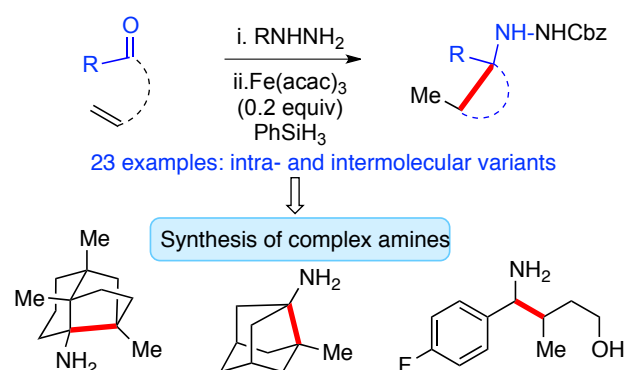


Hydrogen Atom Transfer (HAT)-Triggered Iron-Catalyzed Intra- and Intermolecular Coupling of Alkenes with Hydrazones: Access to Complex Amines

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ABSTRACT: A novel methodology for the coupling of alkenes with aldehyde- or ketone-derived Cbz-hydrazones to form a new C-C bond through a radical process is described. The sequence comprises an initial in situ generation of an iron hydride followed by a hydrogen atom transfer to an alkene, a coupling with a hydrazone and a final reduction of the nitrogen-centered radical. Hydrogenation of the obtained hydrazines renders amines, including valuable *tert*-alkyl amines.

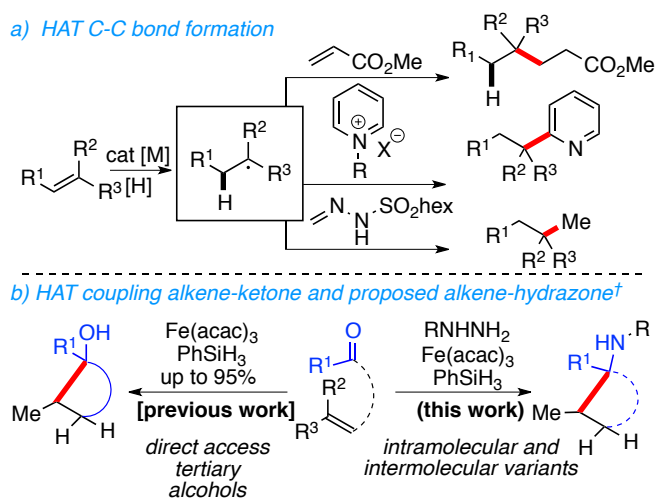


KEYWORDS: *HAT*, iron catalysis, α -*tert*-amines, C-C bond formation, radical processes, synthetic methods

The use of radicals in the formation of carbon-carbon bonds is the flagship reaction of radical chemistry applied to organic synthesis.¹ A landmark in this continuously growing field was the metal-catalyzed generation of radicals from alkenes through a hydrogen atom transfer (HAT)² to

initiate coupling reactions. In these radical reactions Fe(III), and to a lesser extent Mn (III) or Co(II), are used with silanes in EtOH³ to generate the promoter metal hydride able to carry out a HAT to an alkene, the initial step prior to the radical coupling that allows C-C bond construction. Applying these conditions, initially using Fe(acac)₃ as the catalyst and PhSiH₃ as the reductant, the inter- and intramolecular coupling of electron-neutral and -rich alkenes with alkenes bearing an electron-withdrawing group was developed in 2014 by Baran's group,⁴ who laid down the groundwork for the study of other radical acceptors and their application in total synthesis.⁵ Apart from previous diene cross coupling reactions now recognized as C-C bond-forming HAT processes,⁶ other notable achievements in this field involve the use of other types of alkenes,⁷ alkynes,⁸ pyridinium salts,⁹ *p*-quinone methides,¹⁰ sulfonylhydrazones,¹¹ and ketones¹² as radical acceptors (Scheme 1).

Scheme 1. Hydrogen Atom Transfer and Carbon-Carbon Formation from Alkenes



[†] The depicted coupled compounds come from alkenes in which R², R³ = H.

After our studies of a new HAT-initiated radical cyclization of alkene-tethered ketones catalyzed by $\text{Fe}(\text{acac})_3$ leading to alcohols (Scheme 1b), we hoped to expand the tool-box of radical acceptors for alkene HAT processes by exploring the usefulness of the $\text{C}=\text{N}$ double bond (hydrazone functionalization). We were particularly drawn to the potential of this alkene hydrohydrazinoalkylation method (Scheme 1b) to access the structurally important α -tertiary amine (ATA) structural motif after cleavage of the hydrazine N-N bond. This constitutional unit features prominently in alkaloids¹³ and pharmaceuticals such as the anti-virals amantadine and memantine,¹⁴ as well as constituting a potentially interesting building block to gain access to new catalysts¹⁵ (Figure 1).

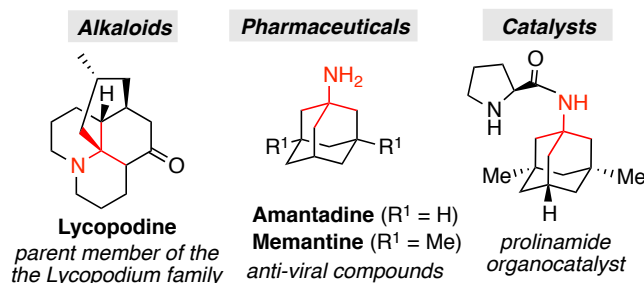


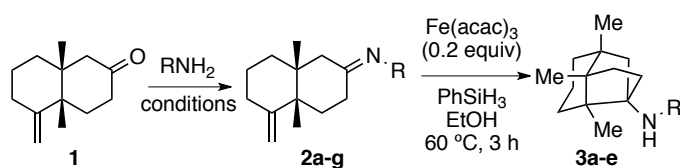
Figure 1. Selected examples of interesting molecules bearing an α -tertiary amine motif

Classical strategies for the alkylation of $\text{C}=\text{N}$ bonds through radical-based methods involve atom transfer conditions (*e.g.* the $\text{Et}_3\text{B}/\text{O}_2$) or reductive processes (*e.g.* tin reagents), alkyl iodides being the typical source of the carbon-centered radical, which promotes the addition that can take place upon several types of $\text{C}=\text{N}$ bonds (*e.g.* hydrazones, oximes) to form the new $\text{C}-\text{C}$ bond.¹⁶ Moreover, in 2007 Carreira¹⁷ reported a cobalt-catalyzed regioselective hydroalldoximation of unactivated alkenes, and recently Molander¹⁸ introduced a photoredox-based addition from alkylsilicate radical precursors to sulfonylimines.

In this communication we report a new approach to products containing α,α -disubstituted and α,α,α -trisubstituted amines (ATA, α -*tert*-amines)¹³ via intramolecular HAT-promoted reactions from alkene-tethered hydrazones leading to amino-substituted cyclic compounds; additionally, the implementation of the cross-coupling version of this iron-catalyzed process opens a new way to access amine compounds.

To study the feasibility of this radical process, ketone **1** was converted to a series of corresponding C=N derivatives (hydrazones, oximes, imines, compounds **2a-g**), which were submitted to radical cyclization conditions using Fe(acac)₃ (0.2 equiv) and PhSiH₃ in EtOH at 60 °C for 3 h. As outlined in Table 1, the results of the HAT-promoted intramolecular radical reaction depend on the nature of the alkene-tethered C=N moiety.

Table 1. Substrate Screening for the Intramolecular Coupling of Type 2 Compounds



Entry	R	yield [%]	yield [%]
1	NHCbz	2a (97)	3a (98)
2	NHBoc	2b (82)	3b (90)
3	OMe	2c (98) ^a	3c (87)
4	NHPh	2d (98) ^a	3d (19) ^c
5	NMe ₂	2e (98) ^a	3e (8)
6	NH ₂	2f (50) ^a	--- ^d
7	Bn	2g (55) ^a	--- ^d
8	NHCbz	2a (97)	3a (91) ^e

9	NHCbz	-	3a (93) ^f
10	H		4 (85) ^g

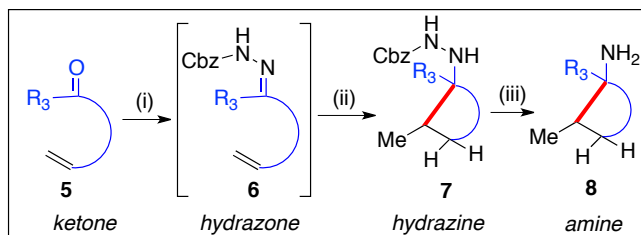
^a Used without purification, and yield determined by NMR (conversion). ^b Used after chromatography. ^c Isolated in its azo form. ^d Complex mixture. ^e Room temperature instead of 60 °C. ^f Combined yield for the one-pot procedure from ketone **1**. ^g Compound **4** is the α -*tert*-amine obtained from hydrogenation of *N*-Cbz hydrazine **3a**.

Initially, we tested a Cbz-protected hydrazone as the radical acceptor and were delighted that the formation of hydrazone **2a** and its subsequent radical cyclization proceeded smoothly with almost quantitative conversion for both coupling steps (**1** → **2a** → **3a**, Table 1, entry 1). The *N*-Boc hydrazone **2b** (entry 2) and methyl oxime **2c** (entry 3) also performed well, albeit with slightly reduced yields. On the other hand, the use of unprotected alkyl or aromatic substituted hydrazones gave poor results for the cyclization step (entries 4-6). The use of a *N*-benzylimine (entry 7) proved unsuccessful, giving a complex mixture of products. Finally, we evaluated some modifications for the synthesis of the Cbz-protected hydrazine **3a**. The reaction could also be efficiently carried out at room temperature with just a slight reduction in yield (entry 8) and proceeded almost as well if the hydrazone intermediate **2a** was not isolated prior to cyclization (entry 9). The latter reaction conditions were therefore the best for the overall process, allowing the coupled hydrazino-substituted tricyclic compound **3a** (91%) to be synthesized directly from ketone **1a**. Sequential cleavage of the carbamate and hydrazine bonds in **3a** under hydrogenation conditions furnished α -*tert*-amine **4** in 85% yield (Table 1, entry 10)

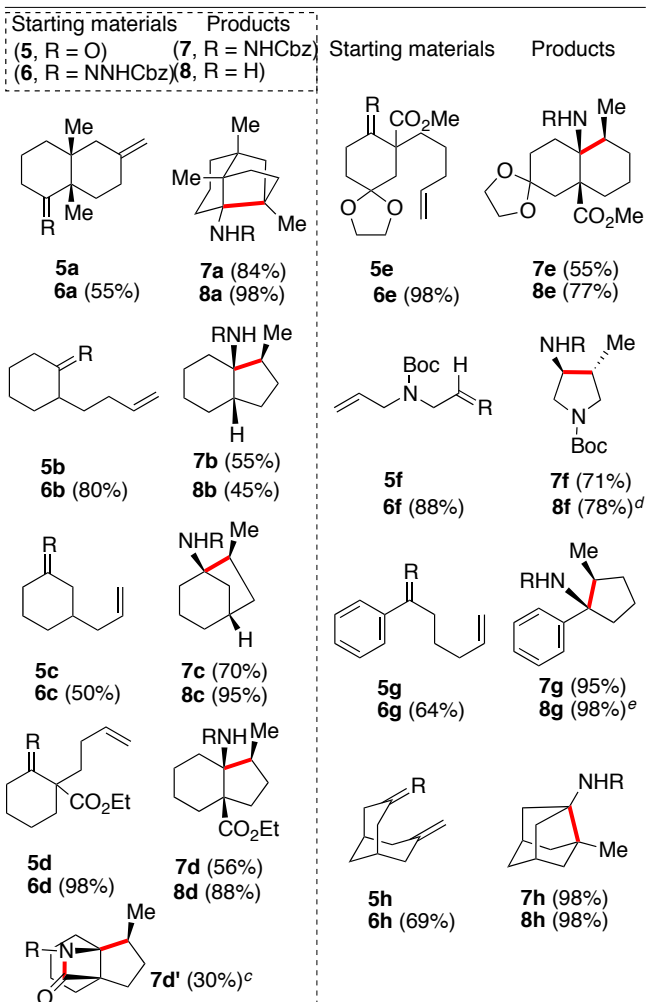
Encouraged by these positive results, we investigated the scope of the intramolecular hydrohydrazination of alkenes using the relatively unexplored hydrazones derived from benzyl carbamate and carbonyl compounds¹⁹ (Table 2). Structurally diverse *N*-Cbz-protected hydrazones

(**6a-g**) were synthesized from a variety of ketones (**5a-h**) containing a mono- or disubstituted alkene tether, and submitted to the same reaction conditions as above to promote the HAT-initiated cyclization process. Hydrazines **7a-h** were obtained in 55-90% yield, being deprotected to the corresponding amine (*i.e.* compounds **8**, see Table 2). The coupling of compound **5h** (R = NOME) through an aza-Prins cyclization leading to C-C bond formation reported by Iwabuchi results in reversed regioselectivity.²⁰ Nitrogen-substituted quaternary centers have usually been synthesized with multiple manipulations and rarely through a direct C–C disconnection as enabled here.¹³ Moreover, despite their simplicity, the majority of the compounds listed in Table 2 are new chemical entities. Among them, 3-noramantadine **8h**, a constitutional isomer of the pharmacologically valuable amantadine,¹⁴ is of particular interest since it constitutes a new congener of the structural family of adamantane-based M2 channel inhibitors. Moreover, **8h** is a rigid, achiral, tricyclic amine, which could constitute a platform to design new catalysts.

Table 2. Scope of the Intramolecular Coupling^{a,b}



(i) NH_2NHCbz , EtOH; (ii) $\text{Fe}(\text{acac})_3$, PhSiH_3 , EtOH, 60 °C, 3 h; (iii) H_2 , Pd-C, MeOH, 20 °C, 24 h



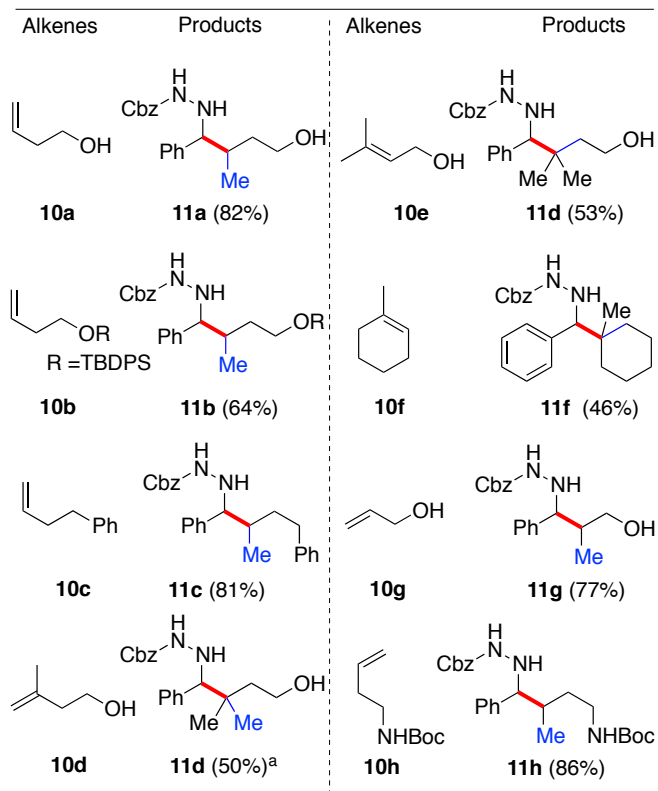
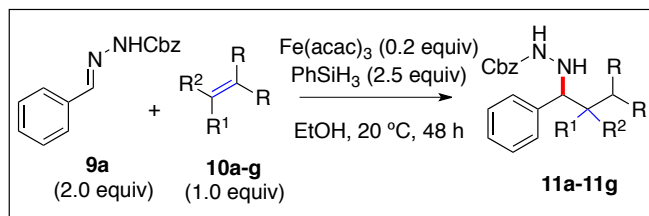
^a The synthesis of all ketones (**5a-5h**) has been previously reported (see SI). ^b For compounds with two possible epimers the major one is depicted. ^c Compound **7d'** was formed by lactamization of **7d**. ^d Compound **8f** was isolated as the corresponding amine. ^e The hydrogenation of the hydrazine **7g** was carried out with Raney-nickel

Given the widespread nature of amines, we sought to extend the reaction from the intra- to the more challenging intermolecular version. Hydrazone **9a** was chosen as the radical acceptor model

and its reaction with 3-buten-1-ol (**10a**) as the radical precursor was evaluated by varying several parameters (see SI, Table S1). As before, the best results were obtained using only 0.2 equiv of Fe(acac)₃, differing in that the reaction time increased to 48 h, the performance was better at room temperature, and 2 equiv of hydrazone was used. In these reaction conditions, hydrazine **11a** was isolated in 82% yield (Table 3).

Having established the optimum conditions, the scope of the reaction was tested on other alkenes while keeping the hydrazone constant (*i.e.* compound **9a**). Examples of this cross coupling with mono-, di-, and trisubstituted olefins (**10a-10g**) are shown in Table 3. As expected, when the substitution degree in the alkene increased, the coupling yield diminished. Finally, the reaction was carried out from 3-butenylamine **10h**, leading to the amino hydrazine **11h** in excellent yield.

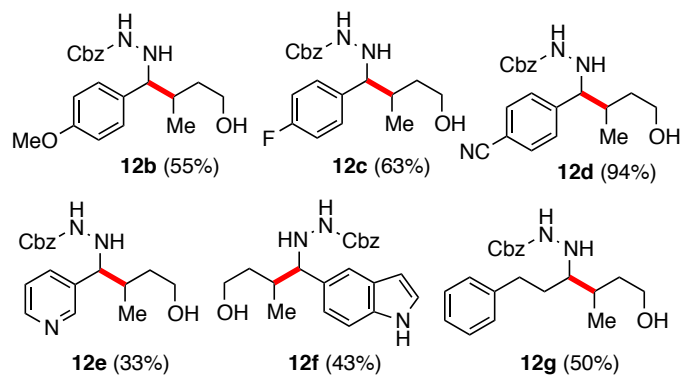
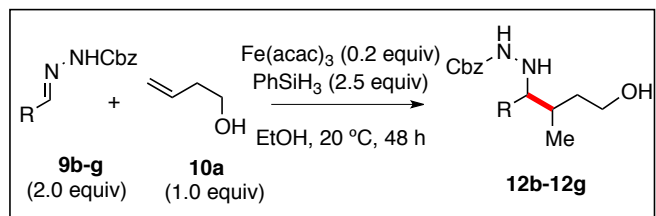
Table 3. Intermolecular Coupling Reaction: Variation of the Alkene Component



^a Reaction time: 72 h. At 48 h, the yield was lower (37%)

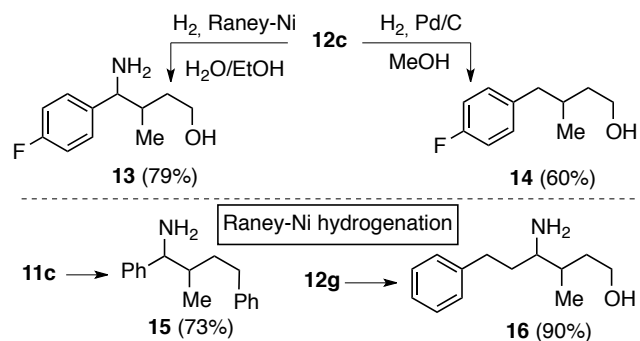
Finally, we studied the scope of the intermolecular reaction using several aldehyde-derived hydrazones under our standard conditions (Table 4).

Table 4. Intermolecular Coupling: Variation of the Hydrazone Component



Hydrogenolysis of the N–N bond using Raney-Ni²¹ from *N*-Cbz hydrazine **12c** allowed the isolation of the benzylic amine **13** in 79% yield; also from **12c**, but using Pd/C in MeOH as the catalyst, an additional cleavage of the C–N bond took place to give **14** in 60% yield (Scheme 2). Retrosynthetically, the latter process involves the formation of a Csp³–Csp³ bond by coupling of an alkene and a benzaldehyde. Finally, hydrazines **11c** and **12g** rendered primary amines **15** and **16**, respectively, when using Raney-Ni in the hydrogenolysis reaction.

Scheme 2. Hydrogenation of *N*-protected hydrazines



In summary, we have shown that an iron-mediated HAT reaction can be successfully employed to reductively couple a wide variety of unactivated alkenes with hydrazones, both intra- and intermolecularly. The resulting *N*-Cbz hydrazine compounds were easily transformed to the corresponding amines through a hydrogenation process. Given the ubiquitous nature of the amine functionality and the novel disconnection approach to achieve nitrogen-containing compounds here reported, we believe this methodology should find a broad range of applications, ranging from the synthesis of natural products to the development of new pharmaceuticals and catalysts.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and spectral data for all new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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