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## Preview

# Ketone C–C Bond Activation meets the Suzuki-Miyaura Cross-Coupling

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## SUMMARY

In a recent issue of *J. Am. Chem. Soc.*, Dong and coworkers report that ketones can participate as electrophiles in the Suzuki-Miyaura cross-coupling reaction under Rh(I) catalysis. Building on their previous work and Jun's original accounts, they have shown that activation of carbon-carbon bonds of unstrained ketones is a versatile process that can engage in cross-coupling reaction with aryl boronates.

## DISCUSSION

The formation of C–C bonds is the most fundamental step of organic chemistry. The union of two molecules to build a larger carbon backbone or the formation of new C–C bonds within a substrate to generate a more complex product is the essence of the vast majority of synthetic approaches. Many of the most celebrated reactions that are found among the basic toolset of the organic chemist fall in this category. The rich chemistry of aldol condensations, the addition of organometallic nucleophiles to electrophiles, pericyclic reactions, as well as transition metal catalyzed cross-coupling reactions have become classic transformations that are still key in most syntheses.

The popularization of transition metal catalyzed cross-coupling reactions has completely transformed the way we think about disconnecting molecular targets, and advances during the last years have allowed the use of a wide range of carbon nucleophiles and electrophiles. Among these the Suzuki-Miyaura cross-coupling is arguably one of the most popular reactions, having found broad application in industry, and one widely studied and used in research laboratories thanks to the stability and versatility of organoboron nucleophiles. In traditional Suzuki-Miyaura reactions, aryl halides or pseudo-halides act as the electrophile; however, more recent developments have expanded the scope of coupling partners to less reactive bonds, such as aryl methyl ethers, phenols or esters.<sup>1–3</sup>

The activation of C–C bonds has often relied on the strain relief associated with the cleavage of such bonds as its driving force.<sup>4</sup> Despite the inherent difficulty in the activation of unstrained C–C bonds, many efforts have successfully tackled this enormous challenge. Actually, several transition metal catalyzed methodologies have been developed to activate different unstrained C–C bonds. Among these we can find the C–C single bonds next to most carbonyl derivatives, alcohols, ethers, amines, nitriles, alkynes, etc. A long list of transition metals has been used for the catalytic activation of such bonds, giving rise to a varied collection of transformations that include fragmentations, rearrangements and cross-couplings.<sup>5</sup> Early reports from Jun showed that metal-organic cooperative catalysis using 2-amino-3-picoline and a Rh(I) catalyst can achieve oxidative addition to C–C bonds in unstrained ketones, unleashing new reactivity modes for one of the most widespread functional groups in nature.<sup>6</sup> Thanks to this pioneering work, the cross-coupling of ketones and imines with alkenes was achieved.<sup>7,8</sup>

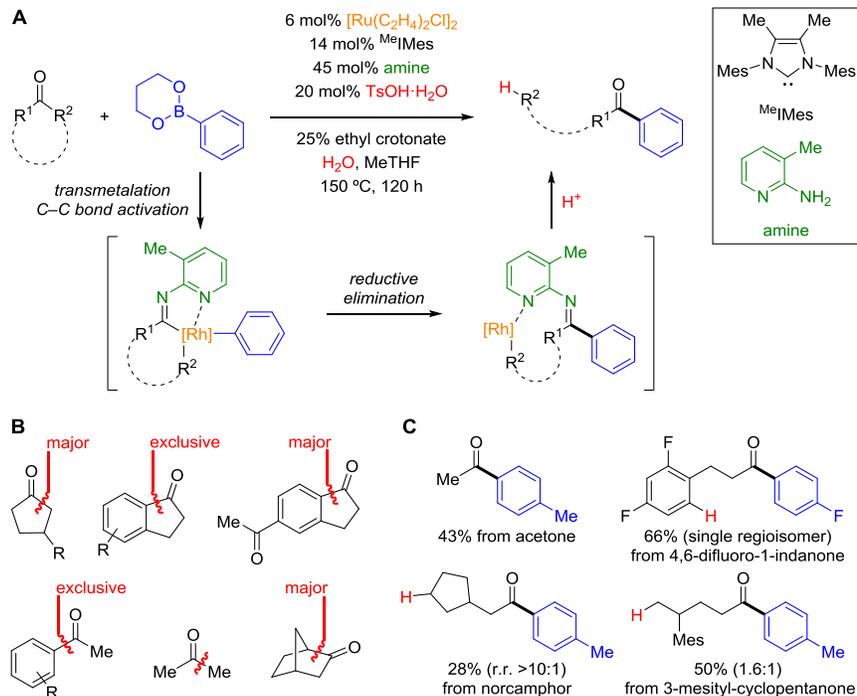
Recently, Dong and collaborators have reported in *J. Am. Chem. Soc.* that C–C bond activation under 2-amino-3-picoline and Rh(I) cooperative catalysis allows to cross-couple linear and unstrained cyclic ketones with aryl boronic ester nucleophiles.<sup>9</sup> The fine tuning of conditions from their previous reports on ketone C–C bond activations allowed the

development of a useful catalytic system. The use of catalytic amounts of acid and amine (Scheme 1A) were essential to unlock this reactivity. Moreover, <sup>Me</sup>IMes proved to be a superior ligand to IMes in this transformation, which had been the ligand of choice in previous accounts.<sup>10</sup> Clearly, one of the strengths of this method is the broad scope of ketones that participate in the transformation, which includes acetone and other common feedstocks (Scheme 1B). Thanks to this, a versatile route to a diverse family of alkyl aryl ketone products is provided (Scheme 1C).

The site selectivity shows a clear trend in cyclic ketones with the most substituted side of the carbonyl being more prone to activation of the C–C bond. Surprisingly, even  $\beta$ -substituents clearly dictate this preference regardless of their electronic nature and the same trend is observed in all cases, albeit with different levels of selectivity. For instance, alkyl and aryl groups give rise to very poor selectivities (1.6:1 or lower), whereas a more electronically biased ester group leads to high regiocontrol (>10:1). On the other hand, benzyl acetone, as the only reported example of an unsymmetrical linear dialkyl ketone, shows a slight preference for cleavage of the smaller methyl substituent. When site selectivity depends solely of electronic effects, complete regiocontrol is achieved. Thus, alkyl aryl ketones always lead to exclusive cleavage of the C<sub>sp2</sub>–C<sub>sp2</sub> bond. Such is the case of 1-indanones and acetophenones, in which Rh(I) always cleaves the bond between the carbonyl and the aryl group, showcasing the potential of the method and its high synthetic value.

Activation of C–C bonds under transition metal catalysis can occur via two different mechanisms, namely oxidative addition or  $\beta$ -carbon elimination assisted by a directing group. In their recent report, Dong and collaborators provide evidence for the mechanism of ketone C–C bond activation, which along with previous theoretical calculations supports that oxidative addition of a Rh(I) species takes place (Scheme 1A).<sup>9,10</sup> This discards the alternative pathway involving  $\beta$ -carbon elimination after 1,2-addition of the aryl nucleophile into the ketone or imine substrates.

Dong's report clearly improves the perspective of ketones being used in cross-coupling technologies involving C–C bond activation and opens up a vast new chemical landscape for the Suzuki-Miyaura cross-coupling. Currently, the method suffers from low conversions after very long reaction times and in most examples yields range from low to moderate. Moreover, the site regioselectivity for unsymmetrical dialkyl ketones can be marginal with the present catalytic system. However, discrimination between aryl and alkyl substituents is superb and renders the method truly synthetically useful. Hopefully, future advances will bring the discovery of even more powerful and selective catalysts that allow the transformation to occur much faster and in higher yields while achieving high selectivity in all substrates.



**Scheme 1. Rhodium-catalyzed Suzuki-Miyaura cross-coupling of aryl boronates and a diverse range of unstrained ketones.**

(A) Standard conditions for the coupling and intermediates of the proposed mechanism.

(B) Scope of ketones used in the study with the preferred C–C bond for activation highlighted.

(C) Selected examples of products.

## AUTHOR CONTRIBUTIONS

X.J.-B. and I. L. wrote the manuscript.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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