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ARTICLE

Suzuki–Miyaura Coupling of Unstrained Ketones *via* Chelation-Assisted C–C Bond Cleavage

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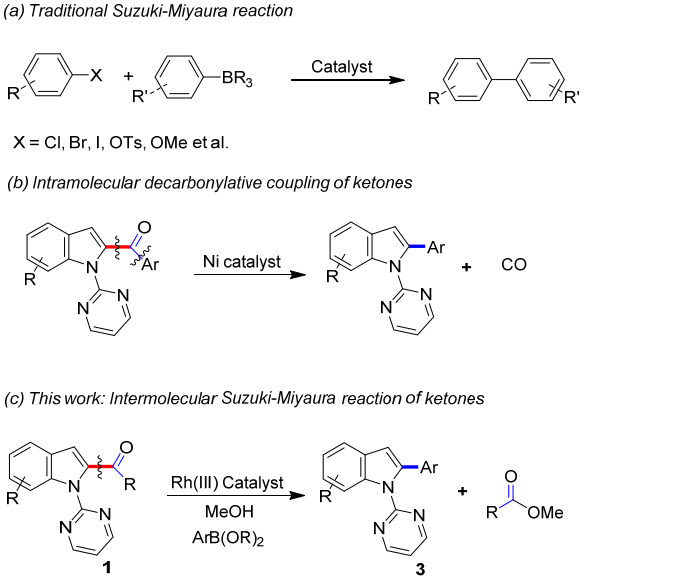
Herein, we report that unstrained ketones can be efficiently employed as electrophiles in Suzuki–Miyaura reactions via catalytic activation of unstrained C–C bonds assist by an N-containing directing group. A wide range of aromatic ketones directly coupled with boronic ester with excellent functional group tolerance. This strategy provides an alternative and versatile approach to constructing biaryls from unstrained ketones.

Introduction

The Suzuki–Miyaura reaction is a useful and versatile method for the construction of C–C bonds.[1] The reaction is particularly important for the preparation of unsymmetrical biaryl compounds, which are frequently encountered as core structural motifs in pharmaceuticals, agrochemicals, and organic materials. The classic Suzuki–Miyaura reaction employs halogen-containing aromatic compounds such as aryl halides as electrophilic coupling partners, while aromatic boron compounds serve as nucleophilic coupling partners (Scheme 1a).[2] Given the increasing importance of this transformation, substantial attention has focused on extending the scope of electrophiles in the Suzuki–Miyaura reaction.[3,4] An innovative scenario, in which a carbonyl group functions as leaving group, through C–C bond cleavage, and is simultaneously involved in the Suzuki–Miyaura reaction, is of particular interest.

The development of efficient methods for coupling ketones with transition-metal-catalyzed C–C bond cleavage has become an important goal in organic synthesis.[5] Using this bond-forming manifold, C–C bonds typically considered inert can be harnessed in generic acyl or aryl–metal reactivity pathways. Given that ketones are ubiquitous synthons in biologically active compounds and common functional groups in organic synthesis, the discovery of new catalytic reactivity through C–C cleavage undoubtedly has significant potential in various fields of chemistry.



Scheme 1 Design of Suzuki–Miyaura reaction of ketones via C–C bond cleavage.

The formation of a stable chelate has been frequently used as a driving force for the catalytic cleavage of unstrained C–C bonds in ketones, including in the pioneering works of Suggs,[6] Jun,[7] and Murai[8] and the recent works of Douglas,[9] Dong,[10] Shi,[11] and others.[12] Recently, our group developed a nickel-catalyzed intramolecular decarbonylation process through C–C cleavage assisted by an *N*-containing directing group (Scheme 1b).[13] Given the unique nature of this bond cleavage, we considered whether such an activation mode could be extended to other transformations, such as intermolecular cross-coupling. Therefore, we were motivated to merge a transmetalation process and directed C–C activation, envisaging that a subsequent reductive elimination would furnish a general cross-coupling reaction between unstrained ketones and arylboronic acid derivatives (Scheme 1c).

Results and discussion

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† Electronic Supplementary Information (ESI) available: Experimental procedures, mechanistic details, spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

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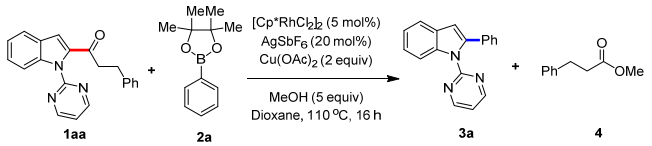
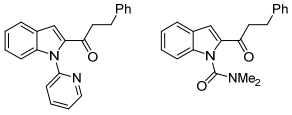
Initially, *N*-pyrimidyl 2-indolylketone **1aa** was chosen as the model substrate for coupling with arylboronate **2a**. After an extensive survey of reaction conditions, the desired coupling product (**3a**) was ultimately obtained in 83% yield (Table 1, entry 1). The optimized catalytic system contained 5 mol% $[Cp^*RhCl_2]_2$, 20 mol% $AgSbF_6$, and 5 equiv. MeOH. $Cu(OAc)_2$ (2 equiv) was used as the oxidant with dioxane as the solvent. A series of control experiments were conducted to gain further insight to this reaction. The presence of the rhodium catalyst system, $[Cp^*RhCl_2]_2$, and $Cu(OAc)_2$ proved to be critical because the reaction did not proceed at all in their absence (entries 2 and 3). In the absence of $AgSbF_6$, **3a** was only formed in less than 30% yield (entry 4). MeOH served as a reactant, with the yield dropping to 52% when no MeOH was added (entry 5). Solvent effects were also examined (entries 6–8), showing that dioxane was the optimal reaction solvent. In addition to pyrimidine, several other coordinating groups were tested. A comparable result was achieved when replacing the pyrimidyl group with a pyridyl group (entry 9), while no product was observed when the pyrimidyl group was replaced with weakly coordinating group, such as urea (entries 10). Remarkably, under the optimized reaction conditions, **1aa** afforded the desired C–C activation product **3a** without any observable C–H activation products at the C-7 position; thus displaying complete regioselectivity. The high regioselectivity is likely due to the formation of more stable five-membered metallacycle complexes.[14]

Table 1 Optimization of reaction conditions[a]



1aa 2a 3a 4

Entry	Change from standard conditions	Yield (%)[b]
1	None	83
2	without $[Cp^*RhCl_2]_2$	0
3	without $Cu(OAc)_2$	0
4	without $AgSbF_6$	32
5	without MeOH	52
6	solvent = THF	30
7	solvent = toluene	0
8	solvent = DMF	0
9	**5a** instead of **1aa**	64
10	**5b** instead of **1aa**	0

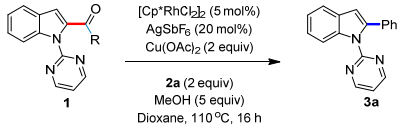


5a 5b

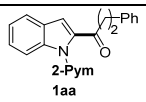
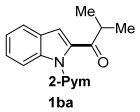
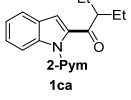
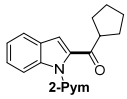
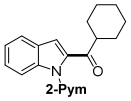
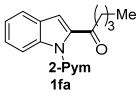
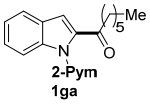
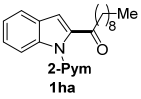
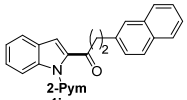
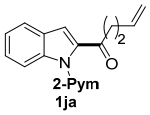
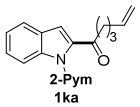
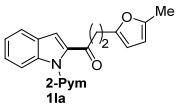
[a] Standard conditions: **1aa** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), MeOH (5 equiv), $Cu(OAc)_2$ (2 equiv), dioxane (2 mL), 110 °C, 16 h. [b] Isolated yields.

With the optimized reaction conditions in hand, we next examined the substrate scope of this process (Table 2). An array of acyclic and cyclic secondary aliphatic ketones (**1ba**–**1ea**) was applied to the coupling reactions. Linear aliphatic ketones (**1fa**–**1ha**) also showed good compatibility in the reaction. Two indole ketone derivatives bearing short and long alkenyl substituted alkyl chains (**1ja** and **1ka**) reacted in high yields. Functional groups, such as a furan (**1ja**) and ketone (**1ma**) were also coupled smoothly. Furthermore, coupling unsaturation ketone (**1na**) worked well and the corresponding product was isolated in 46% yield.

Table 2 Variation of the ketone substituents[a,b]



1 3a

Entry	Substrate	Yield of **3a**
1	 **2-Pym 1aa**	83%
2	 **2-Pym 1ba**	52%
3[c]	 **2-Pym 1ca**	54%
4[c]	 **2-Pym 1da**	69%
5[c]	 **2-Pym 1ea**	67%
6[c]	 **2-Pym 1fa**	63%
7	 **2-Pym 1ga**	72%
8	 **2-Pym 1ha**	78%
9	 **2-Pym 1ia**	51%
10[c]	 **2-Pym 1ja**	46%
11[c]	 **2-Pym 1ka**	51%
12	 **2-Pym 1la**	65%

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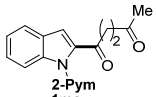
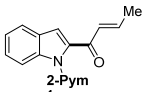
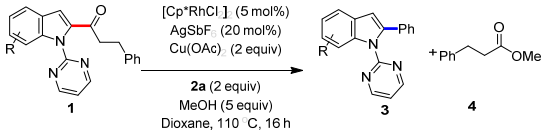
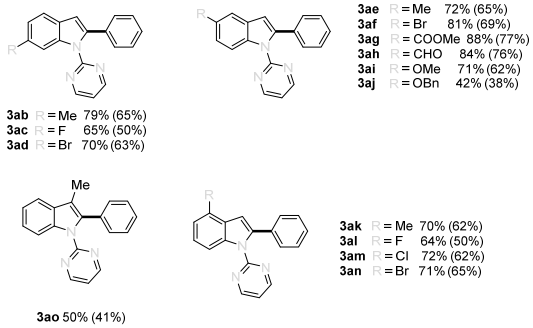
13	 2-Pym 1ma	65%
14	 2-Pym 1na	46%

[a] Standard conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), MeOH (5 equiv), $Cu(OAc)_2$ (2 equiv), dioxane (2 mL), 110 °C, 16 h. [b] Isolated yields. [c] The reaction was run for 48 h.

Next, the functional group tolerance of various 2-indolylketones was examined (Table 3). To our delight, a broad scope of substrates bearing various groups at 3−6 positions were well tolerated in the reaction and gaving the corresponding products in good to moderate yields. Notably, fluoride (**1ac** and **1al**), bromide (**1ad** and **1af**), chloride (**1am**), methoxy (**1ai**), benzyloxy (**1aj**), ester (**1ag**), and aldehyde (**1ah**) groups were well tolerated. Notably, bromo and chloro groups offer the opportunity for further transformations using other traditional cross-coupling reactions.

Table 3 Scope of indoles[a,b,c]

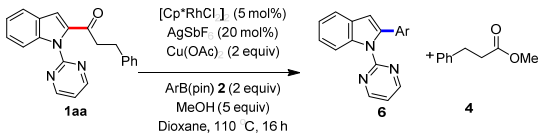


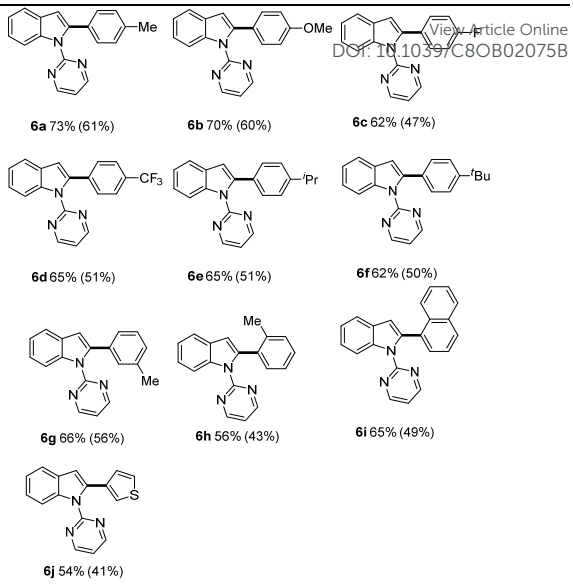


[a] Standard conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), MeOH (5 equiv), $Cu(OAc)_2$ (2 equiv), dioxane (2 mL), 110 °C, 16 h. [b] Isolated yields. [c] The number in brackets refers to the corresponding isolated yield of **4**.

The reaction scope with respect to the boronic ester was examined using **1aa** as the substrate (Table 4). Both electron-rich and electron -deficient aryl groups can be introduced with comparable efficiency. Methoxy (**2b**), fluoride (**2c**) or trifluoromethyl (**2d**) functional groups could be introduced into the substrates, leading to various coupling products. Furthermore, heteroarylboronic ester **2j** successfully reacted in the cross-coupling.

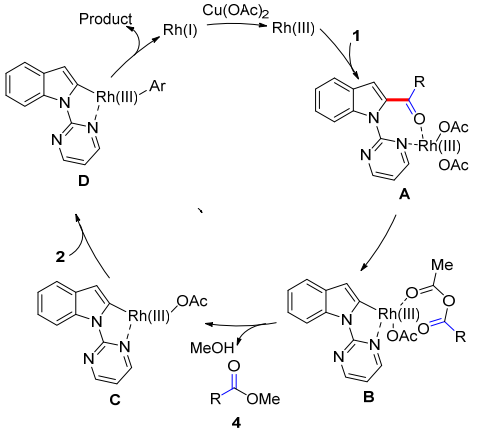
Table 4 Scope of boronic ester [a,b,c]





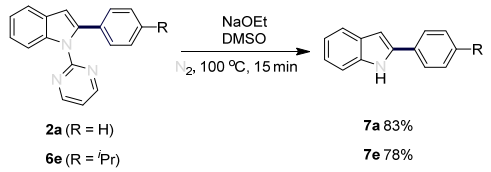
[a] Standard conditions: **1aa** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), MeOH (5 equiv), $Cu(OAc)_2$ (2 equiv), dioxane (2 mL), 110 °C, 16 h. [b] Isolated yields. [c] The number in brackets refers to the corresponding isolated yield of **4**.

A plausible reaction mechanism is shown in Scheme 2. Firstly, $[Cp^*RhCl_2]_2$ can undergo ligand exchange with $AgSbF_6$ and $Cu(OAc)_2$ to give a cationic acetate-ligated Rh(III) Lewis acid species, which coordinates with substrate **1** in a bidentate fashion to form complex **A**. Complex **A** would undergo electrophilic C–C bond cleavage to form rhodacycle **B** through formation of a mixed anhydride. Under the action of methanol, anhydride is further converted to ester **4**. Subsequent transmetallation of **C** with the arylboronate **2** would form **D**, which would undergo reductive elimination to afford product **3** and a Rh(I) species that is reoxidized to a Rh(III) species by $Cu(OAc)_2$ to complete the catalytic cycle.



Scheme 2 Plausible Mechanism.

Finally, we attempted to remove the directing group from the products (Scheme 3). Upon treatment of **2a** and **6d** with NaOMe in dimethylsulfoxide (DMSO) at 100 °C,[15] the corresponding N-H indoles **7a** and **7e** were obtained in 83 and 78% yields, respectively.



2a (R = H) **7a** 83%
6e (R = ^{i}Pr) **7e** 78%

Scheme 3. Removal of the Directing Group on Indoles

Conclusions

We have described the development of a Suzuki–Miyaura reaction between simple ketones and arylboronates *via* the Rh-catalyzed activation of unstrained C–C bonds. Various substituted indole derivatives were obtained in moderate to good yields. Further efforts to expand the scope of this reaction are currently underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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