C–H Activation Hot Paper

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# Manganese-Catalyzed Direct Nucleophilic C($sp^2$)–H Addition to Aldehydes and Nitriles

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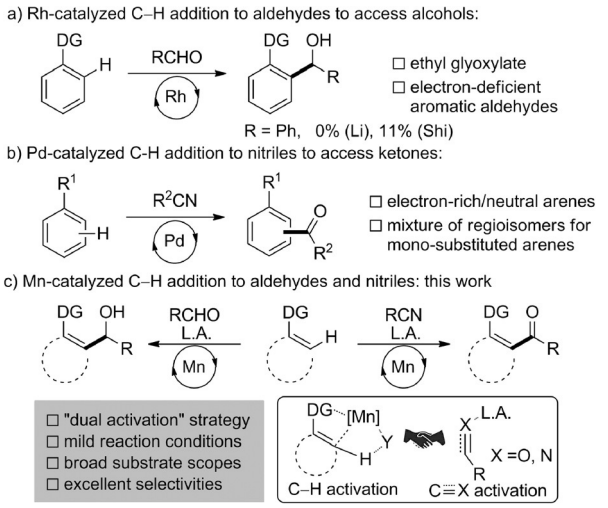
***Abstract:*** *Herein, a manganese-catalyzed nucleophilic addition of inert C($sp^2$)–H bonds to aldehydes and nitriles is disclosed by virtue of a dual activation strategy. The reactions feature mild reaction conditions, excellent regio- and stereoselectivity, and a wide substrate scope, which includes both aromatic and olefinic C–H bonds, as well as a large variety of aldehydes and nitriles. Moreover, mechanistic studies shed light on possible catalytic cycles.*

Transition-metal-catalyzed functionalization of inert C–H bonds, which are ubiquitous in organic molecules, has witnessed an explosive advance in the past three decades.[1] The redox reactivity of transition metals (e.g. $Pd^{II}/Pd^{IV}$, $Pd^{II}/Pd^{0}$, $Rh^{III}/Rh^{I}$) contributes significantly to the diversity of C–H transformations. In contrast, the redox-neutral reactivity of the organometallic intermediate formed by C–H activation with electrophiles has been less explored, in particular for aryl–Pd species, until the recent achievements by Yu et al.[2] Meanwhile, the redox-neutral direct nucleophilic addition of inert C–H bonds to polar multiple bonds has recently attracted more attention since substrates bearing such polar unsaturated bonds often contain various heteroatoms and are essential building blocks for the synthesis of highly functionalized complex molecules.[3] In this context, the transition-metal-catalyzed direct nucleophilic C–H addition to aldehydes is highly desirable for alcohol synthesis. However, there are a few challenges to achieving efficient catalytic turnovers for such a process: 1) low nucleophilicity of the C–M (M = transition metal) bond formed by C–H activation, 2) insertion of aldehydes into the C–M bond is reversible,[4] and 3) the transition-metal alkoxide species resulting from insertion is recalcitrant to release of the transition metal for the next catalytic cycle, but undergoes side reactions such as β-hydride elimination.[5] To circumvent these pitfalls, the groups of Miura, Takai, and Shi successfully shifted the equilibrium of the C–H addition to aldehydes forward by addition of external silanes, thus affording the corresponding silylethers as final products.[6] Alternatively, directing groups were employed as intramolecular traps for the metal alkoxides to form stable cyclic products.[7] In comparison with these trapping strategies, the direct nucleophilic C–H addition of arenes to aldehydes to access alcohols has been little explored. Specifically, the groups of Li and Shi independently demonstrated a rhodium-catalyzed alcohol synthesis through C–H addition to aldehydes (Scheme 1 a).[8] Nevertheless, the scope with respect to the aldehyde was limited to electron-deficient ones, while electron-neutral and electron-rich aldehydes exhibited very low reactivity, if any at all.[8] Therefore, it remains an unmet challenge to develop a general Grignard-type nucleophilic C–H addition to aldehydes.




***Scheme 1.*** Transition-metal-catalyzed direct nucleophilic C–H addition to aldehydes/nitriles. DG = directing group, L.A. = Lewis acid.

Along the same lines, the direct nucleophilic addition of inert C–H bonds to nitriles has also met with very limited success so far because of the relatively low propensity of the C≡N bond to nucleophilic attack. Larock et al. elegantly demonstrated the palladium-catalyzed synthesis of ketones by C–H addition of arenes to nitriles (Scheme 1 b).[9a,b] Unfortunately, the reaction was only applicable to electron-rich and electron-neutral arenes, and a mixture of regioisomers was formed when monosubstituted benzenes were used. Later on, the groups of You and Wang reported the palladium-catalyzed addition of indoles and thiophenes to nitriles to furnish 3-acylindoles and 2-acylthiophenes, respectively.[9c–e] Regrettably, the substrates were limited to electron-rich arenes. An electropalladation pathway for the C–H activation of arenes might account for the observed reactivity and selectivity of these systems. Therefore, the direct nucleophilic C–H addition of arenes, in particular the electron-neutral and electron-deficient ones, to nitriles with controllable regioselectivity is still in high demand. As part of

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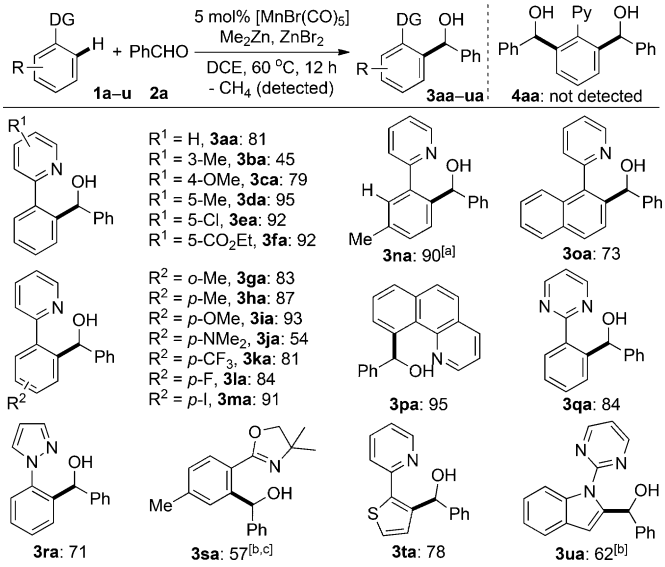
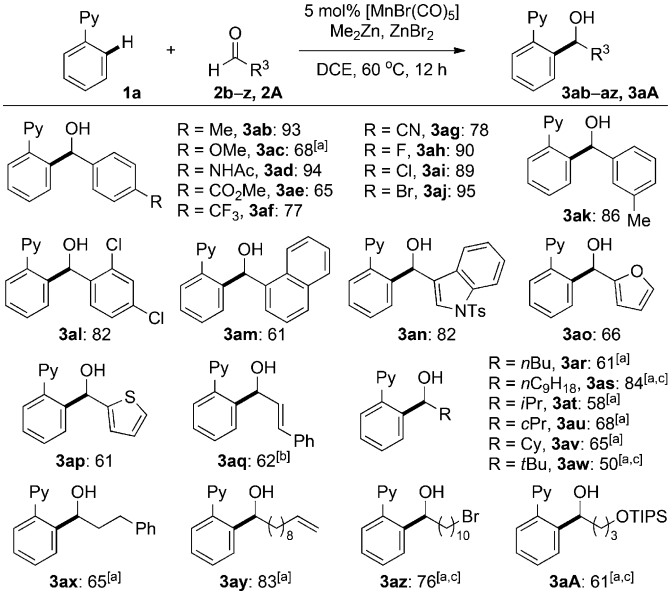
our ongoing interest in earth abundant manganese catalyzed C–H activation,[10,11] herein we disclose a manganese-catalyzed C–H nucleophilic addition to aldehydes and nitriles by a strategy of dual activation, namely, merging C–H activation by a transition-metal catalyst and aldehyde/nitrile activation by a Lewis acid (Scheme 1c). Importantly, this protocol is suitable for both aromatic and olefinic C–H bonds, and is applicable to a wide range of aldehydes and nitriles.

At the outset, 2-phenylpyridine (**1a**) and benzaldehyde (**2a**) were selected as model substrates. After an extensive survey of reaction parameters, it was found that the synergetic use of dimethylzinc ($Me_2Zn$) and zinc bromide ($ZnBr_2$) was essential for accessing the expected product **3aa** with high efficiency (Scheme 2).[12] Finally, **3aa** was obtained in 81% yield upon isolation by using mild reaction conditions. Importantly, the double-addition product **4aa** was not detected during the entire optimization process. Also, the evolution of methane ($CH_4$) was confirmed by GC analysis. We then investigated the scope with respect to the arene. A wide range of functional groups (OMe, $NMe_2$, $CO_2Et$, $CF_3$, F, Cl, I, etc.) was well tolerated at different positions of the 2-arylpyridines (**3ba**–**ma**). When two C–H bonds were available on the benzene moiety, the C–H addition occurred at the sterically more accessible site with high regioselectivity (**3na**). 1-Pyridylnaphthalene and benzo[*h*]quinoline were also suitable substrates, thus giving the corresponding products smoothly (**3oa**,**pa**). Arenes containing other directing groups such as pyrimidine, pyrazole, and oxazoline also worked well (**3qa**–**sa**). Heteroarenes bearing thiophene and indole skeletons successfully delivered the corresponding products **3ta** and **3ua**. Of note, the formation of **3ua** is complementary to traditional Friedel–Crafts reactions, which usually give 3-indolyl alcohols.[13]



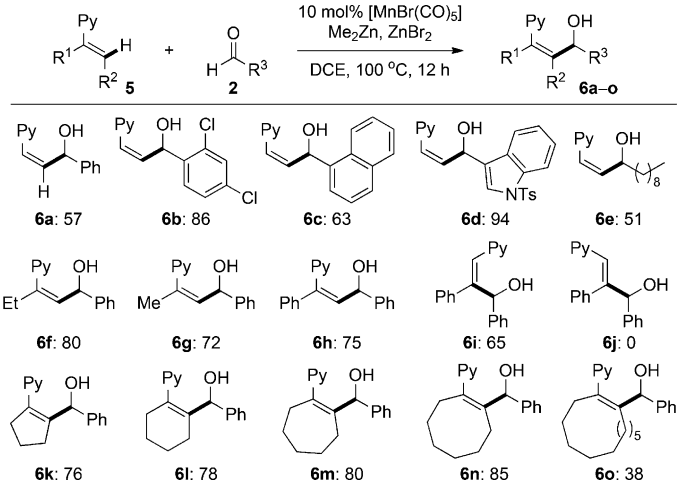

***Scheme 2.*** Scope with respect to the arene. Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), $[MnBr(CO)_5]$ (0.025 mmol), $Me_2Zn$ (0.75 mmol), $ZnBr_2$ (0.5 mmol), DCE (5 mL), 60 °C, 12 h. Yields are those of the isolated products. [a] Major regioisomer was shown, **3na**/**3na′** = 12:1. [b] 100 °C. [c] 10 mol% $[MnBr(CO)_5]$. DCE = 1,2-dichloroethane.

The scope with respect to the aldehyde was further tested (Scheme 3). In sharp contrast to the rhodium-catalyzed protocols,[8] the present reaction was suitable for not only electron-deficient aldehydes but also electron-neutral and electron-rich ones (**3ab**–**aj**). Different substitution patterns of aldehydes had no obvious influence on the reaction outcome (**3ak**–**al**). The sterically demanding 1-naphthaldehyde and various heteroaromatic aldehydes bearing indole, furan, and thiophene rings were all compatible with this reaction (**3am**–**ap**). Remarkably, α,β-unsaturated cinnamaldehyde gave only the 1,2-addition product **3aq**, without any of the 1,4-addition product. The more challenging aliphatic aldehydes were next explored. It turned out that a variety of primary, secondary, and even tertiary aliphatic aldehydes, both acyclic and cyclic, were amenable to this protocol at increased temperature (**3ar**–**ax**). Importantly, functionalities such as an olefin, alkyl bromide, and silylether were well tolerated (**3ay**–**aA**).

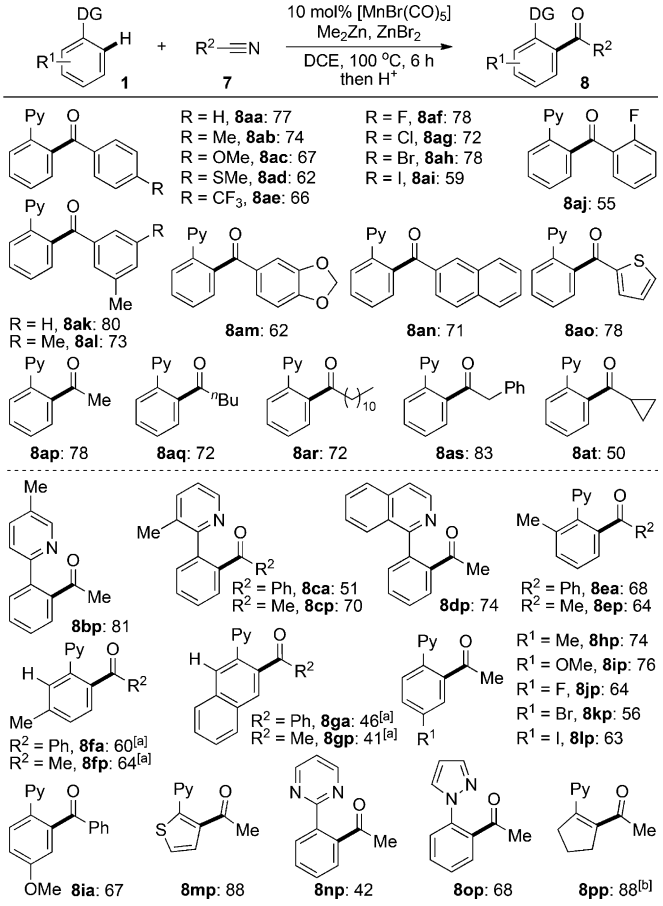



***Scheme 3.*** Scope with respect to the aldehyde. Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $[MnBr(CO)_5]$ (0.025 mmol), $Me_2Zn$ (0.75 mmol), $ZnBr_2$ (0.5 mmol), DCE (5 mL), 60 °C, 12 h. Yields are those of the isolated products. [a] 100 °C. [b] Single isomer. [c] 10 mol% $[MnBr(CO)_5]$. TIPS = triisopropylsilyl, Ts = 4-toluenesulfonyl.

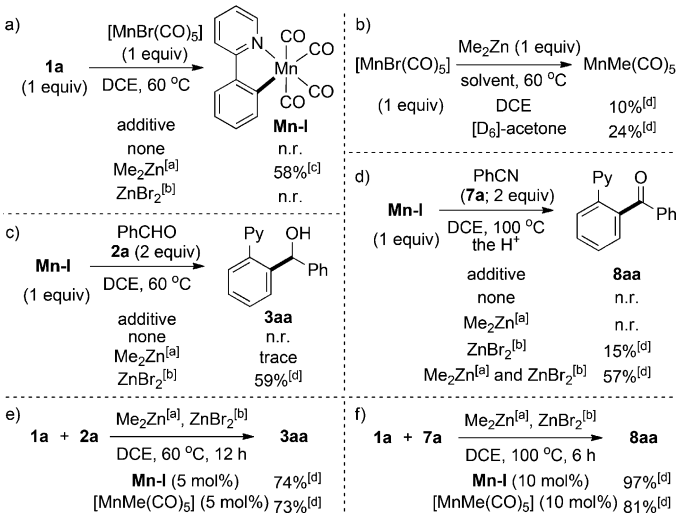
Next, we pursued the possibility of direct nucleophilic addition of olefinic C–H bonds to aldehydes (Scheme 4). Gratifyingly, the expected product **6a** was obtained as the sole *Z* stereoisomer from 2-vinylpyridine and **2a**. Again, aromatic, heteroaromatic, and aliphatic aldehydes were all amenable to this reaction (**6b**–**e**). The configuration of **6c** was unambiguously confirmed by single-crystal X-ray diffraction analysis.[12] 1,1-Disubstituted olefins could also deliver the corresponding products smoothly with perfect stereoselectivity (**6f**–**h**). The *E*-configured 1,2-disubstituted olefin containing a C–H bond *cis* to the pyridine group was a suitable substrate,




***Scheme 4.*** Olefinic C–H addition to aldehydes. Reaction conditions: **5** (0.5 mmol), **2** (1.0 mmol), $[MnBr(CO)_5]$ (0.05 mmol), $Me_2Zn$ (0.75 mmol), $ZnBr_2$ (0.5 mol), DCE (5 mL), 100 °C, 12 h. Yields are those of the isolated products.




***Scheme 5.*** Nucleophilic C–H addition to nitriles. Reaction conditions: **1** (0.5 mmol), **7** (1.0 mmol), $[MnBr(CO)_5]$ (0.05 mmol), $Me_2Zn$ (0.75 mmol), $ZnBr_2$ (0.5 mol), DCE (0.5 mL), 100 °C, 6 h, then HCl (2 mL, 3 M), 100 °C, 2 h. Yields are those of the isolated prodcuts. [a] Single regioisomer. [b] Hydrolysis by $H_2O$.




***Scheme 6.*** Mechanistic experiments. [a] 1.5 equiv [b] 1.0 equiv [c] Yield of isolated product. [d] Yield determined by $^1H$ NMR spectroscopy.

while the *Z*-configured one failed to give any product as expected (**6i** versus **6j**). Trisubstituted olefins bearing varied ring sizes underwent the desired C–H addition, thus successfully affording the allylic alcohols **6k–o** with fully substituted C=C bonds.

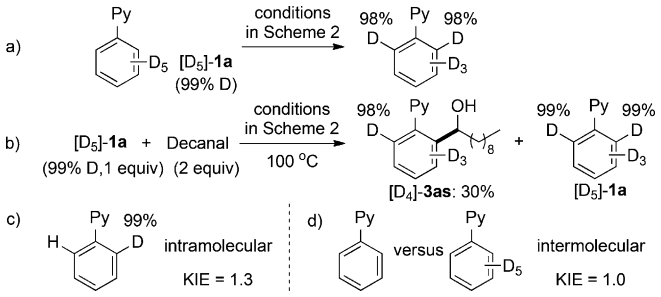
Encouraged by the above results, we then explored the manganese-catalyzed C–H nucleophilic addition of arenes to nitriles bearing the more challenging C≡N bonds. To our delight, the expected reactions occurred smoothly under similar reaction conditions, thus affording ketones after acidic hydrolysis (Scheme 5). A multitude of aromatic nitriles were amenable to this protocol and the reaction demonstrated a good tolerance of functional groups (**8aa–ai**). The *ortho*- and *meta*-substituted benzonitriles, 2-naphthonitrile, and 2-thiophenenitrile were all suitable substrates (**8aj–ao**). Importantly, aliphatic nitriles worked equally well in the reaction (**8ap–at**). Then, the scope with respect to the arene was examined. The reaction was applicable to various pyridinyl arenes of different substitution patterns. Of note, only the addition products derived from sterically less congested C–H bonds were obtained when two positions were available in the substrates (**8fa**,**ga** and **8fp**,**gp**). Other directing groups such as pyrimidine and pyrazole were also effective for this reaction (**8np**,**op**). Moreover, addition of the olefinic C–H bond to acetonitrile took place successfully, thus affording an α,β-unsaturated ketone (**8pp**) in high yield.

To shed light on the possible reaction mechanism, a series of experiments was conducted. Initially, the stoichiometric reaction of **1a** and $[MnBr(CO)_5]$ was examined and no reaction occurred (Scheme 6a). The addition of $Me_2Zn$ to the reaction resulted in the formation of the manganacycle **Mn-I** in 58% yield upon isolation, while $ZnBr_2$ did not show any effect. To further explore the role of $Me_2Zn$, $[MnBr(CO)_5]$ was treated with $Me_2Zn$ in DCE and $[D_6]$acetone (Scheme 6b), and $[MnMe(CO)_5]$ was detected in 10 and 24% yield (NMR), respectively.[14] Then, the reaction of **Mn-I** with **2a** was checked and no reaction occurred (Scheme 6c). It was $ZnBr_2$ this time, rather than $Me_2Zn$, that enhanced the reaction efficiency significantly.[15] These results clearly indicated that $Me_2Zn$ was indispensable for the C–H activation

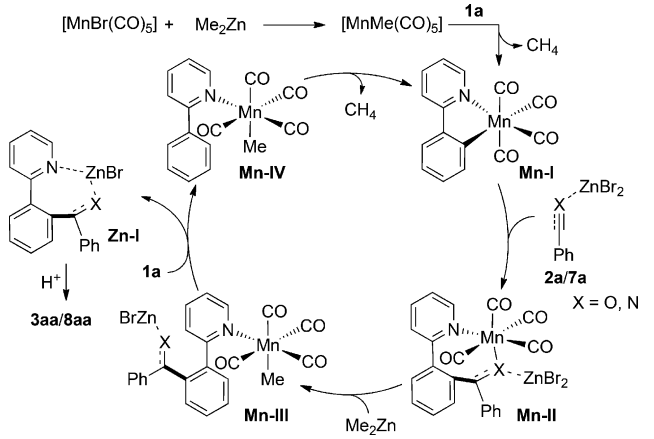
step, whereas $ZnBr_2$ was essential to the aldehyde-activation step. The reaction of **Mn-I** and benzonitrile (**7a**) demonstrated a similar tendency and a more profound synergetic effect of $Me_2Zn$ and $ZnBr_2$ (Scheme 6d). Importantly, both **Mn-I** and $[MnMe(CO)_5]$ catalyzed the reactions to give the expected products in comparable yields (Scheme 6e,f), and thus suggested that they are possible reaction intermediates.

To further probe the nature of the C–H activation step, deuterium-labeling experiments were carried out. First, the sole treatment of $[D_5]$2-phenylpyridine ($[D_5]$-**1a**) under the reaction conditions gave no obvious deuterium loss at the *ortho* positions of $[D_5]$-**1a** (Scheme 7a). Second, when $[D_5]$-**1a** was employed to react with decanal, almost no H–D scrambling was observed at the *ortho* positions of both the product $[D_4]$-**3as** and the remaining $[D_5]$-**1a** (Scheme 7b). These results indicated the C–H activation step is irreversible in the reaction. Third, intramolecular and intermolecular kinetic isotope effect (KIE) values were measured to be 1.3 and 1.0, respectively (Scheme 7c,d), and implied that the cleavage of the C–H bond was not involved in the rate-determining step. These results are in sharp contrast to those of previous manganese systems.[11]




***Scheme 7.*** Deuterium-labeling experiments.

Based on these observations and literature clues,[14] a tentative reaction mechanism is depicted in Scheme 8. $[MnBr(CO)_5]$ reacts first with $Me_2Zn$ to afford $[MnMe(CO)_5]$, which undergoes cyclomanganation with **1a** to give the manganacycle **Mn-I**. The insertion of either **2a** or **7a**, activated by $ZnBr_2$, results in the formation of the seven-membered manganacycle **Mn-II**. Ligand metathesis of **Mn-II** with $Me_2Zn$ gives the methylmanganese species **Mn-III**, which reacts further with **1a** to generate **Mn-IV** and release zinc species **Zn-I**. The ensuing C–H activation in **Mn-IV** regenerates **Mn-I** with the evolution of $CH_4$,[12] thus closing the catalytic cycle. Hydrolysis of **Zn-I** provides either **3aa** or **8aa**.




***Scheme 8.*** A plausible reaction mechanism.

In conclusion, the manganese-catalyzed Grignard-type nucleophilic addition of $C(sp^2)$–H bonds to aldehydes/nitriles to access alcohols/ketones was developed by using a strategy of dual activation, which circumvents the limitations of previous rhodium and palladium catalytic systems.[8,9] It also features mild reaction conditions, broad substrate scope, and excellent regio- and stereoselectivity. Further explorations on the direct C–H transformations using this manganese catalyst system are underway in our laboratory.

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*Angew. Chem.* **2015**, *127*, 13863–13867

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[15] The following Lewis acids were also effective: $Yb(OTf)_3$: 10%, $SbF_3$: 9%, $AgBF_4$: 30%, $MgBr_2$: 48%.

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