

To address this question, a series of control experiments was carried out with aromatic hydrazones **52a**, **52b**, and **52c**, using Mn-mediated radical addition of iodide **53**. From

hydrazones **52a** and **52b**, the expected products **54a** and **54b** were obtained in moderate yield (ca. 40%), confirming that the electron-rich methoxyaryl substituent was compatible with the coupling. Pyridine-containing hydrazone **52c**, however, gave none of the desired coupling product **54c**, indicating that heteroaromatic nitrogen may have interfered with the Mn-mediated coupling reaction.

When attempting the coupling of iodide **50** (eq. 2) with simplified hydrazones en route to quinine, another issue of compatibility arose. Although OH and OTBS groups were already known to be well-tolerated, the couplings of **50** were inefficient. This raised suspicion about the potential side reactions of an alkene moiety in the radical intermediate. Despite changing the identity of the spectator functional groups, or the roles of the two precursors, so that the alkene was in the radical acceptor (e.g., **55a**–**55d**), the reaction remained inefficient. Yields of the desired product remained generally less than 30% despite extensive efforts toward improvement. Finally, a control experiment with saturated iodide **50c** revealed that the alkene indeed was detrimental to the success of this coupling. It is unclear whether this incompatibility is a general one or a peculiarity of the examples shown in Scheme 18.

In summary, there are some useful functional groups bearing either acidic protons (alcohol) or electrophilic centers (alkyl chloride, ester) which are tolerated as spectators in the Mn-mediated radical addition reaction. These compatibilities complement those of other chiral amine synthesis methods involving strongly nucleophilic (and basic) organometallic reagents, thereby offering some useful options for synthetic design. Ethers and silyl ethers are also compatible. Selected examples involving pyridines and alkenes as spectator groups revealed some complications, the scope of which remain unclear, so for synthetic design purposes, these types of moieties may need to be introduced later in the route.

2.7.2. Stereoconvergence for Flexibility in Synthetic Application—Considering the examples discussed above, it is clear that the Mn-mediated radical additions offer useful functional group compatibilities in both the radical precursor and *N*-acylhydrazone acceptor. And, 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 Table 4.[60] Thus, stereoconvergent construction of alternative C–C bonds at the chiral amine stereocenter (Scheme 19) can be readily conceived, so that the roles of these precursors can be chosen on the basis of synthetic strategy rather than rather than on the basis of functional group limitations of the methodology. Such strategic flexibility contributes to the synthetic potential of these radical addition reactions.

3. Asymmetric Catalysis of Radical Addition

Although the forgoing sections have illustrated the viability of stereocontrolled radical addition to C=N bonds as a route to chiral amines, imparting the stereocontrol through asymmetric catalysis remains a challenge. To date, most efforts toward this goal have required very high catalyst loading (usually stoichiometric) or have limited scope. In this section, a summary of these studies illustrates some of the highlights and limitations.

Naito reported the first asymmetric radical additions to C=N bonds with a non-covalent mode of stereocontrol. Building upon earlier work exploiting chiral glyoxylate imines as radical acceptors in the presence of Lewis acids, Naito employed Lewis acids bearing a chiral bisoxazoline ligand for addition to achiral glyoxylate oxime ether **56** (Scheme 20). With $MgBr_2$ and ligand **58**, enantioselectivity up to 52% ee was obtained at stoichiometric loading.[61] Jorgensen published an alternative approach, attempting catalysis with a combination of Cu(I) and to lBINAP (**59**).[62] Unfortunately this gave very low enantioselectivity, with a yield lower than the catalyst loading.

We sought to demonstrate the first example of catalytic asymmetric induction in radical addition to C=N bonds. Our effort toward this goal was built upon the two-point binding motif of *N*-acylhydrazones (Figure 6), which could potentially transmit stereocontrol from chiral ligands accompanying a Lewis acid.

The first successes exploited additions of isopropyl iodide, with radical initiation by triethylborane and oxygen. Using valerolactam-derived achiral *N*-acylhydrazone acceptor **60a** (Table 6), highly enantioselective isopropyl radical additions were promoted by one equivalent each of Lewis acid and bisoxazoline ligand **62**. With $InCl_3$, $Mg(ClO_4)_2$, and $Cu(OTf)_2$ as the Lewis acids only modest yields of **61** were obtained (entries 1–3), but selectivities in the range of 57–66%ee set a new standard for selectivity in radical additions to C=N bonds.[63] Using benzene/CH_2Cl_2 as the solvent (entry 4), the selectivity increased further, to 95%ee (66% yield). The less polar solvent system presumably facilitated the assembly of a ternary complex from the 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.

A series of radical precursors and acceptors were employed, showing some versatility accompanied by high enantioselectivity (Table 7).[63] Using stoichiometric amounts of the preformed aquo complex Cu(*t*Bu-Box)$(H_2O)_2(OTf)_2$, isopropyl additions to *N*-acylhydrazones prepared from benzaldehyde, *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde were highly enantioselective (entries 1 and 2). Additions of various radicals, including chloromethyl, to **60a** were also successful (entries 3–6). Turnover of the chiral catalyst was examined by lowering the catalyst loading (Table 7, entries 8–10). The yield remained high, while enantioselection decreased. However, the yield and enantioselection (74% yield, 46%ee) at 10 mol% catalyst loading showed evidence of catalyst turnover — the first example of asymmetric catalysis in radical addition to C=N bonds.

The glyoxylic oxime ether **62** was subjected by Jang et al. to radical addition of several simple alkyl iodides in with triethylborane/oxygen initiation in the presence of Cinchona alkaloid salts of hypophosphorous acid (Scheme 21).[64] Although an excess of the Cinchona alkaloid was required, transmission of stereochemical information was confirmed. A stereocontrol model was proposed with a combination of hydrogen bonding and pi stacking to activate the radical acceptor and constrain its structure.

More recently, the Jang group has reported that *N*-benzoylhydrazones are also suitable substrates for stereocontrolled radical addition in the presence of Cinchona alkaloids.[65] With hydrazones prepared from a series of substituted benzaldehydes (Scheme 22), very high enantioselectivities (98–99%ee) were observed using the *O*-benzyl alkaloid derivative **68** (40 mol%). The high selectivity observed with aromatic hydrazones was not retained during addition to the *N*-benzoylhydrazone prepared from octanal (80%ee, not shown). Cyclohexyl, *tert*-butyl, and adamantyl radical additions were effective, but the use of primary radical (from *n*-octyl iodide) was detrimental to both efficiency and selectivity (55% yield, 81%ee).

Binaphthol-derived chiral Bronsted acids have been exploited to catalyze addition to *N*-aryl imines (Scheme 23).[66] In these reactions, the use of 30 mole % of catalyst **71** was sufficient to promote addition of isopropyl and *tert*-butyl iodides to imine **69** with enantiomeric excesses in the 73–84% range, although the isolated yields were moderate. As in most reactions using the triethylborane-oxygen initiation system, the products were accompanied by significant amounts of the ethyl adduct (**76**, R = Et, from triethylborane).

4. Summary

Radical addition to imino compounds has emerged as a general approach with broad versatility that complements non-radical methodology. Our work has discovered and elaborated this concept into synthetically useful methodology: First, highly stereoselective intermolecular additions of alkyl iodides to chiral hydrazones in the presence of $Mn_2(CO)_{10}$ accomodate a broad range of functionality, including esters and unprotected hydroxyl groups which may not be compatible with carbanion chemistry. The viability of this strategies for stereocontrol has now been established in applications to target-directed synthesis. Secondly, we have developed a means of catalytic asymmetric induction; excellent enantioselectivity is obtained at stoichiometric loading, and moderate enantioselectivity is observed in conditions which demonstrate catalyst turnover. Although these are promising results, a method for asymmetric catalysis in radical addition to C=N bonds which offers high turnover numbers and broad scope is still an unmet challenge.

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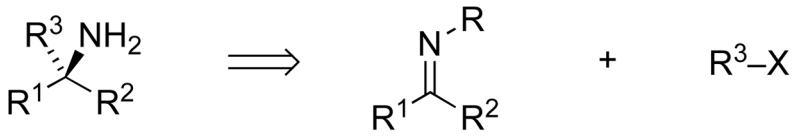


Fig. 1.

Disconnecting a C–C bond of a chiral amine suggests an imino compound (e.g., imine, oxime, hydrazone, etc.) and an organic halide as precursors.

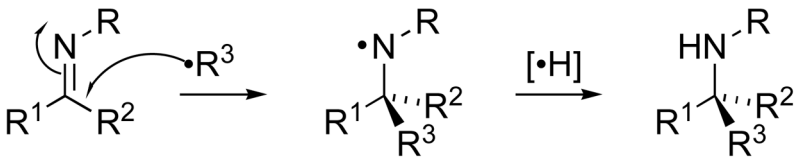


Fig. 2.
Radical Addition to Imino Compounds.

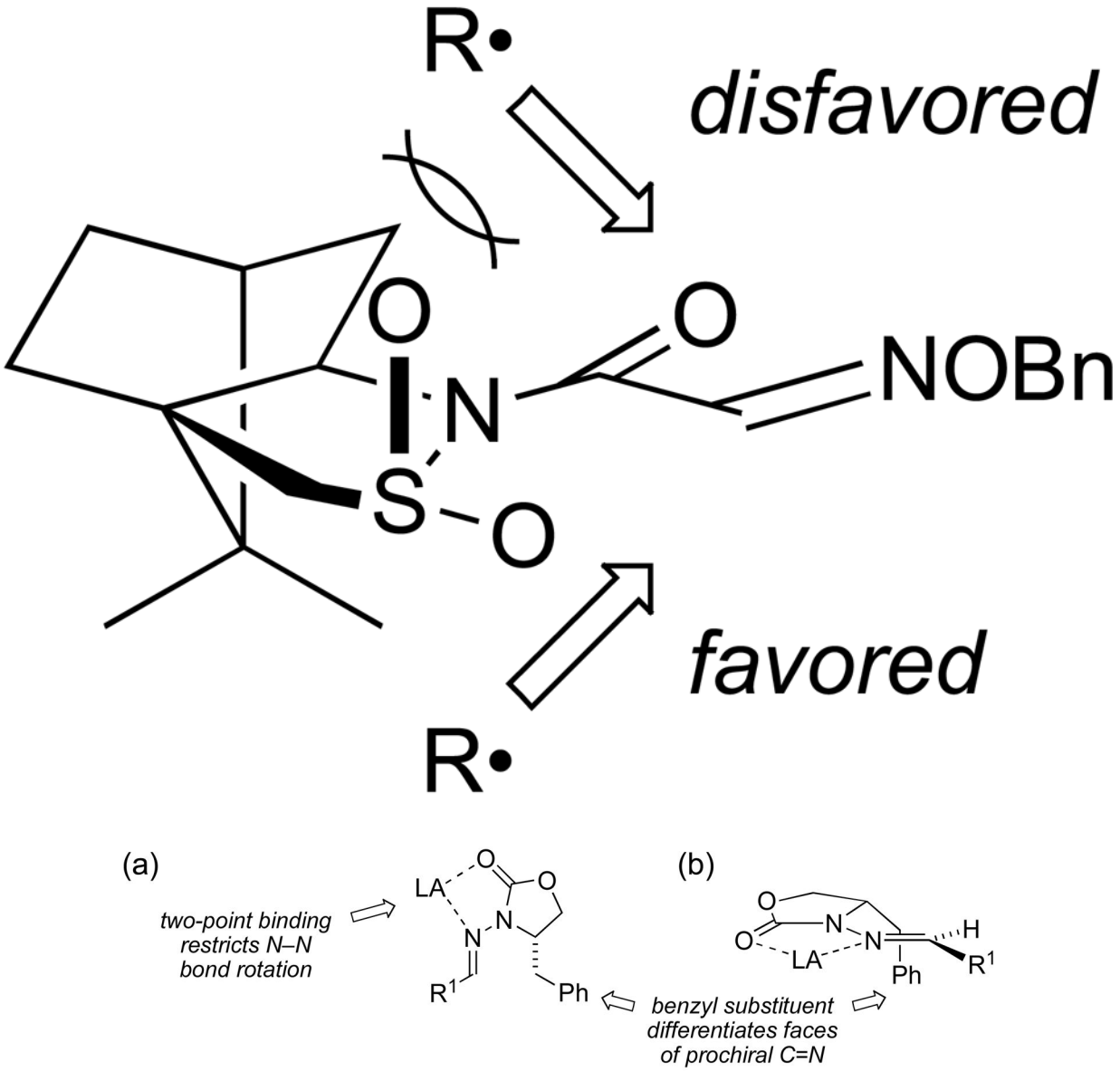


Fig. 3.

Naito stereocontrol model proposed for additions to camphorsultam-functionalized glyoxylic oxime ethers.

(a) Lewis acid chelation induces rigidity and electron-deficiency into the *N*-acylhydrazone radical acceptor (LA = Lewis acid). (b) Benzyl substituent of 4-benzyl-2-oxazolidinone provides facial diferentiation of the C=N bond.

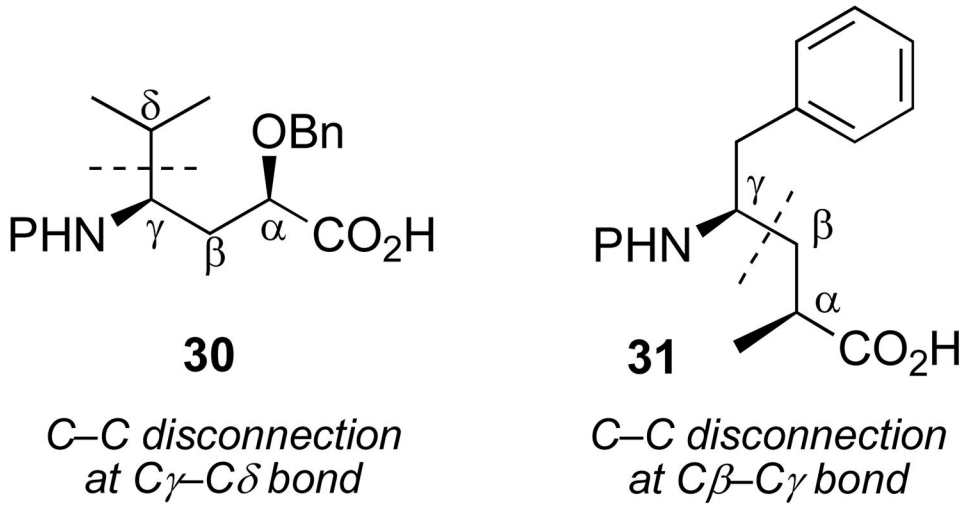


Figure 4.
Representative γ-amino acids with strategic bond disconnections at the γ–δ and β–γ carbons.

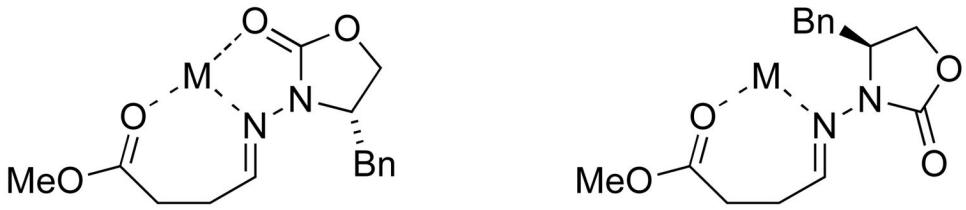


Fig. 5.

Some hypothetical multipoint binding of a Lewis acid by N-acylhydrazones bearing additional ester functionality

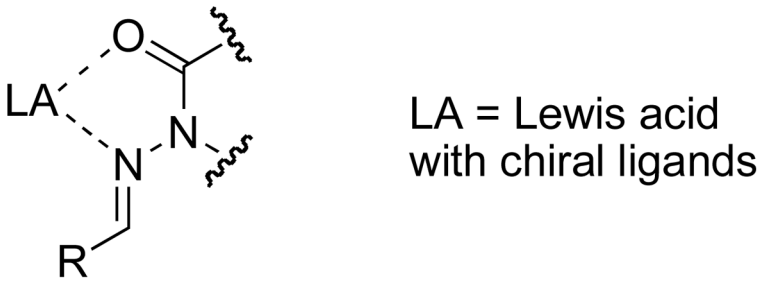
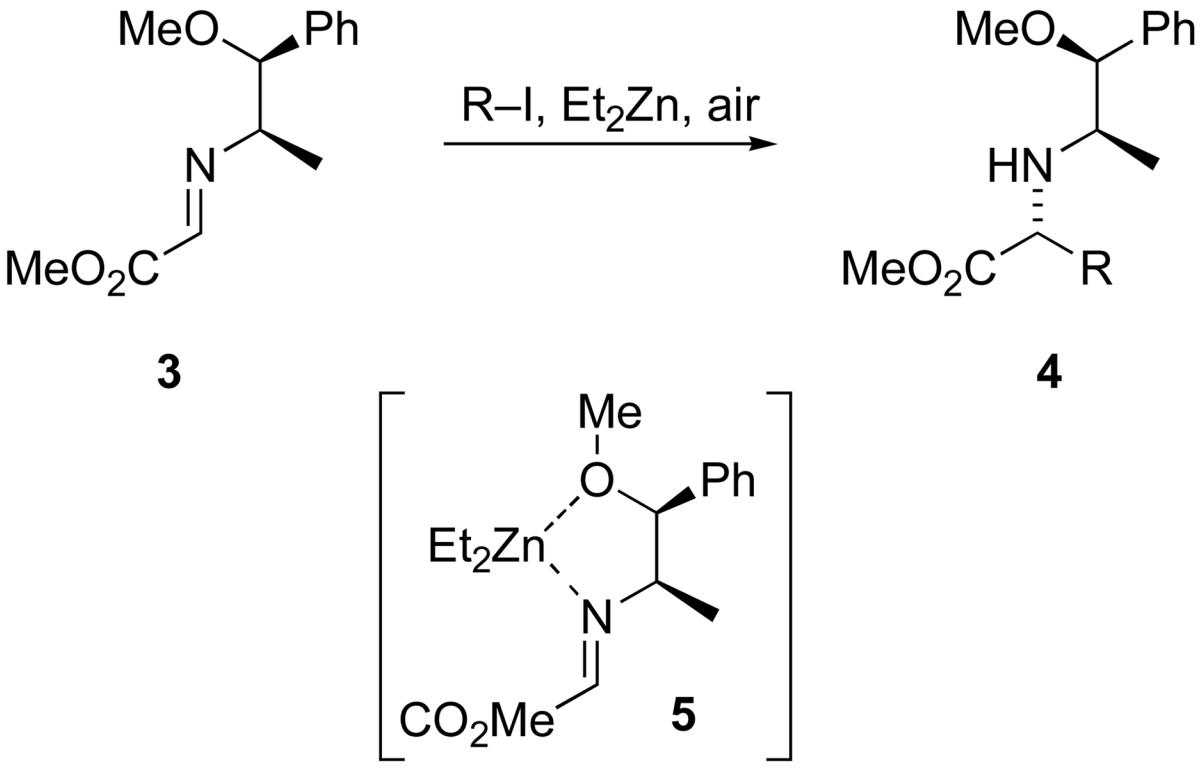
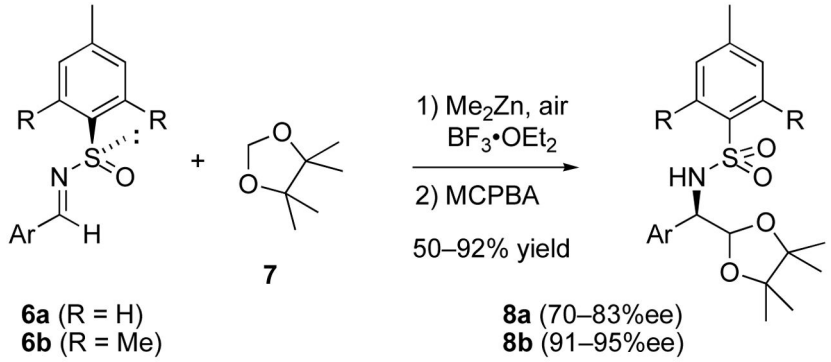


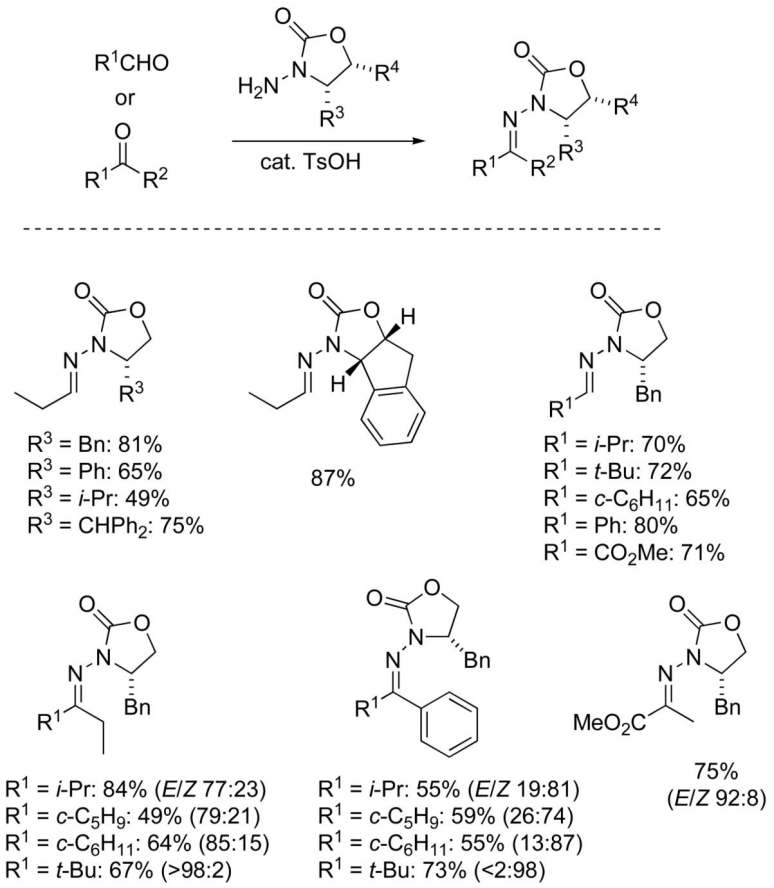
Fig. 6.
Two-point binding of a Lewis acid by a generalized *N*-acylhydrazone structure.



Scheme 1.
Radical addition to glyoxylate imines.

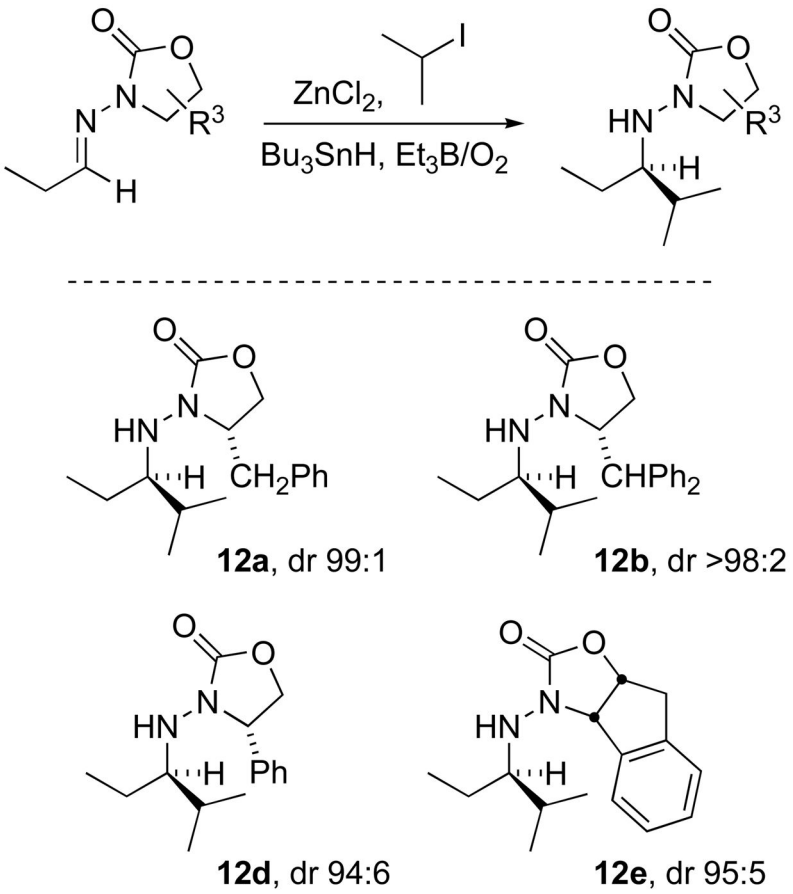


Scheme 2.
Radical addition to *N*-sulfinylimines



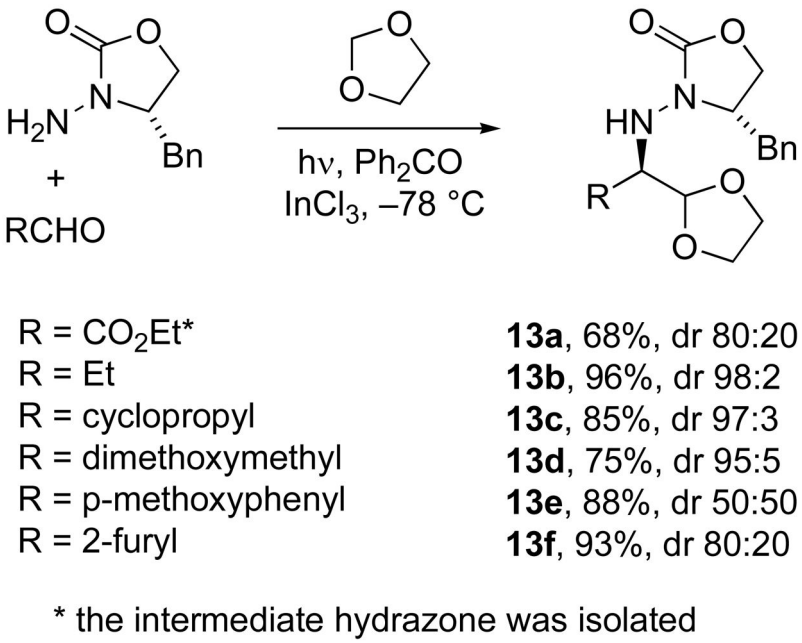
Scheme 3.

Representative preparations of chiral *N*-acylhydrazones

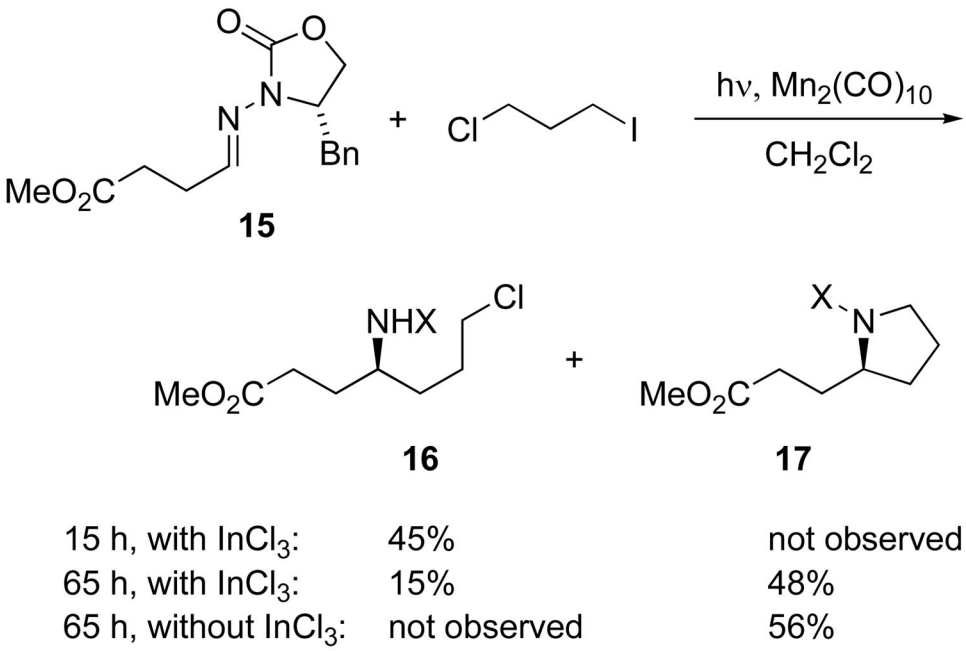


Scheme 4.

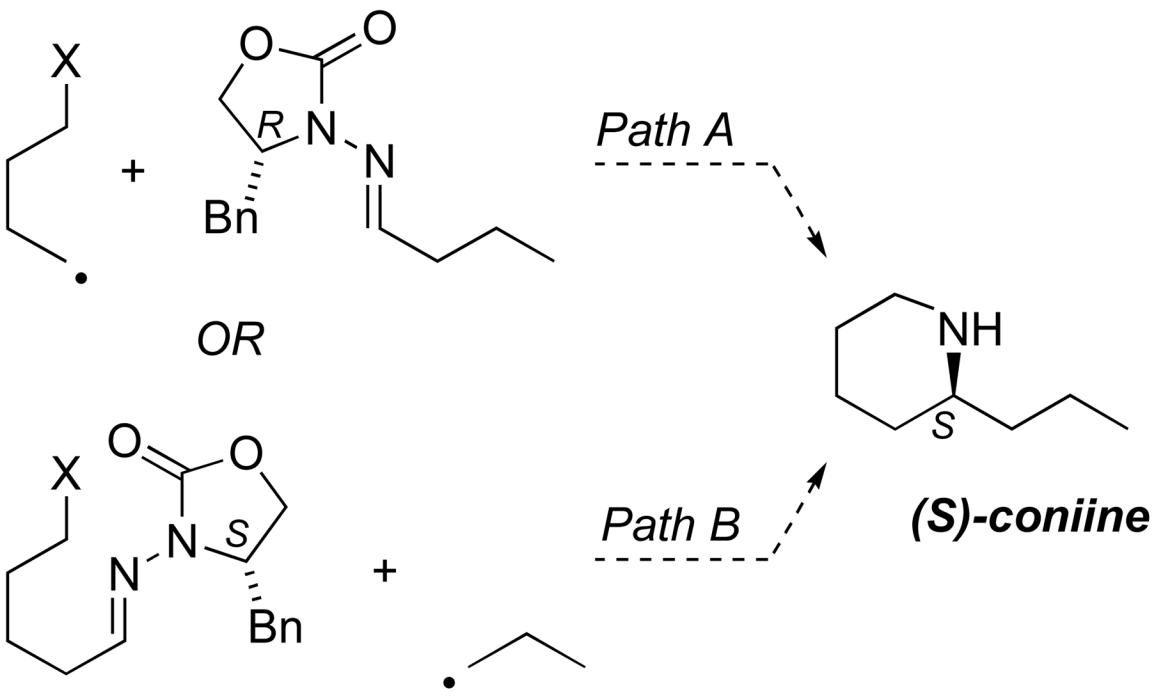
Role of oxazolidinone substituents on diastereoselectivity in isopropyl radical addition



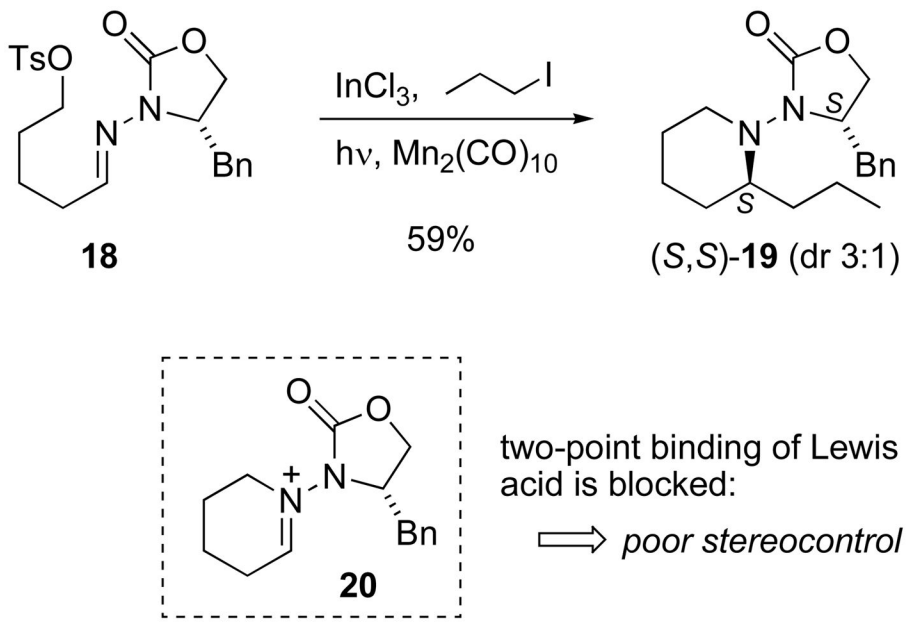
Scheme 5.
A one-pot condensation–radical addition of *N*-acylhydrazones



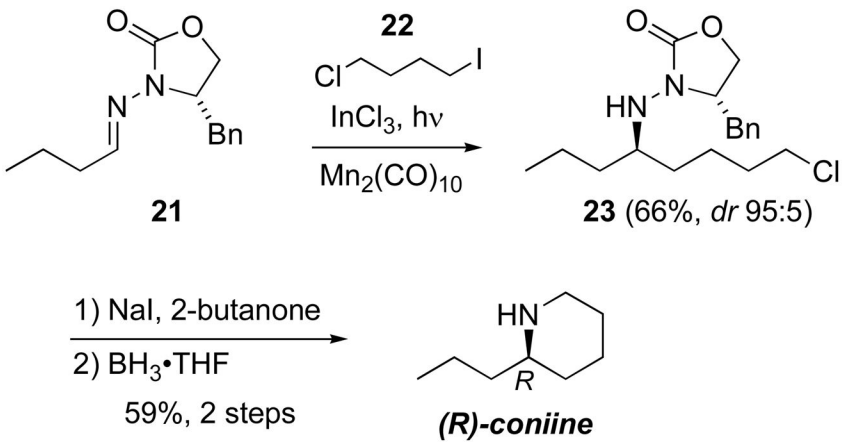
Scheme 6.
Control of stepwise annulation



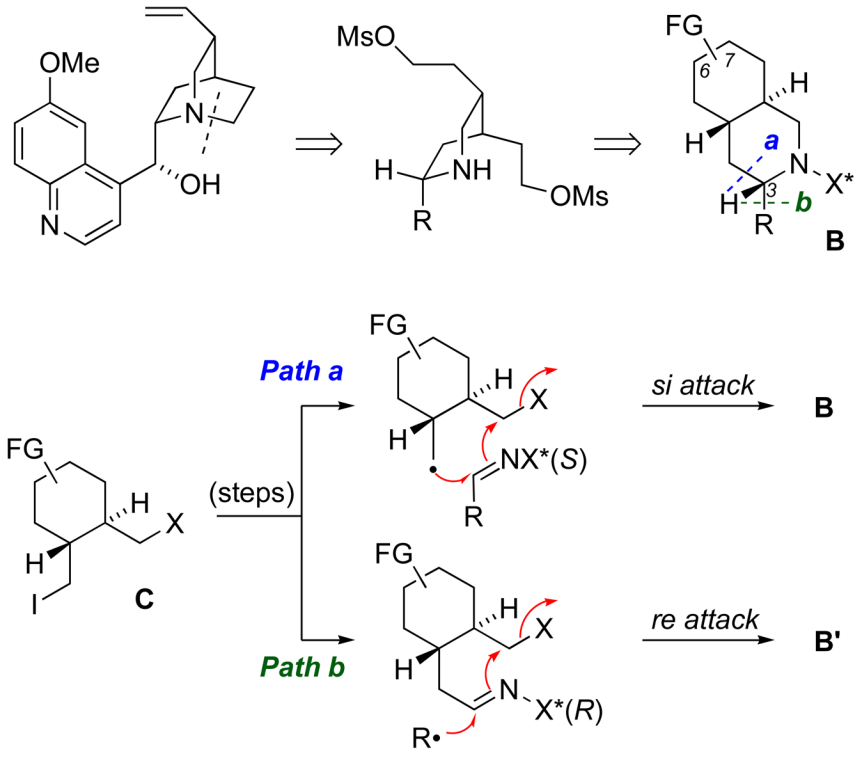
Scheme 7.
Retrosynthetic disconnection of coniine



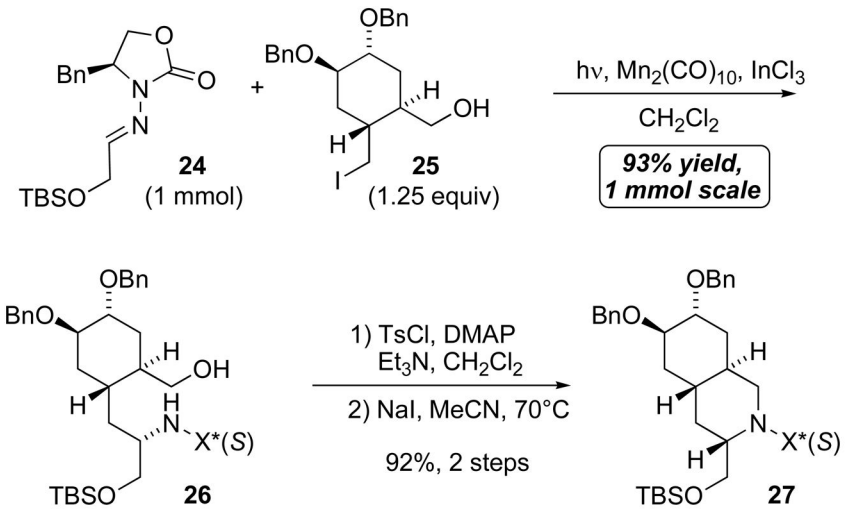
Scheme 8.
Radical addition to 5-tosyloxypentanal hydrazone **18**



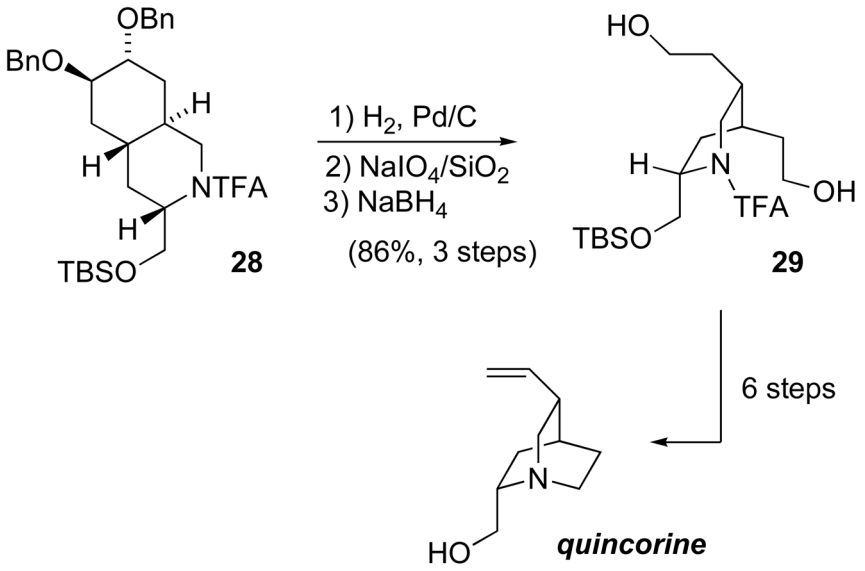
Scheme 9.
Synthesis of (*R*)-coniine



Scheme 10.
Retrosynthetic analysis of quinine

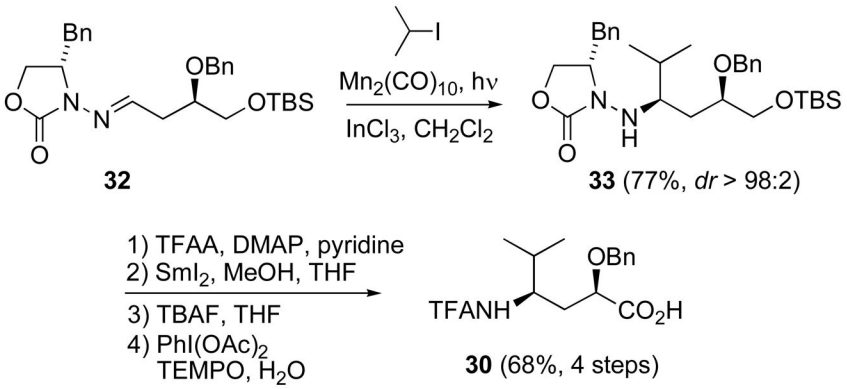


Scheme 11.
Mn-mediated radical addition en route to quinine



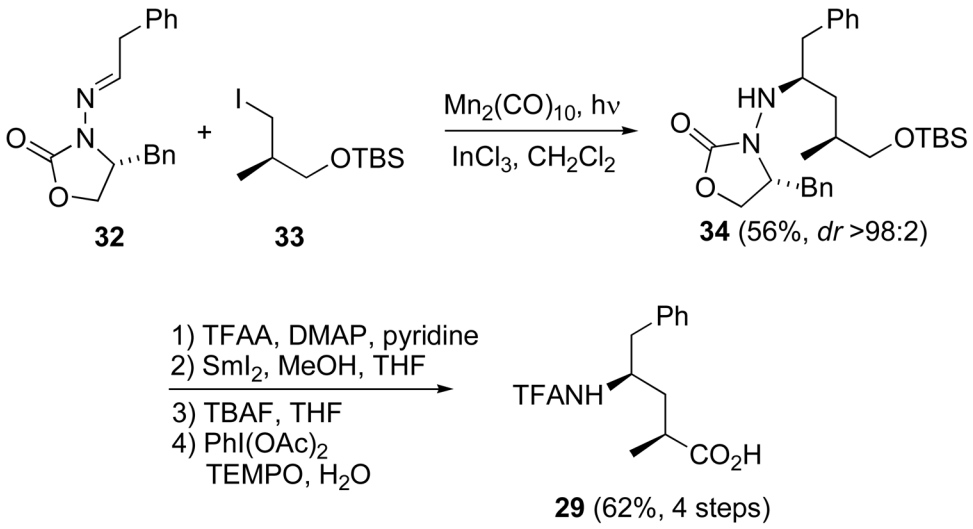
Scheme 12.

Conversion of quinolizidine **28** to quincorine



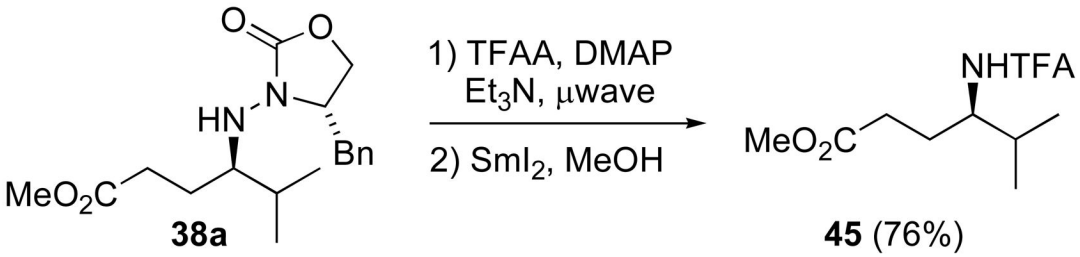
Scheme 13.

Addition to a β-alkoxyhydrazone without β-elimination

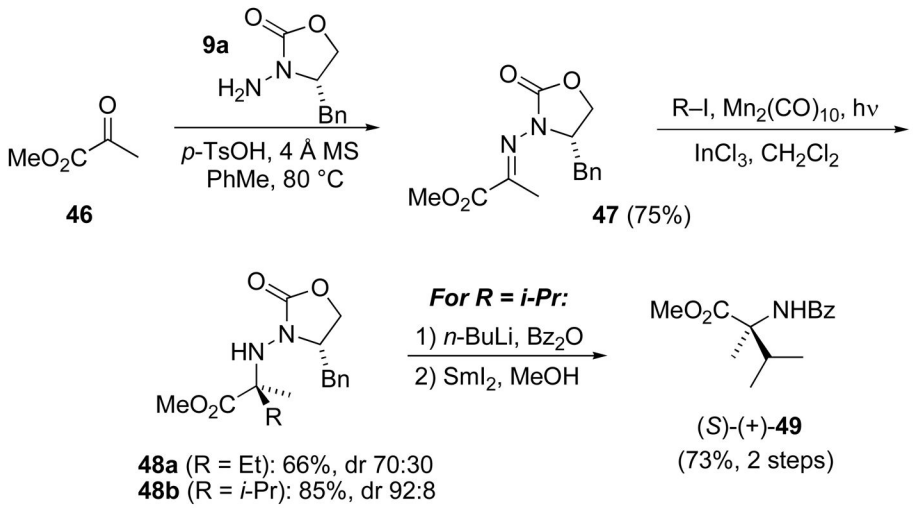


Scheme 14.

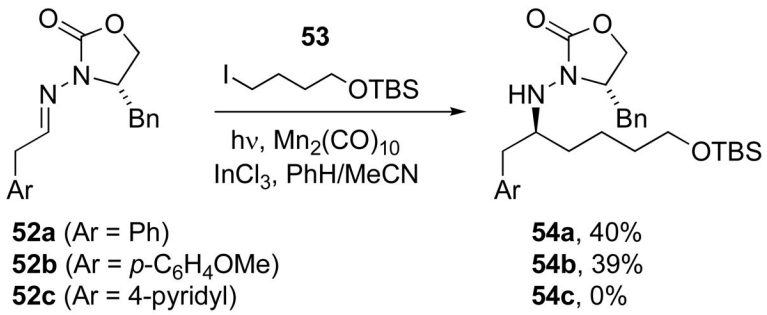
Addition of a 3-silyloxyalkyl iodide to an *N*-acylhydrazone



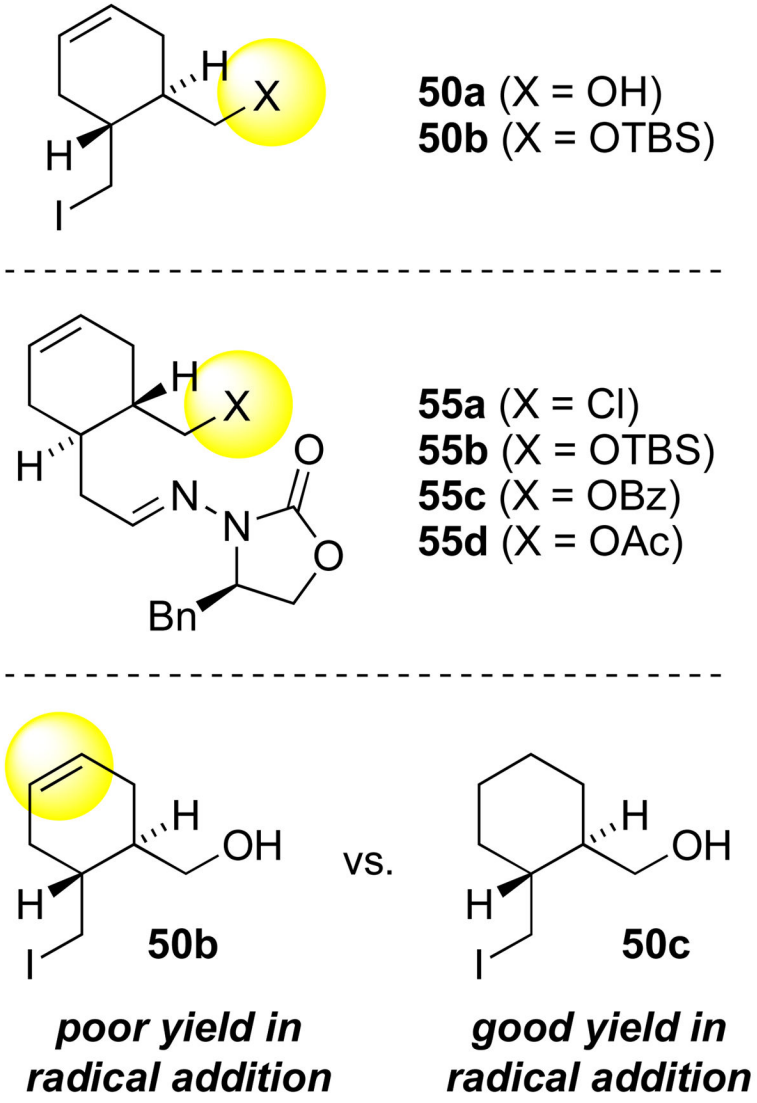
Scheme 15.
Conversion of radical adduct to *N*-trifluoroacetamide



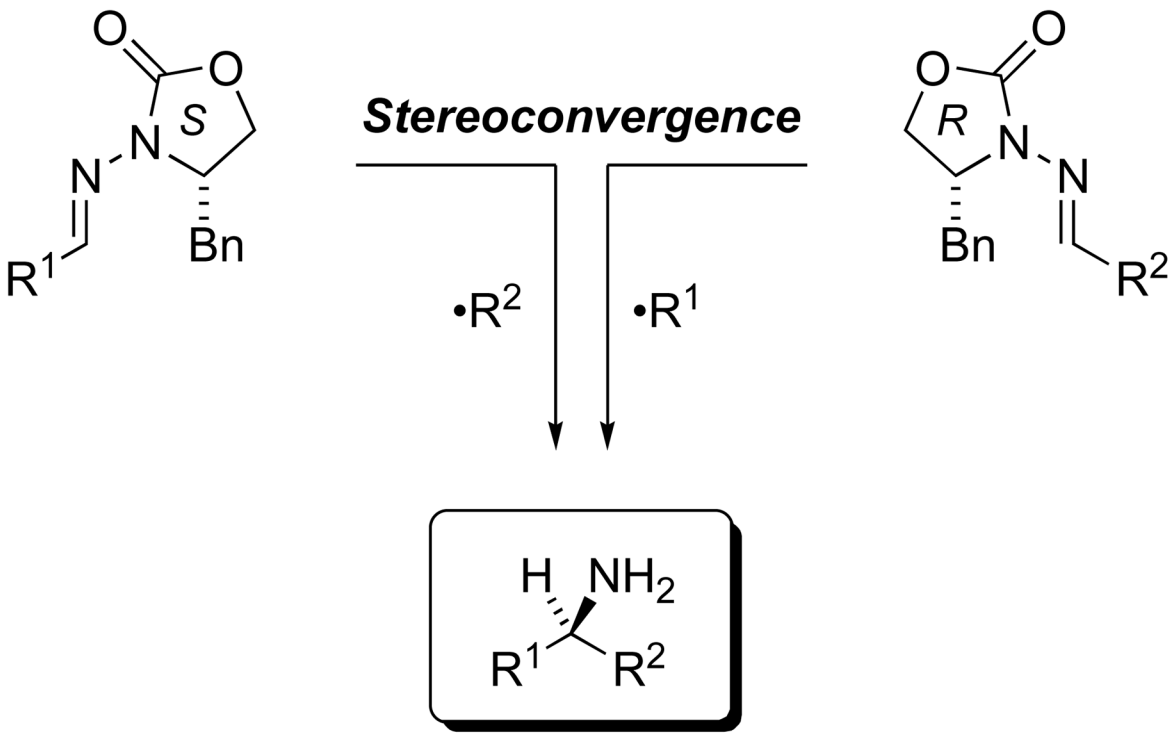
Scheme 16.
Radical addition to ketimine **47**



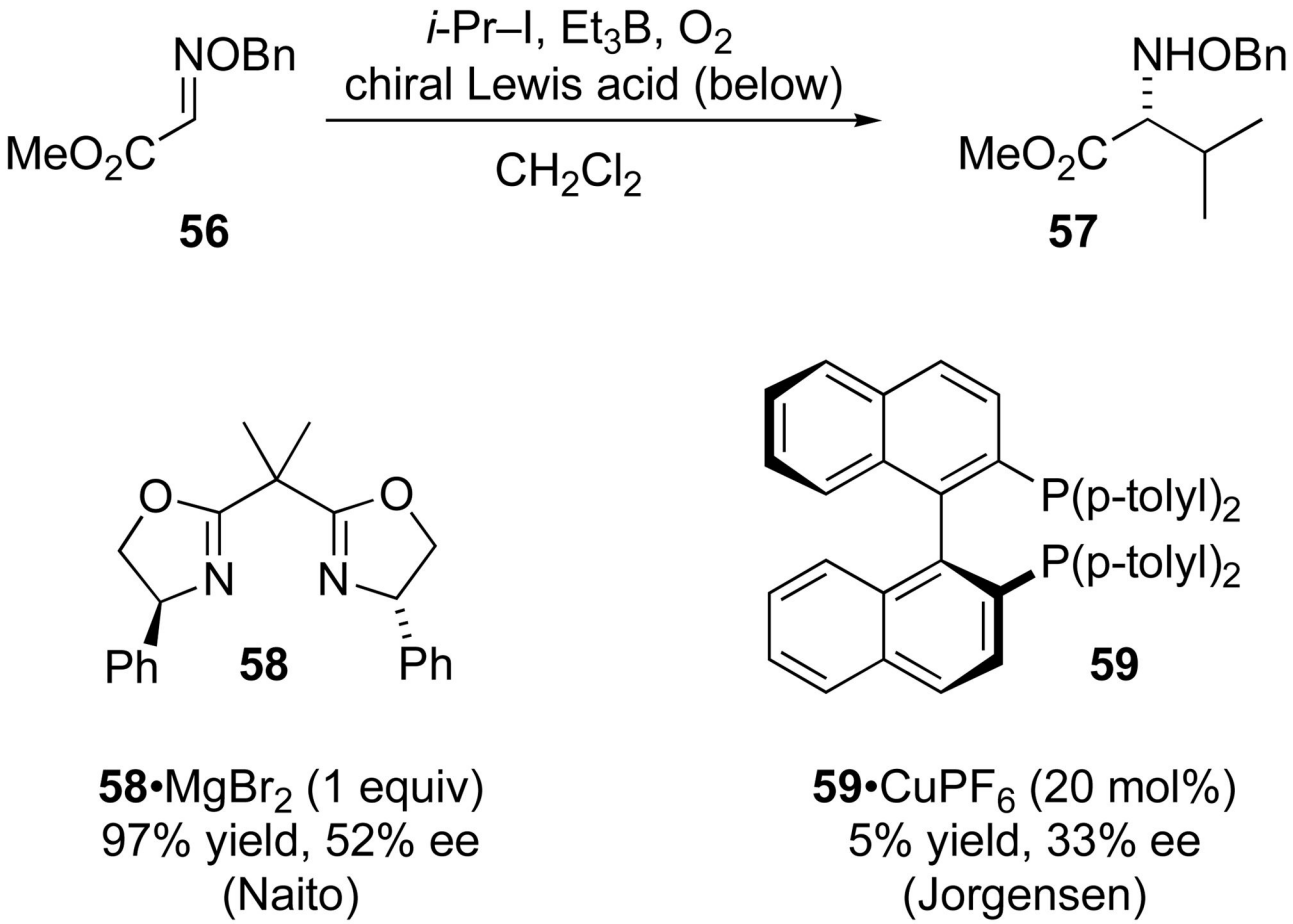
Scheme 17.
Control experiments with electron-rich aromatics



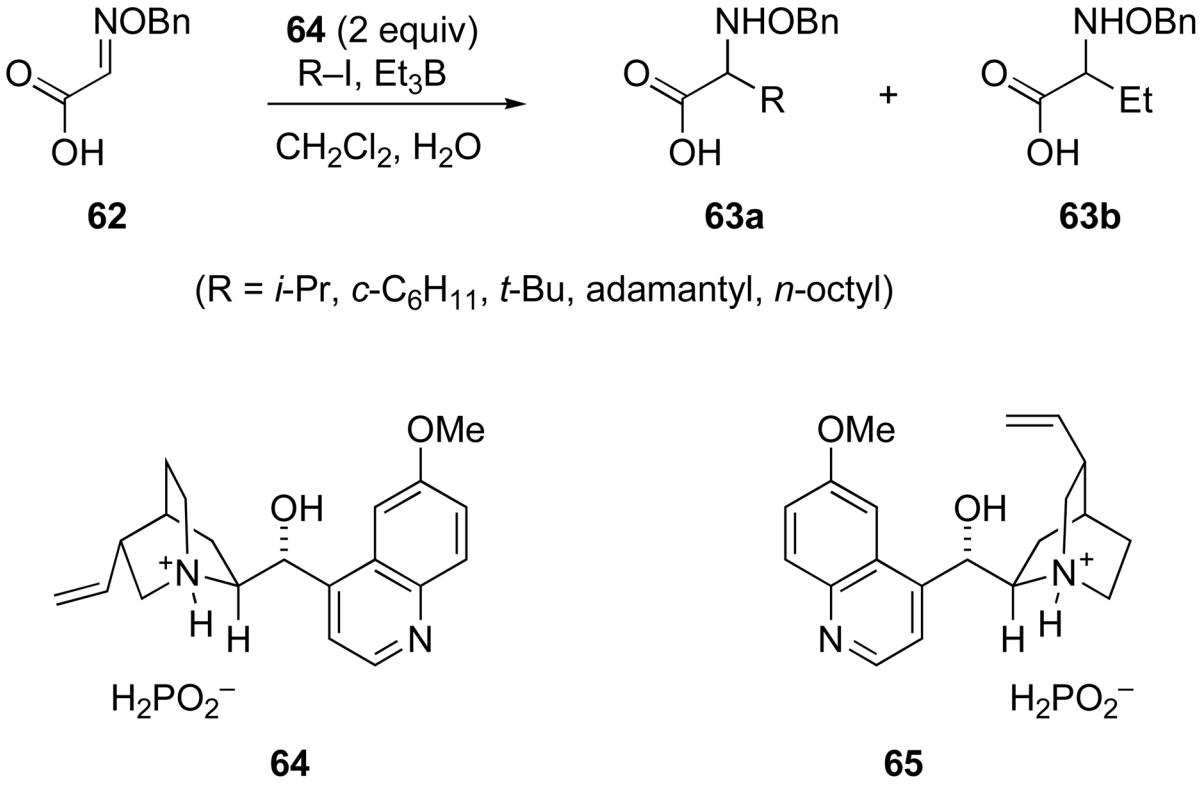
Scheme 18.
Functionality variations in Mn-mediated coupling attempts for quinine synthesis



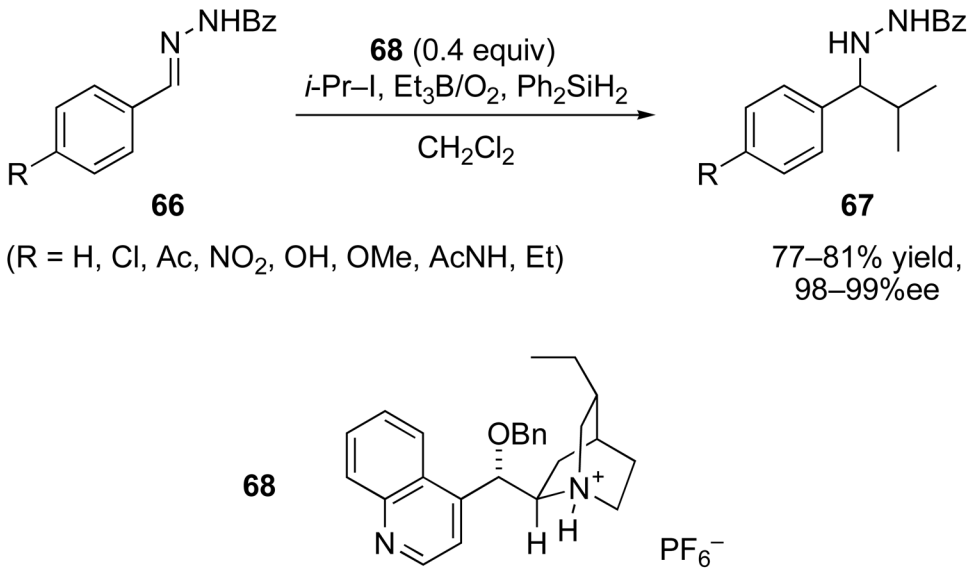
Scheme 19.
Stereoconvergent routes to chiral amines



Scheme 20.
Asymmetric addition of isopropyl iodide to glyoxylate oxime ether

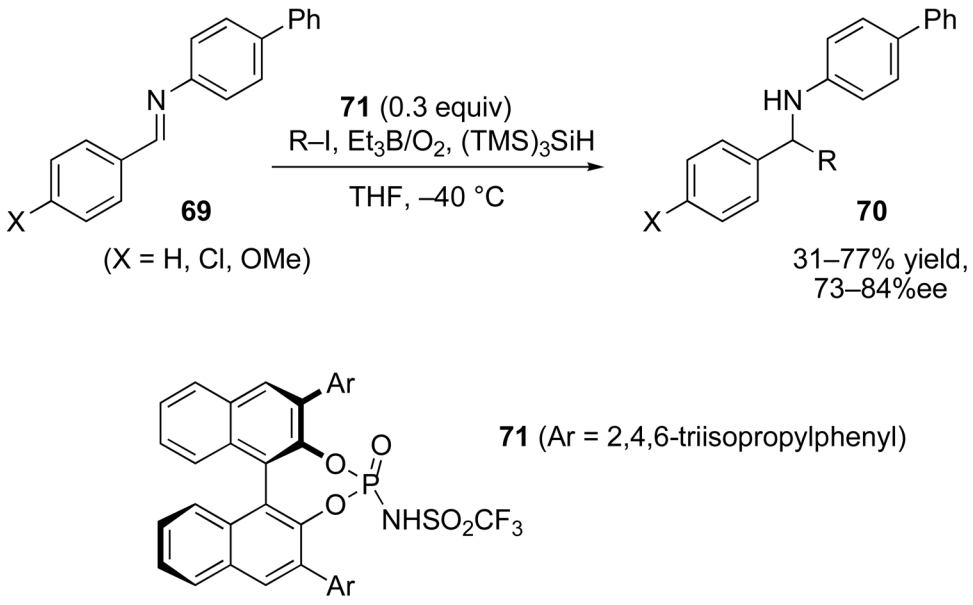


Scheme 21.
Radical addition in the presence of cinchona alkaloid salts of hypophosphorous acid.



Scheme 22.

Catalytic asymmetric radical addition to *N*-benzoylhydrazones in the presence of a cinchona alkaloid salt

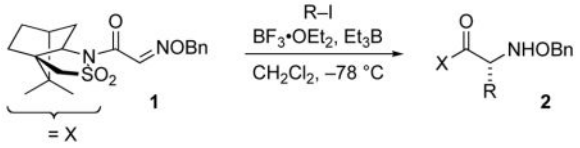


Scheme 23.

Binaphthol-derived Bronsted acid catalyst for asymmetric radical addition to *N*-arylimines

Table 1

Radical Addition to Chiral Glyoxylic Oxime Ethers.



Entry	R^1	Yield[a]	dr[b]
1	Et	80%	95:5
2	*i*-Bu	83%	97:3
3	*i*-Pr	80%	96:4
4	*s*-Bu	69%[c]	>98:2
5	*c*-C_6H_{11}	86%	96:4
6	*t*-Bu	83%	>98:2
7	$AcO(CH_2)_4$	41%[d]	>98:2
8	$Cl(CH_2)_4$	15%[d]	>98:2

[a] Isolated yield.

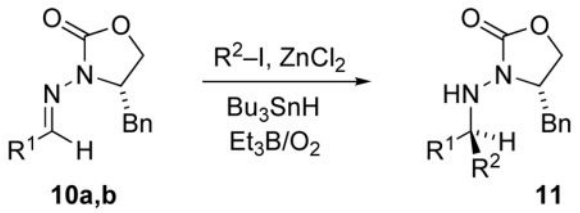
[b] dr = diastereomer ratio.

[c] Obtained as 1:1 mixture of diastereomers.

[d] Major product was ethyl addition.

Table 2

Tin-Mediated Radical Addition to Chiral *N*-Acylhydrazone **10a** in the Presence of $ZnCl_2$



10a,b **11**

Entry	R^1	R^2	Product, Yield[b] (*dr*)
1	Et (**10a**)	*i*-Pr	**11a**, 60% (99:1)
2	Et (**10a**)	*c*-C_5H_9	**11b**, 59% (96:4)
3	Et (**10a**)	*c*-C_6H_{11}	**11c**, 28% (97:5)
4	Et (**10a**)	*t*-Bu	**11d**, 54% (95:5)
11	Ph (**10b**)	*i*-Pr	**11e**, 42% (99:1)
12	Ph (**10b**)	*c*-C_5H_9	**11f**, 59% (96:4)
13	Ph (**10b**)	*c*-C_6H_{11}	**11g**, 30% (99:1)
14	Ph (**10b**)	*t*-Bu	**11h**, 83% (93:7)

Reaction conditions: Bu_3SnH (5 equiv) and O_2 (7mL/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 → rt.

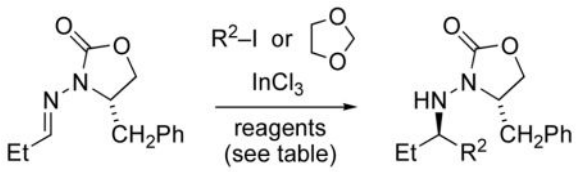
[a] Recovered hydrazone, %.

[b] Isolated yield, %.

[c] Not determined.

Table 3

Tin-Free Radical Additions to **10a** in the Presence of $InCl_3$



Entry	R^2	Method	Yield[a]
1	Et	A	33%
2	*i*-Pr	A	75%[b]
3	*c*-C_5H_9	A	47%
4	*c*-C_6H_{11}	A	56%
5	$ClCH_2$	A	33%
6	1,3-dioxolan-2-yl	B	87%[c]
7	1,3-dioxolan-2-yl	C	96%[d]

Reaction conditions: A: As in Table 2, minus Bu_3SnH. B: 1,3-dioxolane, Ph_2CO, $InCl_3$, hν, −78 °C. C: Same as B, except one-pot; *N*-acylhydrazone prepared and used *in situ*.

[a] Isolated yield.

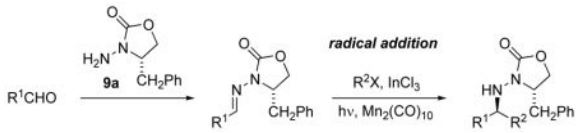
[b] *dr* >95:5 (^1H NMR).

[c] *dr* 91:9 (Alonso, ref. 36).

[d] *dr* 98:2 (Alonso, ref. 36).

Table 4

Mn-Mediated Radical Additions to *N*-Acylhydrazones.



entry	aldehyde (or acetal)	yield, hydrazone[a]	halide R^2X	yield, radical addition[b]	*dr*
1	CH_3CH_2CHO	81%	CH_3CH_2I	85%	-
2			CH_3I	48%[c,d] (*S*)	95:5[e]
3			*n*-PrI	66% (*R*)	94:6[e]
4			*n*-BuI	78% (*R*)	95:5[e]
5			$n\text{-}C_5H_{11}I$	79% (*R*)	96:4[e]
6			*i*-BuI	54%[c] (*R*)	95:5[f]
7			*i*-PrI	75% (*R*)	95:5[f]
8			$ClCH_2I$	63% (*R*)	93:7[e]
9			$Cl(CH_2)_3I$	52% (*R*)	96:4[f]
10			$Cl(CH_2)_4I$	55% (*R*)	96:4[e]
11			Cl_2CHBr	38%[c,d] (*R*)	98:2[f]
12	CH_3CHO	66%	CH_3CH_2I	66% (*R*)	95:5[e]
13	*n*-PrCHO	87%		63% (*S*)	95:5[e]
14	*n*-BuCHO	89%		72% (*S*)	97:3[e]
15	$n\text{-}C_5H_{11}CHO$	88%		77% (*S*)	97:3[e]
16	*i*-BuCHO	85%		65% (*S*)	95:5[f]
17	$ClCH_2CH(OMe)_2$	85%		57% (*S*)	93:7[e]
18	$Cl(CH_2)_3CHO$	95%		60% (*S*)	93:7[f]
19	$Cl(CH_2)_4CHO$	89%		62% (*S*)	97:3[e]
20	$Cl_2CHCH(OEt)_2$	54%		34%[c] (*S*)	89:11[f]

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Reaction conditions: (1) Aldehyde or acetal (5–10 equiv), **9a**, *p*-toluenesulfonic acid, CH_2Cl_2, rt. (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.

[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.

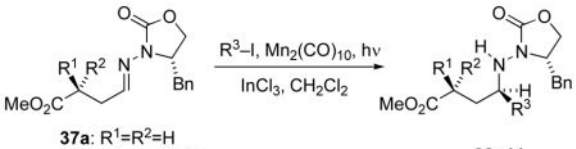
[d] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used in removal of Mn byproducts.

[e] Ratio by HPLC (Chiralcel OD, 2-PrOH/hexane).

[f] Ratio by ^1H NMR.

Table 5

Additions of Alkyl Iodides to γ-Hydrazonoesters



37a: R^1=R^2=H
37b: R^1=H, R^2=Me
37c: R^1=R^2=Me
37d: R^1=H, R^2=OBn

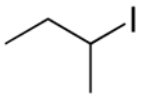
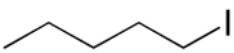
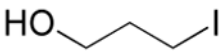
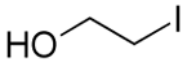
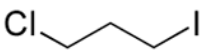
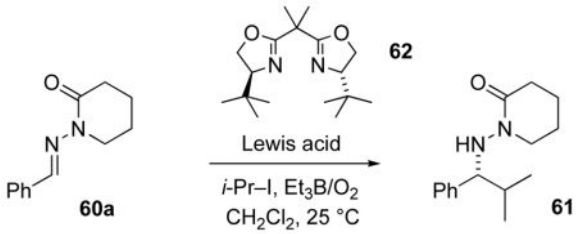
entry	hydrazone	iodide R^3I	product, yield	*dr*
1	**37a**	*i*-PrI	**38a**, >99%	94:6
2	**37b**		**38b**, 98%	95:5
3	**37c**		**38c**, 96%	99:1
4	**37d**		**38d**, 96%	90:10
5	**37a**		**39**, 82%	--
6			**40**, 66%	94:6
7			**41**, 37%	96:4
8			**42**, 61%	97:3
9			**43**, 33%	96:4
10			**44**, 45%	85:15

Table 6

Comparison of Lewis acids in isopropyl addition to **60a**.[a]



entry	Lewis acid	solvent, additive	yield[b]	*ee*[c]
1	$InCl_3$	CH_2Cl_2	33%	57%
2	$Mg(ClO_4)_2$	CH_2Cl_2	41%	66%
3	$Cu(OTf)_2$	CH_2Cl_2	41%	59%
4[d,e]	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1), 4Å MS	66%	**95**%
5[d,e,f]	$Cu(OTf)_2$	PhH/CH_2Cl_2 (2:1), 4Å MS	**94**%	86%

[a] Reaction conditions: Lewis acid (1 equiv), *tert*-butylbisoxazoline ligand (1 equiv), 2-iodopropane (6 equiv), Et_3B/O_2 (6 equiv).

[b] Isolated yield, %.

[c] Enantiomeric excess, determined by HPLC.

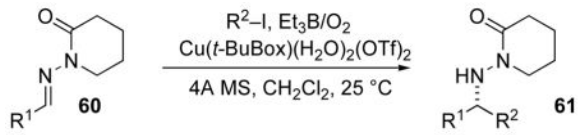
[d] Et_3N was added during workup.

[e] Preformed aquo complex Cu(*t*Bu-Box)$(H_2O)_2(OTf)_2$ was used.

[f] 10 equiv of *i*-PrI and Et_3B were used.

Table 7

Varying the radical precursors and acceptors in Cu(II) catalyzed addition to *N*-acylhydrazones.



a: R^1 = Ph; **b**: R^1 = *p*-$MeOC_6H_4$; **c**: R^1 = *p*-ClC_6H_4

entry	halide	hydrazone	catalyst load	% yield[b]	% *ee*[c]
1	*i*PrI	**60a**	1 equiv	66	95
2	*i*-PrI	**60b**	1 equiv	46	90
3	*i*-PrI	**60c**	1 equiv	53	81
4	EtI[d]	**60a**	1 equiv	88	83
5	*c*-C_5H_9I[d]		1 equiv	86	84
6	*c*-$C_6H_{11}I$[d]		1 equiv	84	89
7	$ClCH_2I$[d]		1 equiv	44[e]	95
8	*i*PrI		0.5 equiv	71	81
9	*i*PrI		0.2 equiv	83	58
10	*i*PrI		0.1 equiv	74	46

[a] Reaction conditions: see Table 6.

[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.