# FUNDAMENTALS AND MODERN ADVANCES IN IRON C-C CROSS-COUPLING

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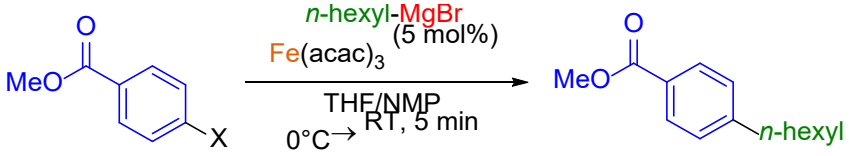
## INTRODUCTION

Cross-coupling reactions have remained a key transformation in chemical synthesis owing to their ability to reliably form carbon-carbon bonds. Cross-coupling chemistry has continued to be dominated by metals such as Pd and Ni for their ligand adaptability, scalability, and well-defined mechanism.[1] Iron provides an attractive alternative to these metals for cross-coupling as its earth abundance is significantly greater than any alternative metal, it is relatively non-toxic, and it can offer complementary reactivity to Pd or Ni, especially in the use of $sp^2$-$sp^3$ cross-couplings.[2]

## A HISTORICAL PERPSECTIVE

Kharasch and coworkers discovered that metal salts, including $FeCl_3$, could catalyze the cross-coupling of arylmagnesium reagents with aryl bromides. This area went largely unexplored until 1971 when Kochi illustrated that $FeCl_3$ could catalyze the coupling of alkenyl bromides and alkyl Grignard reagents with retention of alkene geometry.[3] This reaction was limited to an excess of organomagnesium reagents until 1996, when Cahiez and coworkers demonstrated that the addition of *N*-methyl-pyrrolidinone (NMP) could reduce the necessary equivalents of nucleophile. In 2002, Fürstner greatly expanded the scope of iron-catalyzed cross couplings to include aryl/heteroaryl halides, illustrating high chemoselectivity, even in the presence of reactive functional groups (**Scheme 1**).[5] The scope of iron reactivity was expanded further by utilizing TMEDA as an additive.

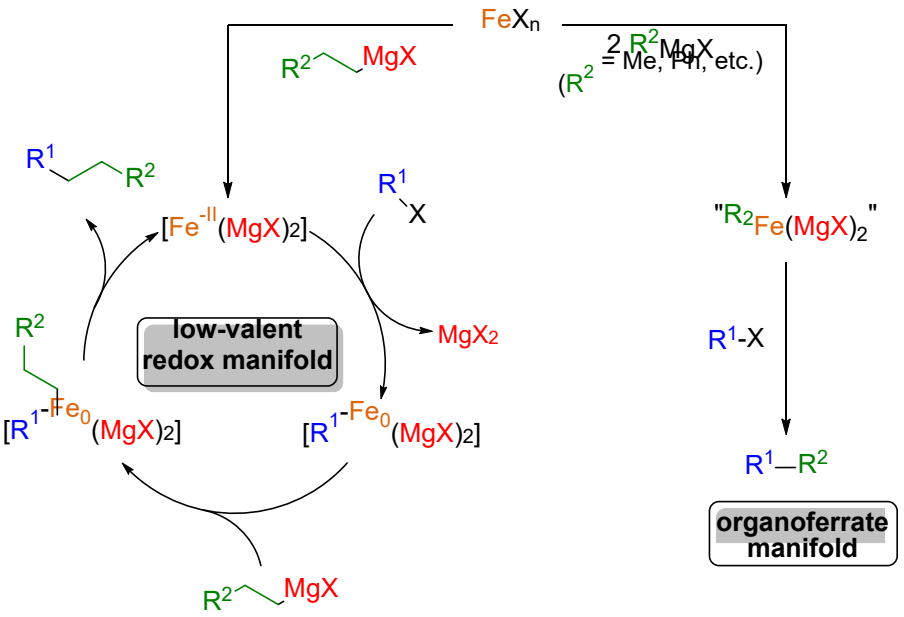



**Scheme 1** Iron-catalyzed cross-coupling of aryl halides and alkyl grignards.

## UNDERSTANDING THE IRON COMPLEX

The mechanism of iron-catalyzed cross-couplings remains ambiguous due to the complex nature of the redox states of iron and difficulty in isolating the active iron species. Fürstner and coworkers approached this problem by successfully isolating different crystal structures of iron at various oxidation states and testing their reactivity in cross-coupling.[6] The crystal structures isolated led them to posit that the presence of a $\beta$-hydride on the organomagnesium reagent led to

a low-valent redox cycle, while Grignard reagents without a β-hydride would operate through an organoferrate manifold (**Scheme 2**). This work would remain the state of the art until techniques such as Mössbauer and EPR spectroscopy were used together to track the oxidation states of elusive intermediates.[7]

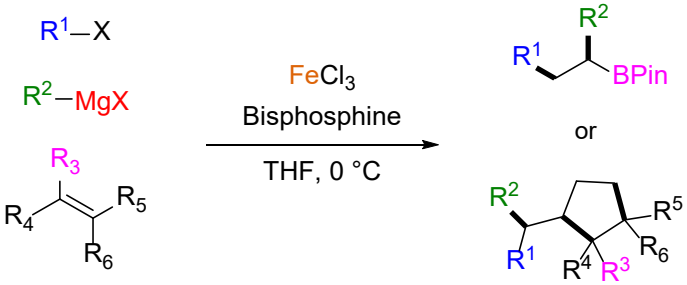



**Scheme 2** Two different pathways for iron reactivity.

Investigations to understand the role of TMEDA with aryl nucleophiles were conducted, with both a homoleptic iron-ate complex and TMEDA-bound iron proposed as operative species.[8]

## MODERN FRONTIERS AND EXPLORATIONS

There are a variety of approaches to further the scope of iron-catalyzed cross-couplings. One novel approach was shown by Gutierrez and co-workers, who disclosed a multicomponent radical cascade reaction using a bisphosphine ligand (**Scheme 3**).[9] The scope of these radical cascades allowed for difunctionalization or annulation depending on the nature of the vinyl species, with mechanistic work illustrating that an Fe(II) species was responsible for alkyl radical generation. Baran and co-workers disclosed a report of an iron-catalyzed cross-coupling between aliphatic redox-active esters and arylzinc complexes. This was capable of coupling primary and secondary acids comparably to nickel; however, iron showed better utility for tertiary acids than nickel. Iron demonstrated higher functional group tolerance as well.




**Scheme 3** Multicomponent radical cascade reaction.

(1) Maseras *et al. Acc. Chem. Res.* **2013**, 46, 2626-2634 (2) Knölker *et al.*; *Chem. Rev.* **2015**, 115, 3170 (3) Kochi, J.; Tamura M.; *J. Am. Chem. Soc.* **1971**, 93, 6, 1487-1489 (4) Cahiez *et al.*; *Pure & Appl. Chem.* **1996**, 68, 53-60 (5) Fürstner *et al.; J. Am. Chem. Soc.* **2002**, 124, 46, 13856-13863 (6) Fürstner *et al.; J. Am. Chem. Soc.* **2008**, 8773-8787 (7) Neidig *et al.*; *Acc. Chem. Res.* **2019**, 52, 140-150 (8) Neidig *et al. Angew. Chem. Int. Ed.* **2022**, 134, e202114986 (9) Gutierrez *et* al *Science*, **2021**. 374, 432-439 (10) Baran *et al. J. Am. Chem. Soc*. **2016**, 138, 11132-11135