Heterocycles

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Manganese-Catalyzed Dehydrogenative [4+2] Annulation of N–H Imines and Alkynes by C–H/N–H Activation**

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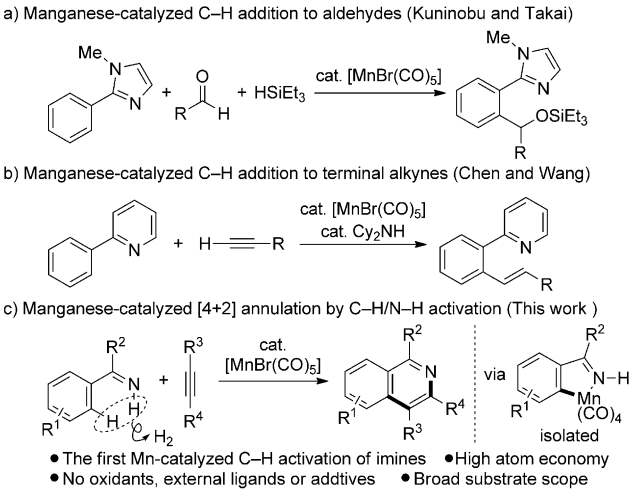
Abstract: *Described herein is a manganese-catalyzed dehydrogenative [4+2] annulation of N–H imines and alkynes, a reaction providing highly atom-economical access to diverse isoquinolines. This transformation represents the first example of manganese-catalyzed C–H activation of imines; the stoichiometric variant of the cyclomanganation was reported in 1971. The redox neutral reaction produces H_2 as the major byproduct and eliminates the need for any oxidants, external ligands, or additives, thus standing out from known isoquinoline synthesis by transition-metal-catalyzed C–H activation. Mechanistic studies revealed the five-membered manganacycle and manganese hydride species as key reaction intermediates in the catalytic cycle.*

Over the past two decades, the strategy based on C–H activation has evolved as a powerful tool to construct functional molecules, and offers an atom- and step-economic alternative to traditional organic synthesis which relies heavily on transformations of various functional groups.[1] So far, second- and third-row transition-metal (e.g., Rh, Pd, Ir, and Ru) catalysts have played a leading role in the area of C–H activation.[2] However, from the viewpoint of sustainable development, it is desirable for chemists to develop more economic alternatives to these precious metals. In line with this, first-row transition metals are naturally abundant and inexpensive, and can be promising candidates for catalyst development in C–H activation reactions.[3]

Manganese is a first-row early transition metal and has been far less studied in the activation of inert C–H bonds, except for the exceptional work on manganese oxo complex promoted C–H oxidation.[4] Despite the fact that stoichiometric cyclometalation reactions of $[MnR(CO)_5]$ ($R = CH_3$, Bn, etc.) have been well documented,[5] significant challenges still remain to achieve an efficient catalytic turnover and further develop new types of C–H transformations beyond the stoichiometric ones. Thus, considerably rare examples of manganese-catalyzed C–C bond-forming reactions by C–H activation have been disclosed recently.[6] Kuninobu and Takai et al. demonstrated a manganese-catalyzed insertion of an aldehyde into a $C(sp^2)$–H bond (Scheme 1a).[6a,b] Our group latter reported a manganese-catalyzed addition of an aromatic C–H bond to a terminal alkyne (Scheme 1b).[6c] Inspired by the stoichiometric cyclomanganation of benzylideneaniline described by Bruce et al. in 1971,[7] we set out to explore manganese-catalyzed C–H transformations of imines. Herein we report a dehydrogenative [4+2] annulation of N-unsubstituted imines and alkynes to expediently furnish isoquinolines by manganese-catalyzed C–H/N–H activation (Scheme 1c). Remarkably, the reaction produces H_2 as the predominant byproduct and eliminates the need for an oxidant. Though rhodium-, ruthenium-, palladium-, and nickel-catalyzed isoquinoline syntheses from imines (or its structural analogues) and alkynes by C–H activation have been reported,[8–11] an external or internal oxidant is generally needed in the reaction to induce catalytic turnover. In principle, the extrusion of H_2 is the most atom-economic, arguably ideal, and unprecedented feature among the reported annulations. Therefore, this manganese-catalyzed reaction provides an important complementary method for isoquinoline synthesis.



Scheme 1. Manganese-catalyzed C–C bond formation by C–H activation.

Initially, bis(4-methoxyphenyl)methanimine (**1a**) and diphenylacetylene (**2a**) were chosen as model substrates and extensive investigations were carried out to define the

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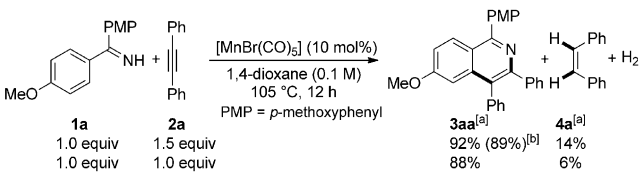
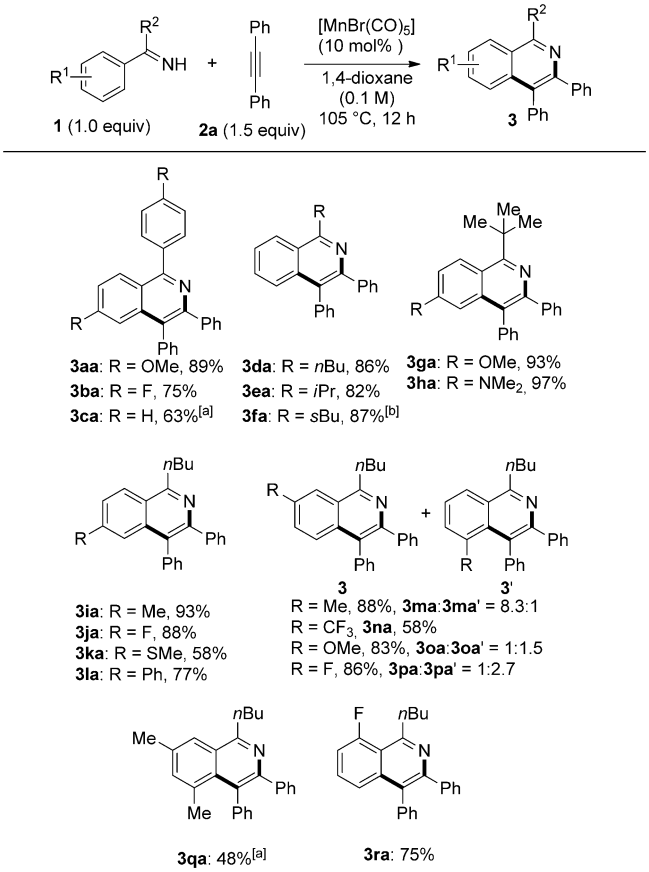


Scheme 2. The model reaction. [a] Yield determined by ^{1}H NMR spectroscopy. [b] Yield of the isolated product. PMP = *para*-methoxyphenyl.

optimal reaction conditions.[12] In the end, treatment of **1a** with 1.5 equivalents of **2a** in the presence of 10 mol% $[MnBr(CO)_5]$ gave the isoquinoline **3aa** in 92% yield, and *cis*-stilbene (**4a**) was formed in 14% (Scheme 2). GC analysis of the atmosphere above the reaction mixture clearly showed the existence of H_2 and CO. Importantly, only 1.0 equivalent of **2a** was sufficient to achieve as high as an 88% yield (determined by NMR spectroscopy) of **3aa** and that of **4a** decreased to 6%.

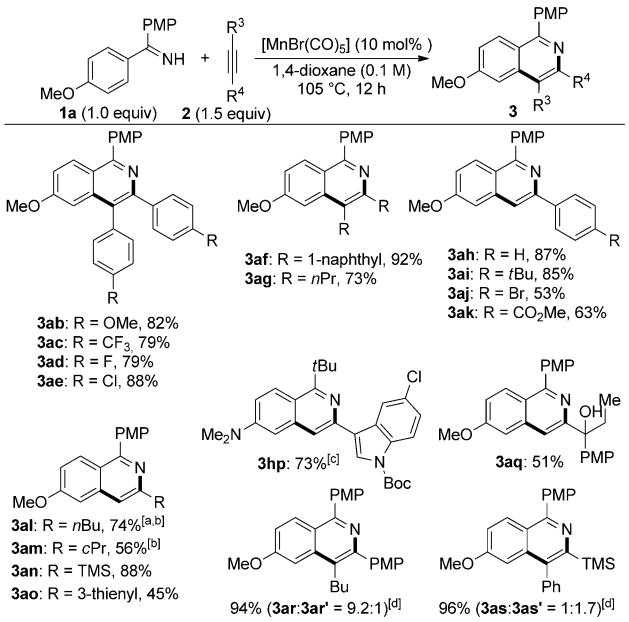
With the optimized reaction conditions established, the scope of imines was first examined (Scheme 3). Both diaryl and aryl alkyl ketimines with a wide array of functional groups and varied substitution patterns reacted readily to give isoquinolines in good yields (**3aa–la**, **3qa**, **ra**). The presence of



Scheme 3. Scope of imines. Reaction conditions: **1** (1.0 mmol), **2a** (1.5 mmol), $[MnBr(CO)_5]$ (0. 1 mmol), 1,4-dioxane (1 mL), 105 °C, 12 h. Yields of the isolated **3** are shown. [a] 15 mol% $[MnBr(CO)_5]$. [b] 24 h.

a *meta*-methyl or *meta*-trifluoromethyl group allowed C–H activation to take place predominantly or exclusively on the less sterically hindered positions (**3ma**, **na**). However, reverse regioselectivities were observed with *meta*-methoxy- and *meta*-fluoro-substituted imines (**3oa′**, **pa′**). This result could be attributed to the secondary directing effect of OMe and F groups.[13]

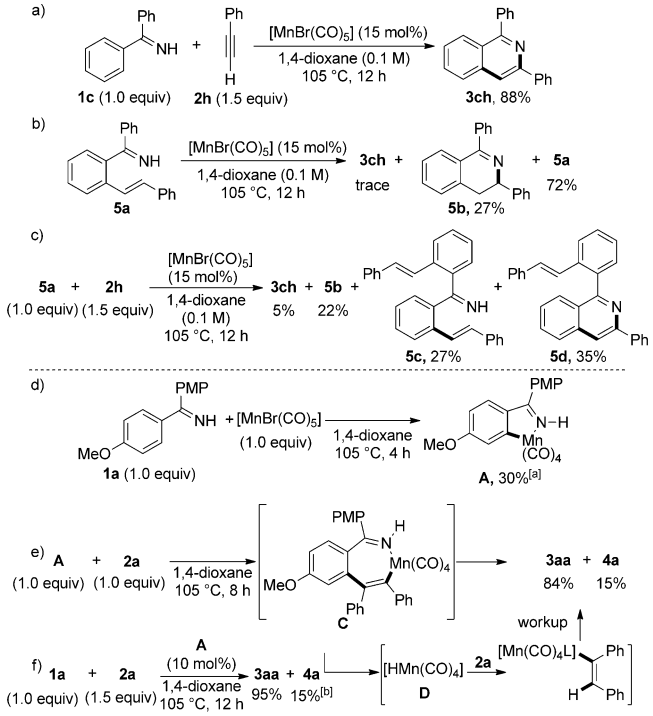
Next, the scope of alkynes was explored using **1a** as the reaction partner (Scheme 4). Various aromatic and aliphatic acetylenes reacted with **1a** readily to form the corresponding isoquinolines in high yields (**3ab–g**, **3ar**, **as**). It is noteworthy



Scheme 4. Scope of the alkynes. Reaction conditions: **1a** (1.0 mmol), **2** (1.5 mmol), $[MnBr(CO)_5]$ (0. 1 mmol), 1,4-dioxane (1 mL), 105 °C, 12 h. Yields of the isolated **3** are shown. [a] 15 mol% $[MnBr(CO)_5]$. [b] 150 °C. [c] Using **1h** in place of **1a**. [d] Major isomer was shown. PMP = *p*-methoxyphenyl.

that terminal alkynes, which are often challenging substrates for rhodium-, palladium-, nickel-, and ruthenium-catalyzed isoquinoline synthesis,[8–11,14] proved to be amenable to the current system. A broad range of terminal alkynes including aromatic (**2h–k**), aliphatic (**2l**,**m**), silylated (**2n**), and heteroaromatic (**2o**,**p**) alkynes, participated smoothly in the reaction to generate **3ah–ao** and **3hp** as single regioisomers in moderate to excellent yields. The terminal alkyne **2q**, containing alcohol functionality, was also suitable for the reaction (**3aq**).

To probe the reaction mechanism, a set of experiments was carried out (Scheme 5).[12] First, the annulation of **1c** with **2h** cleanly produced the isoquinoline **3ch** in 88% yield (Scheme 5a). As a potential intermediate of this reaction, the 2-styryl imine **5a** was prepared and then subjected to the reaction conditions in either the absence or the presence of **2h**. In the first case, unreacted starting material largely remained and only a trace amount of **3ch** as well as 27% of the 3,4-dihydroisoquinoline **5b** was formed (Scheme 5b). In

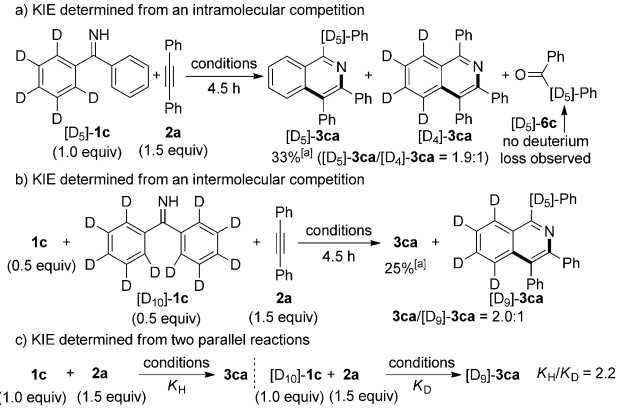


Scheme 5. Probe for possible reaction intermediates. Yields were determined by ^{1}H NMR spectroscopy unless otherwise noted. [a] Yield of the isolated product. [b] Based on **1a**.

the latter case, a complicated mixture of products was generated (Scheme 5c). It can be seen that the conversion of **5a** into **3ch** exhibited very low efficiency and was accompanied by competitive formation of several side products (**5b–d**), which were not detected in the reaction of **1c** with **2h** (Scheme 5a). Therefore, the mechanism involving an alkene intermediate such as **5a** might not be operative in the dehydrogenative annulation.

Second, the stoichiometric reaction of $[MnBr(CO)_5]$ with **1a** afforded the five-membered manganacycle **A** in 30% yield upon isolation (Scheme 5d). The ease of C–H activation here with $[MnBr(CO)_5]$ was striking and contrasted with conventional cyclomanganation achieved by the general use of manganese hydrocarbyls, which were tediously synthesized from $[Mn_2(CO)_{10}]$ and Na/Hg.[5,15] Treatment of **A** with the alkyne **2a** gave **3aa** and **4a** in 85% and 14% yields, respectively, possibly via the intermediacy of the seven-membered manganacycle **C** (Scheme 5e).[16] It is likely that a Mn-H species was responsible for the formation of **4a**. Moreover, a catalytic amount of **A** efficiently promoted the dehydrogenative cyclization of **1a** with **2a** (Scheme 5f), thus affording **3aa** in comparable yield. Collectively, these results indicate the involvement of **A** in the catalytic reaction.

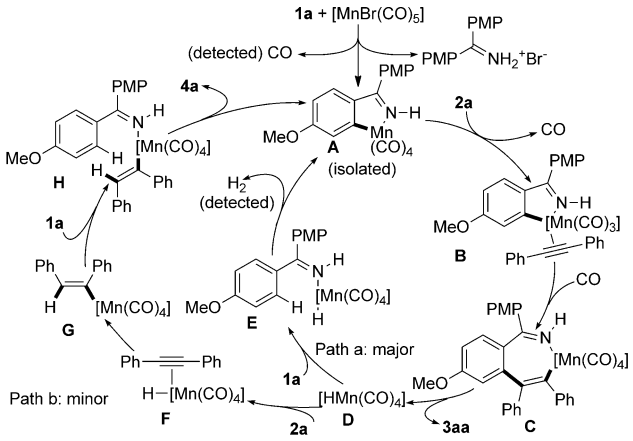
Third, three types of kinetic isotope effect (KIE) experiments were conducted and the KIE values were measured to be 1.9, 2.0, and 2.2 respectively (Scheme 6a–c). In addition, the deuterated ketone $[D_5]$-**6c** from hydrolysis of the unconverted imine was isolated and no deuterium loss was detected, thus indicating the C–H activation step might be an irreversible process. These experiments suggested that the C–H



Scheme 6. KIE experiments. [a] Determined by ^{1}H NMR spectroscopy. Conditions: $[MnBr(CO)_5]$ (10 mol%), 1,4-dioxane, 105 °C

bond cleavage might be directly involved in the rate-determining step.[17]

Based on the above results, a plausible catalytic cycle is proposed in Scheme 7. The reaction commences with cyclomanganation of the imine **1a** with $[MnBr(CO)_5]$ to generate the five-membered manganacycle **A**. Insertion of **2a** into the Mn–C_{aryl} bond of **A** via the manganese alkyne



Scheme 7. A proposed catalytic cycle.

complex **B** forms the seven-membered manganacycle **C**, which is directly transformed into **3aa** with concomitant formation of the manganese hydride species $[HMn(CO)_4]$. There are two possible rationales for this process: 1) metathesis between C(sp^2)–Mn and N–H bonds, and 2) oxidative addition of the N–H bond followed by C–N reductive elimination. Then the coordinatively unsaturated complex **D** combines with **1a** and subsequently regenerates **A** along with elimination of H_2 (Path a). Alternatively, **D** could react with **2a** and **1a** to eventually regenerate **A** and release **4a** through a series of sequential steps (Path b). The H_2-producing pathway (Path a) is deemed to be the major one according to the low yields of **4a** (Scheme 2).

In conclusion, a manganese-catalyzed dehydrogenative [4+2] annulation of N–H imines and alkynes has been

developed to provide an expedient access to isoquinolines. This transformation represents the first example of manganese-catalyzed C–H activation of imines and features the high atom economy, broad substrate scope, and a very simple catalytic system. The mild reaction conditions obviate the need of any oxidants, external ligands, or additives, thus tolerating diverse functional groups. Through the mechanistic study, the key reaction intermediates have been identified and the ability of manganese(I) to catalytically induce C–H bond cleavage and C–C and C–N bond formation, has been recognized. Based on the above knowledge, further exploration on manganese catalysis in the field of C–H activation is currently underway in our laboratory.

Experimental Section

General procedure: In an oven-dried Schlenk tube under N_2 atmosphere, a mixture of the imine **1** (1.0 mmol), alkyne **2** (1.5 mmol), $[MnBr(CO)_5]$ (0.1 mmol), and anhydrous 1,4-dioxane (10 mL) was stirred at 105 °C for 12 h. The solvent was then removed in vacuo and the product **3** was isolated by column chromatography on silica gel.

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