Suzuki-Miyaura Coupling of Simple Ketones via Activation of Unstrained Carbon-Carbon Bonds

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b02462 • Publication Date (Web): 13 Apr 2018

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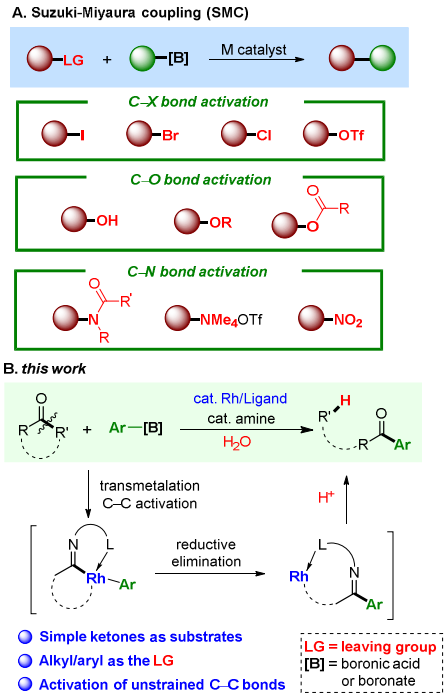
Supporting Information Placeholder

ABSTRACT: Here, we describe that simple ketones can be efficiently employed as electrophiles in Suzuki–Miyaura coupling reactions via catalytic activation of unstrained C−C bonds. A range of common ketones, such as cyclopentanones, acetophenones, acetone and 1-indanones, could be directly coupled with various arylboronates in high site-selectivity, which offers a distinct entry to more functionalized aromatic ketones. Preliminary mechanistic study suggests that the ketone α-C−C bond was cleaved via oxidative addition.

Cross-coupling reactions catalyzed by transition metals have greatly influenced bond-disconnection strategies in modern organic synthesis.[1] In particular, the Suzuki–Miyaura coupling (SMC), the coupling between organoboranes and carbon electrophiles[2a], represent one of the most frequently utilized reactions in pharmaceutical, agrichemical and material research[2b], which is largely attributed to the wide availability, decent stability and excellent reactivity of boron reagents. Classical SMC reaction employs organohalides or pseudohalides as electrophiles (Scheme 1A). Given the increasing importance of this transformation, substantial attentions have been paid on extending the scope of electrophiles for SMC.[3-5] The recent advance of nickel catalysis has allowed aryl ethers, phenols and esters to serve as electrophiles for SMC through C–O bond activation.[3] In addition, use of aryl amides, ammonium salts and nitro compounds has also been demonstrated via a metal-mediated C–N bond activation.[4] Apart from cleaving the more polarized C–X (X = halogen), C–O and C–N bonds, SMC reactions via activation of less polar, *unstrained C–C bonds in common feedstock* would be highly valuable, which however remained a challenge to date.[6,7]

Transition metal-catalyzed C−C bond activation has become an emerging area for enabling novel transformations of organic molecules.[8,9] Small ring systems are commonly employed to drive the C−C bond cleavage process through strain relief,[9a,b] consequently leading to valuable methods for building bridged and fused rings.[9c] In contrast, catalytic activation of less- or non-strained systems has been rather challenging, especially in a constructive manner.[8d,10] As an initial step towards the goal of developing synthetically useful methods via activating unstrained C−C bonds, we recently reported a catalytic tandem C−C/C−H activation of 3-arylcyclopentanones.[11] In this reaction, 3-arylcyclopentanones underwent oxidation addition into α C−C bonds through an *in situ* generated ketimine intermediate, a mode of reactivity originally discovered by Jun,[8i,10b,10c] followed by an intramolecular C−H metalation and reductive elimination, eventually providing functionalized α-tetralones or 1-indanones. This intramolecular reaction shows promise for synthetic applications capitalizing on C−C activation of unstrained systems; however, it would be more broadly useful if an intermolecular cross coupling could be realized with readily available simple ketones as substrates. Hence, we were motivated to merge a transmetalation process and imine-directed C−C activation, and envisaged that subsequent reductive elimination/protonation would furnish a general cross-coupling reaction between simple common ketones and arylboronic acid derivatives (Scheme 1B).

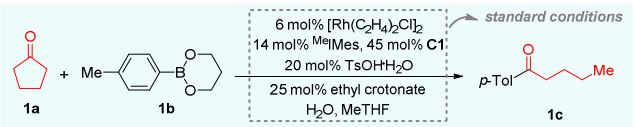
Scheme 1. The Development of Suzuki–Miyaura Coupling (SMC) Reactions



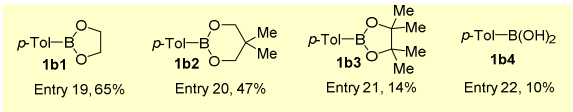
At the outset, cyclopentanone (**1a**) was chosen as the model substrate for the coupling with arylboronate **1b** (Table 1). After an extensive survey of the reaction conditions, the desired coupling product (**1c**) was ultimately obtained in 68% yield (Entry 1). The optimized catalytic system contains 6 mol% $[Rh(C_2H_4)_2Cl]_2$, 14 mol% ^{Me}IMes, 20 mol% $TsOH{\cdot}H_2O$, 45 mol% 2-amino-3-picoline (**C1**) and 25 mol% ethyl crotonate; 2 equiv of H_2O was used as the proton source with MeTHF (2-methyltetrahydrofuran) as the solvent. Note that no additional base was required for this ketone-mediated SMC reaction. A series of control experiments were then carried out to gain more insights to this reaction. It was revealed that the rhodium pre-catalyst and the amine co-catalyst (**C1**) were both crucial, and no product was produced without either of them (Entries 2 and 3). In the absence of $TsOH{\cdot}H_2O$ or

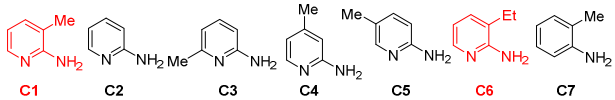
^{Me}IMes, **1c** was only formed in less than 10% yield (Entries 4 and 5). H_2O serves as a reactant, and the yield dropped to 20% when no H_2O was added (Entry 6). The catalytic amount of ethyl crotonate can slightly increase the efficiency, which likely plays a role as a π acid to promote the reductive elimination step (Entry 7).[12] Apart from 2-amino-3-picoline (**C1**), several other amine co-catalysts were also tested. Without the methyl group (Entry 8) or having methyl at other positions (Entries 9-11), the amine co-catalysts were much less active. A comparable result was achieved when replacing the methyl with an ethyl group (Entry 12), while no product was produced when the pyridyl group was replaced by a phenyl group (Entry 13). Compared with the ^{Me}IMes ligand, other NHC ligands also promoted this reaction albeit in lower yields (Entries 14-16). When the reaction temperature was lowered to 130 °C or less arylboronate **1b** was used, the coupling product was still obtained in 46% and 56% yields, respectively (Entries 17 and 18). With regard to the arylboron reagents, 1,3-propanediol-drived boronate (**1b**) offers a nice balance between stability and reactivity. Similar reactivity was observed using glycol-derived arylboronate (**1b1**), but other diol-derived arylboronates or boronic acid was less effective (Entries 19-22).

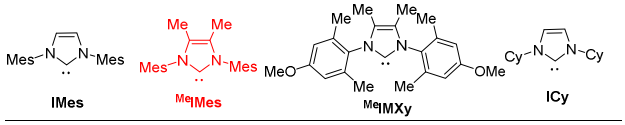
Table 1. Selected Optimization of Reaction Conditions[a]



Entry	Variation	Yield (%)[b]	Entry	Variation	Yield (%)[b]
1	None	68 (67)[c]	10	**C4** instead of **C1**	19
2	w/o $[Rh(C_2H_4)_2Cl]_2$	0	11	**C5** instead of **C1**	11
3	w/o **C1**	0	12	**C6** instead of **C1**	67
4	w/o $TsOHH_2O$	2	13	**C7** instead of **C1**	0
5	w/o ^{Me}IMes	7	14	IMes instead of ^{Me}IMes	58
6	w/o H_2O	20	15	ICy instead of ^{Me}IMes	41
7	w/o ethyl crotonate	59	16	IMxy instead of ^{Me}IMes	61
8	**C2** instead of **C1**	19	17	130 °C	46
9	**C3** instead of **C1**	<1	18	1.5 equiv. **1b**	56







[a]All the reactions were run with 0.2 mmol of **1a**, 0.5 mmol of arylboronate, 0.4 mmol of H_2O and 0.15 mL of MeTHF in a 4 mL vial at 150 °C for 120 h. [b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield; the yield was 40% for 60 h and 59% for 96 h. Ts, *p*-toluenesulfonyl, MeTHF, 2-methyltetrahydrofuran.

The substrate scope of this ketone-mediated SMC reaction was then investigated (Chart 1). Firstly, a series of 1,3-propanediol arylboronates were tested in the reaction with cyclopentanone (Chart 1A). In general, more electron-rich arylboronates worked better probably due to a faster transmetalation process, whereas the more electron-deficient ones gave sluggish reactions (Entries 1-20). A range of functional groups that are known to participate in cross coupling reactions, such as trimethylsilyl (TMS) (Entry 9), aryl chloride (Entry 18), aryl fluoride (Entry 13), methyl ethers (Entries 7 and 15) and phenolic hydroxyl group (Entry 20), were found compatible under the optimized conditions. Interestingly, the strained cyclobutane ring remained intact during the reaction (Entry 6). A number of *para* and *meta*-substituted arylboronates were successfully coupled, but the *ortho*-substituted ones are more difficult likely caused by the steric hindrance during the transmetalation step. Nevertheless, coupling with di- and trisubstituted arylboronates smoothly delivered the corresponding poly-substituted aromatic ketones in modest to good yields (Entries 21-29).

The reactivity of different types of ketones was inspected. 3-Alkyl and aryl substituted cyclopentanones (**2a-4a**) are competent substrates (Chart 1B), in which both the C1−C2 and C1−C5 bonds can be activated (Entries 30-32). Surprisingly, the site-selectivity slightly favored the more sterically hindered side, though the exact reason is unclear. In addition, 3-ester substituted cyclopentanone (**5a**) and norcamphor (**6a**) showed excellent site-selectivity at the bulkier side to give the desired coupling products, albeit in low yields (Entries 33 and 34). Ring-fused cyclopentanone (**7a**) also worked; the low reactivity is presumably caused by the steric hindrance of the ketone substrate (Entry 35). To extend the scope of the ketone component, substituted 1-indanones were found to be an efficient class of substrates in this reaction (Chart 1C). The discovery was rather unexpected as aryl ketones are typically less reactive due to the larger conjugated π system compared to the corresponding alkyl ketones. To the best of our knowledge, *C−C activation of 1-indanones has not been reported to date*. Although 1-indanones have two different α-C−C bonds, gratifyingly the C−C cleavage/coupling occurred exclusively at the C(aryl)−C(carbonyl) bond to provide dihydrochalcone derivatives up to 75% isolated yield. The substituents on 1-indanones exhibit great influence on the reactivity, in which the electron-deficient 1-indanones were typically more efficient substrates than the electron-rich ones. When 1-indanone bearing an acetyl group (**13a**) was employed, dihydrochalcone (**41c**) and *p*-methylacetophenone (**42c**) were isolated in 62% total yield with a ratio of 1.8:1, which suggests that the reactivity of the carbonyl in 1-indanone appears to be higher than the one in acetophenone.

Besides cyclic ketones[13], a range of acyclic ketones also expressed considerable reactivity (Chart 1D). Various acetophenones (**16a-22a**) can react with arylboronate **1b** to provide the "aryl-exchanged" products. While the conversions were moderate, high brsm yields were obtained in these reactions. Again, the C−C cleavage occurred exclusively at the C(aryl)−C(carbonyl) bond and the electron-deficient acetophenones gave higher conversion than the electron-rich ones. It is noteworthy that the potential

Scheme 2. Synthetic Utilities of the Ketone-SMC Reaction

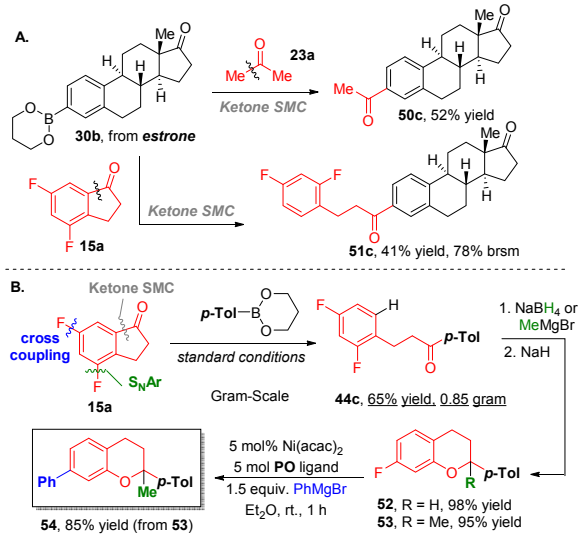
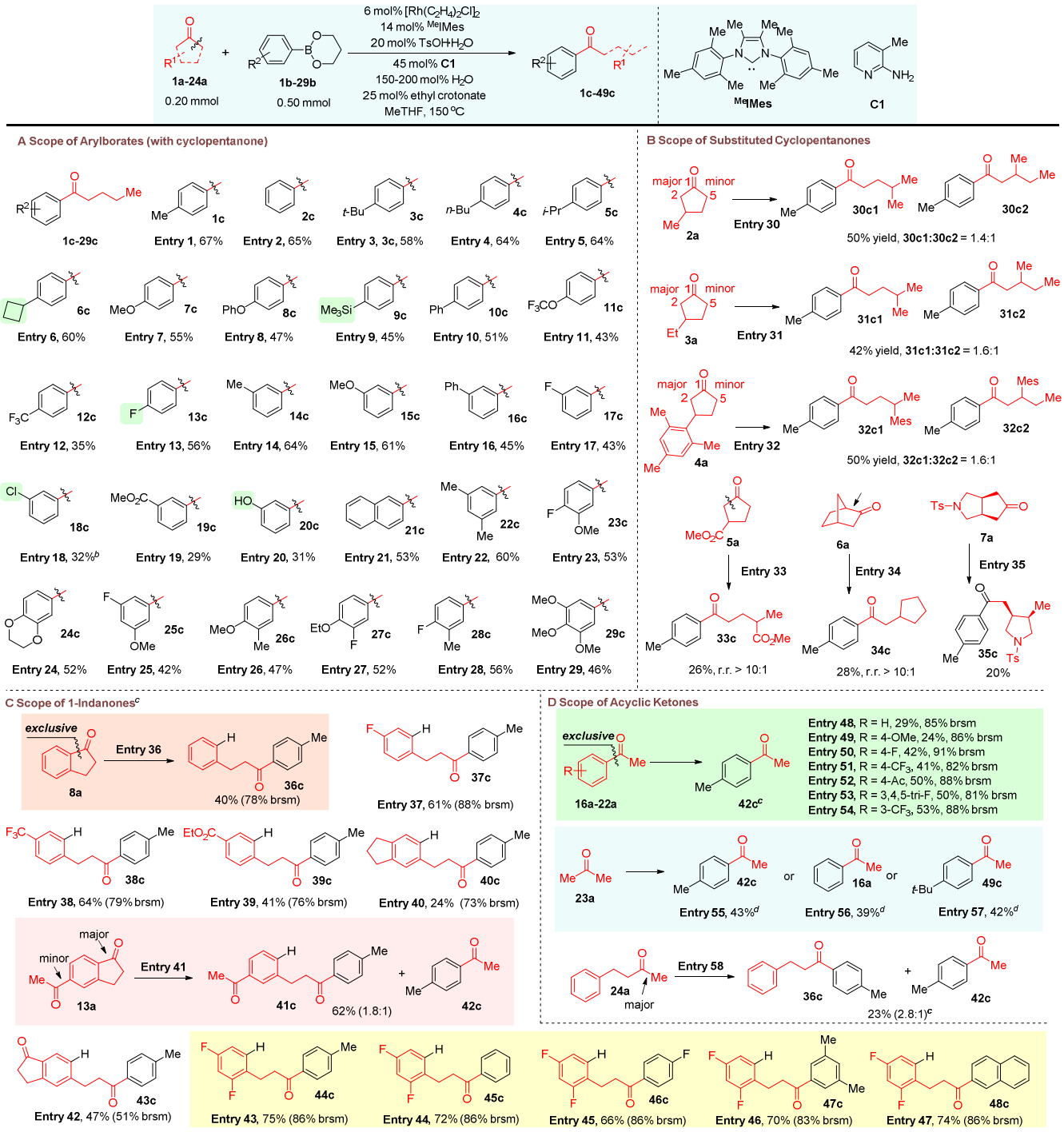


Chart 1. Scope of the Ketone SMC Reaction[a]



[a]All the reactions were run on 0.2 mmol scale under the standard conditions depicted in Table 1 unless otherwise noted. [b]140 °C using IMes as the ligand. [c]Using 150 mol% of H_2O. [d]Arylboronates were used as the limiting reagents; arylboronate (0.2 mmol, 1.0 equiv) and acetone (2 mmol, 10 equiv) were used; ethyl crotonate and H_2O were not added in these reactions; 0.10 mL MeTHF (instead of 0.15 mL) was used. See Supporting information for more experimental details. brsm, based on recovered starting material; r.r.: regioisomer ratio.

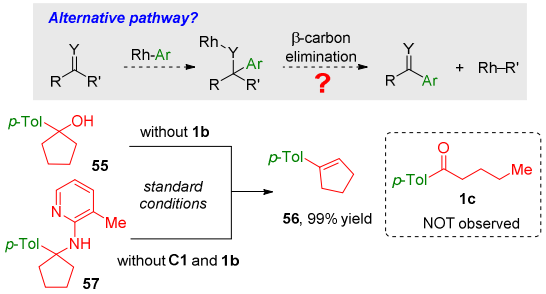
ortho C–H arylation directed by the carbonyl group[14] was not observed. Moreover, the *simplest ketone*, i.e. *acetone*, was also a suitable substrate to give acceptable yields of the coupling products (Entries 55-57). Finally, the unsymmetrical acyclic aliphatic ketone (**24a**) afforded a mixture of dihydrochalcone (**36c**) and *p*-methylacetophenone (**42c**) with a ratio of 2.8:1 (Entry 58).

The utility of this ketone-mediated SMC reaction was first examined in the derivatization of steroid natural products (Scheme 2A). For examples, reactions between arylboronate **30b** and acetone or 1-indanone **15a** smoothly provided two ketone-derived estrone analogues *without the need for strong acylating agents*. In addition, the reaction was scalable (Scheme 2B). On a gram scale the coupling product **44c** was afforded in 65% yield from commercially available 1-indanone **15a**. After reduction or 1,2-addition with ketone **44c**, the resulting alcohols underwent intramolecular nucleophilic aromatic substitution to deliver the corresponding chromane derivatives **52** and **53** in excellent yields. The remaining fluoride on the arene can further undergo

Kumada-type coupling with Grignard reagents under Nakamura's conditions.[15] As a result, the whole synthetic sequence provides a rapid and modular approach to access functionalized chromanes, a common structural motif found in bioactive compounds.[16]

To gain insights about how the C−C bond is cleaved in this ketone-SMC reaction, control experiments were carried out (Scheme 3). In addition to oxidative addition of Rh(I) into ketone α C−C bond, a potential alternative way involves 1,2-addition of the aryl nucleophile into the carbonyl or imine intermediate, followed by a β-carbon elimination process.[17] To investigate the hypothetical β-carbon elimination pathway, tertiary alcohol **55** and amine **57** were independently synthesized, which were then subjected to the standard conditions (in the absence of ketone and boronate reactants). The desired SMC product **1c** was not observed; instead, olefin **56** was produced in a quantitative yield. Combining the fact that olefin **56** was not observed in our standard ketone-SMC reactions (Table 1), the β-carbon elimination pathway is unlikely. Hence, the results of these control experiments are consistent with our hypothesis (Scheme 1B) that the C−C bond cleavage involves oxidative addition with a Rh(I) species.

Scheme 3. Control Experiments to Examine an Alternative *β*-Carbon Elimination Pathway



In summary, we describe the development of a SMC reaction between simple ketones and arylboronates via Rh-catalyzed activation of unstrained C−C bonds. While the efficiency of the reaction still has room for further improvement, the general applicability is nevertheless encouraging. The use of unstrained C−C bond as electrophiles in cross couplings should have broad implications. Detailed mechanistic study (experimental and computational) and efforts to accelerate the reaction rate is ongoing.

ASSOCIATED CONTENT

Supporting Information Experimental procedures; spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This project was supported by NIGMS (R01GM109054). Y. X. acknowledges the International Postdoctoral Exchange Fellowship Program 2015 from the Office of China Postdoctoral Council (No. 38 Document of OCPC, 2015).

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