

Manganese-Catalyzed Direct Nucleophilic C(sp²)-H Addition to Aldehydes

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Checker: Shu-Bo Hu

Date: 2015/12/09

Wang, C.-Y. *et al.*
Angew. Chem. Int. Ed. **2015**, *54*, 13659.



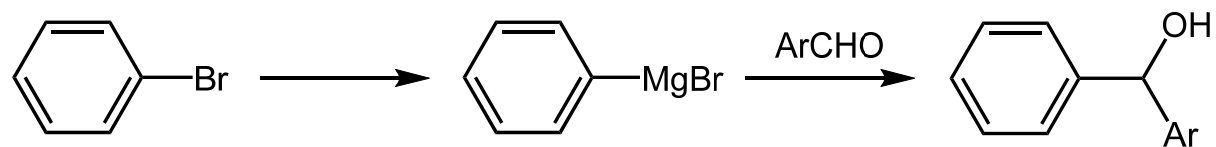
王从洋
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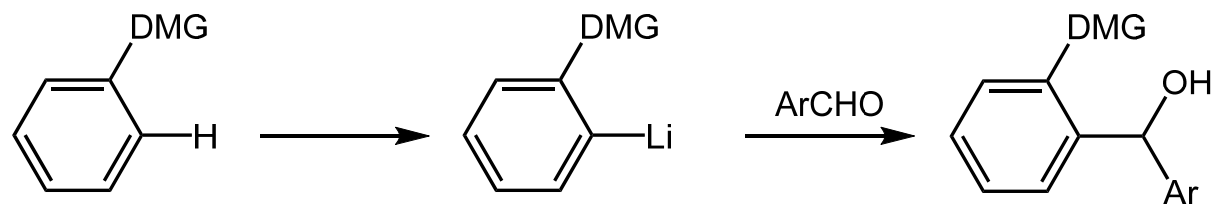
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- ◆ **Rh-catalyzed C-H addition to aldehydes**
- ◆ **Mn-catalyzed C-H addition to aldehydes**
- ◆ **Summary**

Introduction

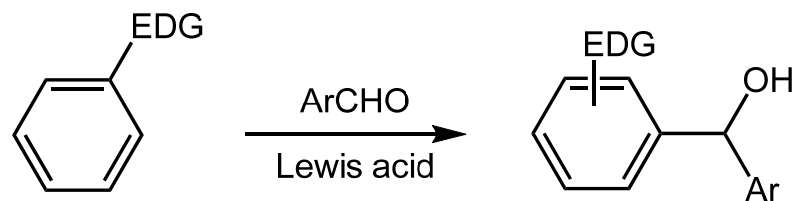
a) Grignard reaction



b) Snieckus's DoM

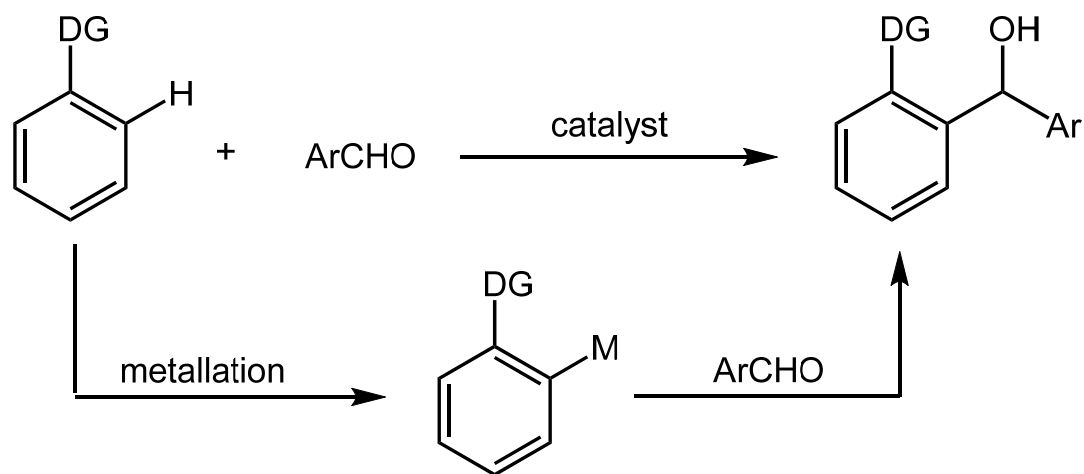


c) Friedel-Crafts arylation reaction



Introduction

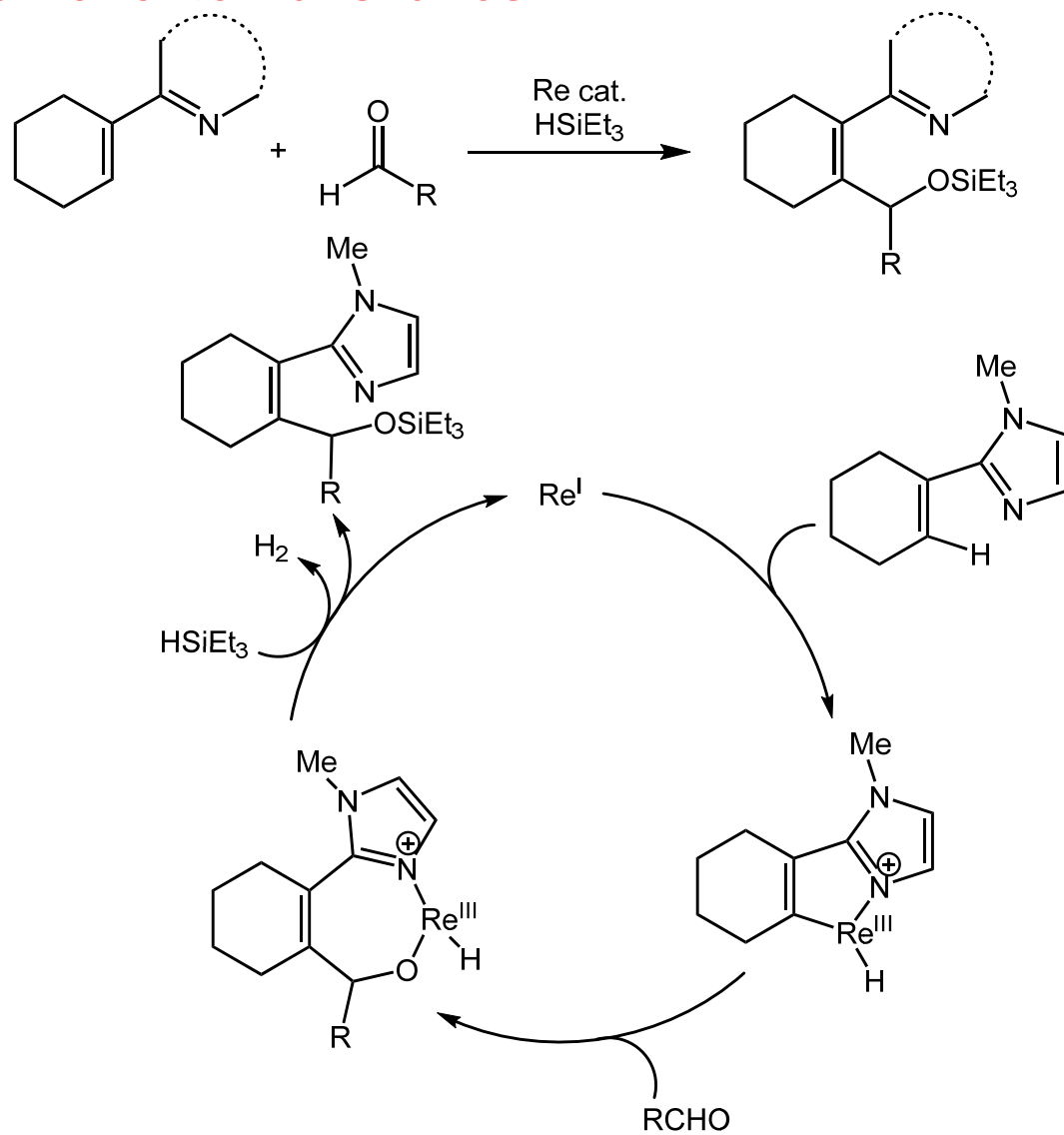
Nucleophilic C-H addition to aldehyde by C-H activation



M = Rh, Ir, Pd, Mn, etc

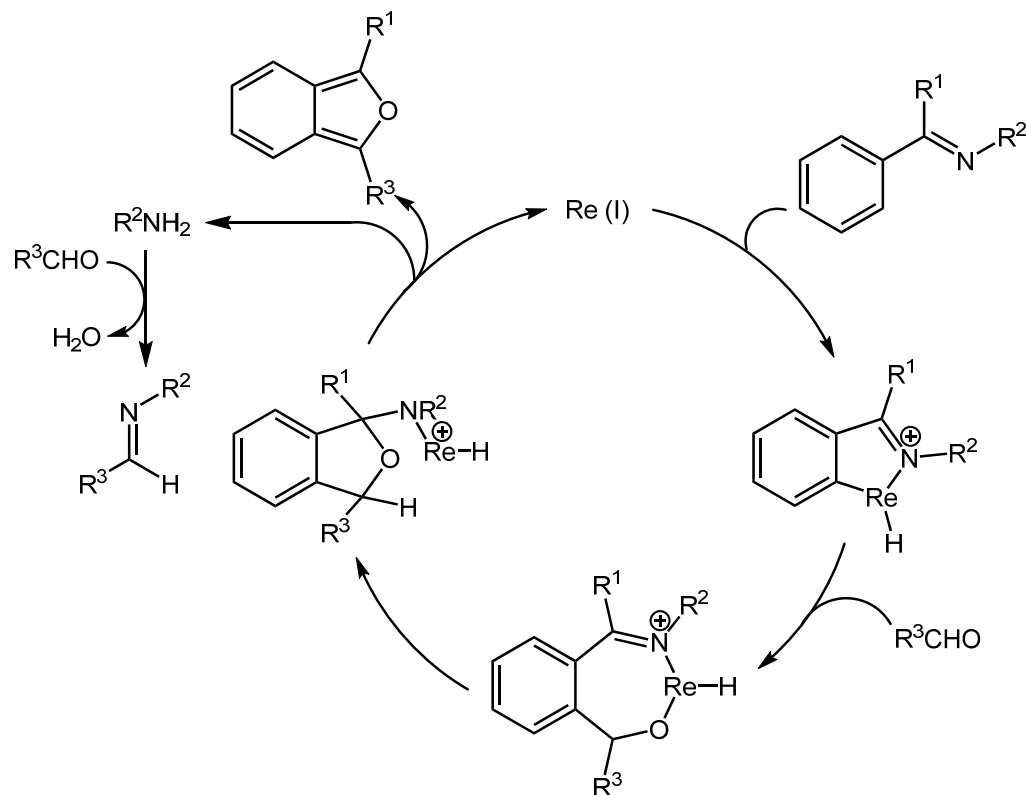
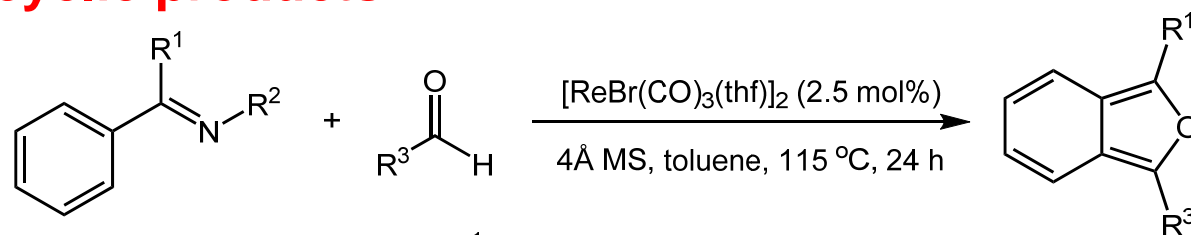
Introduction

Addition of external silanes



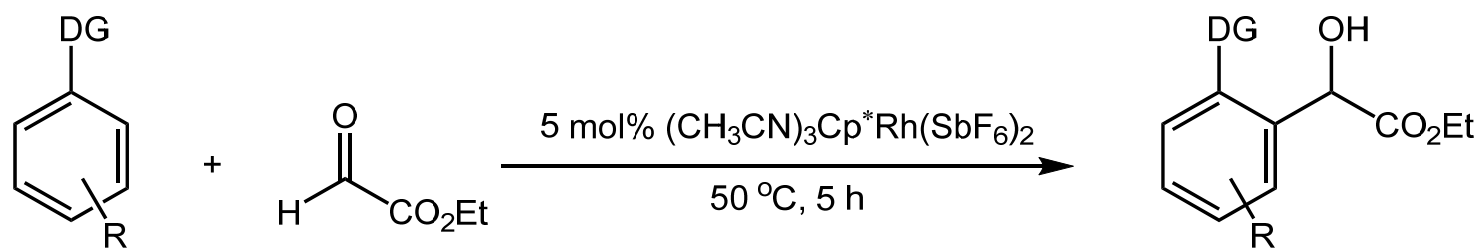
Introduction

Directing groups as intramolecular traps for the metal alkoxides to form cyclic products



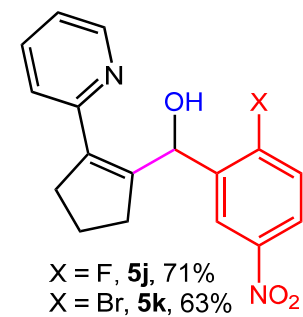
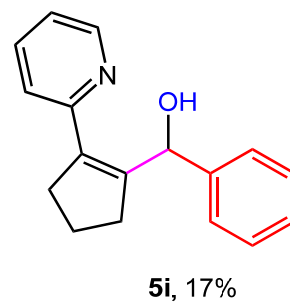
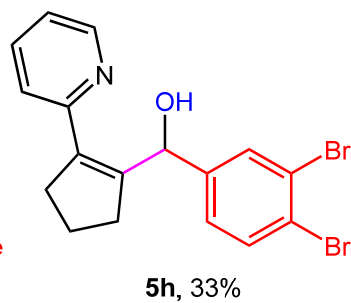
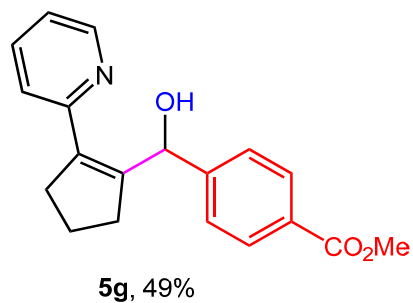
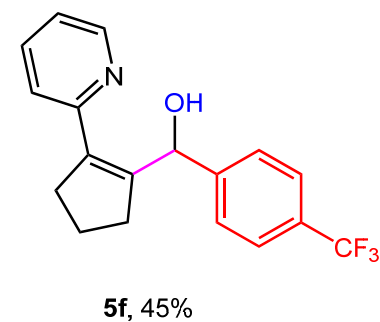
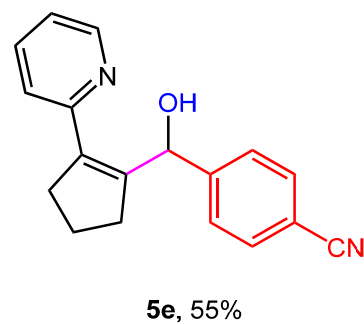
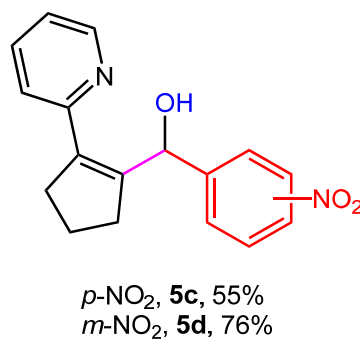
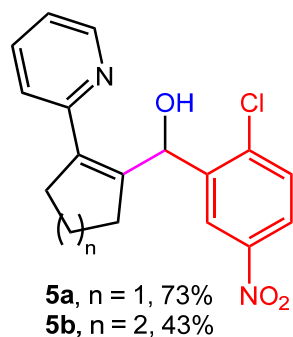
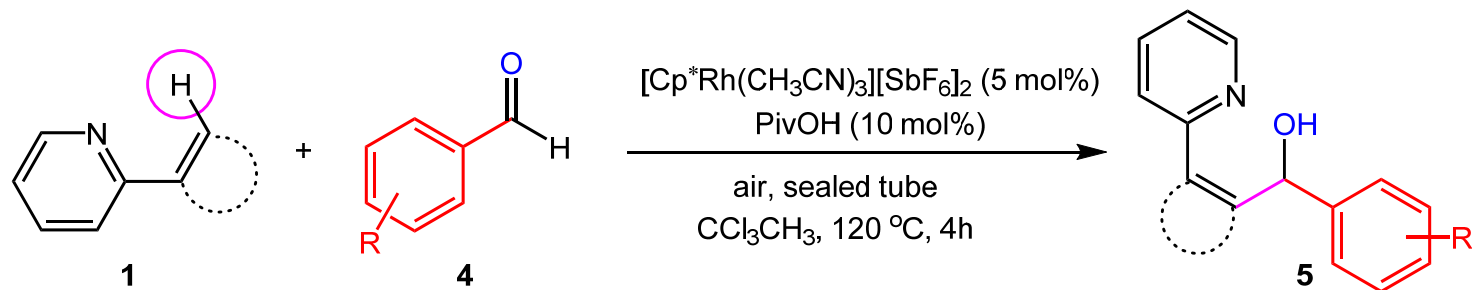
Takai, K. *et al.* *J. Am. Chem. Soc.* **2006**, *128*, 12376.

Rh-catalyzed C-H addition to aldehydes

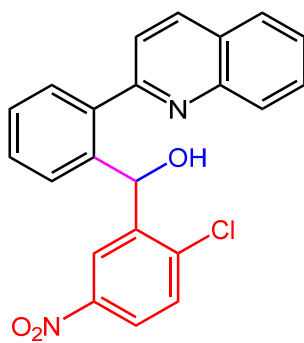
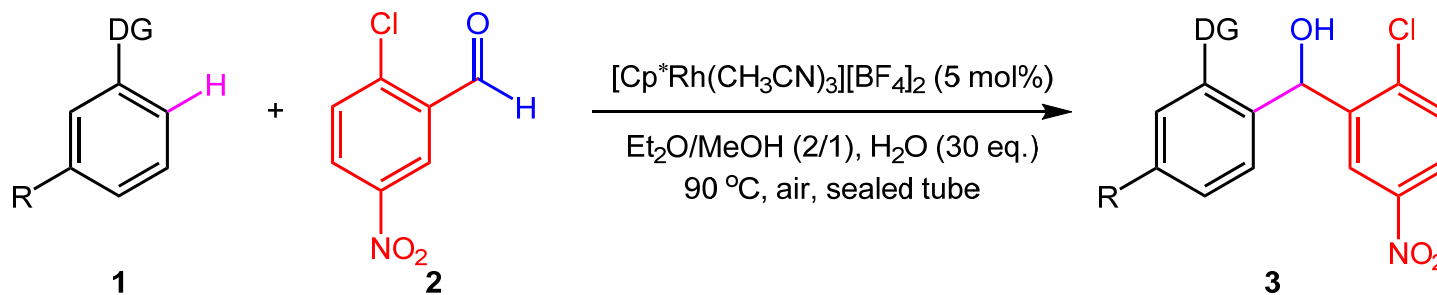


Li, C.-J. *et al. Adv. Synth. Catal.* **2011**, 353, 1269.

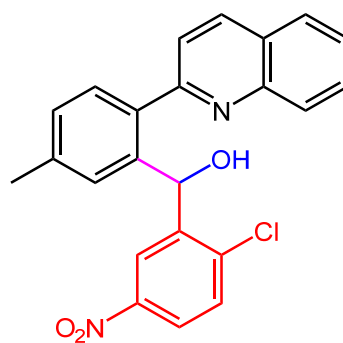
Rh-catalyzed C-H addition to aldehydes



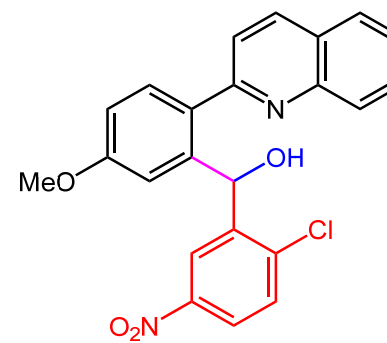
Rh-catalyzed C-H addition to aldehydes



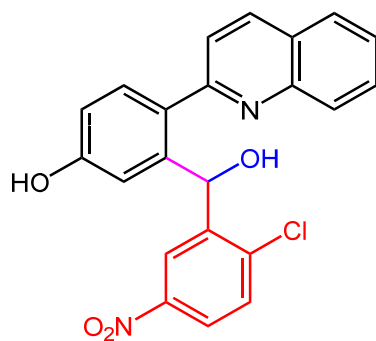
3a, 77% (10 h)



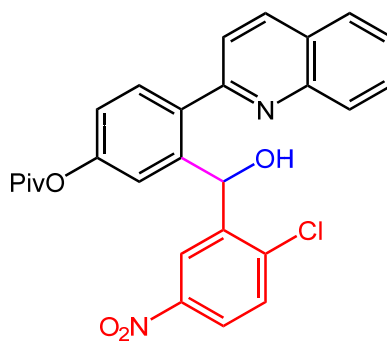
3b, 77% (10 h)



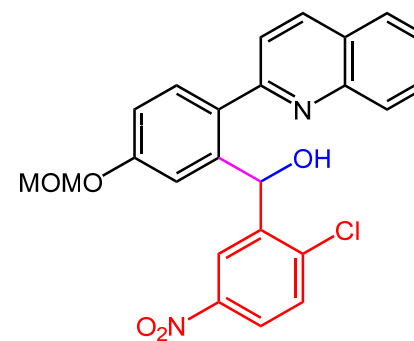
3c, 82% (10 h)



3d, 84% (10 h)

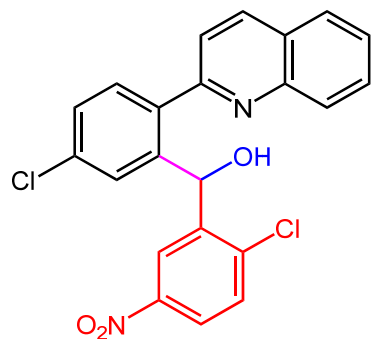


3e, 79% (24 h)

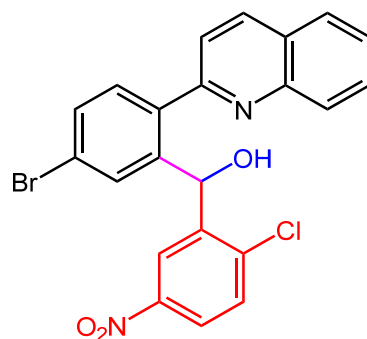


3f, 75% (24 h)

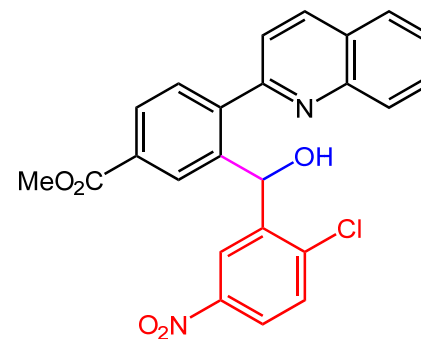
Rh-catalyzed C-H addition to aldehydes



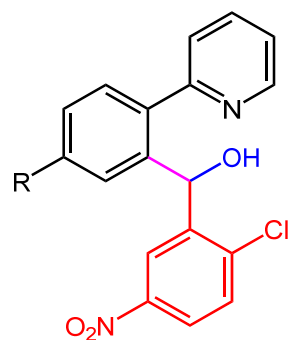
3g, 74% (72 h)



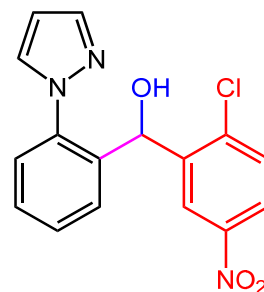
3h, 85% (24 h)



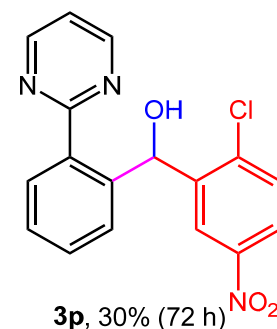
3i, 90% (48 h)



R = H, **3j**, 69% (10 h)
R = Me, **3k**, 62% (10 h)
R = ^tBu, **3l**, 58% (10 h)
R = OMe, **3m**, 74% (10 h)
R = OH, **3n**, 57% (10 h)

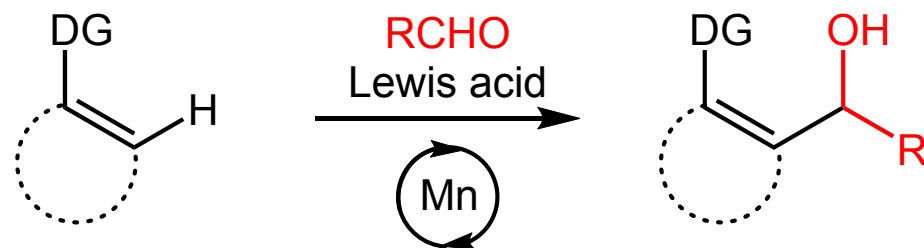


3o, 40% (72 h)



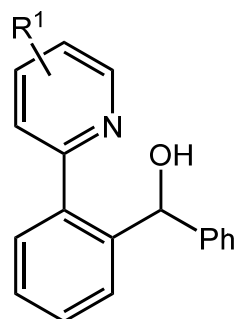
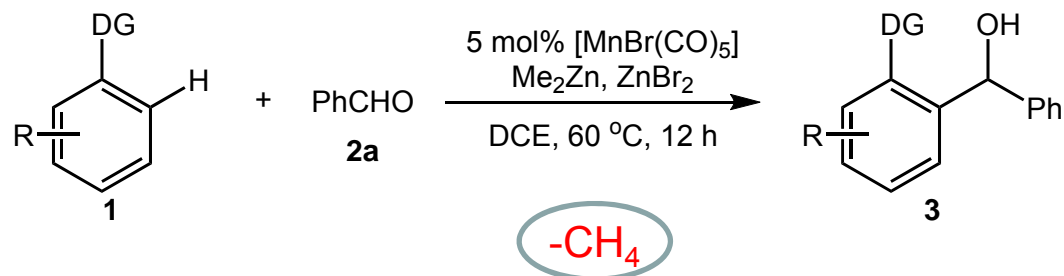
3p, 30% (72 h)

Mn-catalyzed C-H addition to aldehydes

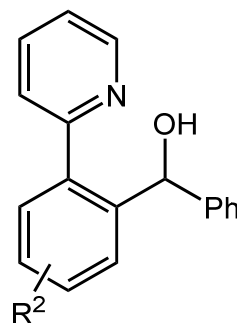


- ❑ “Dual activation” strategy
- ❑ Mild reaction conditions
- ❑ Broad substrate scopes
- ❑ Excellent selectivities

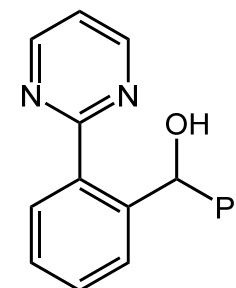
Scope with respect to the arene



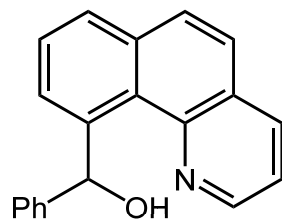
R₁ = H, **3aa**, 81%
R₁ = 3-Me, **3ba**, 45%
R₁ = 4-OMe, **3ca**, 79%
R₁ = 5-Me, **3da**, 95%
R₁ = 5-Cl, **3ea**, 92%
R₁ = 5-CO₂Et, **3fa**, 92%



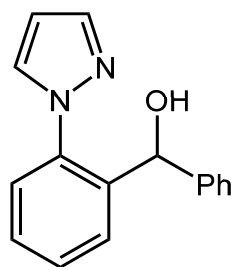
R₂ = *o*-Me, **3ga**, 83%
R₂ = *p*-Me, **3ha**, 87%
R₂ = *p*-OMe, **3ia**, 93%
R₂ = *p*-NMe₂, **3ja**, 54%
R₂ = *p*-CF₃, **3ka**, 81%
R₂ = *p*-F, **3la**, 84%
R₂ = *p*-I, **3ma**, 91%



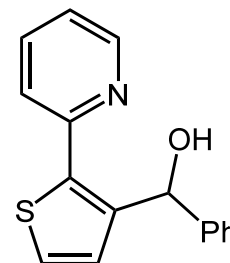
3na, 84%



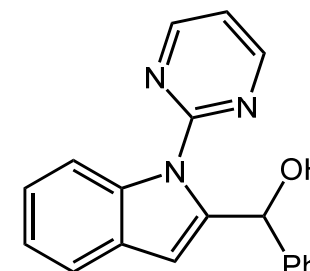
3oa, 95%



3pa, 71%

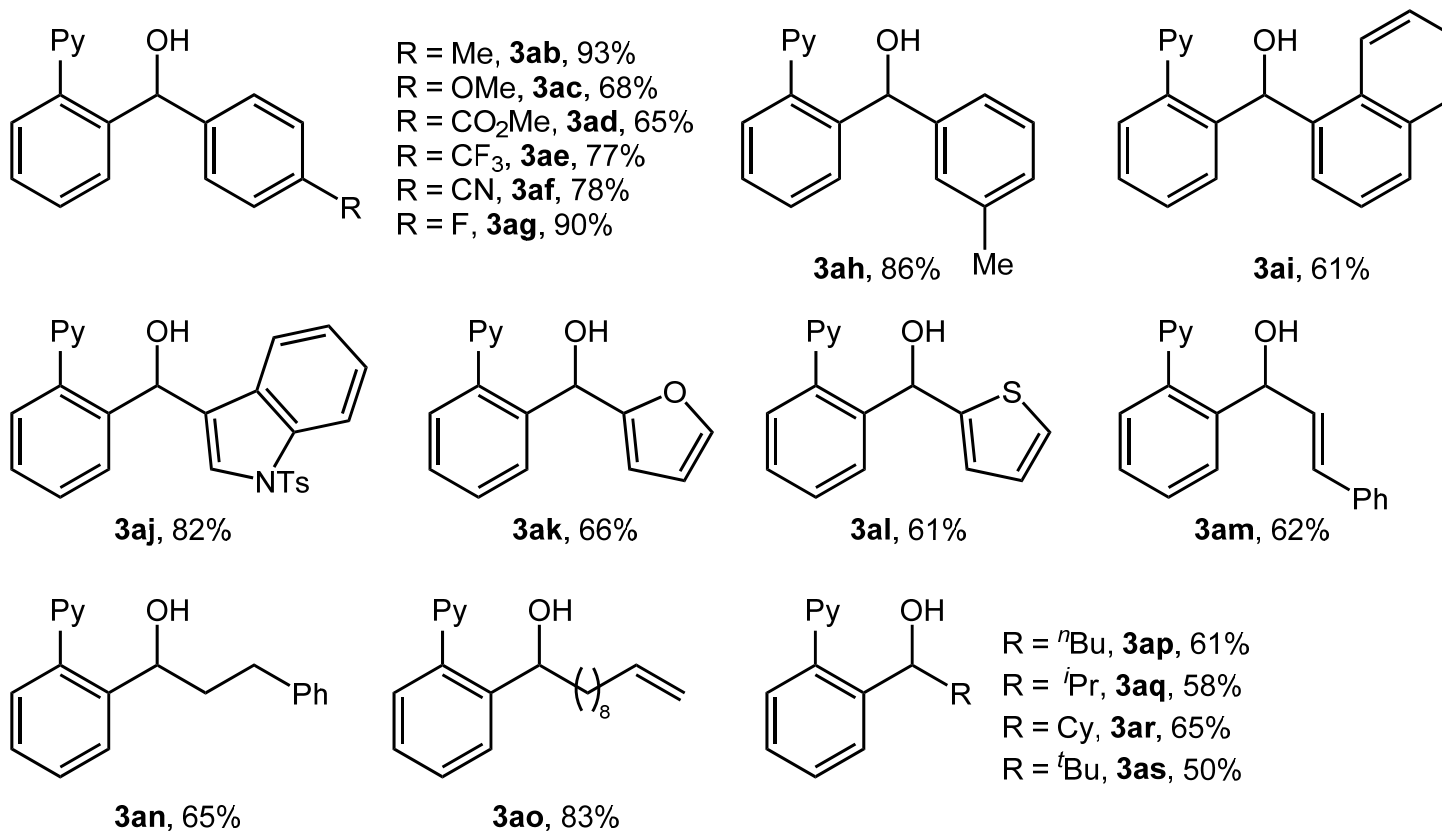
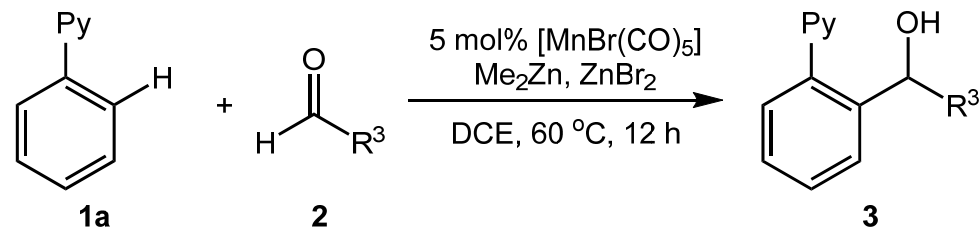


3qa, 78%

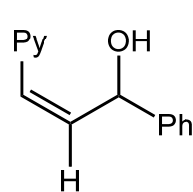
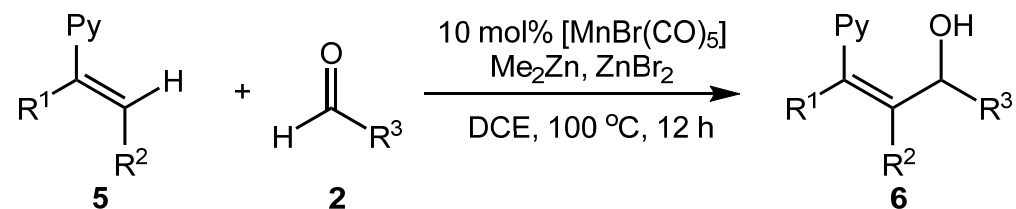


3ra, 62%

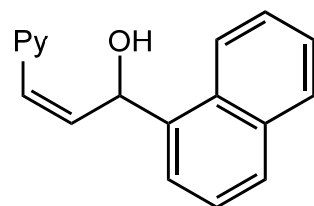
Scope with respect to the aldehyde



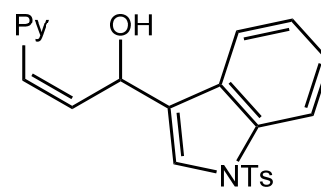
Olefinic C-H addition to aldehydes



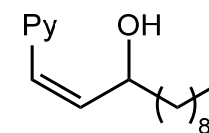
6a, 57%



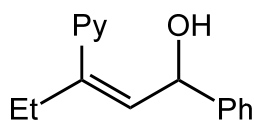
6b, 63%



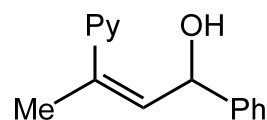
6c, 94%



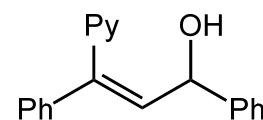
6d, 51%



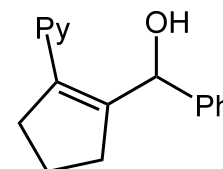
6e, 80%



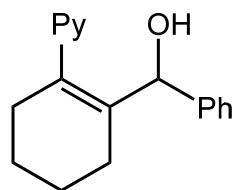
6f, 72%



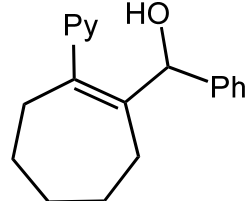
6g, 75%



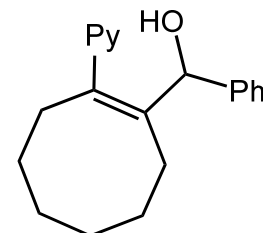
6h, 76%



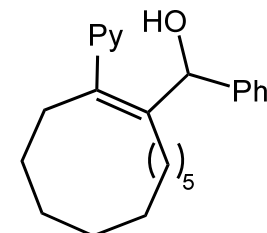
6i, 78%



6j, 80%



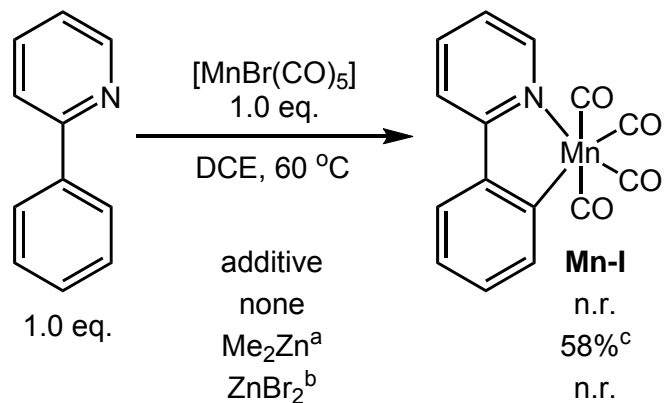
6k, 85%



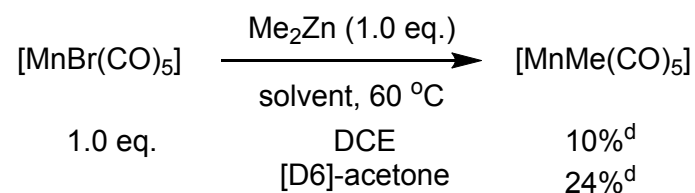
6l, 38%

Mechanistic experiments

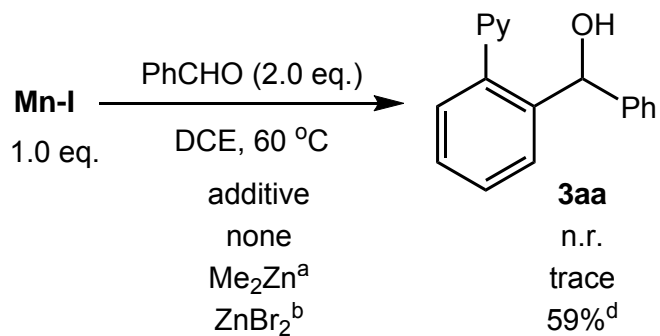
a)



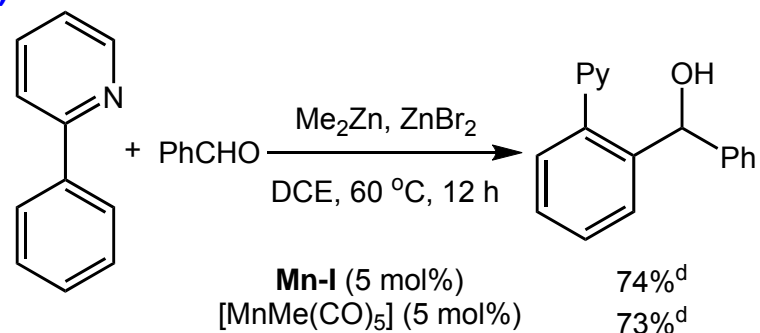
b)



c)

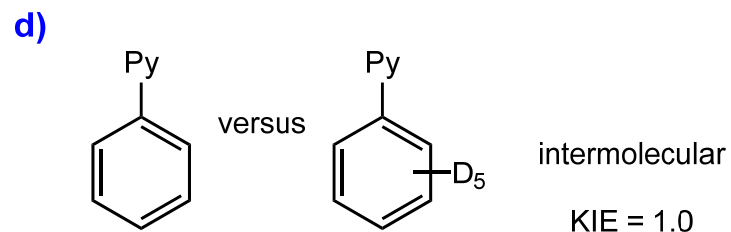
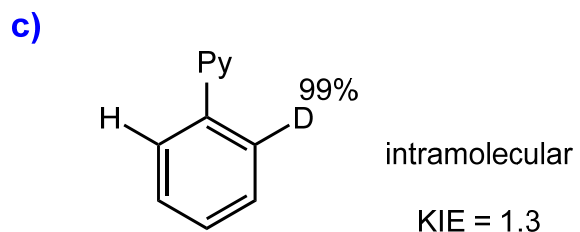
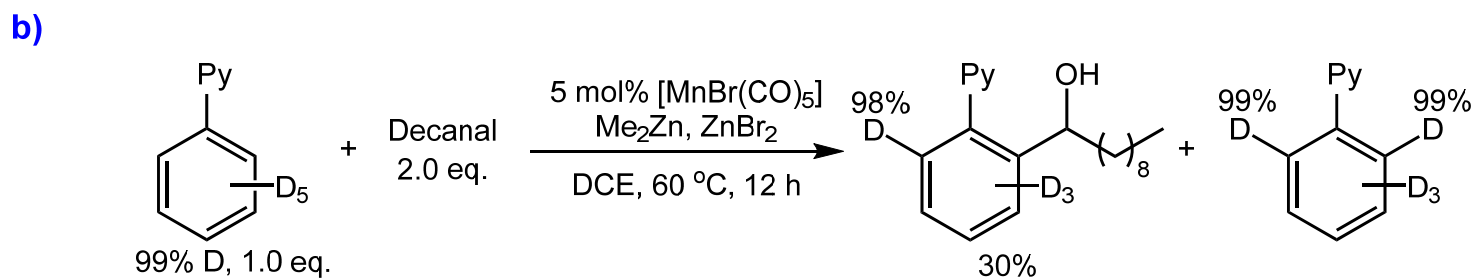
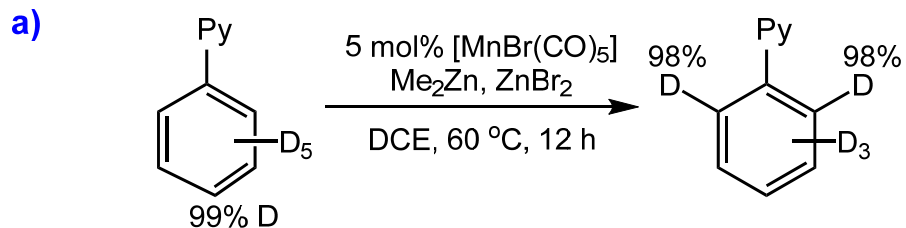


d)

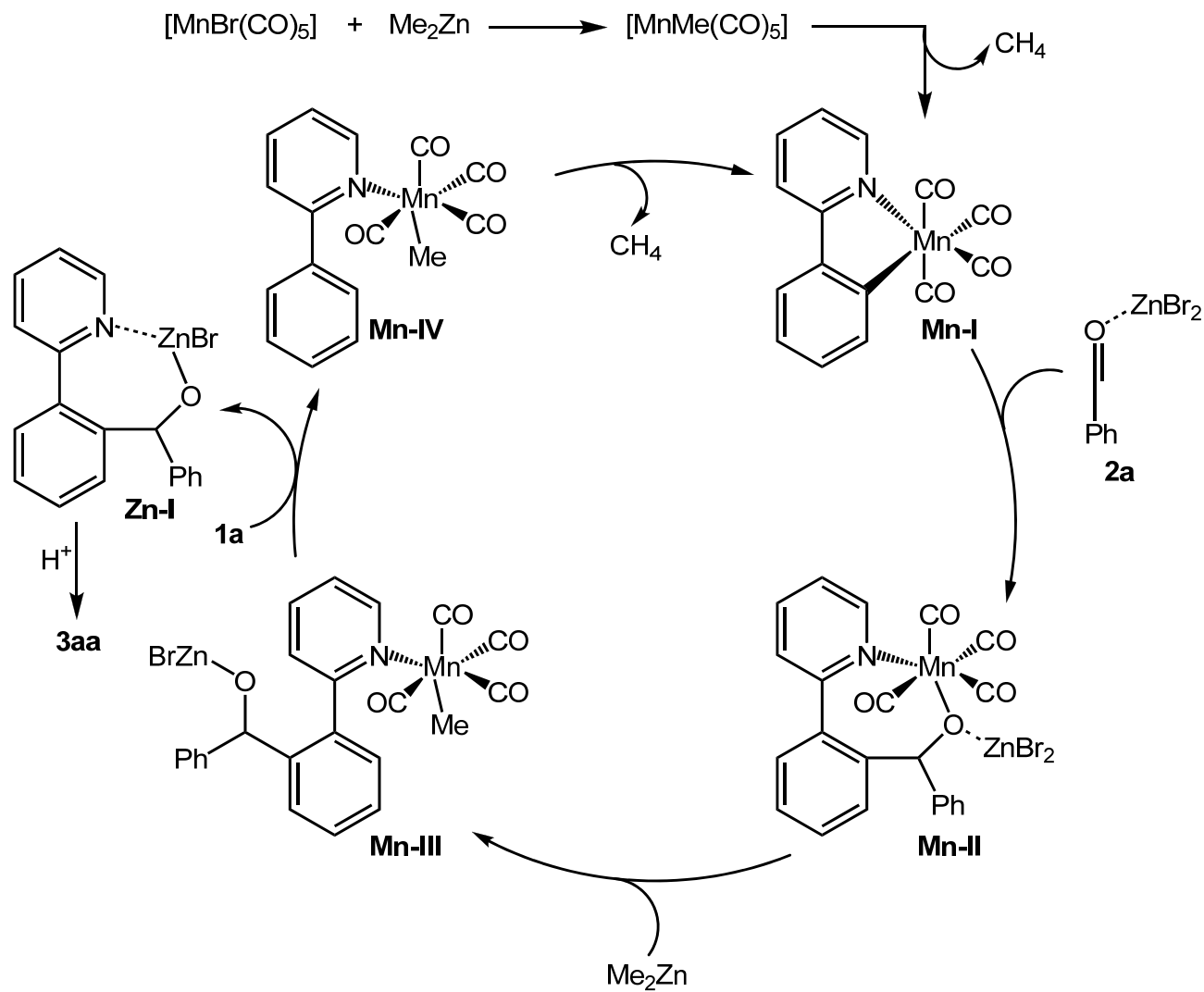


^a 1.5 eq. ^b 1.0 eq. ^c Yield of isolated product. ^d Yield determined by ¹H NMR spectroscopy.

Deuterium-labeling experiments

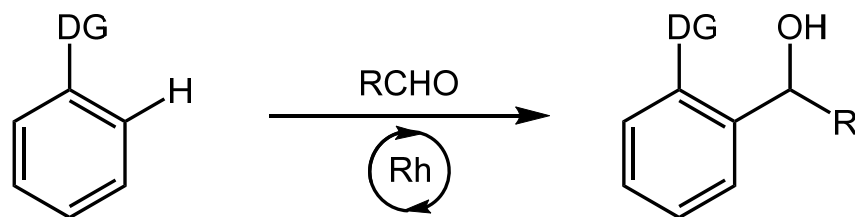


Proposed catalytic pathway

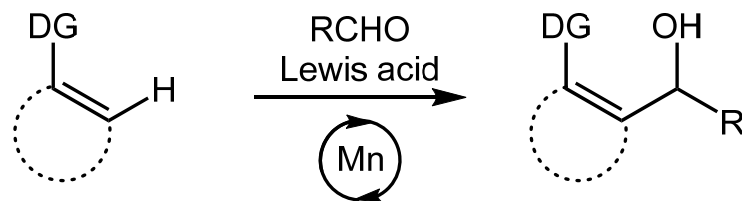


Summary

- Rh-catalyzed C-H addition to aldehydes to access alcohols:



- Mn-catalyzed C-H addition to aldehydes to access alcohols:



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. The redox reactivity of transition metals (e.g. Pd^{II}/Pd^{IV}, Pd^{II}/Pd⁰, 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. 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.

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 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. 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. Alternatively, directing groups were employed as intramolecular traps for the metal alkoxides to form stable cyclic products.

In conclusion, the manganese-catalyzed Grignard-type nucleophilic addition of C(sp²)-H bonds to aldehydes to access alcohols/ketones was developed by using a strategy of dual activation, which circumvents the limitations of previous rhodium and palladium catalytic systems. 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.