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Rhodium-Catalyzed Interconversion of Quinolinyl Ketones with Boronic Acids via C−C Bond Activation

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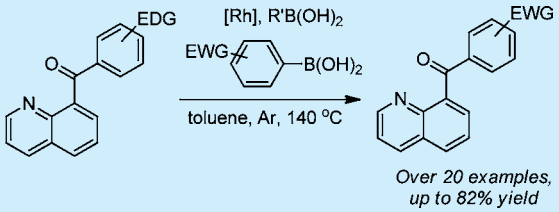
Supporting Information

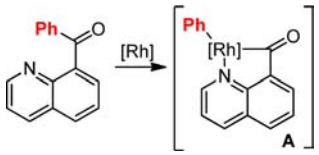
ABSTRACT: A rhodium-catalyzed cross-coupling of aryl and aliphatic quinolinyl ketones with boronic acids has been developed. Proceeding via quinoline-directed carbon−carbon σ bond activation, the transformation demonstrates tolerance of a range of functional groups on both the ketone and aryl boronic acid substrates, providing good to excellent yields of the new ketones, particularly those containing electron-withdrawing substituents. Catalyst reactivity is dependent on quinolinyl ketone substrates, with alkyl ketones requiring $Rh(PPh_3)_3Cl$ instead of the more reactive $[Rh(C_2H_4)_2Cl]_2$. With the use of K_2CO_3 as an additive, methyl boronic acid is also a competent substrate, giving rise to an unprecedented methylation technique.



In the past two decades, metal-catalyzed carbon−hydrogen (C−H) activation has transitioned from esoteric phenomena to a widely used synthetic strategy.[1] With C−H activation becoming a highly established practice, one could envision a similar evolution in the utility of other inert moieties, including the carbon−carbon (C−C) single bond.[2] Despite the vast potential in the synthesis of both small and complex molecules, the selective metal-catalyzed activation and subsequent functionalization of C−C σ-bonds remains largely in the early stages of development.[3] Chiefly due to the kinetic and thermodynamic stability of the C−C bonds, current methods often require harsh reaction conditions and highly reactive substrates,[4,5] such as strained ring systems,[6] to promote activation.[7] One successful strategy, the use of directing groups, has facilitated reactivity by bringing transition metal catalysts into close proximity to desired activation sites, thus overcoming the inherent stability of the C−C bond.[8,9] Suggs and Jun demonstrated the feasibility of utilizing an 8-substituted quinolinyl ketone as a substrate for C−C activation,[10,11] and a variety of transformations have utilized transition metal catalysts to activate and functionalize aryl ketones through both intra- and intermolecular reactions.[12] In particular, the functionalization of the quinolinyl ketone with a tethered alkene has been used to great effect by Douglas and co-workers[13] and has subsequently been the subject of intensive mechanistic studies by our group to identify primary intermediates and to profile the kinetic behavior of the reaction.[14,15]

Despite an increased interest in developing new synthetic practices that utilize C−C bond activation, current methodologies are largely intramolecular. The development of intermolecular cross-coupling reactions that proceed through C−C bond activation has the potential to revolutionize the way the synthetic target disconnections are approached and offers a new opportunity to selectively install a wide array of carbon−carbon and carbon−heteroatom bonds. It was our intent to utilize the well characterized quinolinyl ketone system as the focal point of our studies, with the intent that the putative rhodium(III) acyl intermediate formed upon C−C bond activation could readily be intercepted with nucleophiles beyond alkenes (Scheme 1).[16] Due to their synthetic diversity and general availability, boronic acid reagents offer a desirable cross-coupling partner for myriad cross-coupling reactions[17] and served as a starting point for developing new C−C activation methods.

Scheme 1. Proposed Rh(III) Intermediate



Utilizing a similar strategy, Wang and co-workers have reported the use of 8-substituted quinolinyl ketones as successful substrates for the activation and functionalization of methyl and aryl ketones with aryl boronic acids.[18] While the methodology explores a variety of substitutions, it fails to demonstrate reactivity with electron-deficient boron reagents or *ortho*-substituted quinolinyl ketones and requires stoichiometric CuI. Herein we report the development of a rhodium-catalyzed cross-coupling of boronic acids with quinolinyl ketones that offers a complementary and broadened substrate scope compared to current methodologies (Scheme 2). Furthermore, the newly developed protocol permits the use of alkyl boronic acids, which has not been reported in C−C bond activation and functionalization methodologies to date.

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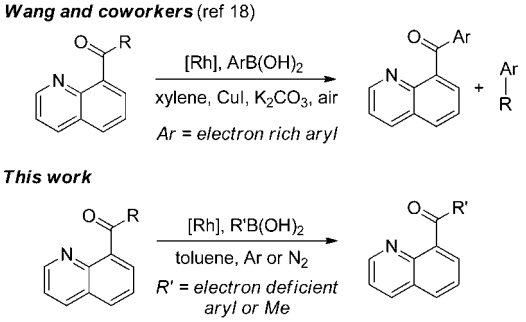
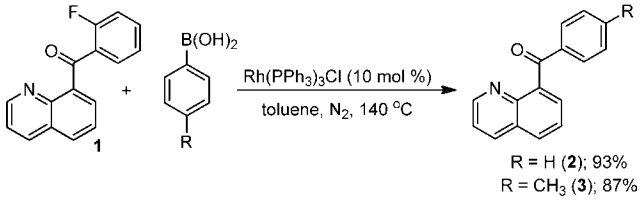
Scheme 2. Rhodium-Catalyzed Cross-Coupling of Boronic Acids and Quinolinyl Ketones Proceeding via Carbon−Carbon Single Bond Activation



Beyond our group's inquiry into the catalytic cycle of the intramolecular carboacylation of quinolinyl ketones, we have also explored mechanistic aspects of Pd-catalyzed β-aryl elimination.[19] Most notably, we observed the dramatic selectivity obtained with *ortho*-fluorinated aryl substituents, which cleave over 75 times more rapidly than unadorned phenyl rings, an effect attributed to the stabilization of a Pd-aryl intermediate.[20] With this information, we envisioned combining the success of the quinolinyl ketone directing group with the influence of the *ortho*-fluorinated aryl ring to promote C−C bond activation and stabilization of the rhodium-aryl intermediate for interception with an appropriate organometallic intermediate.

As proof of principle, the *ortho*-fluorinated quinolinyl ketone **1** was subjected to an excess of phenyl boronic acid in the presence of 10 mol % Wilkinson's catalyst, in toluene at 140 °C for 48 h. Much to our delight, **1** readily undergoes C−C bond activation and cross-coupling to generate phenyl (quinolin-8-yl)methanone (**2**) in 93% conversion based on GC/MS (Scheme 3). The reaction proceeds with a similarly high

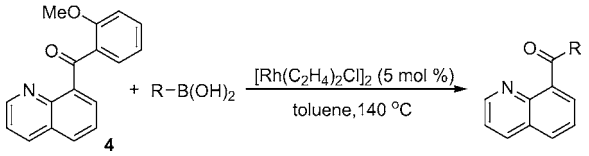
Scheme 3. Proof of Principle



conversion using tolyl boronic acid, ensuring that an interconversion process is active, rather than a simple defluorination process.[21] To further explore the transformation and to probe the necessity of the *ortho*-fluorine substituent, our efforts focused on the development and optimization of conditions for a variety of quinolinyl ketones. After significant experimentation, it was determined that the use of 2.5 equiv of boronic acid and 10 mol % of $[Rh(C_2H_4)_2Cl]_2$ in toluene at 140 °C provides the most consistent ketone exchange over a range of substrates.[22] As will be further illustrated, it has been observed that some form of electronic or steric driving force is necessary to achieve effective conversion.

Once satisfactory reaction conditions were established, efforts focused on the expansion of the substrate scope. While a number of quinolinyl ketones are compatible with the reaction conditions (*vide infra*), 2-methoxy quinolinyl ketone **4** was identified as a promising substrate with which to explore a variety of commercially available boronic acids as cross-coupling agents. As seen in Table 1, electron-deficient aryl

Table 1. Scope of Boronic Acids for Cross Coupling with an Electron-Rich Quinolinyl Ketone



entry[a]	R	product	yield (%)[b]
1	3,5-$(F_3C)_2C_6H_3$	**5**	47 (>95)
2	4-CNC_6H_4	**6**	38 (84)
3	4- $F_3CC_6H_4$	**7**	82 (98)
4	4-$CO_2MeC_6H_4$	**8**	53 (95)
5	4-C(O)Me C_6H_4	**9**	57 (80)
6	3-$NO_2C_6H_4$	**10**	30 (74)
7	3-$CF_3C_6H_4$	**11**	46 (77)
8	3-$C(O)MeC_6H_4$	**12**	40 (85)
9	2-naphthyl	**13**	33 (88)
10	Ph	**2**	52 (67)
11	Me	**14**	(<10)

[a]Reaction conditions: (2-methoxyphenyl)(quinolin-8-yl)methanone **4** (0.11 mmol), aryl boronic acid (0.28 mmol), $[Rh(C_2H_4)_2)Cl]_2$ (0.006 mmol), toluene (2 mL), N_2, 140 °C, 48 h. [b]Value in parentheses is product formation based on conversion of **4** by GC/MS analysis.

boronic acids served as robust coupling partners in the transformation. Fluorinated aryl boronic acids worked well in the reaction, as did those containing nitro and cyano groups. Reaction conditions also tolerated ketones and esters, which generated over 85% of the desired product. Due to the structural similarity of starting materials and products, isolation via column chromatography is challenging and results in reduced yields relative to high conversions. Notably, 2-naphthyl boronic acid was a suitable cross-coupling partner in the reaction (entry 9), but less than 15% product was observed with the use of bulkier substrates such as 1-naphthyl or *o*-tolyl boronic acids. Attempts to use phenyl boronic acid or more electron-rich species such as 4-methoxy or 4-thiomethyl boronic acid provided the desired products in diminishing yields despite efforts to increase the conversion through alteration of the reaction conditions.

Notably, the success of our methodology with electron-deficient species is in marked contrast to the system described by Wang and co-workers, for which there are no examples of the use of electron-deficient boronic acids.[18] To more accurately compare and contrast these reaction conditions a series of experiments were performed with identical substrates. Utilizing Wang's conditions, the electron-deficient 4-(trifluoromethyl)phenylboronic acid reacts with the 2-methoxy quinolinyl ketone **4** to produce only 9% of the converted ketone, whereas reaction under our conditions yields **7** in 82% yield.[23] In contrast, our conditions yield no appreciable product utilizing electron-rich 4-methoxyphenyl boronic acid with quinolinyl ketone **2**, whereas the conditions of Wang provide the exchanged product in 51% yield. These results illustrate the complementary nature of the two approaches.

As alluded to previously, our exploration of quinolinyl ketone substrates indicated that the conversion to neutral or electron-rich ketones was problematic. This deficiency can be addressed in part through the use of alkyl ketones, particularly the

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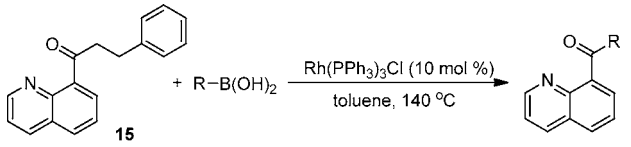
phenethyl substituted quinolinyl ketone **15**. The activation of alkyl ketones presents both benefits and challenges, as the facile nature of β-hydride elimination not only can provide a thermodynamic driving force but also holds the potential for undesired polymerization of metal−alkyl intermediates. While the use of $[Rh(C_2H_4)_2Cl]_2$ failed to provide the desired product in appreciable yields, $Rh(PPh_3)_3Cl$ efficiently catalyzed the transformation without side products formed via β-hydride elimination. Similar to the reactivity of aryl substituted boronic acids, the phenethyl derivative is compatible with an array of electron-deficient aryl boronic acid moieties. Moreover, the reaction proceeds efficiently with phenylboronic acid (Table 2, entry 3) and tolerates the electron-rich 4-methoxyphenyl-boronic acid (entry 4), albeit in decreased yields, demonstrating the increased substrate scope available via this approach. Unfortunately, the reaction still does not provide appreciable yields of sterically hindered ketones (entry 9).

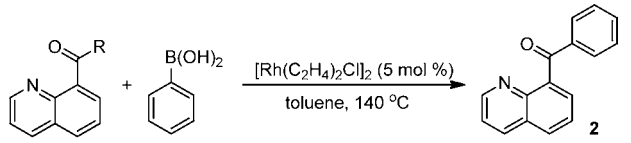
Table 2. Scope of Boronic Acid in Cross-Coupling with an Alkyl Quinolinyl Ketone



entry[a]	R	product	yield (%)[b]
1	4-CNC_6H_4	**6**	78 (92)
2	4-$F_3CC_6H_4$	**7**	57 (75)
3	Ph	**2**	63 (85)
4	4-$MeOC_6H_4$	**16**	33 (51)
5	4-$SMeC_6H_4$	**17**	<10 (43)
6	4-MeC_6H_4	**3**	56 (62)
7	4-FC_6H_4	**18**	36 (58)
8	3-$MeOC_6H_4$	**19**	52 (73)
9	2-$MeOC_6H_4$	**4**	(<5)

[a]Reaction conditions: ketone **15** (0.10 mmol), aryl boronic acid (0.24 mmol), $Rh(PPh_3)_3Cl$ (0.010 mmol), toluene (2 mL), N_2, 140 °C, 48 h. [b]Value in parentheses is product formation based on conversion of starting materials by GC/MS analysis.

Scheme 4. Representative Quinolinyl Ketone Substitution in Coupling with Phenyl Boronic Acid

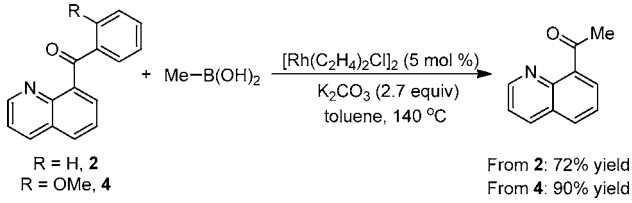


Starting Material	Yield of **2**
R = Me, (**14**)	60%
R = 2-$OMeC_6H_4$ (**4**)	52%
R = 2-FC_6H_4 (**1**)	93%

2-fluorophenyl- (**1**) and 2-methoxyphenyl (**4**) quinolinyl ketones react efficiently with phenyl boronic acid, providing 93% and 42% yields of **2**, respectively. Likewise, methyl quinolinyl ketone **13** can be utilized as a competent starting material, producing the desired product **2** in 60% yield.

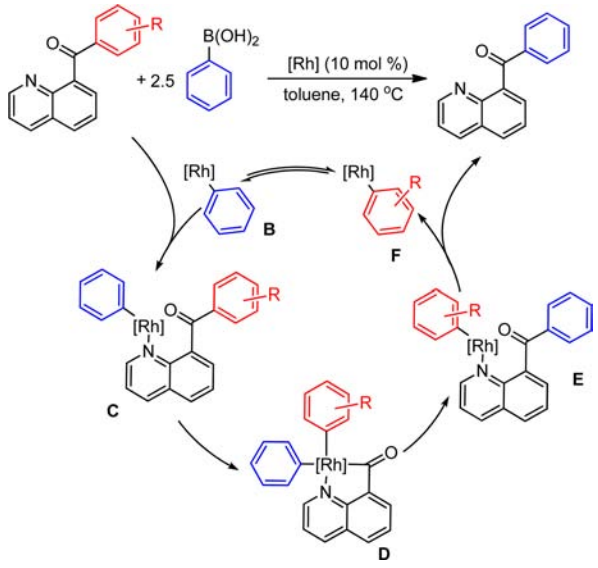
In light of the successful activation and cross-coupling of alkyl ketones, we hypothesized that alkyl boron reagents could be likewise suitable cross-coupling partners. To develop this methodology, methyl boronic acid was utilized as a representative substrate with quinolinyl ketones **2** and **4** (Scheme 5). Under conditions similar to those utilized with aryl boronic acids, no reactivity was observed. In the presence of K_2CO_3, however, the reaction proceeded efficiently, generating the methyl quinolinyl ketone in 72% yield from the phenyl quinolinyl ketone and 90% yield from the 2-methoxy substrate. Furthermore, it was observed that this transformation required an inert atmosphere, as only a stoichiometric amount of product is observed when the reaction is performed in air, even in the presence of K_2CO_3. Unfortunately, efforts to expand reactivity to other alkyl boronic acids have proven unsuccessful.[22]

Scheme 5. Utilization of Methyl Boronic Acid



Although a detailed mechanistic investigation has yet to be pursued, it is hypothesized the reaction proceeds through a mechanism closely related to that proposed by Douglas and co-workers[13] and previously studied in detail within our lab.[14] Initial transmetalation of the boronic acid with the rhodium catalyst produces rhodium(I) aryl intermediate **B** (Scheme 6).

Scheme 6. Hypothetical Catalytic Cycle



Upon coordination of the active Rh(I) species to the Lewis basic quinoline (intermediate **C**), the metal center is in proximity to the aryl−ketone bond and undergoes carbon−carbon single bond activation through a formal oxidative addition process to generate diaryl rhodium(III) metalacycle **D**. Reductive elimination with the new aryl substituent and subsequent dissociation generates the product and rhodium-

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(I)−aryl complex **F**, which can undergo transmetalation with additional boronic acid starting material to regenerate intermediate **B**.[24]

Notably, it is hypothesized that the rhodium(III) acyl intermediate **D** contains two aryl groups. This species can undergo reductive elimination to generate a biaryl byproduct, the starting material, or the desired product. Substrate-specific electron or steric effects presumably dictate the selectivity of the reductive elimination pathway, as only traces of biaryl species are observed in the reaction. As there are no clearly irreversible steps within the catalytic cycle, it is hypothesized that the extent of product formation is largely driven by the excess of boronic acid and the relative stability of the boronic acids and quinolinyl ketone. Work is underway to further elucidate trends in substrates to promote a broader scope of productive reductive elimination and product formation.

In summary, we have developed a method that efficiently cross-couples both alkyl and aryl substituted quinolinyl ketones with boronic acids. The reaction is tolerant of a variety of electron-deficient aryl boron reagents, which overcomes current limitations in C−C bond activation and functionalization methodologies. The reaction proceeds without the use of oxidants and in a catalytic fashion. Finally, the use of methyl boronic acid as a cross-coupling agent provides evidence for the feasibility of installing sp^3 functionality at ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01434.

Experimental data, optimization data, characterization information, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(21) It should be noted that Suzuki-like coupling was observed for a number of boronic acid substrates, precluding the general use of the *ortho*-fluorinated quinolinyl ketone.

(22) Results from the optimization process can be found in the Supporting Information.

(23) See ref 18. Quinolinyl ketone (0.05 mmol), boronic acid (0.125 mmol), CuI (0.1 mmol), K_2CO_3 (0.1 mmol), and $Rh(PPh_3)_3Cl$ (10 mol %) in xylene (0.5 mL) at 130 °C under air.

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