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Ru-Catalyzed Selective C(sp^3)–H Monoborylation of Amides and Esters

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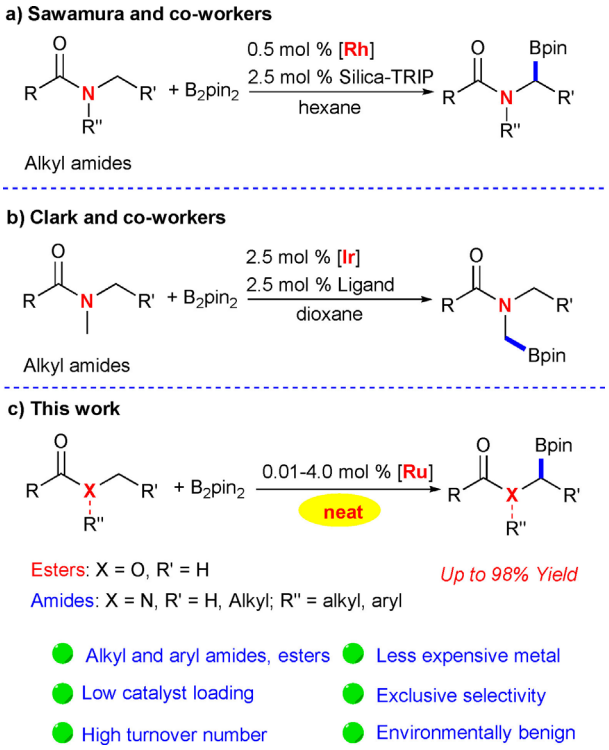
A ruthenium-catalyzed method has been developed for the C(sp^3)–H monoborylation of various unactivated alkyl and aryl amides and challenging esters, with a low-cost and bench-stable boron source, providing boronates with exclusive selectivity, high efficiency, and high turnover number (up to 8900). This novel strategy may offer a versatile and environmentally friendly alternative to current methods for selective C(sp^3)–H borylation that employ even more expensive metals, such as iridium and rhodium.

Amido- and alkoxyboronic acids are value-added units in the structures of pharmaceuticals and biologically active molecules, such as Bortezomib and Ixazomib.[1] The frequently used procedures for the preparation of these important derivatives involve the reactions of aryllithium or Grignard reagents with organoboron nucleophiles.[2] However, these systems usually suffer from poor functional group tolerance and require multistep syntheses. Therefore, for the synthesis of boronic acids, it is desirable continue development of synthetic strategies with high efficiency and atom economy.

An alternative approach for the preparation of amido- and alkoxyboronic acids is to directly catalyze borylation of C(sp^3)–H bonds in amides and esters, which is a desirable strategy in terms of high atom efficiency.[3] Despite the impressive achievements in borylation processes, the selective borylation of C(sp^3)–H bonds in unactivated carboxamides still poses challenges and mainly concerns the use of catalyst systems based on the noble metals Rh and Ir.[4]

In 2012, Sawamura and co-workers reported an efficient method that involved a combination of the [{Rh(OMe)(cod)}$_2$] complex (cod = 1,5-cyclooctadiene) with a silica-supported triarylphosphine ligand to facilitate C(sp^3)–H borylation of alkyl amides to give amidoboronate esters, albeit along with geminal bisborylation products in several cases (Scheme 1 a).[5] This work represented a breakthrough in the borylation of N-adjacent C(sp^3)–H bonds in carboxamides, but the substrate scope was restricted to alkyl amides. Moreover, excess amides and volatile organic solvent were required for good conversions. Very recently, similar transformations were reported by Clark and co-workers, who used an iridium catalyst to form α-amidoboronate esters at 120 °C (Scheme 1 b).[6] However, the system showed lower catalytic efficiency than the Rh catalyst.



Scheme 1. C(sp^3)–H borylation of amides and esters. a) Rhodium-catalyzed borylation of amides.[5] b) Iridium-catalyzed borylation of amides.[6] c) This work.

Avoiding the use of organic solvents is clearly an important characteristic of green synthesis.[7] To our knowledge, selective C(sp^3)–H borylation of amide derivatives by using eco-friendly processes has not been reported to date. Furthermore, in contrast to the borylation of amide derivates, the catalytic C(sp^3)–H borylation of less reactive esters also remains unreported. The main challenge in this regard is the issue of electronic properties, given to the different electronic delocalizations in amides and esters (Scheme 2).[8]

Ruthenium is an attractive alternative to established iridium and rhodium catalysts, because it is approximately ten times less expensive.[9] Although a large number of Ru complexes have been used in versatile catalytic transformations, to our knowledge there are no reports on Ru-catalyzed borylation of amides and esters. On the basis of our interest in exploring the selectivity,[10] we report herein the Ru-catalyzed exclusive C(sp^3)–H borylation of inert amides (Scheme 1 c). Importantly, the ruthenium catalyst is also effective for C(sp^3)–H borylation

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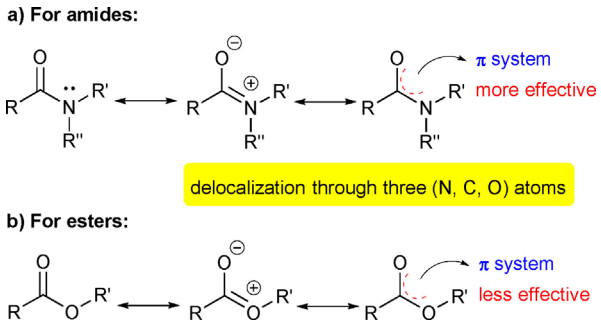
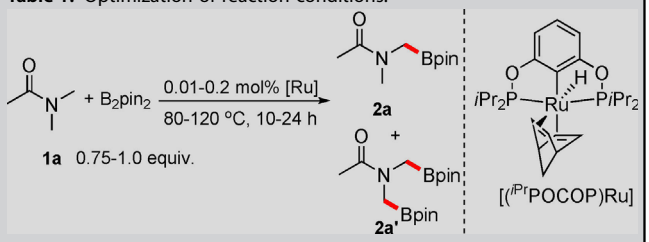


Scheme 2. Electronic properties of amides (a) and esters (b).

of challenging alkyl and aryl esters with bis(pinacolato)diboron (B_2pin_2).

Our initial study of the catalytic activity of several ruthenium complexes focused on the controlled reduction of dimethylacetamide (**1 a**) with B_2pin_2 (Table 1). The most effective catalyst was [(^{iPr}POCOP)Ru], which gave a good yield of the monoborylated product **2 a** under the standard conditions (Table 1, entry 1).The highly catalytic activity of the pincer [(^{iPr}POCOP)Ru] catalyst is partly attributed to its high thermal stability.[11] In contrast, when the reaction was performed with [Ru(acac)$_3$], [$Ru_3(CO)_{12}$], [(Cp*$RuCl_2$)$_2$] [{Ir(cod)Cl}$_2$] or even [$Rh(PPh_3)_3Cl$], the process was inefficient (Table 1, entries 2–6). Notably, [{Ir(cod)Cl}$_2$] and [$Rh(PPh_3)_3Cl$] were previously reported to be highly efficient catalysts for the C(sp^3)–H borylation of unactivated alkanes.[3] The [(^{iPr}POCOP)Ru]-catalyzed borylation of **1 a** also proceeded efficiently in organic solvents, such as THF, DME, Et_2O, and PhMe (Table 1, entries 7–10, 45–68%). Further optimization revealed that extending the reaction time to 24 h further improved the yield to 95% with only 0.05 mol% of [(^{iPr}POCOP)Ru] (Table 1, entry 11). However, when the reaction temperature (Table 1, entry 12), the catalyst loading (entry 13), or the amount of B_2pin_2 (entry 14) was lowered, the yield of **2 a** decreased as well.

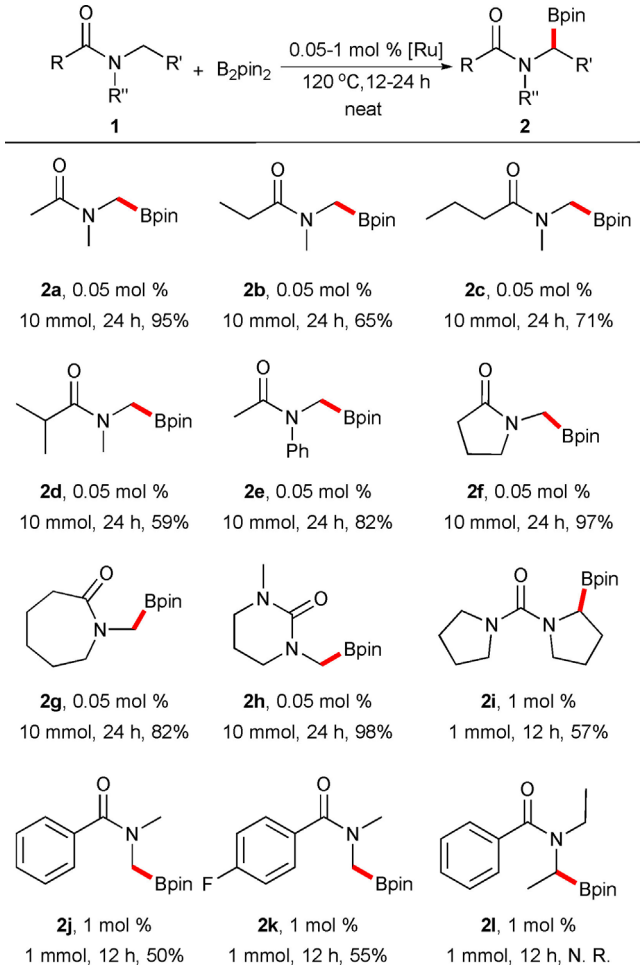
Table 1. Optimization of reaction conditions.[a]



Entry	[Ru]	[Ru] [mol%]	Solvent	Yield **2 a** [%]	Yield **2 a′** [%]
1	[(^{iPr}POCOP)Ru]	0.2	neat	73	0
2	[Ru(acac)$_3$]	0.2	neat	trace	0
3	[$Ru_3(CO)_{12}$]	0.2	neat	trace	0
4	[(Cp*$RuCl_2$)$_2$]	0.2	neat	trace	0
5	[{Ir(cod)Cl}$_2$]	0.2	neat	trace	0
6	[$Rh(PPh_3)_3Cl$]	0.2	neat	trace	0
7	[(^{iPr}POCOP)Ru]	0.2	THF	68	0
8	[(^{iPr}POCOP)Ru]	0.2	DME	45	0
9	[(^{iPr}POCOP)Ru]	0.2	Et_2O	57	0
10	[(^{iPr}POCOP)Ru]	0.2	PhMe	48	0
11[b]	[(^{iPr}POCOP)Ru]	0.05	neat	95	0
12[b,c]	[(^{iPr}POCOP)Ru]	0.05	neat	56	0
13[b]	[(^{iPr}POCOP)Ru]	0.01	neat	39	0
14[b,d]	[(^{iPr}POCOP)Ru]	0.05	neat	69	0

[a] Reaction conditions: **1 a** (1.0 mmol), B_2pin_2 (1.0 equiv.) and [Ru] (0.01–0.2 mol%), 120 °C, 10 h. Yields refer to isolated products. [b] t = 24 h. [c] T = 80 °C. [d] B_2pin_2 (0.75 equiv.).

Utilizing the optimized reaction conditions, we examined the substrate scope with respect to various amides for the monoborylation reaction (Scheme 3). The catalytic system mediated C(sp^3)–H borylation of both linear and cyclic alkyl amides with B_2pin_2 (**1 a**–**g**), delivering the corresponding isolated monoborylated products in good to excellent yields with only 0.05 mol% loading of [(^{iPr}POCOP)Ru]. Interestingly, bisborylation products were not formed in the reactions of ureas (**1 h**, **1 i**), even when 2.0 equivalents of B_2pin_2 were used. Significantly, our catalyst system enabled, for the first time, the highly efficient and selective monoborylation of *N*,*N*-dimethylbenzamide derivatives in useful yields (**1 j**, **1 k**). The bisborylation processes did not occur at the second *N*-methyl group in amides or ureas, which may indicate that intramolecular coordination of the carbonyl oxygen to the B atom may disturb

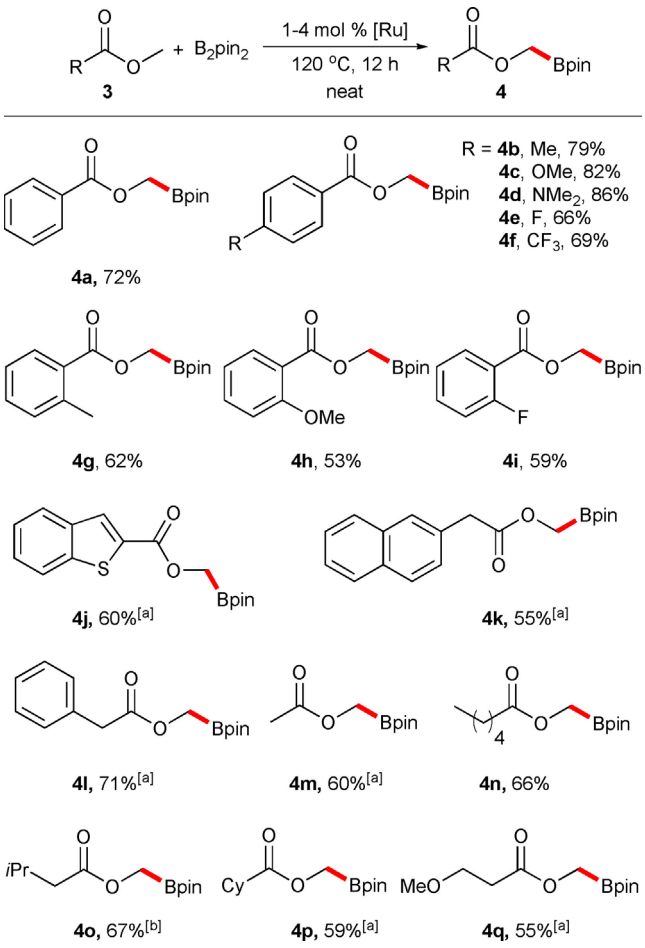


Scheme 3. Substrate scope for monoborylation of amides. Reaction conditions: **1** (1–10 mmol), B_2pin_2 (1.0 equiv.), [(^{iPr}POCOP)Ru] (0.05 mol-1.0%), neat, 120 °C, 12–24 h. Yields shown refer to isolated products.

the binding of the Ru center to the carbonyl. Unfortunately, increasing the size of the substituents at N or by using acyl-, alkene-, or ester-substituted amides destroyed the catalytic efficiency of the borylation (**1 l** and Scheme S1 in the Supporting Information).

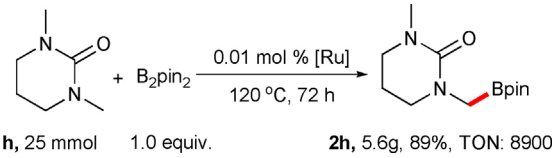
In light of the high activity of [(^{iPr}POCOP)Ru] in the catalytic borylation of amides and ureas, we next tested the catalytic systems applicability to the less reactive ester species (Scheme 2). Compared with carboxamides, the selective monoborylation of O-adjacent C(sp^3)–H bonds in esters is more difficult, which is due to the lower activity of these C(sp^3)–H bonds.

With the optimized reaction conditions in hand (see the Supporting Information), we explored the scope of reactions with respect to ester species (Scheme 4). Most reactions were conducted at 120 °C with catalyst loadings of 1.0 mol% and the low-cost B_2pin_2 as boron source. Reactions of substrates bearing methyl (**3 b**), ether (**3 c**), amino (**3 d**), fluoro (**3 e**), and trifluoromethyl (**3 f**) functional groups proceeded in a chemo- and site-selective manner. In addition, substituents at the *ortho* position on the aromatic ring (**3 g**–**i**) were all tolerated and afforded the desired products in good yields with exclusive selectivity. Notably, the heterocyclic ester **3 j** was also a suitable substrate for this reaction and a series of linear and cyclic alkyl esters (**3 k**–**q**) could also undergo selective monoborylation. However, some limitations of the scope were observed; borylation of acyl-, nitrile-, and nitro-containing amides could not proceed (Scheme S2). Furthermore, the attempted borylations of alkyne-, alkene-, bromo- or iodo-substituted amides also resulted in no product, even when the reaction was carried out at high temperature.



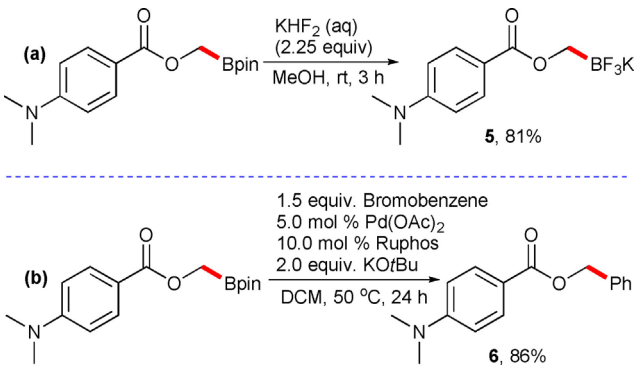
Scheme 4. Substrate scope for monoborylation of esters. Reaction conditions: **3** (1.0 mmol), B_2pin_2 (1.0 equiv.), [(^{iPr}POCOP)Ru] (1.0 mol%), 120 °C, 12 h. Yields shown refer to isolated products. [a] [Ru] (2.0 mol%). [b] [Ru] (4.0 mol%).

With the highly active catalyst in hand, we sought to demonstrate the synthetic utility of the borylation process (Scheme 5). In the presence of only 100 ppm (0.01 mol%) of catalyst, the borylation of **1 h** (25 mmol) could proceed at 120 °C, and afforded **2 h** in 89% yield after 72 h. This result corresponded to a turnover number (TON) of 8900, which, to our knowledge, represents the highest turnover number for any metal-catalyzed C(sp^3)–H borylation of **1 h** with B_2pin_2.[12]



Scheme 5. Large-scale reaction.

Following the borylation, boronic ester **4 d** could be smoothly converted into the corresponding organotrifluoroborate by treatment with KHF_2 (Scheme 6). Moreover, a mild protocol for the cross coupling of **4 d** with bromobenze was also developed and gave the isolated product **6** in good yield.



Scheme 6. Functionalization of boronic ester **4 d**.

The time courses of the C(sp^3)–H monoborylations of **1 a** and **3 a** catalyzed by [(^{iPr}POCOP)Ru] are shown in Figure 1. After 24 and 12 h, the yields of **2 a** and **4 a** were 95% and 72%, respectively. However, a substantial decrease in the reaction time was detrimental in both cases, and the yields of the two products were significantly diminished. These results clearly suggest that the reaction time has a significant impact on these borylation transformations.

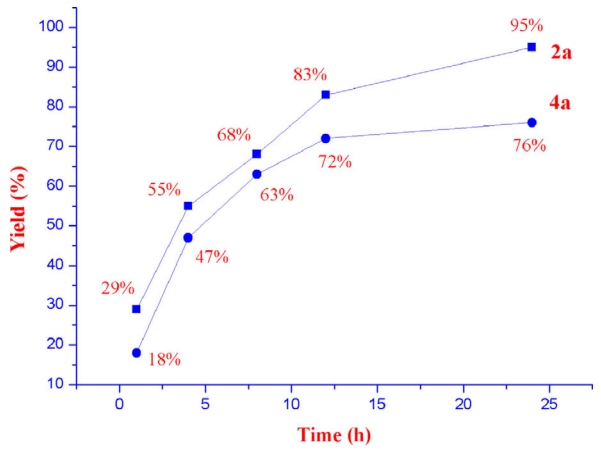
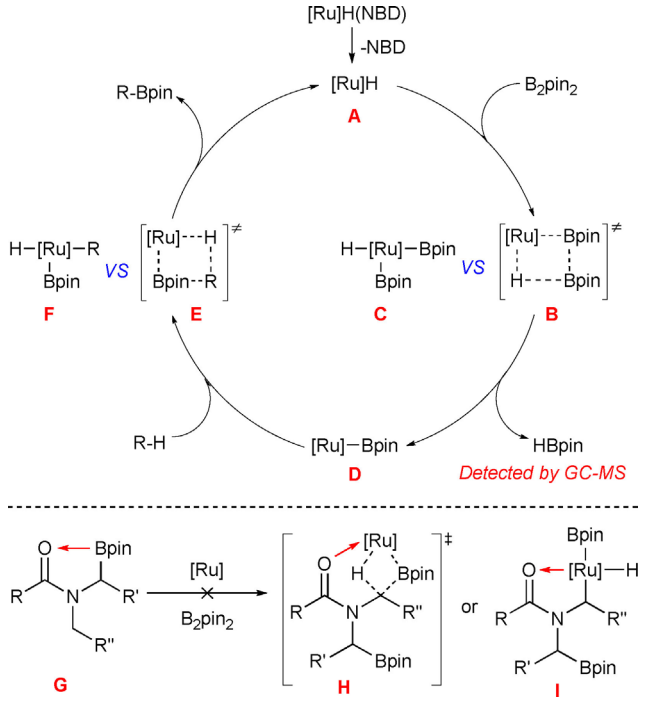


Figure 1. Time courses of the C(sp^3)–H monoborylations of **1a** and **3a**. Reaction conditions: **1a** (10.0 mmol), B_2pin_2 (1.0 equiv.), [(^{iPr}POCOP)Ru] (0.05 mol%), neat, at 120 °C, 1–24 h. **3a** (1.0 mmol), B_2pin_2 (1.0 equiv.), [(^{iPr}POCOP)Ru] (1.0 mol%), neat, at 120 °C, 1–24 h. Yields shown are of isolated products.

Based on the previous works[13] and free-radical control experiments (see the Supporting Information), we propose the mechanism of the borylaton process depicted in Scheme 7. According to reports on Ru systems, the Ru^{II} complexes are not prone to two-electron oxidation.[14] The d^6 [Ru]H center is not isoelectronic with the d^8 [Ir] center. Thus, these results indicate that oxidative addition of B–B/C–H bonds to **A**/**D** via discrete Ru^{IV} intermediates **C**/**F** is unlikely. Therefore, we propose that B–B/C–H bond activation proceeds by σ-bond metathesis through two four-coordinate, 14-electron Ru^{II} species **B** and **E**. Following dissociation from the resulting **E** regenerate **A** and the desired borate. Similar C–N bonds activation by σ-bond metathesis through the Ru^{II} transition state were reported previously.[15] Further in-depth tests and computational studies are currently underway to distinguish the two pathways.



Scheme 7. Proposed mechanism.

Based on the previous report[5] and the signal of the ^{11}B NMR spectrum,[16] the intramolecular coordination of the carbonyl oxygen to the B atom (**G**) may disturb the binding of the Ru center to the carbonyl (**H** or **I**), which will lead to the failure in bisborylation processes at the second *N*-ethyl group of amides or ureas. This suggests that the exclusive selectivity in the C(sp^3)–H monoborylation of amides is likely.

In conclusion, we have developed a new approach for the selective monoborylation of inert C(sp^3)–H bonds in alkyl and even aryl carboxamides, using a thermally robust and active pincer Ru complex in the absence of additives and solvents. Featuring environmentally benign utility, high efficiency, and exclusive selectivity, this catalytic strategy has also been applied to selective ester monoborylations to form the corresponding aryl and alkyl boronates.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amides · borylation · C–H activation · ester · ruthenium

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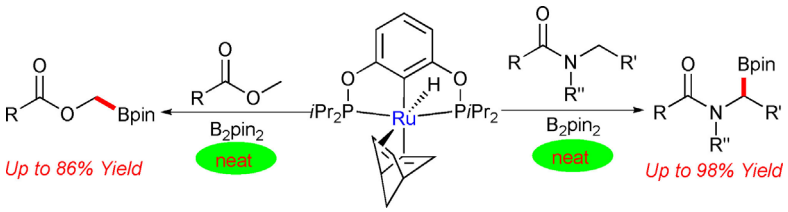

Plan B: A ruthenium-catalyzed method has been developed for the C(sp^3)–H monoborylation of various unactivated alkyl and aryl amides and challenging esters with a low-cost and bench-stable boron source, providing boronates with exclusive selectivity, high efficiency, and turnover numbers of up to 8900.