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One-Pot C−H Formylation Enabled by Relay Catalysis of Manganese(I) and Iron(III)

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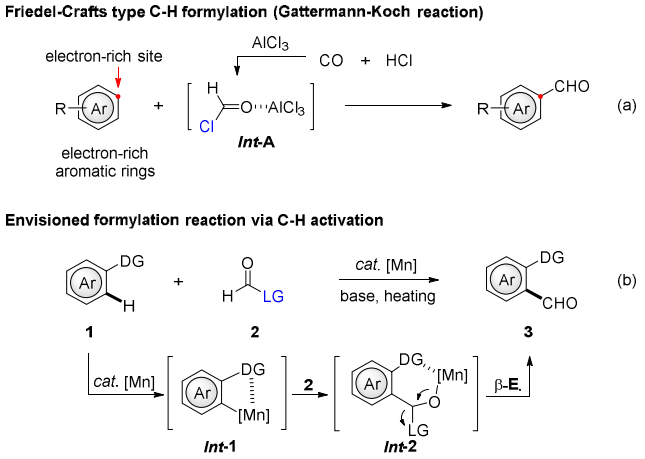
ABSTRACT: A practical one-pot C−H formylation approach enabled by the relay catalysis of manganese(I) and iron(III) has been developed. The effect of the directing group exhibited that 2-pyrimidinyl was a suitable directing group to promote the C−H hydroxymethylation, and also compatible in the subsequent aerobic oxidation. This formylation reaction, in which water is the only byproduct, showed high selectivity and efficiency across a broad substrate scope. The use of non-noble transition metals to promote relay catalysis provides a practical and scalable approach to C−H formylation. The loading of the manganese(I) catalyst could be decreased to as low as 0.5 mol% on a 5-gram scale reaction.

KEYWORDS: Manganese • Iron • C−H formylation • hydroxymethylation • aerobic oxidation

Transition metal-catalyzed transformations have become ubiquitous in the functionalization and assembly of pharmaceuticals and materials.[1] During the past few decades, noble metal complexes have been at the core of catalysis.[2] In contrast, the application of non-noble transition metal-based complexes (*e.g.* iron and manganese), which are abundant in Earth's crust, inexpensive, and of low toxicity, unfortunately remains relatively scarce.[3] Recent years have witnessed the significant progress, and catalysis based on non-noble transition metals has been increasingly developed in many fields, including C–H activation,[4] modern oxidation,[5] cross-coupling,[6] olefin functionalization reactions[7] and so on. For example, instead of using complexes of 4d or 5d noble metals, C–H activation based on manganese, achieved by the groups of Kuninobu and Takai,[8] Wang,[9] Ackermann,[10] our group[11] and others,[12] has been employed to promote a diverse range of transformations, and thus has attracted great attention.[13]

The formyl group is an essential functional group in organic chemistry, which is ubiquitous in various natural products, pharmacologically active substances, and cosmetics.[14] Moreover, the formyl group can be easily transformed into many other functional groups.[15] However, efficient methodologies for introducing formyl group into molecules are limited, especially those utilizing C–H bonds. Traditional Friedel–Crafts type C–H formylation reactions can be limited to electron-rich aromatic systems, and site-selectivity is dictated by electronic effects (Scheme 1a).[16] In the Gattermann–Koch reaction, a Friedel–Crafts catalyst is used under forcing conditions with carbon monoxide (CO) and hydrochloric acid (HCl) to generate the key intermediate ***Int*-A** *in situ*, possessing a chlorine atom as a leaving group. Inspired by this formylation approach, we envisioned that intermediate ***Int*-1**, generated via manganese-catalyzed C–H activation of **1**, would undergo nucleophilic addition to the formyl group in **2**, to generate cyclic intermediate ***Int*-2** (Scheme 1b). The formylation product could then be obtained by trans-β-elimination from ***Int*-2**,[10d,11d] in which site-selectivity could be conveniently controlled by a suitable directing group to



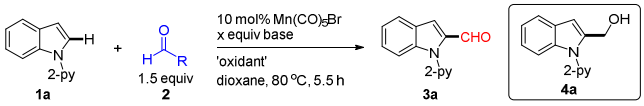
Scheme 1. Envisioned transformations for the C-H formylation reactions

overcome the inherent site-selectivity and reactivity of the aromatic substrates. To the best of our knowledge, a formylation methodology using C–H activation has not been reported so far. To achieve this approach, two significant challenges must be overcome: 1) The newly formed aldehyde **3** might also serve as an electrophile which is reactive with ***Int*-1** to form alcohols;[8a,9d] 2) The bidentate coordination to manganese in ***Int*-2** could potentially stabilize this complex, and thus fail to undergo *trans*-β-elimination to deliver **3**.[8a]

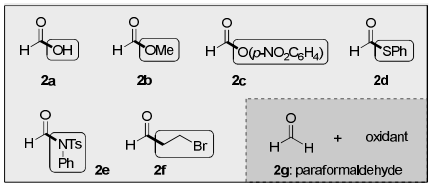
Based on this initial concept, we started screening coupling partners **2** with *N*-(2-pyridyl)indole **1a** as the standard substrate. When formic acid (**2a**) or methyl formate (**2b**) were employed using $Mn(CO)_5Br$ (10 mol%) as the catalyst in dioxane at 80 °C, no formylation product (**3a**) was detected, only recovering **1a** in 80 and 92% yield, respectively (Table 1, entries 1 and 2). A *p*-nitrophenoxyl group, which has been applied as a good leaving group in NHC chemistry,[17] did not favor the formation of the desired product **3a** (Table 1, entry 3). Other types of leaving groups, including S-, N-, or C-

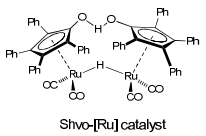
containing moieties were further studied, however similar results were observed (Table 1, entries 4-6).[18] With these negative results in hand, we deduced that the *trans*-β-elimination step from ***Int*-2** may be, as anticipated, difficult to induce. As an alternative approach, we elected to use formaldehyde together with an external oxidant, instead of an internal leaving group. The reaction of **1a** with formaldehyde would generate alcohol **4a** as the intermediate, which could then be readily oxidized to aldehyde **3a** *in situ* or afterwards. When the reaction was conducted with paraformaldehyde (3 equiv) and BQ (1.2 equiv, BQ = 1,4-benzoquinone), the desired product **3a** was observed in 4% yield, with alcohol **4a** in 52% yield (Table 1, entry 7). No obvious improvement was achieved with additional Shvo-[Ru] (2 mol%) as a hydrogen transfer catalyst (Table 1, entry 8).[19] The aerobic oxidation enabled by Fe(III)/TEMPO catalysis, which has emerged as a green and efficient method to oxidize alcohols to the corresponding aldehydes, was then examined.[20] The reaction

Table 1. Optimization of the reaction conditions[a]



Entry	2	'Oxidant' (equiv)	Base (equiv)	Yield of **3a** (%)[b]	Recovery of **1a** (%)[b]
1	**2a**[c]	-	Cy_2NH (1.5)	-	80
2	**2b**[c]	-	Cy_2NH (0.2)	-	92
3	**2c**	-	Cy_2NH (1.5)	-	99
4	**2d**	-	Cy_2NH (1.5)	-	88
5	**2e**[d]	-	Cy_2NH (0.2)	-	96
6	**2f**	-	Cy_2NH (1.5)	-	77
7	**2g**[c]	BQ (1.2)	Cy_2NH (0.2)	4[e]	16
8	**2g**[c]	Shvo-[Ru] (0.02)+BQ (1.2)	Cy_2NH (0.2)	5[f]	22
9	**2g**[c]	[Fe]/TEMPO (0.15)[g]+air	Cy_2NH (0.2)	25[h]	18
10	**2g**[c]	[Fe]/TEMPO (0.15)[g]+air	NaOAc (0.1)	43[i]	-
11	**2g**[c]	[Fe]/TEMPO (0.15)[g,j]+air	NaOAc(0.1)	78 (75)	-

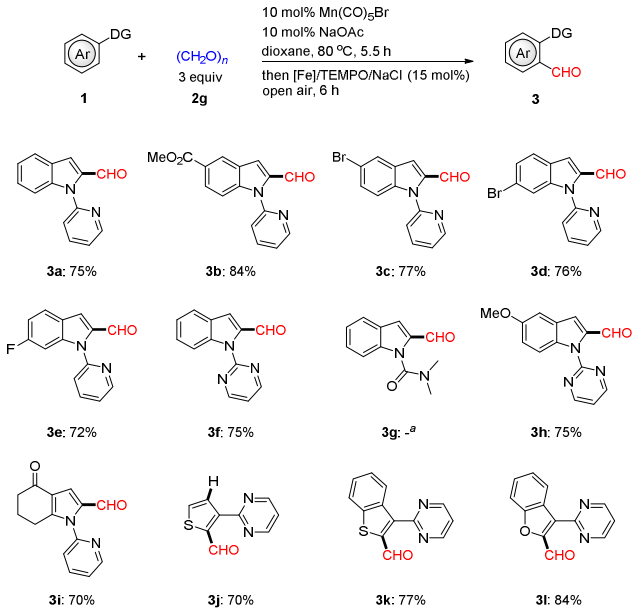




[a]The reactions were carried out using **1a** (0.2 mmol), 2 (1.5 equiv.), $[MnBr(CO)_5]$ (10 mol%), and base in dioxane (1 mL) at 80 °C for 5.5 h. [b]Yields determined by ^{1}H NMR analysis using mesitylene as the internal standard. Value in the parentheses is the isolated yield. [c]**2** (3 equiv) was used. [d]The reaction was conducted with additional $ZnBr_2$ (0.5 equiv) at 100 °C. [e]Hydroxymethylation product **4a** was detected in 52% yield. [f]**4a** was detected in 50% yield. [g]$Fe(NO_3)_3{\cdot}9H_2O$ (15 mol%) and TEMPO (15 mol%) were added afterwards, and the reaction was then stirred at room temperature for additional 6 h under open air conditions. [h]**4a** was detected in 40% yield. [i]**4a** was detected in 44% yield. [j]Additional NaCl (15 mol%) was added. LG = leaving group. BQ = 1,4-benzoquinone. Ts = *p*-toluenesulfonyl.

gave the desired product **3a** in 25% yield, with 40% yield of **4a**, by adding $Fe(NO_3)_3{\cdot}9H_2O$ (15 mol%) and TEMPO (15 mol%) for additional 6 h at room temperature under air. The yield of **3a** was further improved to 43% yield by changing the base to NaOAc (10 mol%) (Table 1, entry 10). To our delight, the addition of NaCl (15 mol%) led to the formation of the desired product **3a** in 75% yield (Table 1, entry 11).[20a] It should be noted that the selective C–H formylation of indoles at 2-position cannot be achieved with previously reported methods, which due to their Friedel–Crafts mechanism lead only to the formylation at the 3-position.[16]

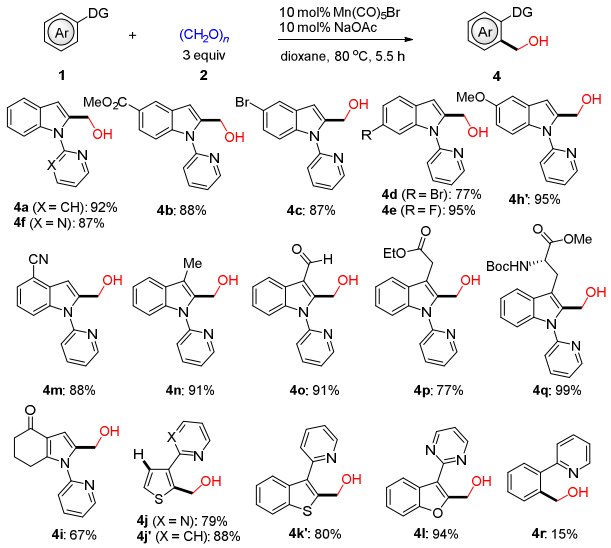
With the optimal reaction conditions in hand, we began substrate scoping studies (Scheme 2). Functional groups, such as 5-CO_2Me and 5-Br on the benzene ring were well tolerated to afford the corresponding products **3b** and **3c** in 84 and 77% yield, respectively. Electron-withdrawing groups, such as 6-Br and 6-F, were also compatible, leading to **3d** and **3e** in good yields. A survey of other directing groups showed that this approach works equally well with 2-pyrimidinyl (2-pym) as the directing group, as shown by the formation of **3f** in 75% yield. However, a carbamoyl-based directing group failed to promote the transformation. It is noteworthy that substrate **1h** with electron-donating 5-MeO group afforded the corresponding product **3h** in 75% yield, with 2-pyrimidinyl as the directing group (for details, see Scheme 4). Finally, this C–H formylation approach could be successfully extended to pyrrole, thiophene, benzothiophene, and benzofuran systems.



Scheme 2. Substrate scope for the C–H formylation. The reaction was carried out using **1** (0.2 mmol), $(CH_2O)_n$ (3 equiv.), $[MnBr(CO)_5]$ (10 mol%), and NaOAc (10 mol%) in dioxane (1 mL) at 80 °C for 5.5 h, then $Fe(NO_3)_3{\cdot}9H_2O$ (15 mol%), TEMPO (15 mol%), and NaCl (15 mol%) were added into the reaction mixture, and the reaction was run for additional 6 h at room temperature under open air conditions. [a]**1g** was recovered in 95% yield.

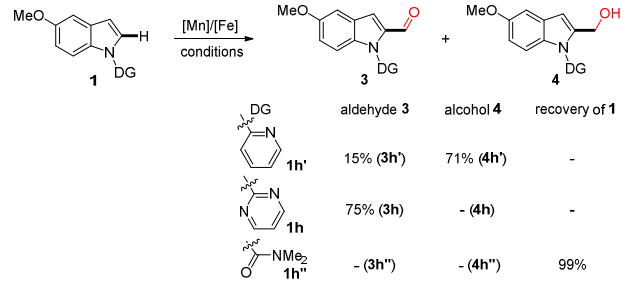
Given the fact that the hydroxymethyl group is also ubiquitous in many natural products, pharmaceuticals, and biologically active compounds,[21] we then studied the substrate scope for the manganese(I)-catalyzed C–H hydroxyl-methylation reaction (Scheme 3). Pleasingly, the product **4**

could be easily produced and isolated without requiring the use of a stoichiometric electrophilic quencher, such as silianes[8a] or zinc reagents[9d]. The analogues substituted with 5-CO_2Me, 5-Br, 6-Br, 6-F, 5-MeO, and 4-CN groups all reacted smoothly. Functional groups, such as methyl, formyl, and 2-ethoxy-2-oxoethyl groups at the 3-positon of the indole moiety were also nicely tolerated. (*S*)-Tryptophan derivative **1q** gave the hydroxymethylated product **4q** in 99% yield. Finally, pyrrole, thiophene, and benzothiophene, and benzofuran derivatives were also effectively employed in this protocol. However, only 15% yield of the hydroxymethylated product **4r** was obtained from 2-phenylpyridine.



Scheme 3. Substrate scope for the C–H hydroxymethylation reaction. For detailed conditions, see SI.

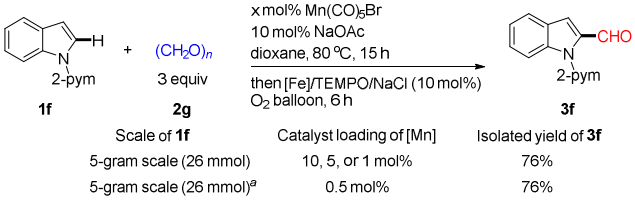
With electron-donating 5-MeO substituent at the benzene ring of indole, the reaction of **1h'** under the Mn(I) and Fe(III) relay catalysis afforded the formylation product **3h'** in only 15% yield, but with 71% formation of alcohol **4h'** (Scheme 4). It became evident that the 2-pyridyl directing group could promote the C–H activation, but does not favor the aerobic oxidation of alcohol **4h'** to aldehyde **3h'**. The loss of activity of the iron catalyst was postulated to be due to strong bidentate coordination and the formation of a stable inactive complex.[8a] This problem could be overcome by replacing the 2-pyridyl group with the slightly weaker coordinating 2-pyrimidinyl directing group. Hence, the reaction of **1h** afforded the corresponding product **3h** in 75% yield. However, the even more weakly coordinating carbamoyl group failed to promote the C–H hydroxymethylation reaction, as shown by the recovery of **1h''** in 99% yield. Therefore, a suitable directing group is crucial for this transformation, especially for



Scheme 4. The effect of directing groups. For detailed conditions, see SI. DG = directing group.

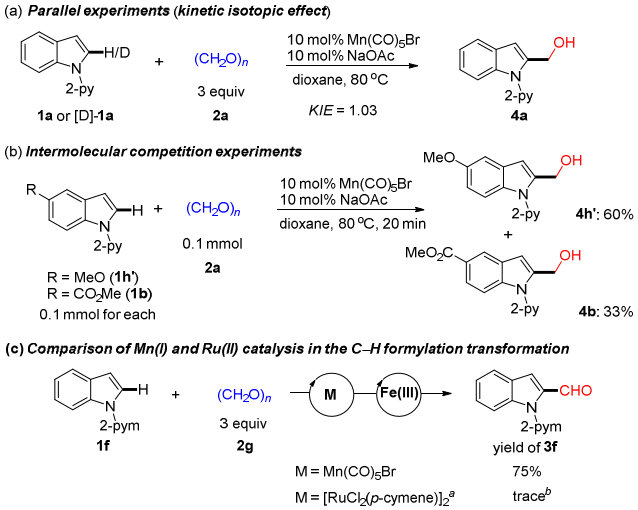
those based on electron-rich systems. Similar results could be observed for other aromatic systems, such as thiophene and benzothiophene.

Next, on a 5 gram-scale reaction, the catalyst loading of $Mn(CO)_5Br$ could be reduced to 5 mol%, and the formylation product **3f** was isolated in 76% yield (Scheme 5). Encouraged by these results, we pushed the limits of catalyst loading further, and found that the C–H formylation reaction of **1f** could again be performed on a 5-gram scale to produce **3f** in the same yield (76%), with only 0.5 mol% of $Mn(CO)_5Br$. To the best of our knowledge, this is the lowest catalyst loading of $[Mn(CO)_5Br]$ catalyst reported in C–H activation to date.[8-13,4k]



Scheme 5. Scale-up synthesis of 3f from 1f. For detailed conditions, see SI. [a]*C* = 0.4 M.

To gain a deeper insight into the mechanism of manganese(I)-catalyzed C–H hydroxymethylation, the kinetic isotope effect (KIE) was determined from two parallel kinetic experiments to have a value of 1.03 (Scheme 6a).[22] These results indicate that the C–H bond cleavage is not involved in the rate-determining step. Moreover, intermolecular competition experiments indicated that electron-rich indoles are more reactive in this transformation (Scheme 6b). Ruthenium(II) catalyst was also reported to promote the C–H hydroxymethylation reaction.[23,21b] However, the combination of ruthenium(II) and iron(III) catalysis did not furnish the aldehyde, indicating the incompatibility of ruthenium(II) and iron(III) catalysis for a similar C–H formylation protocol (Scheme 6c). Finally, a robustness screen was applied to exhibit the functional group and heterocycle tolerance of this methodology (see the Supporting Information).[24]



Scheme 6. Mechanistic Studies. [a]Reaction conditions were employed as reported in ref. (24), then $Fe(NO_3)_3{\cdot}9H_2O$ (15 mol%), TEMPO (15 mol%), and NaCl (15 mol%) were added into the reaction mixture, and the reaction was run for additional 6 h at room temperature under open air. [b]**1f** was recovered.

In conclusion, we have developed a one-pot C−H formylation approach enabled by the relay catalysis of manganese(I) and iron(III) with high selectivity and efficiency (just 0.5 mol% Mn-catalyst on a 5-gram scale reaction). This relay catalysis proceeds via a sequential manganese(I)-catalyzed C−H hydroxymethylation and iron(III)-catalyzed aerobic oxidation process, from which water was produced as the only byproduct. Paraformaldehyde, employed as *C1* source in the reaction, is also of low-cost and easy to handle. The compatibility of manganese(I) and iron(III) catalysis was crucial to realize this one-pot transformation, which was used to formylate a broad scope of substrates, including indole, pyrrole, thiophene, benzothiophene, and benzofuran systems.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org, which included NMR data and characterization (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) H. Knözinger, K. Kochloefl, Heterogeneous Catalysis and Solid Catalysts, Wiley-VCH, Weinheim, **2002**.

(2) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation. *Chem. Rev*. **2010**, *110*, 624-655. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions. *Chem. Rev*. **2011**, *111*, 1780-1824.

(3) (a) Thoi, V. S.; Sun, Y.; Long, J. R.; Chang, C. J. Complexes of earth-abundant metals for catalytic electrochemical hydrogen generation under aqueous conditions. *Chem. Soc. Rev*. **2013**, *42*, 2388-2400. (b) Ran, J.; Zhang, J.; Yu, J.; Jaroniecc, M.; Qiao, S. Z. Earth-abundant cocatalysts for semiconductor-based photocatalytic water splitting. *Chem. Soc. Rev*. **2014**, *43*, 7787-7812. (c) Hunter, B. M.; Gray, H. B.; Müller, A. M. Earth-Abundant Heterogeneous Water Oxidation Catalysts. *Chem. Rev*. **2016**, *116*, 14120-14136. (d) Wang, D.; Astruc, D. The recent development of efficient Earth-abundant transition-metal nanocatalysts. *Chem. Soc. Rev*. **2017**, *46*, 816-854.

(4) (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C−H bond activation strategy for C−C and C−N bond formation. *Chem. Soc. Rev*. **2011**, *40*, 5068-5083. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C−H Transformation via Iron Catalysis. *Chem. Rev*. **2011**, *111*, 1293-1314. (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. Recent developments in natural product synthesis using metal-catalysed C–H bond functionalization. *Chem. Soc. Rev*. **2011**, *40*, 1885-1898. (d) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon−Carbon Bonds by Oxidizing Two Carbon−Hydrogen Bonds. *Chem. Rev*. **2011**, *111*, 1215-1292. (e) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions. *Acc. Chem. Res*. **2012**, *45*, 788-802. (f) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc. Chem. Res*. **2015**, *48*, 1053-1064. (g) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C–H Activation. *ACS Catal*. **2016**, *6*, 498-525. (h) Gensch, T.; Klauck, F. J. R.; Glorius, F. Cobalt-Catalyzed C−H Thiolation through Dehydrogenative Cross-Coupling. *Angew. Chem. Int. Ed*. **2016**, *55*, 11287-11291. (i) Shang, R.; Ilies, L.; Nakamura, E. Iron-Catalyzed C–H Bond Activation. *Chem. Rev*. **2017**, *117*, 9086-9139. (j) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C–H Bond Addition to Carbonyls, Imines, and Related Polarized π Bonds. *Chem. Rev*. **2017**, *117*, 9163-9227. (k) Gensch, T.; James, M.; Dalton, T.; Glorius, F. Increasing Catalyst Efficiency in C−H Activation Catalysis. *Angew. Chem. Int. Ed*. **2018**, *57*, 2296-2306.

(5) J.-E. Bäckvall, *Modern Oxidation Methods*, Wiley-VCH, Weinheim, **2004**.

(6) (a) Cahiez, G.; Moyeux, A. Cobalt-Catalyzed Cross-Coupling Reactions. *Chem. Rev*. **2010**, *110*, 1435-1462. (b) Xia, Y.; Qiu, D.; Wang, J. Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chem. Rev*. **2017**, *117*, 13810-13889.

(7) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev*. **2016**, *116*, 8912-9000.

(8) (a) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. Manganese-catalyzed insertion of aldehydes into a C−H bond. *Angew. Chem. Int. Ed*. **2007**, *46*, 6518-6520. (b) Sueki, S.; Wang, Z.; Kuninobu, Y. Manganese- and Borane-Mediated Synthesis of Isobenzofuranones from Aromatic Esters and Oxiranes via C–H Bond Activation. *Org. Lett*. **2016**, *18*, 304-307.

(9) (a) Zhou, B.; Chen, H.; Wang, C. Mn-Catalyzed Aromatic C–H Alkenylation with Terminal Alkynes. *J. Am. Chem. Soc*. **2013**, *135*, 1264-1267. (b) He, R.; Huang, Z. T.; Zheng, Q. Y.; Wang, C. Manganese-catalyzed dehydrogenative [4+2] annulation of N–H imines and alkynes by C−H/N−H activation. *Angew. Chem. Int. Ed*. **2014**, *53*, 4950-4953. (c) Zhou, B.; Ma, P.; Chen, H.; Wang, C. Amine-accelerated manganese-catalyzed aromatic C–H conjugate addition to α,β-unsaturated carbonyls. *Chem. Commun*. **2014**, *50*, 14558-14561. (d) Zhou, B.; Hu, Y.; Wang, C. Manganese-Catalyzed Direct Nucleophilic C(sp^2)–H Addition to Aldehydes and Nitriles. *Angew. Chem. Int. Ed*. **2015**, *54*, 13659-13663. (e) Hu, Y.; Wang, C. Manganese-catalyzed bicyclic annulations of imines and α,β-unsaturated esters via C−H activatio. *Sci. China Chem*. **2016**, *59*, 1301-1305. (f) Yang, X.; Jin, X.; Wang, C. Manganese-Catalyzed *ortho*-C–H Alkenylation of Aromatic N–H Imidates with Alkynes: Versatile Access to Mono-Alkenylated Aromatic Nitriles. *Adv. Synth. Catal*. **2016**, *358*, 2436-2442. (g) Zhou, B.; Hu, Y.; Liu, T.; Wang, C. Aromatic C–H addition of ketones to imines enabled by manganese catalysis. *Nat. Commun*. **2017**, *8*, 1169.

(10) (a) Liu, W.; Bang, J.; Zhang, Y.; Ackermann, L. Manganese(I)-Catalyzed C–H Aminocarbonylation of Heteroarenes. *Angew. Chem. Int. Ed*. **2015**, *54*, 14137-14140. (b) Liu, W.; Zell, D.; John, M.; Ackermann, L. Manganese-Catalyzed Synthesis of cis-β-Amino Acid Esters through Organometallic C–H Activation of Ketimines. *Angew. Chem. Int. Ed*. **2015**, *54*, 4092-4096. (c) Liu, W.; Richter, S. C.; Zhang, Y.; Ackermann, L. Manganese(I)-Catalyzed Substitutive C–H Allylation. *Angew. Chem. Int. Ed*. **2016**, *55*, 7747-7750. (d) Ruan, Z.; Sauermann, N.; Manoni, E.; Ackermann, L. Manganese-Catalyzed C–H Alkynylation: Expedient Peptide Synthesis and Modification. *Angew. Chem. Int. Ed*. **2017**, *56*, 3172-3176. (e) Meyer, T. H.; Liu, W.; Feldt, M.; Wuttke, A.; Mata, R. A.; Ackermann, L. Manganese(I)-Catalyzed Dispersion-Enabled C−H/C−C Activation. *Chem. Eur. J*. **2017**, *23*, 5443-5447. (f) Liang, Y.-F.; Müller, V.; Liu, W.; Münch, A.; Stalke, D.; Ackermann, L. Methylenecyclopropane Annulation by Manganese(I)-Catalyzed Stereoselective C−H/C−C Activation. *Angew. Chem. Int. Ed.* **2017**, *56*, 9415-9419. (g) Wang, H.; Lorion, M. M.; Ackermann, L. Air-Stable Manganese(I)-Catalyzed C−H Activation for Decarboxylative C−H/C−O Cleavages in Water. *Angew. Chem. Int. Ed.* **2017**, *56*, 6339-6342.

(11) (a) Lu, Q.; Klauck, F. J. R.; Glorius, F. Manganese-catalyzed allylation via sequential C–H and C–C/C–Het bond activation. *Chem. Sci*. **2017**, *8*, 3379-3383. (b) Lu, Q.; Greßies, S.; Cembellín, S.; Klauck, F. J. R.; Daniliuc, C. G.; Glorius, F. Redox-Neutral Manganese(I)-Catalyzed C−H Activation: Traceless Directing Group Enabled Regioselective Annulation. *Angew. Chem. Int. Ed.* **2017**, *56*, 12778-12782. (c) Lu, Q.; Greßies, S.; Klauck, F. J. R.; Glorius, F. Manganese(I)-Catalyzed Regioselective C−H Allenylation: Direct Access to 2-Allenylindoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 6660-6664. (d) Zhu, C.; Schwarz, J. L.; Cembellín, S.; Greßies, S.; Glorius, F. Highly Selective Manganese(I)/Lewis Acid Cocatalyzed Direct C−H Propargylation Using Bromoallenes. *Angew. Chem. Int. Ed*. **2018**, *57*, 437-441. (e) Lu, Q.; Cembellín, S.; Greßies, S.; Singha, S.; Daniliuc, C. G.; Glorius, F. Manganese(I)-Catalyzed C−H (2-Indolyl)methylation: Expedient Access to Diheteroarylmethanes. *Angew. Chem. Int. Ed*. **2018**, *57*, 1399-1403.

(12) (a) Yahaya, N. P.; Appleby, K. M.; Teh, M.; Wagner, C.; Troschke, E.; Bray, J. T. W.; Duckett, S. B.; Hammarback, L. A.; Ward, J. S.; Milani, J.; Pridmore, N. E.; Whitwood, A. C.; Lynam, J. M.; Fairlamb, I. J. S. Manganese(I)-Catalyzed C−H Activation: The Key Role of a 7-Membered Manganacycle in H-Transfer and Reductive Elimination. *Angew. Chem. Int. Ed*. **2016**, *55*, 12455-12459. (b) Wang, C.; Wang, A.; Rueping, M. Manganese-Catalyzed C−H Functionalizations: Hydroarylations and Alkenylations Involving an Unexpected Heteroaryl Shift. *Angew. Chem. Int. Ed*. **2017**, *56*, 9935-9938. (c) Chen, S.-Y.; Han, X.-L.; Wu, J.-Q.; Li, Q.; Chen, Y.; Wang, H. Manganese(I)-Catalyzed Regio- and Stereoselective 1,2-Diheteroarylation of Allenes: Combination of C−H Activation and Smiles Rearrangement. *Angew. Chem. Int. Ed.* **2017**, *56*, 9939-9943. (d) Chen, S.-Y.; Li, Q.; Liu, X.-G.; Wu, J.-Q.; Zhang, S.-S.; Wang, H. Polycyclization Enabled by Relay Catalysis: One-Pot Manganese-Catalyzed C−H Allylation and Silver-Catalyzed Povarov Reaction, ChemSusChem **2017**, *10*, 2360-2364. (e) Chen, S.-Y.; Li, Q.; Wang, H. Manganese(I)-Catalyzed Direct C–H Allylation of Arenes with Allenes, *J. Org. Chem*. **2017**, *82*, 11173-11181.

(13) For reviews, see: (a) Wang, C. Manganese-Mediated C–C Bond Formation via C–H Activation: From Stoichiometry to Catalysis. *Synlett* **2013**, 1606-1613. (b) Liu, W.; Ackermann, L. Manganese-Catalyzed C–H Activation. *ACS Catal*. **2016**, *6*, 3743-3752. (c) Hu, Y.; Zhou, B.; Wang, C. Inert C–H Bond Transformations Enabled by Organometallic Manganese Catalysis, *Acc. Chem. Res*. **2018**, *51*, 816-827. (d) Cano, R.; Mackey, K.; McGlacken, G. P. Recent advances in manganese-catalysed C–H activation: scope and mechanism. *Catal. Sci. Technol*. **2018**, *8*, 1251-1266.

(14) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Springer: Heidelberg, Germany, **2007**.

(15) (a) Arundale, E.; Mikeska, L. A. The Olefin-Aldehyde Condensation. The Prins Reaction. *Chem. Rev*. **1952**, *51*, 505-555. (b) Lawrence, N. J. Aldehydes and ketones. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1739-1750.

(16) (a) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. Formylating agents. *Chem. Rev*. **1987**, *87*, 671-686. (b) Wu, W.; Su, W. Mild and Selective Ru-Catalyzed Formylation and Fe-Catalyzed Acylation of Free (N–H) Indoles Using Anilines as the Carbonyl Source. *J. Am. Chem. Soc*. **2011**, *133*, 11924-11927. (c) Chen, J.; Liu, B.; Liu, D.; Liu, S.; Cheng, J. The Copper-Catalyzed C-3-Formylation of Indole C−H Bonds using Tertiary Amines and Molecular Oxygen. *Adv. Synth. Catal*. **2012**, *354*, 2438-2442.

(17) Chen, X.; Fong, J. Z. M.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B.-A.; Chi, Y. R. Carbene-Catalyzed Dynamic Kinetic Resolution of Carboxylic Esters. *J. Am. Chem. Soc*. **2016**, *138*, 7212-7215.

(18) (a) Haraguchi, R.; Tanazawa, S.-g.; Tokunaga, N.; Fukuzawa, S.-i. Palladium-Catalyzed Formylation of Arylzinc Reagents with S-Phenyl Thioformate. *Org. Lett*. **2017**, *19*, 1646-1649. (b) Haraguchi, R.; Kusakabe, A.; Mizutani, N.; Fukuzawa, S.-i. Transition-Metal-Free Formylation of Allylzinc Reagents Leading to α-Quaternary Aldehydes. *Org. Lett*. **2018**, *20*, 1613-1616.

(19) Conley, B. L.; Pennington-Boggio, M. K.; Boz, E.; Williams, T. J. Discovery, Applications, and Catalytic Mechanisms of Shvo's Catalyst. *Chem. Rev*. **2010**, *110*, 2294-2312.

(20) (a) Ma, S.; Liu, J.; Li, S.; Chen, B.; Cheng, J.; Kuang, J.; Liu, Y.; Wan, B.; Wang, Y.; Ye, J.; Yu, Q.; Yuan, W.; Yu, S. Development of a General and Practical Iron Nitrate/TEMPO-Catalyzed Aerobic Oxidation of Alcohols to Aldehydes/Ketones: Catalysis with Table Salt. *Adv. Synth. Catal*. **2011**, *353*, 1005-1017. (b) Liu, J.; Xie, X.; Ma, S. Aerobic Oxidation of Propargylic Alcohols to α,β-Unsaturated Alkynals or Alkynones Catalyzed by $Fe(NO_3)_3{\cdot}9H_2O$, TEMPO and Sodium Chloride in Toluene. *Synthesis*, **2012**, *44*, 1569-1576. (c) Liu, J.; Ma, S. Aerobic oxidation of indole carbinols using $Fe(NO_3)_3{\cdot}9H_2O$/TEMPO/NaCl as catalysts. *Org. Biomol. Chem*. **2013**, *11*, 4186-4193. (d) Liu, J.; Ma, S. Room temperature $Fe(NO_3)_3{\cdot}9H_2O$/TEMPO/NaCl-catalyzed aerobic oxidation of homopropargylic alcohols. *Tetrahedron* **2013**, *69*, 10161-10167. (e) Liu, J.; Ma, S. Iron-Catalyzed Aerobic Oxidation of Allylic Alcohols: The Issue of C=C Bond Isomerization. *Org. Lett*. **2013**, *15*, 5150-5153. (f) Liu, J.; Ma, S. Aerobic Oxidation of Propargyl Alcohol: A Convenient Method for the Synthesis of Propiolaldehyde. *Synthesis* **2013**, *45*, 1624-1626. (g) Zhai, D.; Chen, L.; Jia, M.; Ma, S. One Pot Synthesis of γ-Benzopyranones via Iron-Catalyzed Aerobic Oxidation and Subsequent 4-Dimethylaminopyridine Catalyzed 6-*endo* Cyclization, *Adv. Synth. Catal*. **2018**, *360*, 153-160.

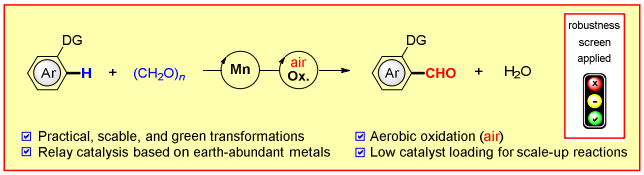
(21) For selected examples, see: (a) Roesch, K. R.; Larock, R. C. Synthesis of Isoquinolines and Pyridines by the Palladium/Copper-Catalyzed Coupling and Cyclization of Terminal Acetylenes and Unsaturated Imines: The Total Synthesis of Decumbenine B. *J. Org. Chem*. **2002**, *67*, 86-94. (b) Zhang, G.-F.; Li, Y.; Xie, X.-Q.; Ding, C.-R. Ru-Catalyzed Regioselective Direct Hydroxymethylation of (Hetero)Arenes via C–H Activation. *Org. Lett*. **2017**, *19*, 1216-1219.

(22) For details, see the Supporting Information.

(23) Wu, Y.; Zhou, B. Ruthenium-Catalyzed Direct Hydroxymethylation of Aryl C–H Bonds. *ACS Catal.* **2017**, *7*, 2213-2217.

(24) (a) Collins, K. D.; Glorius, F. A robustness screen for the rapid assessment of chemical reactions. *Nat. Chem*. **2013**, *5*, 597-601. (b) Collins, K. D.; Glorius, F. Intermolecular Reaction Screening as a Tool for Reaction Evaluation. *Acc. Chem. Res*. **2015**, *48*, 619-627. (c) Gensch, T.; Teders, M.; Glorius, F. Approach to Comparing the Functional Group Tolerance of Reactions. *J. Org. Chem*. **2017**, *82*, 9154-9159.

TOC graphic


DG
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DG
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robustness screen applied
Practical, scable, and green transformations
Relay catalysis based on earth-abundant metals
Aerobic oxidation (air)
Low catalyst loading for scale-up reactions