

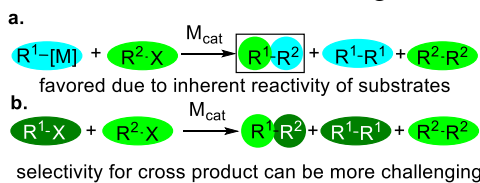
NICKEL-CATALYZED, CROSS-ELECTROPHILE COUPLING

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INTRODUCTION

Formation of carbon-carbon bonds via metal-catalyzed cross-coupling has revolutionized the field of organic chemistry.¹ Despite the broad scope of this reaction, some drawbacks exist. Fewer carbon nucleophiles are commercially available than the corresponding electrophiles. Functional group tolerance can be limited due to reactive organometallic species, especially with organo-magnesium and -zinc reagents. An alternative is to eliminate the need for preformed organometallic species through cross-coupling two electrophiles.² The main challenge is selectively forming cross-product over dimerization. Unlike coupling of electrophiles and nucleophiles, where the former selectivity adds through oxidative addition and the latter through transmetalation, both electrophiles compete for oxidative addition to the

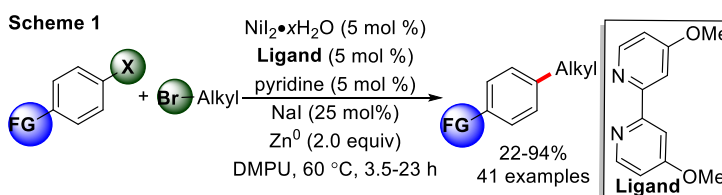


metal catalyst (Figure 1).² When the electrophiles are sufficiently alike, a statistical mixture of products is formed. Four general strategies to overcome dimerization have been developed: (1) utilizing excess of one reagent, (2) electronic differentiation of partners, (3) steric matching of catalyst-substrate, and (4) choice

of reaction parameters to favor radical chain process.²

METALS AS STOICHIOMETRIC TERMINAL REDUCTANTS

One example of each style of cross-coupling is presented herein: C(sp²)-C(sp³), C(sp²)-C(sp²) and C(sp³)-C(sp³). High chemoselectivity in coupling alkyl halides and aryl halides has been accomplished by Weix and Everson (Scheme 1).³ Halides are selectively coupled in the presence of other electrophiles (sulfonates and carbonyls) and acidic hydrogens (alcohol and Boc-protected amine). Substrates bearing both a nucleophile and an electrophile were selectively coupled at the electrophilic carbon, allowing for the incorporation of nucleophilic moieties such as organotin (-SnMe₃), organoboron (-Bpin), and organosilicon (-SiMe₂OH).³

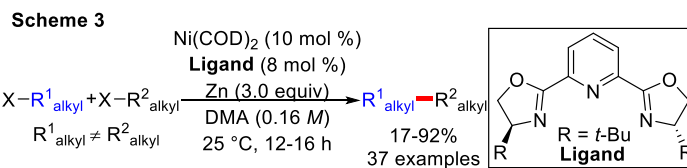


Four general mechanisms have been invoked for cross-electrophile coupling: (1) *in situ* formation of organometallic reagents, (2) disproportionation metathesis of nickel intermediates, (3) intermediate reduction of nickel, (4) no intermediate reduction of nickel (includes radical chain mechanism). Weix and Biswas demonstrated that organic reductants can be used in place of Zn or Mn metal, eliminating the possibility of *in situ* organometallic formation. In a separate experiment, two isolated nickel(II)

complexes resulting from the oxidative addition of each coupling partner are subjected to coupling conditions. The major product results from homocoupling, indicating that disproportionation metathesis is not the operative mechanism. Radical clock experiments suggest a radical chain mechanism is operating. Through extensive mechanistic investigation, Weix and Biswas show that oxidation of aryl halides first occurs through a two electron process followed by addition of the alkyl halide via a radical chain process.⁴

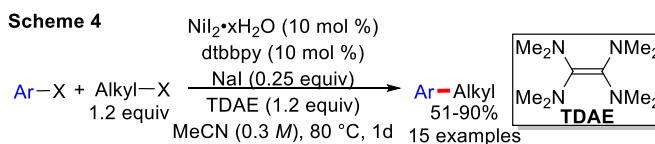
Recently Duan and co-workers have applied cross-electrophile coupling to the synthesis of 2,2'-bipyridines (Scheme 2).⁵ These compounds can be difficult to access with isohypsic Pd-catalyzed cross-coupling because of irreversible coordination of the product to the metal catalyst. Performing these reactions under cross-electrophile conditions is advantageous, as the zinc serves two purposes: as a terminal reductant and chelation metal to sequester the product, avoiding catalyst poisoning, and allowing for low nickel catalyst loading.

In 2011, Gong and co-workers developed the first cross $C(sp^3)-C(sp^3)$ coupling with unactivated primary and secondary halides (Scheme 3).⁶ The scope of coupling includes tolerance of imides, ester, alkene, acetal and alcohol functionality.



NON-METALS AS STOICHIOMETRIC TERMINAL REDUCTANTS

The majority of cross-electrophile couplings have the best selectivity in amide or urea solvents. Weix and co-workers have carried out cross-electrophile couplings in acetonitrile by using an organic compound, *tetrakis*(dimethylamino)ethylene (TDAE), as a terminal reductant.⁷ Diarylmethanes and easily reducible substrates were accessed with these conditions (Scheme 4).



OUTLOOK

The use of radical precursors and/or dual catalysis can offer another way to differentiate alkyl coupling partners. Organic reductants can tolerate easily reducible moieties on the coupling partners.

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