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Functional Group Interconversion: Decarbonylative Borylation of Esters for the Synthesis of Organoboronates

Lin Guo and Magnus Rueping*

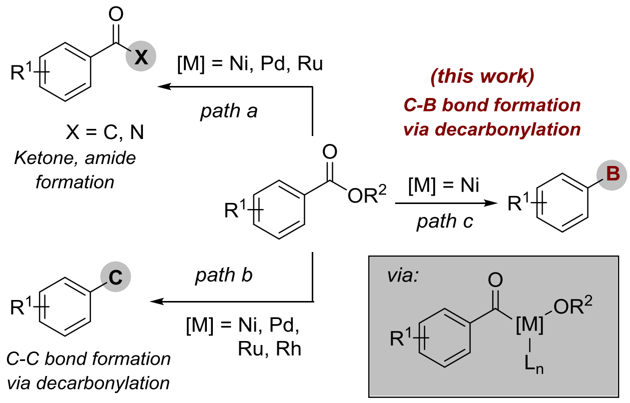
Abstract: A new and efficient nickel-catalyzed decarbonylative borylation reaction of carboxylic acid esters with bis(pinacolato)-diboron has been developed. This transformation allows access to structurally diverse aryl as well as alkenyl and alkyl boronate esters with high reactivity, broad substrate scope and excellent functional group tolerance. Further experiments show that this protocol can be carried out on gram scale and applied to orthogonal synthetic strategies.

Organoboroncompounds are widely recognized as essential synthetic building blocks in modern organic synthesis. They have been attracting increasing attention due to their wide range applicability to C-X (X = C, N and O) bond-forming reactions and ease of handling.[1] Traditional methods for the preparation of organoboron compounds involve the reaction of either organolithium or Grignard reagents with boron-centered electrophiles.[2] Recent years have witnessed the development of transition-metal catalyzed boryl substitution of aryl halides[3] and arene C-H borylations[4] with high functional group tolerance. In addition, base-mediated[5] or photoinduced[6]borylation of aryl halides as well as the Sandmeyer-type borylation of anilines[7] have also been developed. However, the above-mentioned methods have limitations includingthe utilization of expensive metal catalysts and environmentally less favorableorganohalides or aniline derivatives. As an alternative, further research has recently made a significant breakthrough in the borylation reaction through cleavage of inert bonds (such as C-O,[8] C-N and C(CO)N,[9] C-CN,[10] and C-F bonds[11]).

Esters, as one of the most commonly used class of carboxylic acid derivatives, are cheap and abundant in nature. Compared with the traditional methods, the utilization of esters as coupling counterparts has received recently considerable attention since it avoids the production of corrosive halide-containing wastes. One such endeavor involves the cross-coupling of pivalate esters that proceeds through nickel-mediated activation of aryl C-O bonds. In contrast, since the initial study by Yamamoto in 1980,[12] the cleavage of acyl C-O bonds in esters remains still underdeveloped (Scheme 1).

Until now, esters have merely been employed as coupling electrophiles for the conversion to ketones and amides via acyl C-O bond activation (Scheme 1, *path a*)[13] or carbon-carbon and carbon-silicon bond formation via a decarbonylative pathway, [14] which proceeds with loss of the carbonyl moiety in the form of CO (Scheme 1, *path b*).[15] Despite the reported advances, carbon-boron bond forming reactions have never been accomplished via a decarbonylative process starting from esters.

From a synthetic point of view, the ability to promote a decarbonylativeborylation of esters would be highly rewarding, providing a new synthetic approach to useful organoboron compounds from simple precursors.With this consideration in mind we proceeded with the development of a simple and efficientborylation protocol that would allow cleavage of the inherently stable ester group while forming a reactive and versatile boron group. As part of our interest in C-O bond activation and functionalization[16] we herein present the first nickel-catalyzed decarbonylative borylation reaction of esters (Scheme 1, *path c*).[17] This protocol is characterized by its wide scope and excellent functional group tolerance.



Scheme 1. Metal-catalyzed acyl C-O bond activation and functionalization.

The nickel-catalyzed decarbonylativeborylation reaction of phenyl 2-naphthoate (**1a**) with bis(pinacolato)diboron (**2**, B_2pin_2) was selected as a model reaction (Table 1). After the initial evaluation, we found a promising result when employing $Ni(COD)_2$, tri-*n*-butylphosphine and lithium carbonate in toluene, affording the corresponding product **3a** in 18% yield after 12 hours (entry 1). Extension of reaction time and increase of reaction temperature resulted indeed in better yields (entries 2-4). Regarding the role of the supporting ligand, replacement of tri-*n*-butylphosphine by other monodentate and bidentate phosphine ligands under identical reaction conditions dramatically decreased the yield (entries 6-9). The loading ratio of $Ni(COD)_2$ and P^nBu_3 ligand had a slight effect on reactivity, affording **3a** in 75% yield when the ratio was changed from 1:2 to 1:4 (entries 4-5). Further optimizations were performed by

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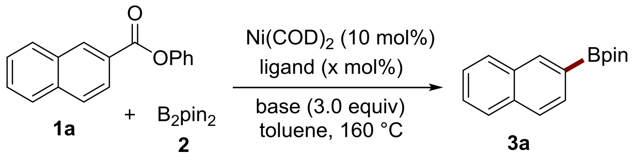
screening various bases, but they all provided unsatisfying results (entries 12-15). Interestingly, the lack of base also provided **3a** in 68% yield. The utilization of 1,4-dioxane instead of toluene as reaction solvent slightly increased the yield to 83% (entry 16). As anticipated, control experiments revealed that the transformation neither proceeds without the nickel catalyst nor in the absence of supporting ligand (entries 10 and 17).

Table 1. Optimization for the decarbonylativeborylation of esters.[a]



L1 (PCy_3) **L2** (P^tBu_3) **L3** (dcype) **L4** (dppf)

Entry	Ligand (xmol%)	Base	Time (h)	Yield (%)[b]
1[c]	P^nBu_3 (40)	Li_2CO_3	12	18
2[c]	P^nBu_3 (40)	Li_2CO_3	24	51
3[c]	P^nBu_3 (40)	Li_2CO_3	36	69
4	P^nBu_3 (40)	Li_2CO_3	36	75
5	P^nBu_3 (20)	Li_2CO_3	36	72
6	**L1** (40)	Li_2CO_3	36	5
7	**L2** (40)	Li_2CO_3	36	< 5
8	**L3** (20)	Li_2CO_3	36	47
9	**L4** (20)	Li_2CO_3	36	15
10	-	Li_2CO_3	36	0
11	P^nBu_3 (40)	-	36	68
12	P^nBu_3 (40)	Na_2CO_3	36	27
13	P^nBu_3 (40)	Cs_2CO_3	36	12
14	P^nBu_3 (40)	CsF	36	29
15	P^nBu_3 (40)	Et_3N	36	35
16[d]	**P^nBu_3 (40)**	**Li_2CO_3**	**36**	**83 (75)[e]**
17[d,f]	P^nBu_3 (40)	Li_2CO_3	36	0

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.30mmol, 2 equiv.), $Ni(COD)_2$ (10mol%), ligand (xmol%), base (0.60 mmol, 3 equiv.) in toluene (1.5 mL) at 160 °C. [b] Determined by ^1H NMR spectroscopy using 1,3,5-$(OMe)_3C_6H_3$ as an internal standard. [c] At 150 °C. [d] Using 1,4-dioxane (1.5 mL) as solvent instead of toluene. [e] Yield after purification. [f] Without $Ni(cod)_2$.

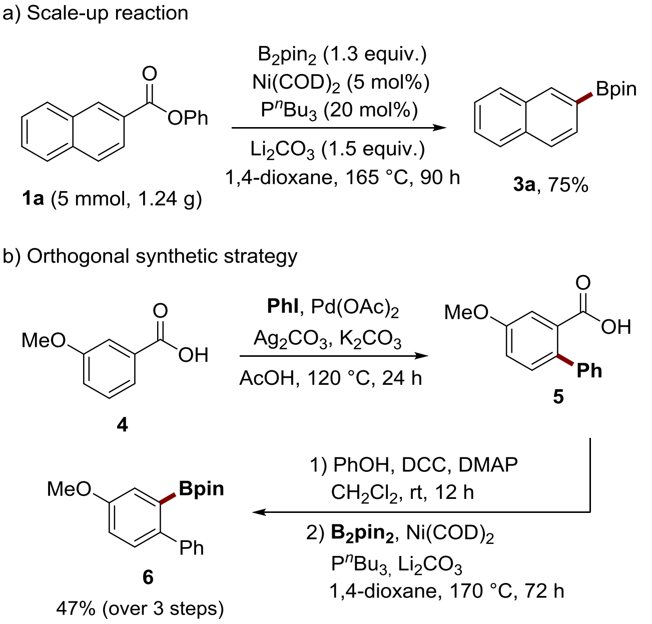
Prompted by these results, we next examined the scope of the boryl substitution with various aryl esters as coupling electrophiles. As shown in Table 2, a wide range of naphthyl (**3a-c**) and phenyl (**3d-u**) esters could be efficiently converted into the corresponding aryl boronic esters by employing bis(pinacolato)diboron (**2**) as the coupling counterpart. Neutral, electron-rich and electron-deficient aryl esters all underwent smoothly the reaction to give the corresponding products in high yields. Biphenyl derivatives and substrates bearing large conjugated systems gave the corresponding products **3d-j** in good to high yields. Additionally, the chemoselectivity profile of this protocol was nicely illustrated by the fact that functional groups such as alkenyl (**3j**), trifluoromethyl (**3i**, **3o**), methyl (**3k**), *tert*-butyl (**3l**), dioxole (**3p**), amine (**3q**) and ketone (**3r**, **3s**) were perfectly tolerated under the developed conditions.

Although nickel catalysts are suitable for borylation events via C-OMe,[8d] C-F[11] or C-NCOR[9a] cleavage, we found that in our case the aryl methyl ether (**3c**, **3m**), fluoride (**3h**, **3n**) or amide (**3u**) did not compete with the decarbonylativeborylation reaction. This notable chemoselectivity is not only a requirement for a useful reaction in general, but additionally important for retrosynthesis planning. Furthermore, also substrate **1t** with a relatively stable methyl ester group was compatible with this methodology, providing **3t** in 57% yield.

As shown in Table 3, this protocol also tolerates α,β-unsaturated esters and unactivated aliphatic esters, affording the corresponding borylated products **3v-x** in moderate yields. The results compiled in Table 2 and Table 3 clearly demonstrate the potential impact of our decarbonylative borylation protocol, even with unactivated substrates.

In terms of the scalability of this method, the decarbonylative borylation of **1a** was conducted on a 5 mmol (1.24 g) scale,[18] as shown in Scheme 2a. With 5 mol% of nickel catalyst, 5 mmol of phenyl 2-naphthoate was converted into 0.96 g (75%) of the corresponding product **3a**. The developed method also enabled us to approach an orthogonal synthetic strategy that makes use of the directing and activating characteristics of the carboxylic acid group. For this purpose, 3-methoxybenzoic acid (**4**) was selectively functionalized at the less-hindered *ortho*-position via carboxylate-directed C-H bond activation.

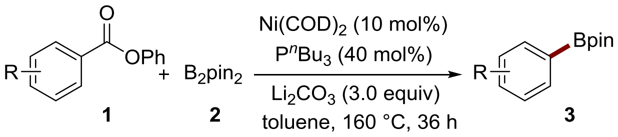
Since there is no available method for the direct conversion of the carboxylic acid group into the very useful boron functional group, the carboxyl group was easily converted into the appropriate phenyl ester, and subsequently to boronate ester by our decarbonylative borylation protocol, affording compound **6** in 47% overall yield after three steps (Scheme 2b).

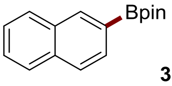

a) Scale-up reaction

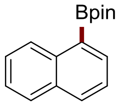
b) Orthogonal synthetic strategy

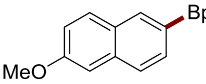
Scheme 2. Scalability and synthetic application.

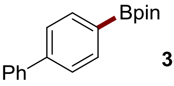
Table 2. Substrate scope for aryl esters.[a,b]

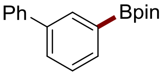


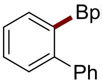

3a, 75%

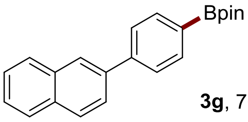

3b, 71%

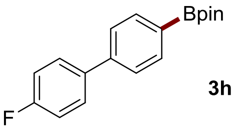

3c, 83%

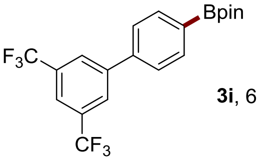

3d, 86%[c]

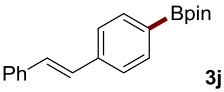

3e, 51%[c]

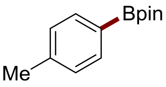

3f, 69%[d]

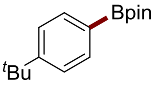

3g, 76%[c]

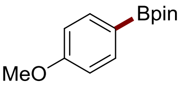

3h, 64%

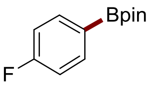

3i, 61%

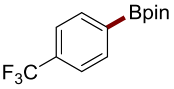

3j, 61%

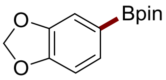

3k, 81%[c]

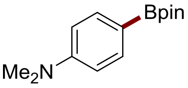

3l, 78%[c]

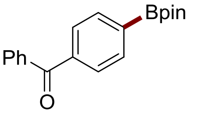

3m, 69%[c]

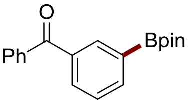

3n, 59%[c]

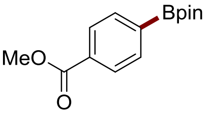

3o, 39%[c]

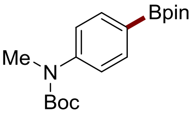

3p, 65%


3q, 38%


3r, 54%

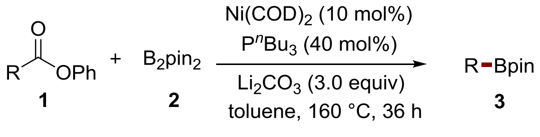

3s, 51%


3t, 57%

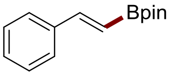

3u, 61%

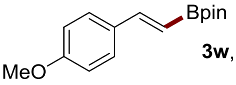
[a] Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), $Ni(COD)_2$ (10 mol%), P^nBu_3 (40 mol%), Li_2CO_3 (0.60 mmol) in toluene (1.5 mL) at 160 °C for 36 h. [b] Isolated yield. [c] At 170 °C. [d] At 170 °C for 72 h.

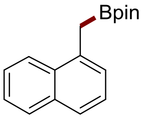
Table 3. Substrate scope for alkenyl and alkyl esters.[a,b]



(R = alkenyl and alkyl)


3v, 49%

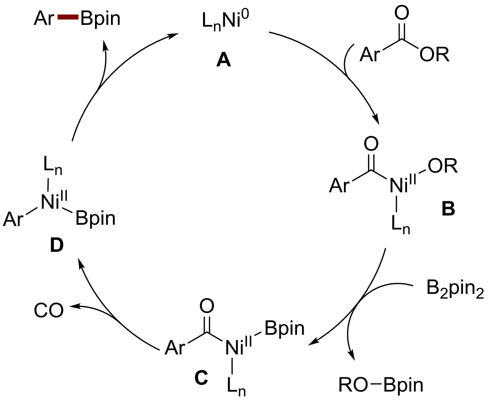

3w, 51%


3x, 32%

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), $Ni(COD)_2$ (10 mol%), P^nBu_3 (40 mol%), Li_2CO_3 (0.60 mmol) in toluene (1.5 mL) at 160 °C for 36 h. [b] Isolated yield.

This reaction sequence is an example of an orthogonal synthetic strategy, which enhances the possibilities for the synthesis of diverse boryl functionalized products from simple precursors and offers the opportunity for further alteration of the easily modifiable boron group.

Based on previous literature reports,[13c,15f] the elementary steps involved in the present nickel-catalyzed borylation of esters are postulated in Scheme 3. The reaction is triggered by oxidative addition of Ni(0) species **A** to the acyl C-O bond of the ester substrate. The resulting acylnickel(II) complex **B** undergoes subsequently a transmetalation step with bis(pinacolato)diboron, generating the acylnickel(II) species **C**. The decarbonylation process is accessed via extrusion of carbon monoxide from intermediate **C**, and subsequent reductive elimination releases the aryl boronate ester product and regenerates the active Ni(0) species **A**. This mechanism is plausible and explains the decarbonylative borylation protocol of carboxylic acid esters.



Scheme 3. Proposed reaction mechanism of the decarbonylative borylation.

In summary, we have developed the first nickel-catalyzed decarbonylative borylation reaction of carboxylic acid esters. This protocol provides a new possibility to cleave a stable ester group while forming a versatile boron group. The broad substrate scope, high reactivity and scalability of the method suggest that this protocol can be a powerful alternative to the existing methodologies for preparing organoboron compounds from readily available precursors. It is important to note that the newly developed protocol shows high chemoselectivity and that functional groups such as C-OMe, C-For C-NCOR previously used in Nickel catalyzed functional group interconversions remain intact. Thus, the developed protocol will be of interest as it allows to replace ester groups which can be used prior the replacement as directing group in Friedel-Crafts reactions or metal catalyzed CH-functionalizations. The method may also be considered in retrosynthesis planning using the ester group as directing group and at the same time placeholder for the boron functionality which if required can easily functionalized to other valuable products. Further mechanistic studies and other related transformations are currently underway in our laboratories.

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Keywords: Decarbonylative cross-coupling • decarboxylation • ester • C-O bond activation • CH borylation

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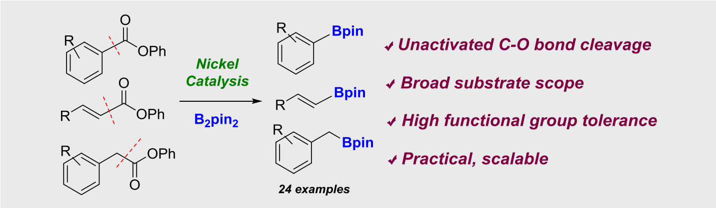

A new and efficient nickel-catalyzed decarbonylative borylation reaction of carboxylic acid esters with bis(pinacolato)diboron was developed. This transformation allows access to structurally diverse aryl as well as alkenyl and alkyl boronate esters with high reactivity, broad substrate scope and excellent functional group tolerance. The protocol can be carried out on gram scale and applied to orthogonal synthetic strategy.

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