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Striving to exploit alkyl electrophiles: challenge and choice in transition metal-catalyzed cross-coupling reactions of sulfones

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For cross-coupling reactions of alkyl electrophiles, alkyl halides, alkyl tosylates, alkyl acetates and alkyl sulfones exhibit high reaction efficiency when various transition metal catalysts and reaction partners are employed. As crystalline and readily available alkyl electrophiles, alkyl sulfones in radical cross-coupling reactions open a new avenue for modularly generating diverse alkyl compounds. It is believed that more transformations using sulfones as electrophiles will be developed in the near future.

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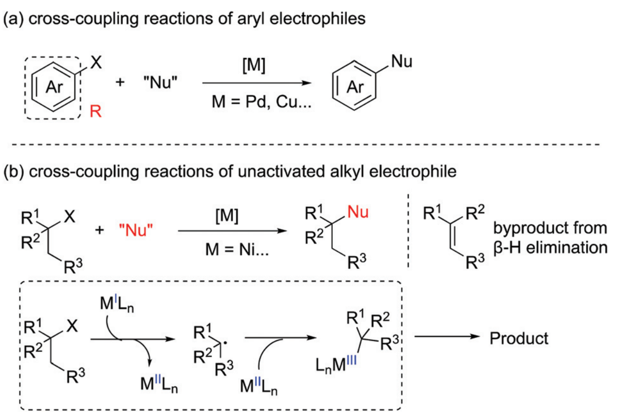
Transition metal-catalyzed cross-coupling reactions are highly attractive due to their versatility toward the formation of carbon–carbon and carbon–heteroatom bonds.[1] Basically, the reaction is usually initiated by the oxidative addition of an electrophile with a transition metal catalyst, and provides the final product through reductive elimination. Previously established achievements showed that various transition metals and different types of ligands have a highly significant impact on cross-coupling reactions, thus giving rise to a range of transition metal catalysis-based name reactions (Scheme 1, eqn (a)). As notable electrophiles, aryl halides and their analogues are well-recognized as efficient reaction partners in many useful transformations, such as Suzuki coupling, Sonogashira coupling, Ullman coupling *etc*. Considering the ubiquity of alkyl groups in many useful molecules, it is unsurprising that alkyl electrophiles used in cross-coupling attract the interest of many chemists.[2]

Alkyl electrophiles, especially secondary alkyl electrophiles and tertiary alkyl electrophiles, always feature β-hydride elimination and hindered oxidative addition, thus it is more difficult for these compounds to undergo a classical two-electron cross-coupling as aryl electrophiles do. Through chemists' unremitting efforts, two protocols to date have been developed to achieve the coupling of alkyl electrophiles.

What came first was the invention of novel reaction systems for promoting the cross-coupling of alkyl electrophiles, especially for unactivated alkyl electrophiles. Recent progress in the development of various transition metal catalysts such as palladium and nickel catalysts *etc*. opened a new door towards the cross-coupling of unactivated alkyl electrophiles.[3–5] In particular, nickel catalysis has proven to be unusually effective for the cross-coupling of unactivated secondary and tertiary alkyl electrophiles.[6]

Mechanistically, the success of coupling unactivated alkyl electrophiles was ascribed to a radical pathway involving "single-electron-induced" oxidative addition (Scheme 1, eqn (b)). Treated with a transition metal catalyst, the alkyl electrophile would be homolyzed into alkyl radicals in the process, and the transition metal, M^{n+}, was oxidized into $M^{(n+1)+}$. Radical recombination of the resulting alkyl radical with $M^{(n+1)+}$ would offer alkyl $M^{(n+2)+}$ species. The following reduc-



Scheme 1 Development of cross-coupling reactions with transition metal catalysis.

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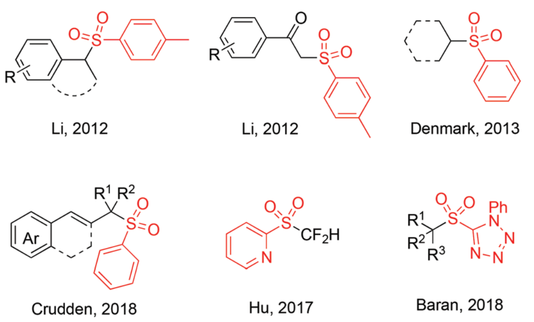
tive elimination would deliver the final product. It is noteworthy that the single-electron-transfer-type addition was effective for the whole process. The above alkyl electrophiles were often alkyl halides and their analogues. To realize the full potential of radical cross-coupling reactions, it is highly desirable to expand the range of electrophiles more widely than alkyl halides, thus spurring chemists to find another way to achieve the cross-coupling of alkyl electrophiles.

Different from other electrophiles, sulfone compounds are often highlighted due to their ready accessibility, convenient manipulation and synthetic versatility for functional elaboration (*i.e.* α-alkylation, fluorination). To the best of our knowledge, α-amino sulfones are well-recognized as efficient electrophiles in nucleophilic substitution reactions. In these reactions, α-amino sulfones serve as stable precursors to reactive *N*-acylimino derivatives. Petrini from Italy summarized the established achievements in 2005.[7] However, other less-reactive alkyl sulfones being used as electrophiles remain rare.

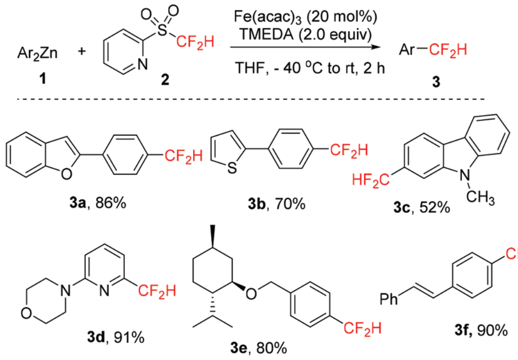
The elegant chemistry using less-reactive alkyl sulfones as alkyl electrophiles was a synthetic milestone for forging $C(sp^3)$–$C(sp^2)$ bonds using nickel or iron catalysis (Scheme 2). In particular, the reactions using alkyl sulfones as electrophiles were extremely efficient for constructing quaternary carbon centers.

The initial work disclosed by Li's group[8] and Crudden's group[9] has stood out for the use of benzylic arylsulfones, allylic arylsulfones, and carbonyl α-tolylsulfones in nickel-catalyzed cross-coupling reactions, which demonstrated the capability of activated alkyl arylsulfones to serve as effective alkyl electrophiles in reactions with Grignard reagents or arylboronic reagents. In addition to nickel catalysis, the first systematic study from Denmark's group revealed that iron catalysis could also enable the coupling of alkyl phenylsulfones. Notably, the use of iron catalysis could expand the reaction greatly to unactivated phenylsulfones with high reaction efficiency.[10]

To achieve mainstream adoption of sulfone-based cross-coupling reactions, Hu's foray into this area centered on developing iron-catalyzed difluoromethylation of arylzinc reagents **1** with difluoromethyl 2-pyridyl sulfone **2**.[11] Investigation of the method's tolerance indicated that Hu's chemistry shone in the preparation of difluoromethylative electron-rich and electron-deficient heterocyclic compounds **3a–3d**. Additionally, alkenyl and chiral components were also compatible. Mechanism studies implied that difluoromethyl 2-pyridyl sulfone **2** had a suitable relative reduction potential to oxidize low-valent iron species, leading to difluoromethyl radicals, 2-pyridyl sulfinate anions and $Fe^{(n+1)+}$ species (Scheme 3).



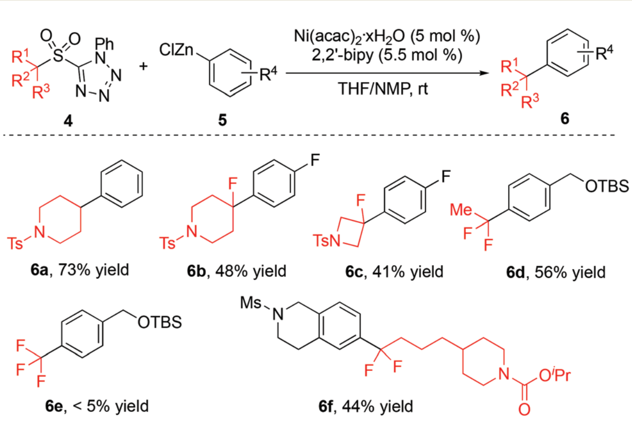
Scheme 2 The developed examples using alkyl sulfones as alkyl electrophiles in cross-coupling reactions.



Scheme 3 Iron-catalyzed difluoromethylation of arylzinc reagents **1** with difluoromethyl 2-pyridyl sulfone **2**.

Concurrent with Hu's report, Baran and co-workers made another breakthrough. By evaluating relative reduction potential, electronegativity and compound size, Baran's group found that an orthogonal redox-active tetrazole sulfone **4** was another uniquely competent alkyl coupling partner in the reaction of arylzinc reagents **5** in the presence of a nickel catalyst and 2,2′-bipy ligand.[12] Baran's chemistry provided a primary advantage for simplifying the retrosynthetic analysis toward complex $C(sp^3)$-fluoro building blocks. As such, the alkyl part in sulfone **4** could be replaced by secondary alkyl, monofluoro-containing tertiary alkyl or difluoro-containing tertiary alkyl groups. A series of products, **6a–6d**, could be achieved in moderate to good yields. The streamlined synthesis of pharmaceutical-oriented fluorinated compound **6f** was also demonstrated, thus proving the robustness of the standard conditions for this radical cross-coupling (Scheme 4).

As evidenced by radical probe reactions and racemic experiments from a chiral sulfone, the alkyl radical was proven to be



Scheme 4 Nickel-catalyzed cross-coupling reactions of alkyl sulfones with organozinc reagents.

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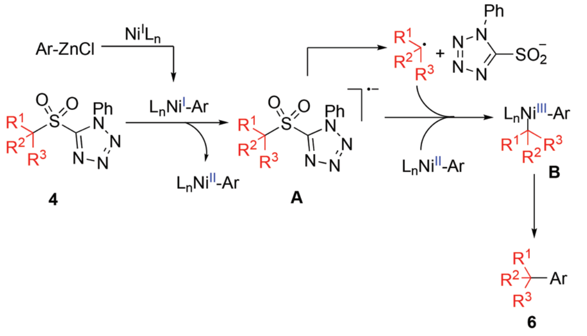

Scheme 5 Plausible mechanism for nickel-catalyzed cross-coupling reactions of alkyl sulfones with organozinc reagents.

the key intermediate (Scheme 5). A single-electron cross-coupling pathway was proposed.

The road to exploiting alkyl electrophiles in cross-coupling reactions is decorated with many landmark findings. Alkyl halides, alkyl tosylates, alkyl acetates, and sulfones exhibited high reaction efficiency when various transition metal catalysts and reaction partners were employed. In particular, tertiary and quaternary carbon motifs could be achieved by using secondary and tertiary alkyl electrophiles. However, the nucleophiles in the established cases of the cross-coupling of alkyl electrophiles focused exclusively on Grignard reagents, organozinc reagents and organoboronic reagents, which points to the improvement needed for wide adoption of the above chemistry. As crystalline and readily handled alkyl electrophiles, alkyl sulfones in radical cross-coupling reactions opened a new avenue for modularly generating diverse alkyl compounds. Using nickel and iron salts as catalysts, alkyl-connecting arylsulfone, pyridylsulfone and tetrazolesulfone proved to be efficient reaction partners in many cross-coupling reactions. It is believed that more transformations using sulfones as electrophiles will be developed in the near future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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