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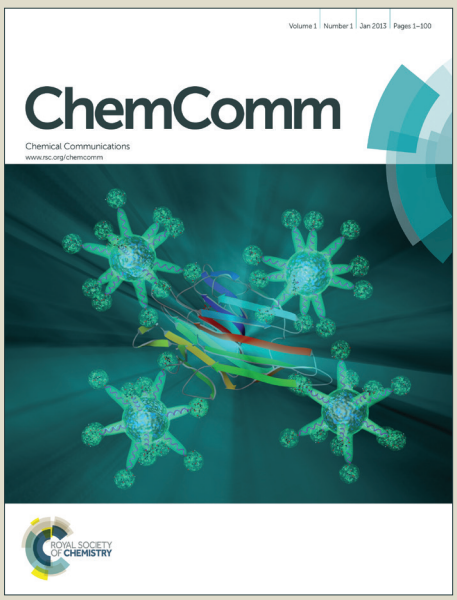

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ARTICLE TYPE

Highly Selective Directed Arylation Reactions via Back-to-Back Dehydrogenative C-H Borylation / Arylation Reactions

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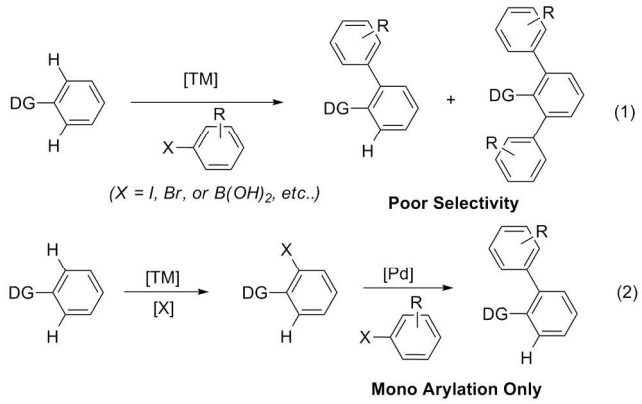
Dimeric rhodium *N*-heterocyclic carbene complexes are demonstrated to be effective catalyst precursors for directed C–H borylation reactions at room temperature. The reactions are highly selective for mono-borylation and can be combined with a one-pot Suzuki–Miyaura coupling to give C–H arylation products with exclusive selectivity for mono-arylation without the requirement for steric blocking groups.

Introduction

Transition metal catalyzed direct C–H arylation reactions have proven to be important alternatives to the more traditional cross coupling procedures which require the preactivation of substrates.[1] Directing groups are commonly incorporated in order to control the regioselectivity of these reactions, however in the absence of steric blocking groups, the presence of multiple *ortho* C–H bonds within an aromatic substrate can result in poor selectivity (Eq. 1).[2] An alternative to the use of blocking groups involves the initial *selective* synthesis of mono borylated substrates by C–H borylation, which are then subjected to traditional methods of cross-coupling procedures such as the Suzuki–Miyaura reaction (Eq. 2). Although this method requires two steps, it can be completed in one pot, and represents a valuable alternative strategy to direct C–H arylation in substrates that otherwise give mixtures of products.

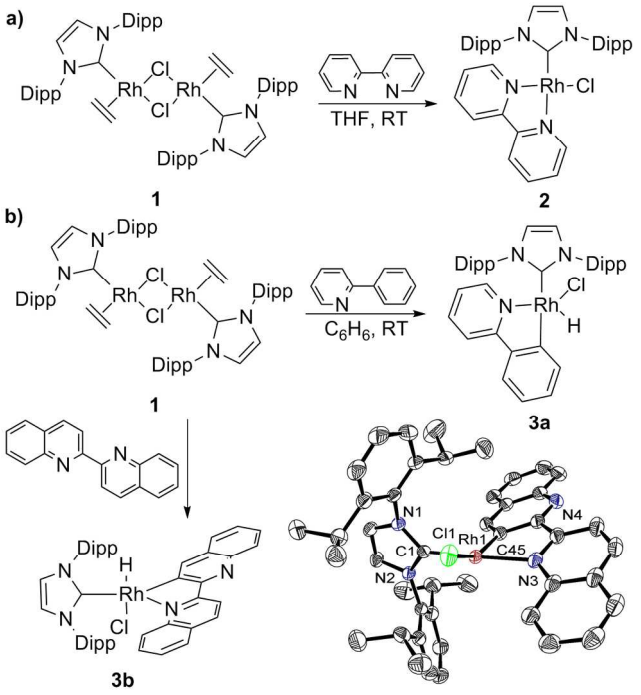


Reliable and robust synthetic routes to boronic acids are extremely important, with C–H borylation routes among the most important.[3] These transformations have predominantly utilized iridium[4] and rhodium[5] catalysts, and the observed regiochemistry is controlled by steric considerations, although directed *ortho* C–H borylations of arenes have also been described.[6] Sawamura and co-workers have recently reported such a reaction using heterogeneous Rh^{I} phosphine complexes as catalysts, which display remarkable activity in the directed C–H borylation of sp^2 and sp^3 C–H bonds under mild conditions, using a wide variety of directing groups.[5g,h] The one limitation of this important advance is the requirement for the specialized SMAP ligands.

N-Heterocyclic carbenes (NHCs) have emerged as an exciting class of ligands, capable of producing highly reactive metal centres through the combination of strong sigma donation, and large steric demand.[7] We[8] and others[9] have recently reported the preparation and use of dimeric Rh^{I} NHC olefin complexes which are remarkable in their high level of unsaturation. Oro and Castarlenas have employed these catalysts in the hydrothiolation of alkynes,[10] in H/D exchange reactions of aromatic α-olefins[11] and in the annulations of alkynes with vinyl pyridines.[12] Herein, we report that these simple, highly reactive catalysts are capable of affecting highly selective, directed C–H borylations. Reactions proceed under mild conditions and with high selectivity. Borylated products can be directly subjected to Suzuki–Miyaura cross coupling reactions the overall process amounts to C–H arylation with complete selectivity for mono arylation.

Results/Discussion

We recently described the reactivity of $[Rh(IPr)(C_2H_4)Cl]_2$ (**1**) towards phosphines and nitrogen derived ligands.[8] For instance, the reaction of 2,2'-bipyridine (Bipy) with **1** resulted in the clean formation of [Rh(IPr)(Bipy)Cl] (**2**) in near quantitative yield (Scheme 1a).[8c] Related complexes were proposed by Chang as likely intermediates in the roll-over C–H alkylation of bipyridine substrates.[13] In accordance with this, when **1** was treated with 2 eq. of 2-phenyl pyridine (2-Ph-pyr) at room temperature, the ^1H NMR displayed a new characteristic hydride resonance at –24.5 ppm ($^1J_{Rh-H}$= 48.9 Hz) indicative of the formation of a Rh^{III}-H complex such as **3a** through C–H activation of 2-Ph-pyr (Scheme 1b).[14] Although attempts to grow X-ray quality crystals of complex **3a** were unsuccessful, single crystals suitable for X-ray diffraction of model complex **3b** were obtained. The X-ray crystal structure clearly demonstrates the successful formation of C–H activated complex **3b**, even at room temperature.



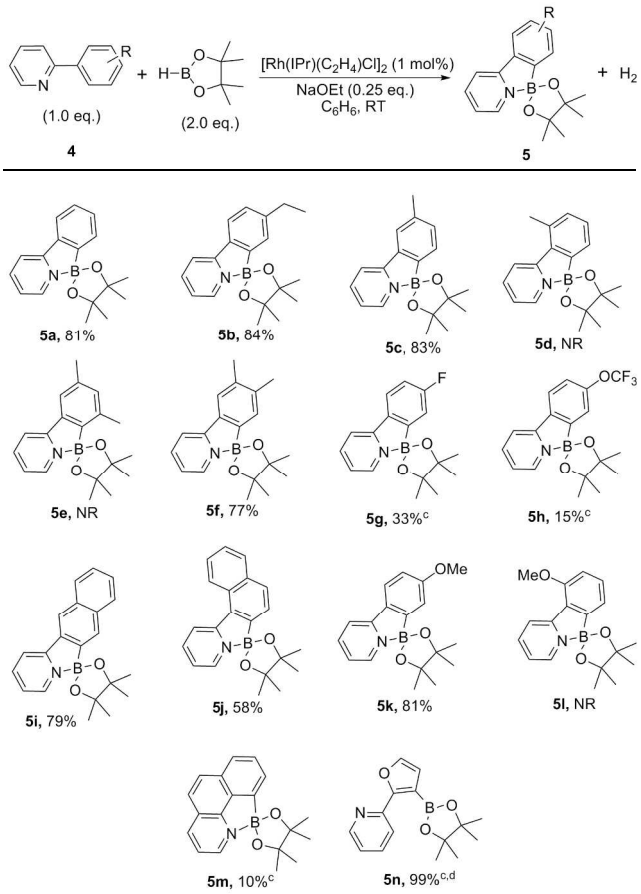
Scheme 1 Stoichiometric reactions of complex **1** with a) Bipy and b) phenyl pyridine, and 2,2' biquinoline and c) X-ray crystal structure of **3b** with ellipsoids at 50%, see SI for details. Dipp= 2,6-diisopropylphenyl.

In addition to several reports of Rh catalysts in C–H activation processes,[1d,15] we were intrigued by the seminal report of Marder, describing the dehydrogenative C–H borylation of simple aromatics with pinacol borane (HBPin) using $[Rh(P^iPr_3)_2ClN_2]$.[5b] It is postulated that the active species in this process is a Rh^I-H complex formed *in-situ* by reductive elimination of ClBPin from the Rh centre, after oxidative addition of HBPin at 140 °C. Since both catalysts should be highly electron rich and coordinatively unsaturated, we were inspired to assess the reactivity of complex **1** in C–H borylation reactions utilizing common directing groups.

The reaction of 2-Ph-pyr with HBPin and 1 mol% of **1** at 25 °C resulted in no observable product. In order to accelerate reductive elimination of ClBPin, KO^{t}Bu, (0.5 eq. relative to substrate) was added to promote loss of ROBPin.[4g,5b,16] This resulted in the immediate evolution of gas, and after 1 hr, the C–H borylated product was observed by ^{1}H NMR in a promising 32% yield. After optimization, (see footnote to Table 1), the yield improved to 91%.[17]

Several substituted 2-phenyl pyridines were subjected to optimized reaction conditions (Table 1). Alkyl substituents in the *meta* and *para* positions of the phenyl ring were well tolerated producing **5b** and **5c** in high yields. However, a single substituent in the *ortho* position, or two in each *meta* position were not tolerated (**5d** and **5e**). This is likely related to the decreased ability of the substrates to cyclometalate with the Rh catalyst.[18] A 3,4-disubstitution pattern had no effect on the reaction, as both products **5f** and **5i** were formed selectively and in high yield. Importantly, despite the excess of HBPin present and two *ortho* protons in the substrates, diborylated products were only observed in trace amounts in select examples.

Table 1 Substrate Scope[a,b]



[a]General Conditions. Substrate (0.5 mmol), NaOEt (0.125 mmol), HBPin (1.0 mmol), **1** (0.005 mmol) in C_6H_6 (0.1 M) for 4 hours. [b]Isolated yields. [c]NMR yields using 1,4-dimethoxybenzene as an internal standard. [d]Due to instability, product could not be isolated, NR = no reaction

We propose that this high selectivity is due to hemilabile coordination of the pyridyl nitrogen to boron, which prevents bonding of the pyridyl nitrogen to Rh and subsequent C–H activation at the second *ortho* position.[6b,f] The X-ray crystal structure of **5b** clearly demonstrates that this coordination occurs in the solid state (Fig. 1), and solution ^{11}B NMR studies show significantly upfield shifted ^{11}B NMR resonances compared to typical sp^2 C-B species, consistent with the presence of this interaction in solution.[6b,f]

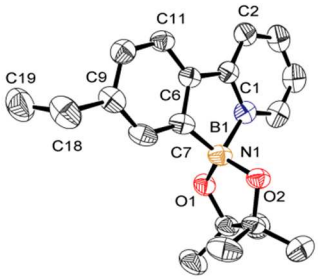


Figure 1 X-ray crystal structure of **5b**, ellipsoids at 50%, see SI for details

A potential mechanism for the observed transformation is presented in Fig. 2. Generation of active catalyst **A** occurs first by salt metathesis with NaOR, followed by oxidative addition of

HBPin and facile reductive elimination of ROBPin.[4g] B–H oxidative addition can then occur resulting in intermediate **B**, which, after loss of H_2, produces Rh^I boryl species **C**. Reaction of **C** with phenyl pyridine results in **D**, which can then release the product and regenerate the active catalyst **A** completing the cycle.

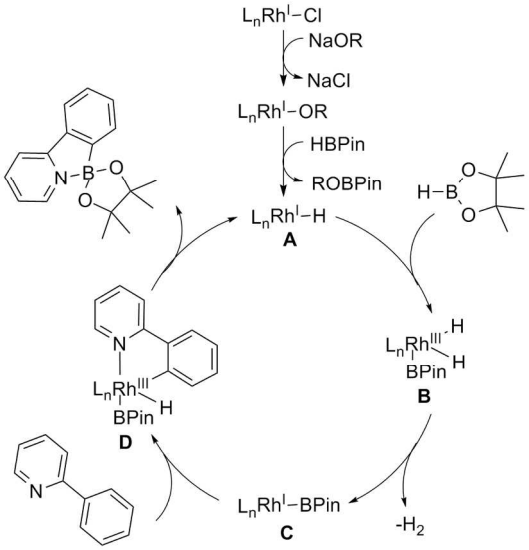
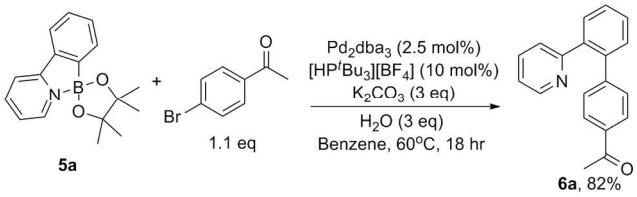


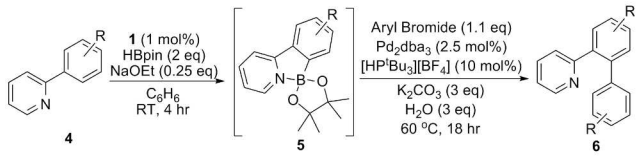
Figure 2 Plausible mechanism for C–H borylation

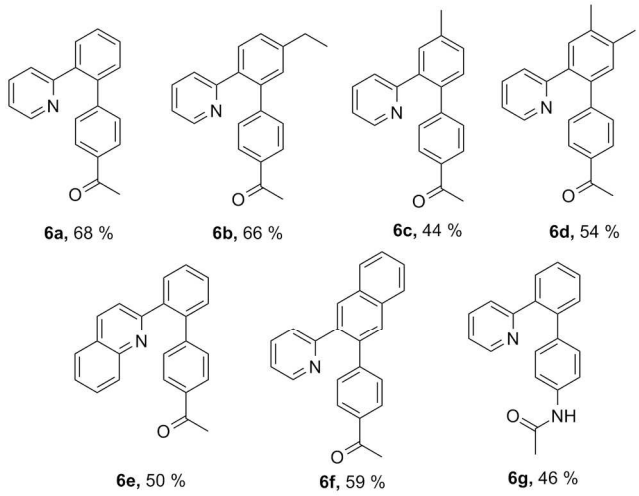
We then sought to explore the possibility of a sequential borylation-arylation, ideally with little to no workup between the two reactions.[19] With this in mind, a catalyst system consisting of Pd_2dba_3 and $[HP^tBu_3][BF_4]$ with K_2CO_3 was applied to isolated product **5a** in benzene at 60 °C. Under these conditions, arylated product **6a** was obtained in 82% isolated yield (Scheme 2).[20] More importantly, a sequential one-pot borylation-arylation requiring no workup was affected merely by the addition of all reagents to the original reaction mixture (Table 2). This sequential process resulted in exclusively monoarylated products in reasonable yields over two steps. Thus several phenyl pyridines were borylated and subsequently monoarylated in one-pot under relatively mild conditions.



Scheme 2 Suzuki-Miyaura coupling reaction on isolated **5a**.

Table 2 One pot borylation-arylation of phenyl pyridines





[a]General Conditions. Substrate (0.5 mmol) NaOEt (0.125 mmol), HBPin (1.0 mmol), **1** (0.005 mmol) in C_6H_6 (0.1 M) for 4 hours. [b]Isolated yield

Conclusions

In conclusion, we have developed a very mild procedure for the directed C–H borylation catalyzed by a highly unsaturated Rh-NHC complex derived from pre-catalyst **1**, giving the desired products in good yields in short time frames. This procedure was combined with a sequential one-pot Suzuki–Miyaura cross-coupling reaction to give the overall C–H arylation product in highly selective manner. The key significance of this report is the relatively simple nature of the Rh complex, which is easily prepared from commercially available $[Rh(C_2H_4)_2Cl]_2$ and IPr. We are currently investigating the scope of other C–H activated processes, and optimizing catalyst performance for the activation of more difficult substrates.

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Notes and references

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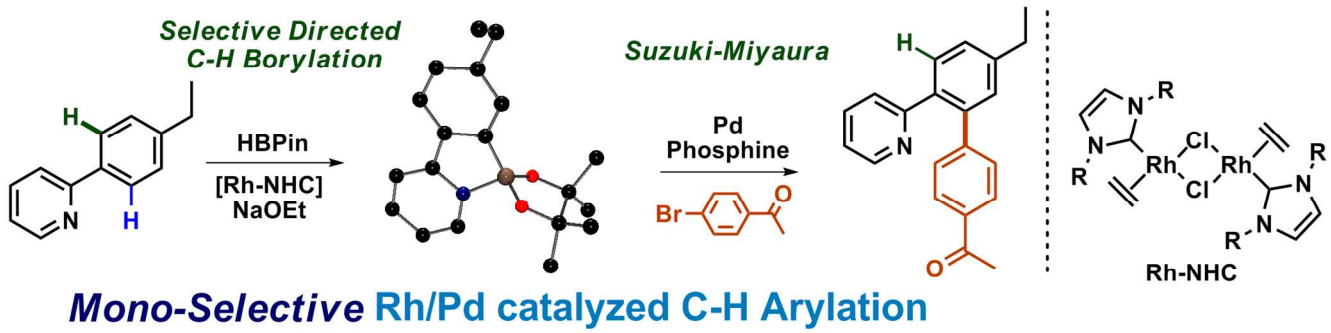

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