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 EtOH\textsuperscript{3} 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)\textsubscript{3} as the catalyst and PhSiH\textsubscript{3} 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,\textsuperscript{4} who laid down the groundwork for the study of other radical acceptors and their application in total synthesis.\textsuperscript{5} Apart from previous diene cross coupling reactions now recognized as C-C bond-forming HAT processes,\textsuperscript{6} other notable achievements in this field involve the use of other types of alkenes,\textsuperscript{7} alkynes,\textsuperscript{8} pyridinium salts,\textsuperscript{9} p-quinone methides,\textsuperscript{10} sulfonylhydrazone,\textsuperscript{11} and ketones\textsuperscript{12} as radical acceptors (Scheme 1).

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

\[ R_1 R_3 R_2 H \]

\[ HAT C-C bond formation \]

\[ R_1 R_3 R_2 H \]

\[ Fe(acac)_3 PhSiH_3 \text{ up to 95%} \]

\[ R_1 R_3 R_2 H \]

\[ RNHNH_2 Fe(acac)_3 PhSiH_3 \]

\[ \text{previous work} \]

\[ \text{direct access tertiary alcohols} \]

\[ \text{this work} \]

\[ \text{intramolecular and intermolecular variants} \]

† The depicted coupled compounds come from alkenes in which \( R_2, R_3 = H \).
After our studies of a new HAT-initiated radical cyclization of alkene-tethered ketones catalyzed by Fe(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 C=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 alkaloids$^{13}$ 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 catalysts$^{15}$ (Figure 1).

![Figure 1](image_url)

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

Classical strategies for the alkylation of C=N bonds through radical-based methods involve atom transfer conditions (e.g. the Et$_3$B/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 C=N bonds (e.g. hydrazones, oximes) to form the new C-C bond.$^{16}$ Moreover, in 2007 Carreira$^{17}$ reported a cobalt-catalyzed regioselective hydroaldoximation of unactivated alkenes, and recently Molander$^{18}$ 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) 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 ºC 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)   | 3c (87)   |
| 4     | NHPh    | 2d (98)   | 3d (19)   |
| 5     | NMe₂    | 2e (98)   | 3e (8)    |
| 6     | NH₂     | 2f (50)   | ---<sup>d</sup> |
| 7     | Bn      | 2g (55)   | ---<sup>d</sup> |
| 8     | NHCbz   | 2a (97)   | 3a (91)   |
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-benzyllimine (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 carbazate 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 Couplinga,b
The synthesis of all ketones (5a–5h) has been previously reported (see SI). For compounds with two possible epimers the major one is depicted. Compound 7d’ was formed by lactamization of 7d. Compound 8f was isolated as the corresponding amine. 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. Hydrazine 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**
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-Ni\textsuperscript{21} 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 Csp\textsuperscript{3}-Csp\textsuperscript{3} 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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