Homogeneous Catalysis

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Iron-Carbonyl-Catalyzed Redox-Neutral [4+2] Annulation of N–H Imines and Internal Alkynes by C–H Bond Activation

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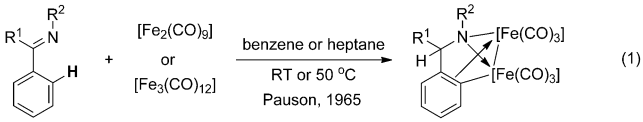
Abstract: *Stoichiometric C–H bond activation of arenes mediated by iron carbonyls was reported by Pauson as early as in 1965, yet the catalytic C–H transformations have not been developed. Herein, an iron-catalyzed annulation of N–H imines and internal alkynes to furnish cis-3,4-dihydroisoquinolines is described, and represents the first iron-carbonyl-catalyzed C–H activation reaction of arenes. Remarkablely, this is also the first redox-neutral [4+2] annulation of imines and alkynes proceeding by C–H activation. The reaction also features only cis stereoselectivity and excellent atom economy as neither base, nor external ligand, nor additive is required. Experimental and theoretical studies reveal an oxidative addition mechanism for C–H bond activation to afford a dinuclear ferracycle and a synergetic diiron-promoted H-transfer to the alkyne as the turnover-determining step.*

Transition-metal-catalyzed direct transformations of inert C–H bonds into C–C and C–X (X = heteroatom) bonds have demonstrated great potential in organic synthesis over the past few decades.[1] Second- and third-row transition metals (such as Pd, Ir, Rh, Ru) have been used successfully in C–H activation reactions in terms of diverse reactivity and controlled selectivity.[1] However, the high cost and rarity of these precious metals necessitate the hunt for new catalysts based on first-row transition metals because of their earth abundance and environmental benign characteristics. Moreover, the unique structures and properties of the first-row transition metals may enable new C–H transformations with unprecedented reactivity and selectivity.[2] In this context, iron is arguably the ideal metal for catalyst development because of its high abundance, low cost, and non-toxicity.[3] Since 2008, the groups of Nakamura and Ilies, Ackermann, Cook, Yoshikai, and others have elegantly disclosed a series of iron-catalyzed C–H activation reactions by using organomagnesium/zinc reagents as key activators, and either dipyridines or diphosphines as essential ligands of iron catalysts.[4]

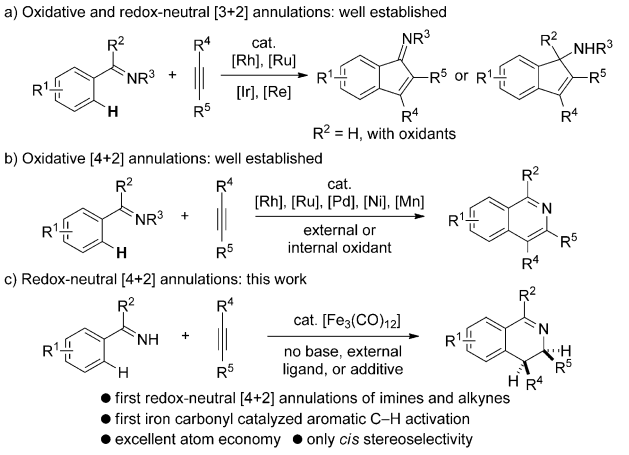
Low-valent iron species formed in situ were frequently proposed to be the truly active catalysts. Regrettably, these key intermediates have not been identified and their defined structures remain elusive so far. In contrast, well-defined iron carbonyl complexes such as $[Fe_2(CO)_9]$ and $[Fe_3(CO)_{12}]$ were showcased by Pauson and others to promote C–H bond activation of aromatic imines as early as in 1965 [Eq. (1)].[5]



(1)

Notably, the reduction of the imino group occurred after the C–H bond activation, thus forming a dinuclear iron complex bearing a 1-ferraisoindoline moiety. However, no iron-carbonyl-catalyzed C–H transformations based on this stoichiometric cycloferration protocol was reported, even after half a century.

The application of C–H activation strategies to the synthesis of heterocycles has recently attracted immense attention, and proved to be very powerful. As illustrated examples, the annulations of imine derivatives with alkynes by C–H activation allow expedient access to various N-heterocycles in a highly efficient manner. Among these, the oxidative and redox-neutral [3+2] cyclizations of imines and alkynes to approach indenimines and indenamines, respectively were achieved through either Rh-, Ru-, Ir-, or Re catalysis (Scheme 1a).[6] Meanwhile, the oxidative [4+2] annulations of imines and alkynes leading to isoquinolines



Scheme 1. Transition-metal-catalyzed annulations of imines and alkynes by C–H bond activation.

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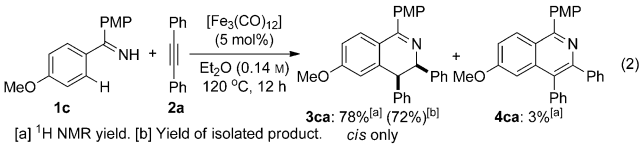
were also well established by using various transition-metal catalysts and proper oxidants (Scheme 1b).[7,8] However, the redox-neutral [4+2] annulations of imines and alkynes to give 3,4-dihydroisoquinolines remain elusive. Herein, we describe the first redox-neutral [4+2] cyclization of N–H imines and internal alkynes to access *cis*-3,4-dihydroisoquinolines by employing iron carbonyls as catalysts (Scheme 1c). This reaction also represents the first iron-carbonyl-catalyzed C–H transformation of arenes since its parent cycloferration reaction was reported in 1965.[5]

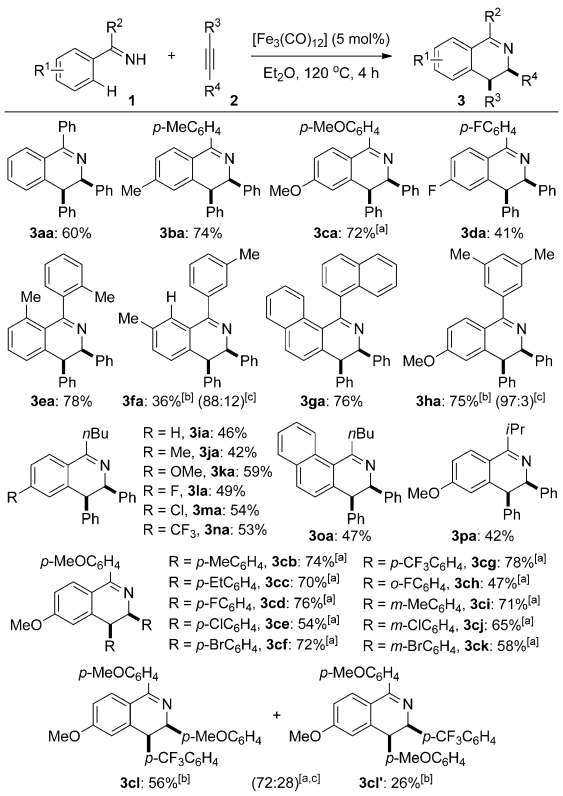
Recently, we reported a manganese-catalyzed dehydrogenative [4+2] annulation of N–H imines and alkynes, thus affording isoquinolines with the evolution of dihydrogen.[8] During the evaluation of various transition-metal catalysts, we serendipitously found that the *cis*-3,4-dihydroisoquinoline **3ca**, rather than the isoquinoline **4ca**, was selectively formed in 78% yield (^{1}H NMR) from the reaction of the N–H imine **1c** and diphenylacetylene (**2a**) in diethyl ether when [$Fe_3(CO)_{12}$] was used as a catalyst instead of [$MnBr(CO)_5$] [Eq. (2); PMP = *para*-methoxyphenyl].[9] Of note, no *trans*-3,4-dihydroisoquinoline product was detected during the optimization process.



[a] ^{1}H NMR yield. [b] Yield of isolated product.

We next investigated the substrate scope (Scheme 2). Both electron-donating and electron-withdrawing groups on N–H imines were tolerated successfully (**3aa**-**da**). An *ortho*-substituted diarylimine showed good reactivity despite its increased steric hindrance (**3ea**). The less sterically congested C–H bond was preferably annulated in the *meta*-substituted imine, albeit in lower yield (**3fa**). The di(naphthalenyl)methanimine **1g** was also a suitable substrate (**3ga**), and an excellent level of regiocontrol was obtained when an unsymmetrical diarylimine was used (**3ha**). Alkyl aryl imines bearing electronically varied groups were also applicable to this reaction (**3ia**–**pa**). A series of aromatic alkynes containing functional groups like F, Cl, Br, and CF_3 in different substitution patterns was all compatible with the reaction conditions (**3cb**–**k**), which allowed further synthetic elaborations. Unfortunately, the reactions of other alkynes such as 4-octyne did not proceed and phenylacetylene failed to give the expected product.[9] Two regioisomers were formed when an unsymmetrical diaryl alkyne was used, and fortunately could be separated by simple chromatography (**3cl**, **3cl′**).

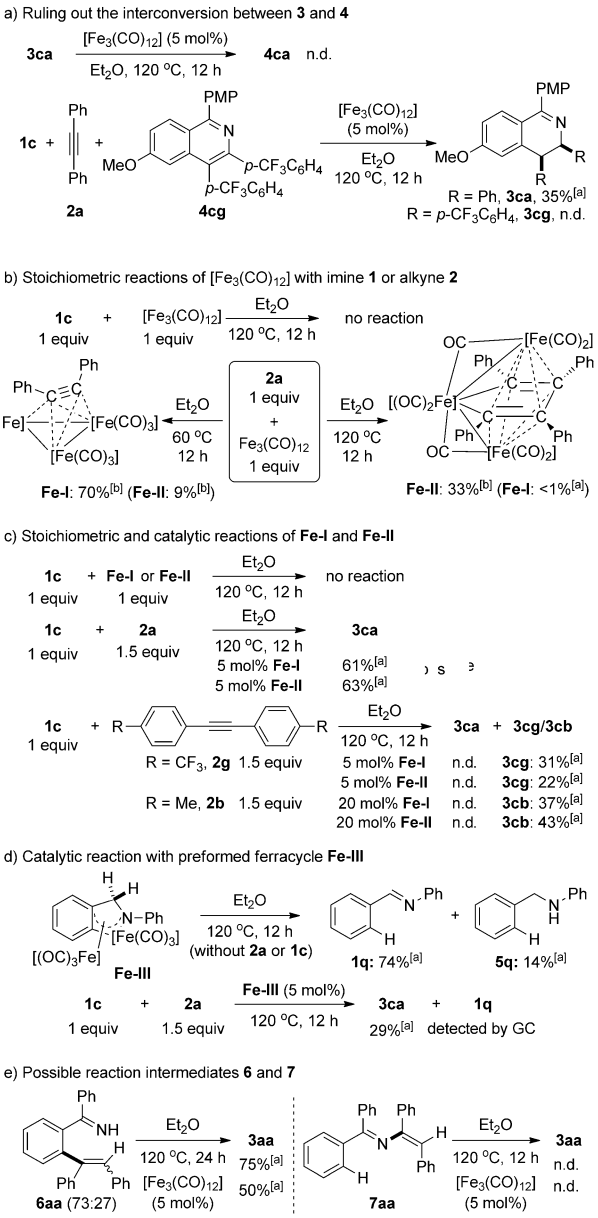
To probe the possible reaction intermediates, a series of mechanistic experiments was carried out. First, the interconversion between **3** and **4** was tested (Scheme 3a). It was shown that no formation of **4ca** was observed from **3ca** under the standard reaction conditions. Meanwhile, only **3ca** was obtained without **3cg** detected when **4cg** was added to the reaction of **1c** and **2a**, and thus ruled out the intermediacy of **4cg** for the formation of **3cg**. Second, a stoichiometric reaction of either the imine **1c** or alkyne **2a** with [$Fe_3(CO)_{12}$]



Scheme 2. Scope with respect to the imines and alkynes. Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), [$Fe_3(CO)_{12}$] (5 mol%), Et_2O (1.6 mL), 120 °C, 24 h. Yield are those of the isolated products. [a] Et_2O (0.25 M). [b] Yield of the pure isolated isomer. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture.

was run (Scheme 3b). No reaction occurred with **1c** and [$Fe_3(CO)_{12}$], whereas the trinuclear iron complexes **Fe-I** and **Fe-II** were selectively generated from reactions of [$Fe_3(CO)_{12}$] and **2a** at 60 and 120 °C, respectively.[10] Although no reaction took place with **1c** and either **Fe-I** or **Fe-II**, they did catalyze the annulation of **1c** with **2a** to afford **3ca** in comparable yields (Scheme 3c). Furthermore, different alkynes, **2g** and **2b**, were reacted with **1c** under the catalysis of either **Fe-I** or **Fe-II** and only **3cg** and **3cb** were formed. Therefore **3ca** was not detected, and suggests that the alkyne moieties in **Fe-I** and **Fe-II** were not involved in the final product. Third, the dinuclear ferracycle **Fe-III** was synthesized by C–H activation from the aldimine **1q** and [$Fe_3(CO)_{12}$][5] and it mainly decomposed to **1q** under the reaction conditions even in the presence of either **2a** or **1c**, which implies the reversibility of the C–H activation and H-migration steps (Scheme 3d). Interestingly, **Fe-III** could also catalyze the annulation of **1c** and **2a**, albeit with lower reactivity. Finally, two possible reaction intermediates, **6aa** and **7aa**,[11] formally arising from the C–H and N–H addition of **1a** to **2a**, respectively, were synthesized and examined under the reaction conditions (Scheme 3e). It turned out the former could deliver product **3aa** with or without [$Fe_3(CO)_{12}$], thus indicating its possible involvement in the reaction.

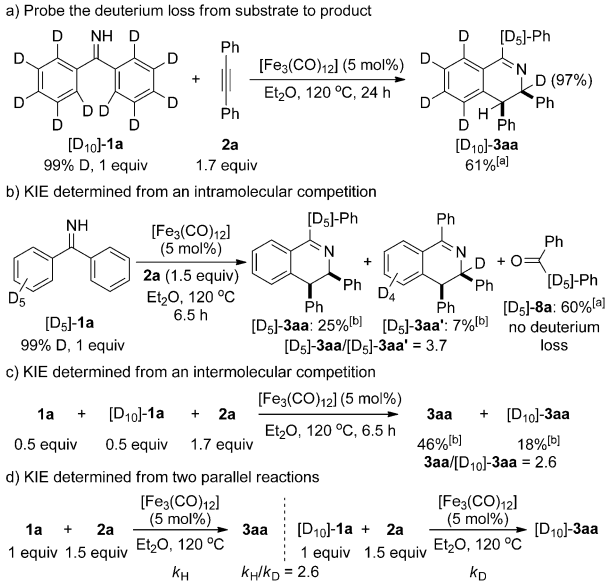
To shed light on the nature of the C–H activation step, several deuterium-labeling experiments were carried out. The reaction of the deuterated imine [D_{10}]-**1a** with **2a** was first



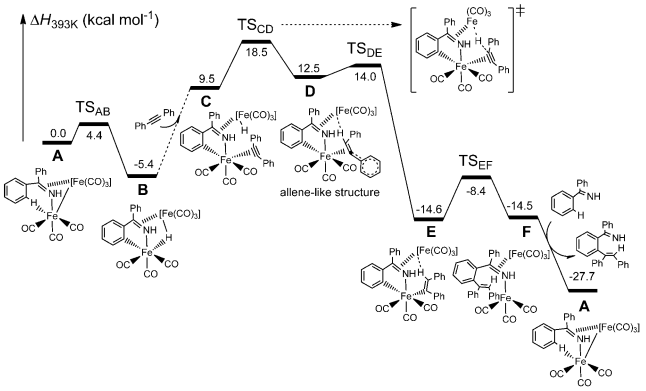
Scheme 3. Mechanistic experiments. ^{1}H NMR yields are shown. The structure of **Fe-II** was confirmed by X-ray crystallographic analysis.[13] [a] Determined by ^{1}H NMR spectroscopy. [b] Yield of isolated product.

examined and the *ortho* D atom was transferred to the 3-position of [D_{10}]-**3aa** with negligible deuterium loss, and suggested a possible oxidative addition pathway for the C–H bond activation step (Scheme 4a). Then, intramolecular, intermolecular, and parallel-reaction kinetic isotope effect (KIE) experiments were performed, thus giving KIE values of 3.7, 2.6, and 2.6 respectively (Scheme 4b–d). These results indicate that the C–H bond cleavage might be involved in the turnover-limiting step or in a prior step with a lower activation barrier.[12]

To explore more details of the reaction mechanism, extensive DFT calculations were conducted on the basis of mononuclear, dinuclear, and trinuclear iron catalytic systems.



Scheme 4. Deuterium-labeling experiments. [a] Yield of isolated product. [b] Yield determined by ^{1}H NMR spectroscopy.



Scheme 5. The most plausible reaction mechanism obtained from DFT calculations.

Through comparison of reaction energetics, we discovered that the dinuclear one is most likely the catalytically active species.[9] The calculated reaction profile of **1a** and **2a** are depicted in Scheme 5. First, the C–H activation step from the **1a**-bound reactant **A** to intermediate **B** proceeds reversibly by an oxidative addition mechanism, with a small activation energy of only 4.4 kcal mol^{-1}. At this step, **2a** is not likely to bind the iron catalyst, otherwise the C–H activation energy becomes considerably larger (exceeding 28 kcal mol^{-1}). This implication is in line with the experimental findings that in alkyne-bound **Fe-I**/**Fe-II**, alkyne moieties were not involved in the final product. After C–H activation, **2a** binds **B** to form the complex **C**, which requires a substantial amount of energy, 14.9 kcal mol^{-1}. The iron-hydride addition to the alkyne from **C** generates **D** with a barrier of 9.0 kcal mol^{-1}, and the alkyne moiety changes to an allene-like structure by assistance of conjugation involving its aromatic substituent. After overcoming a tiny barrier of 1.5 kcal mol^{-1}, **D** easily isomerizes into the more stable alkenyl structure **E**, with a substantial

energy of 27.1 kcal mol^{-1} released. From **E** to **F**, the reductive elimination occurs to form the C–C bond generating **6aa** with barrier of 6.2 kcal mol^{-1} (note that the barrier of this C–C coupling in trinuclear system is more than 33 kcal mol^{-1}),[9] which could deliver the final product **3aa** by electrocyclization according to our experimental study. In total, the turnover-determining step in the whole calculated pathway is the insertion of the alkyne into the iron-hydride bond, which is in agreement with the KIE experiments. Notably, the synergy between the two iron nuclei plays an essential role in both the C–H activation and the H-transfer steps.

In summary, the first redox-neutral [4+2] annulations of N–H imines and internal alkynes was developed by employing iron carbonyl catalysis, which also represents the first iron-carbonyl-catalyzed C–H transformation of arenes since its parent cycloferration reaction reported in 1965. The easily available starting materials, simple catalyst system, sole *cis*-stereoselectivity, and excellent atom economy add more benefits to this protocol. Remarkably, mechanistic studies highlight the essential synergy of dinuclear irons in the oxidative C–H addition and turnover-limiting H-transfer to alkyne steps in the catalytic cycle, and give important hints for future work on dinuclear iron catalysis.

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Keywords: alkynes · annulations · C–H activation · heterocycles · iron

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[13] CCDC 1445220 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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