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Iron-Catalyzed Reductive Coupling of Nitroarenes with Olefins: Intermediate of Iron-Nitroso Complex

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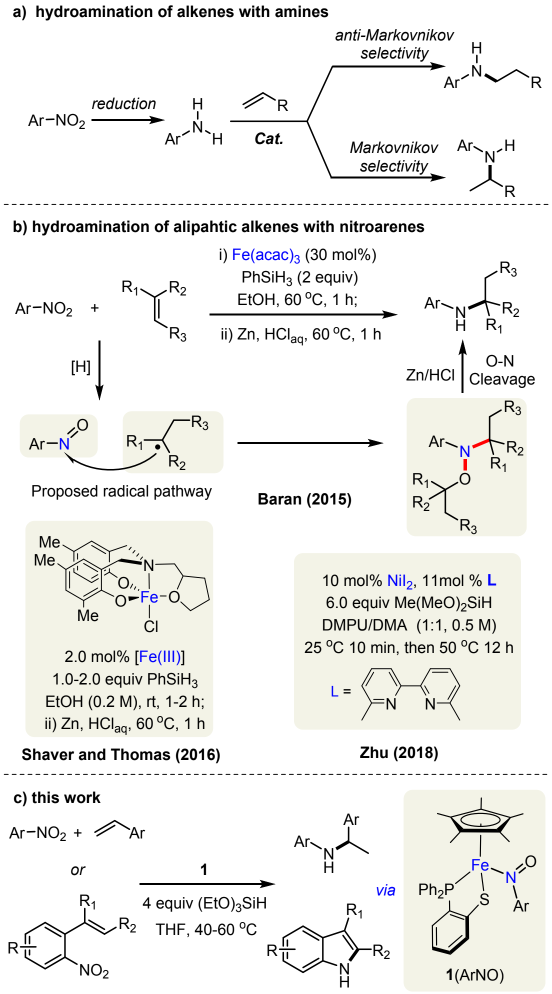
ABSTRACT. Using a single half-sandwich iron(II) compound, Cp*Fe(1,2-$Ph_2PC_6H_4S$)(NCMe) ($Cp^{*-} = C_5Me_5^-$, **1**) as a catalyst, reductive coupling of nitroarenes with olefins has been achieved by a well-defined iron(II)/$(EtO)_3SiH$ system. Through either inter- or intramolecular reductive coupling, various branched amines and indole derivatives have been directly synthesized in one-pot. Mechanistic studies showed that the catalysis is initiated by activation of nitroarenes by the iron(II) catalyst with silane, generating iron-nitrosoarene intermediate for the C–N bond coupling.

KEYWORDS : *Reductive C–N bond coupling, iron catalysis, iron-nitrosoarene intermediate, secondary amines, indoles*

INTRODUCTION

(Hetero)aromatic amines have privileged scaffolds which are widely found in natural products, pharmaceuticals, dyes and industrial fine chemicals.[1-3] Hydroamination through intra- and intermolecular addition of amine N–H bonds to alkenes[4] is an attractive strategy with which to construct new C–N bonds and manipulate (hetero)aryl amines,[5] owing to the widespread availability of alkenes (Scheme 1a). Although regioselective hydroamination via Markovnikov[6] or anti-Markovnikov[7] process is challenging, significant progress has been made in producing linear or branched amines based on transition-metal catalysis.[8] Since aromatic amines are usually obtained from reduction of nitro(hetero)arenes, direct use of nitro(hetero)arenes as nitrogenous partners for the C–N coupling has the great advantage of step economy and easy manipulation,[9] which can offer an appealing process for the construction of C–N bonds.



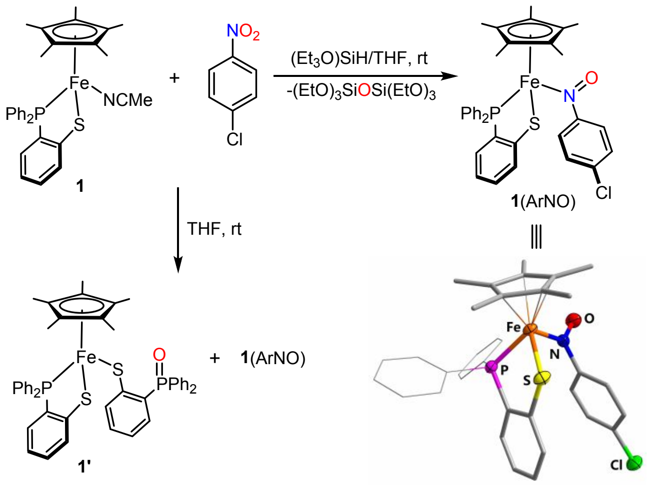
Scheme 1. Approaches to Hydroamination of Alkenes with Nitroarenes

Using a single catalyst or catalyst precursor to realize the reduction of nitro groups, coupled with hydroamination of alkenes in a one-pot protocol is challenging. A breakthrough was made by Baran et al.[10] in 2015, who reported the first use of a simple $Fe(acac)_3/PhSiH_3$ catalytic system to achieve reductive C–N bond formation between nitro(hetero)arenes and aliphatic alkenes, forming various secondary amines in moderate to good yields (Scheme 1b). Subsequently, Thomas and Shaver[11] reported the selective reduction and formal hydroamination of functional nitroarenes with aliphatic alkenes by using a bench-stable amine–bis(phenolate) iron(III) complex (2 mol%) and silane. In these transformations, nitroso compounds was often envisioned as the key intermediate which couples with carbon-centered alkyl radicals generated *in situ* from alkenes. Hu and co-workers reported reductive coupling of nitro(hetero)arenes with numerous alkyl halides to synthesize various (hetero)aryl amines using a $FeCl_2{\bullet}4H_2O$/TMSCl system. [12] In these iron-catalyzed transformations, Zn is required to serve as additional reductant. Recently, Zhu et al. reported an elegant nickel-catalyzed C–N coupling system achieved by merging alkene isomerization and hydroamination.[13]

Although considerable progress have been made in reductive coupling of nitro(hetero)arenes with alkenes, aryl olefins often do not perform well in the iron-catalyzed reductive C–N coupling system, and with the formation of (hetero)aromatic amines in low yields.[10] Using a neutral half-sandwich iron(II) compound, Cp*Fe(1,2-$Ph_2PC_6H_4S$)(NCMe) (Cp^{*-} = $C_5Me_5^-$, **1**)[14] as a catalyst, we report an well-defined iron(II)/$(EtO)_3SiH$ system which achieves reductive hydroamination of nitro(hetero)arenes with alkenes to produce secondary amines and indoles (Scheme 1c). The catalysis is initiated by activation of nitroarenes, generating the iron-nitroso intermediate for the reductive C–N bond coupling.

RESULTS AND DISCUSSION

Activation of Nitroarenes by 1. Metal-nitroso complexes can be derived from the deoxygenation of organic nitro compounds by metal-phosphine[15] or metal-carbonyl precursors.[16] At the outset of this study, we found that **1** reacts readily with nitro(hetero)arenes, affording an iron-nitrosoarene complex that mediates the reduction of nitroarenes to aryl amines by reaction with $(EtO)_3SiH$.

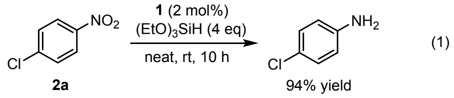


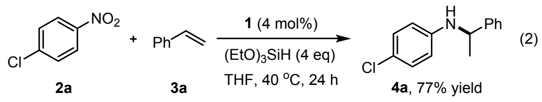
Scheme 2. Activation of Nitroarenes by **1** and the Structure of Iron-Nitrosoarene Intermediate

An addition of **1** to a mixture of 1-chloro-4-nitrobenzene (**2a**) and an equimolar amount of $(EtO)_3SiH$ in THF caused the color of the solution to turn from brown to deep red. According to GC-MS analysis, polysiloxane $(EtO)_3SiOSi(EtO)_3$ (m/z = 342) and 4-chloroaniline was produced, indicating the deoxygenation of the nitro group by hydrosilane. The ^{31}P NMR spectrum of the reaction mixture displayed only a single phosphorus resonance at δ 75. The new iron(II)-nitrosoarene complex, **1**(ArNO) was isolated and identified. Crystallographic analysis revealed the structure of an η^1(N)-nitroso complex,[17] in which the N atom of 4-Cl-C_6H_4NO is coordinated to the iron center

(Scheme 2). The N–O bond length of 1.282(5) Å is slightly increased relative to that in the free 4-Cl-C_6H_4NO molecule, 1.265(3) Å.[18]

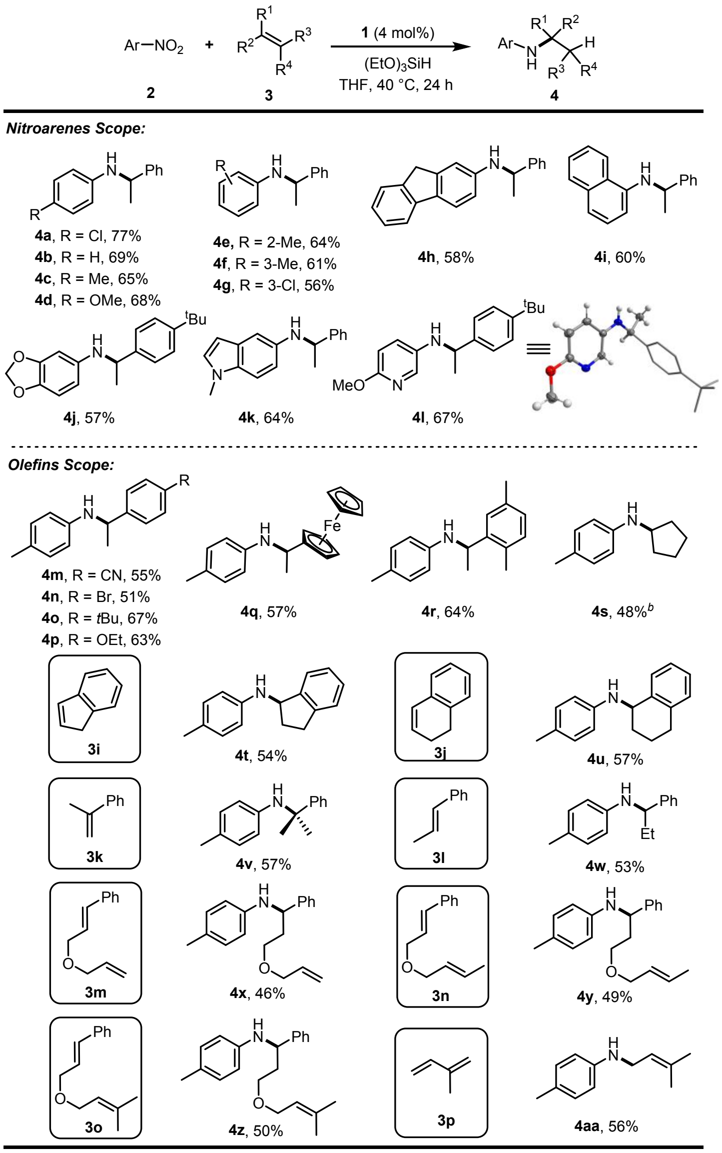
In the absence of $(EtO)_3SiH$, **1** also reacts with **2a** (Scheme 2). In addition to **1**(ArNO), however, a half-sandwich iron(III) species (**1'**) was also crystallized from the reaction mixture (SI, Figure S6). This result indicates that $ArNO_2$ can oxidize the iron complex from Fe(II) to Fe(III), with the phosphine unit serving as a deoxygenation agent.[15] Importantly, **1**(ArNO) reacts further with $(EtO)_3SiH$ to produce *p*-chloroaniline according to GC-MS analysis. The recovery of the organoiron species was deduced from the ESI-MS spectrum, which showed a peak at *m/z* = 484.1147 for Cp*Fe(1,2-$Ph_2PC_6H_4S$). Inspired by the reactivity of **1** and its nitrosoarene derivative, we examined the catalytic reduction of **2a** with $(EtO)_3SiH$ using **1** as the catalyst. With 2 mol% of **1**, compound **2a** was converted to the corresponding primary amine in 94% yield at room temperature (eq 1).





Catalytic Intermolecular C−N Bond Coupling. Subsequently, we examined the reductive C–N bond formation in the reaction between nitro(hetero)arenes and styrene type olefins and found that **1** is capable of catalyzing this challenging transformation. Under the optimized reaction conditions using 4 mol% of **1** and 4 equivalents of $(EtO)_3SiH$ in THF, the intermolecular reductive coupling between **2a** and styrene (**3a**) proceeded well at 40 °C, affording the branched chain amine (**4a**) which was obtained in 77% yield (eq 2). Formation of a linear product was not observed.

Table 1. Scope of Intermolecular C−N Bond Coupling[a]



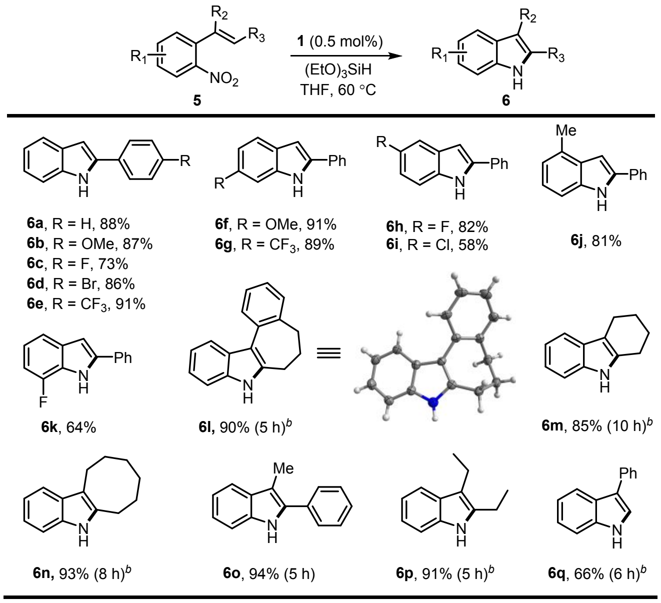
[a]Reaction conditions: nitro(hetero)arene (0.5 mmol), olefin (2.5 mmol), $(EtO)_3SiH$ (2 mmol, 4 equiv), 4 mol% catalyst loading relative to the nitroarene in 0.5 mL of THF at 40 °C for 24 h. Isolated yields were given. [b]60 °C for 8 h.

As shown in Table 1, a series of nitroarenes were subjected to reaction with styrene, and the corresponding branched amines were obtained in moderate to good yields. Various groups at the *para, ortho* or *meta* position on the aromatic ring do not affect this reaction (**4a**-**4g**). Notably, nitro-heteroarenes were used to deliver medicinally relevant building blocks containing indole (**4k**) and pyridine (**4l**) ring systems, the latter of which was confirmed by X-ray crystallographic analysis.

Styrene type alkenes and several aliphatic alkenes are suitable substrates, delivering the corresponding amines in moderate to good yields (Table 1). Electron-donating groups (**4o** and **4p**) at the *para*-position of the phenyl ring appeared to give better yields than electron-withdrawing groups (**4m** and **4n**). Although a cyano group might coordinate to the Fe center and deactivate the catalyst, it is compatible with the reaction, affording the coupled amine product (**4m**) in 55% yield. Aliphatic alkenes are less reactive, and the conversion of cyclopentene (**3h**) provided the amine product (**4s**) in 48% yield. Disubstituted alkenes are all suitable substrates, giving diverse amine products (**4t**-**4w**) in moderate yields. With the substrates (**3m**-**3o**) containing both aromatic and aliphatic alkene moieties, the C–N coupling reaction occurs selectively at the aromatic alkene sites. It is interesting that a 1,4-addition product (**4aa**) was formed selectively in 56% yield when conjugated diene **3p** was used as the substrate. Overall, the present transformation allows the direct amination of aromatic alkenes with nitroarenes to afford branched amines bearing an aryl group in alpha position, which is complementary to the previously described iron-catalyzed reductive coupling of nitroarenes with aliphatic alkenes.[10,11]

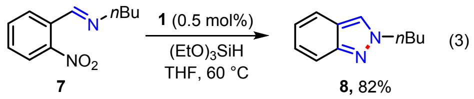
Catalytic Intramolecular C–N coupling. Reductive C–N bond coupling can lead to derivatives of indole, one of the most important heterocycles in organic chemistry.[19] Previous reactions often required strong reductants such as Grignard reagent[20] or $TiCl_3$[21] together with toxic reagents. Therefore, developing efficient catalysts based on earth-abundant metals and under mild reaction conditions is highly desirable.[22] We applied our protocol to the synthesis of indoles by using *o*-nitrostyrenes as the starting materials (Table 2). The intramolecular reductive C–N bond coupling is so efficient that even at 0.5 mol% catalyst loading the indole product **6a** was produced in 88% yield within 6 h at 60 °C. A series of monosubstituted or disubstituted indole derivatives were synthesized in good to excellent yields following this simple procedure.

Table 2*.* Scope of Intramolecular C−N Bond Coupling[a]

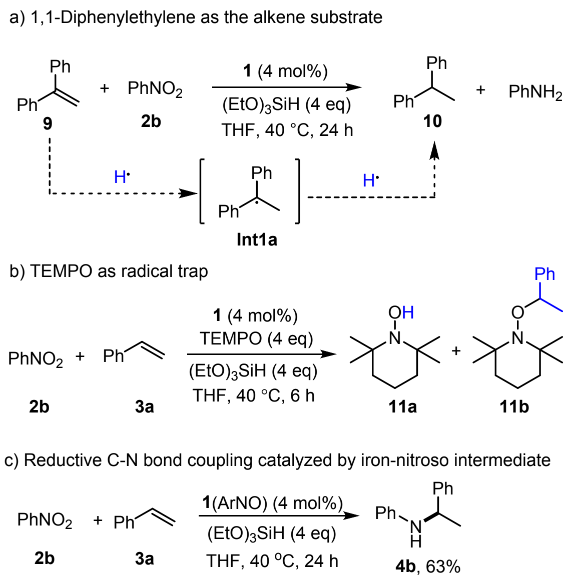


^{a}Reaction conditions: substrates (0.1 mmol), (EtO)$_3$SiH (0.4 mmol), 0.5 mol% catalyst loading relative to the substrates in 4 mL of THF at 60 °C for 6 h, and isolated yields were given. ^{b}80 °C in 1,2-dimethoxyethane.

Functional groups such as −OMe, −F, −Br and −CF$_3$ are all tolerated under the reaction conditions. Nitro compounds with cyclic-alkenes with six to eight membered rings are all suitable substrates, and the fused tricyclic indole derivatives (**6l**-**6n**) were produced in excellent yields in 1,2-dimethoxyethane at 80 ^{o}C. The structure of **6l** containing a seven membered ring was unambiguously established by single crystal X-ray diffraction. Acyclic trisubstituted olefins were converted to 2,3-disubstituted indoles (**6o, 6p**) in very good yields. 3-Phenyl indole (**6q**) was obtained from the corresponding alkene in 66% yield. The catalysis is amenable to a reductive N–N coupling to access an indazole (**8**)[23] from the corresponding aldimine (eq 3).



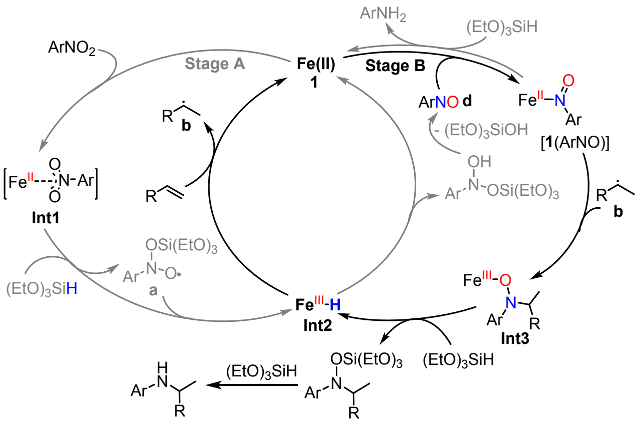
Mechanistic Insights. Several control experiments were conducted to probe the mechanism of the catalysis. When a radical trap, 1,1-diphenylethylene (**9**),[24] was subjected to intermolecular C–N coupling with $PhNO_2$, the reaction was suppressed by productions of 1,1-diphenylethane (**10**) and aniline (Scheme 3a). Such hydrogenation reactions suggest that a stepwise addition of hydrogen radical is involved in the catalysis, probably because the diphenyl stabilized radical (**Int1a**) is not sufficiently active for the C–N coupling with the nitroso intermediate.



Scheme 3. Control Experiments for Mechanistic Study

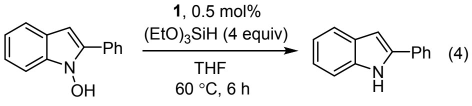
That the catalysis proceeds by a radical mechanism was further supported by the addition of the radical quencher, 2,2,6,6-tetra-methylpiperidine-1-oxyl (TEMPO), to the reductive coupling reaction of **2b** and **3a**. Judging by GC-MS analysis, the desired C–N coupling was indeed interrupted. The hydrogen radical and benzyl radical involved in the coupling were trapped by TEMPO, forming **11a** and **11b**, respectively (Scheme 3b). In contrast, no reaction was detected in the absence of the catalyst. Particularly, the nitroso complex **1**(ArNO) is capable of catalyzing the reductive amination reaction. As examplified by the reaction of **2b** with **3a** (Scheme 3c), the reaction provided **4b** in 63%

yield, comparable to the 69% yield obtained from the reaction using catalyst **1**. This result is indicative of the intermediacy of **1**(ArNO) in the C–N bond coupling.



Scheme 4. Proposed Mechanism for the Iron-Catalyzed Reductive C–N Coupling.

Accordingly, a radical mechanism was proposed for the intermolecular C–N bond coupling (Scheme 4). Based on the dissociation of the MeCN ligand from **1**,[14] we propose that coordination of nitroarene to the iron(II) center leads to the formation of an Fe(II)-substrate adduct (**Int1**) intermediate. In the absence of (EtO)$_3$SiH, **Int 1** undergoes deoxygenation reaction to produce **1'** and **1**(ArNO) (Scheme 2). By the reaction of (EtO)$_3$SiH and **Int 1**, the Fe(III)-H intermediate[25] and an aryl-NO radical (**a**) are generated. Fe(III)-H can react with styrene by donating a hydrogen radical,[26] forming an alkyl radical (**b**) with recovery of the catalyst to the Fe(II) state. The Fe(III)-H could also donate a hydrogen radical in the reduction of a nitro group to the nitroso compound (**d**). Recombination of Fe(II) with **d** leads to the Fe(II)-nitroso intermediate. The benzyl radical then attacks **1**(ArNO) resulting in the formation of an Fe(III) complex (**Int3**), and this is followed by reaction with $(EtO)_3SiH$ to produce the amine product while regenerating the Fe(III)-H species.



6a, 80%

With regard to the intramolecular C−N bond coupling, Driver recently reported a $Fe(OAc)_2$/4,7-$(MeO)_2$Phen/$PhSiH_3$ system for reductive cyclization of *o*-nitrostyrenes into indoles.[22a] They proposed that the catalysis is initiated by the reaction of the iron(II) precursor with the silane to generate iron(II)-hydride species, which is responsible for the reduction of nitrostyrene to nitrosostyrene. In the present case, we propose that the nitrostyrene substrates is directly activated by **1** and subsequently reduced to the nitroso intermediate by silane (Stage A). The intermediacy of *N*-hydroxyindole formed by electrocyclization of nitrosostyrene is usually proposed for such intramolecular C−N bond coupling process.[21,22] Indeed, **1** is capable of catalyzing the transformation of *N*-hydroxyindole to the indole product. For instance, the reaction of *N*-hydroxy-2-phenylindole under the catalytic conditions produced **6a** in 80% yield (eq 4). In contrast, the production of **6a** was not observed in the absence of the iron catalyst.

CONCLUSION

In summary, we have developed an iron(II)-catalyzed reductive coupling of nitro compounds with styrenes under mild conditions. The intermolecular C–N reductive coupling led to diverse branched amines, while an intramolecular transformation efficiently afforded a variety of indole derivatives. In the reported cases of iron-catalyzed reductive C–N couplings, reductive workup with $Zn/HCl_{(aq)}$ is necessary to cleave N–O bond forming the desired products. In the present case, $(EtO)_3SiH$ is the only reducing agent, and the catalysis is initiated by activation of nitroarenes by the iron(II) catalyst with silane. The resultant iron-nitrosoarene intermediate is essential to promote the C–N coupling and a one-pot synthesis of (hetero)aromatic amines. This reaction offered a promising platform for the use of earth-abundant metals for these important radical-type homogeneous transformations.[27]

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information

This contains experimental details, characterization of the products, crystallographic data and cif files (CCDC 1944762-1944765). This information is available free of charge on the ACS Publications website.

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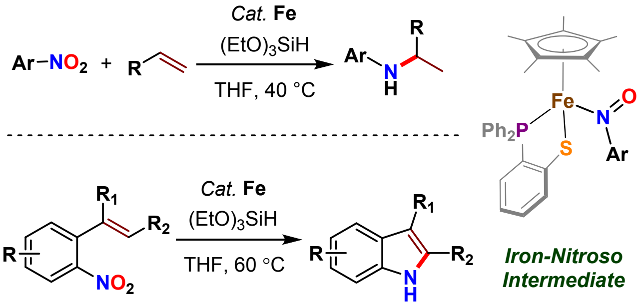
Table of Contents Graphic and Synopsis



Reductive coupling of nitroarenes with olefins has been achieved by a well-defined iron/$(EtO)_3SiH$ catalytic system. By either inter- or intramolecular reductive coupling, diverse branched amines and indole derivatives has been directly synthesized. The catalysis is initiated by activation of nitroarenes, generating the iron-nitroso intermediate for the reductive C–N bond coupling.