

LOW VALENT COBALT CATALYZED C—H FUNCTIONALIZATIONS

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December 6th, 2016

INTRODUCTION

Since Murahashi's 1955 report¹ on the cobalt catalyzed synthesis of phthalimidines from *N*-benzylideneaniline and carbon monoxide, the field of low valent cobalt catalysis has been expanded to include a variety of powerful C—H functionalization methods. Whereas the catalysis of the 4- and 5-d congeners of cobalt typically require temperatures at or in excess of 100 °C, low valent cobalt systems are frequently able to catalyze many of the same transformations at ambient temperature.² Importantly, the reactivity exhibited by low valent cobalt catalysts is often orthogonal to that of the noble metals.

HYDROARYLATION OF ALKYNES AND ALKENES

In 2010, Yoshikai *et al.* reported a ternary catalytic system comprised of a Co(II) precatalyst, a monodentate phosphine ligand, and a substoichiometric quantity of a Grignard reagent (Figure 1).³ Via this system, 2-arylpyridines and aryl ketimines are alkenylated at the *ortho* position. The mechanism of this transformation is initiated by a low valent Co(0) species, which likely exists as a formally negative -ate complex. Remarkably, this reaction proceeds at ambient temperature. Differentially substituted diaryl and dialkyl substituted alkynes are efficiently hydroarylated with predictable regioselectivity, and the imine moiety is readily hydrolyzed to reveal the masked ketone.

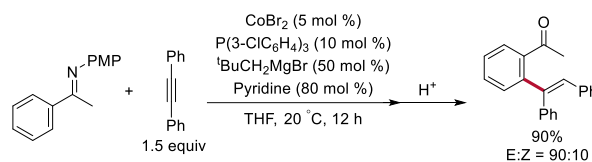


Figure 1: Cobalt catalyzed hydroarylation of alkynes at ambient temperature.

Interestingly, a strong secondary *meta* directing group effect is observed, which enables functionalization of the more hindered *ortho* C—H bond if the *meta* director is Lewis basic. Mechanistic investigations have revealed that the hydrogen atom *ortho* to the imine directing group is fully transferred to the alkyne moiety, indicating that Co(0) activates the *ortho* C—H bond via an oxidative addition type mechanism, then engages in *syn* hydroarylation of the alkyne.⁴

Styrenes readily participate in the hydroarylation reaction, affording the *ortho* alkylated aryl imines.⁵ The regioselectivity of these transformations is often highly tunable, and in the absence of extreme substrate bias, catalyst controlled. Use of *para* substituted monodentate triaryl phosphine ligands produces the branched alkylation product, whereas methoxy substituted triarylphosphine ligands afford the linear product. Development of this system has generated efficient and regioselective conditions that allow access to either the branched or linear alkylation products with selectivities that are often >90:10.⁵

ALKYLATION AND ARYLATIONS

Concomitant with the development of the hydroarylation chemistry, Nakamura *et al.* developed methodology to alkylate benzamides at the *ortho* position using alkyl chlorides.⁶ Unlike the hydroarylation

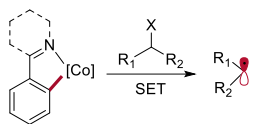


Figure 2: Cobalt metallacyclic intermediates can activate various electrophiles *via* SET.

chemistry, the mechanism of this reaction is thought to proceed via a metalation-deprotonation type C-H activation, and activation of the alkyl chloride likely proceeds via a single electron transfer (SET) from an intermediate cobalt metallacycle to produce an alkyl radical (Figure 2).

Yoshikai and co-workers expanded the scope of this transformation *via* use of alkyl bromides and a *N*-heterocyclic carbene (NHC) Co-catalyst system.⁷ Ackermann further developed this chemistry to produce robust methods for the alkenylation and arylation of *N*-pyrimidine protected indoles and 2-aryl pyridines, also using NHC systems.⁸ Ackermann demonstrated that carbamates, acetates, sulfamates, and phosphates can serve as electrophiles, and acyclic acetates proceed through a stereoconvergent mechanism.

HYDROACYLATIONS

Cobalt catalyzed, intermolecular hydroacylation was first achieved by Brookhart, *et al.*, who developed a method for the hydroacylation of vinyl silanes.⁹ Though extremely efficient, the scope of this reaction was limited entirely to vinyl silanes and unhindered alkyl aldehydes. Dong *et al.*, however, demonstrated that dienes and aldehydes can be hydroacylated under the action of low valent Co catalysis *via* an oxidative cyclization mechanism, providing access to unique hydroacylation regioisomers.¹⁰

CONCLUSION

The mild catalysis of low valent cobalt catalysis provides access to a variety of interesting materials, and offers reactivity that is divergent from noble metal catalysis.

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