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Nickel-Catalyzed 1,1-Alkylboration of Electronically Unbiased Terminal Alkenes

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Abstract: An unprecedented, nickel-catalyzed, 1,1-alkylboration of electronically unbiased alkenes has been developed, providing straightforward access to secondary aliphatic boronic esters from readily available materials under very mild reaction conditions. The regioselectivity of this reaction is governed by a unique pyridyl carboxamide ligated catalyst, rather than the substrates. Moreover, this transformation shows excellent chemo- and regio-selectivity and remarkably good functional group tolerance. We also demonstrate that under balloon-pressure, ethylene can also be utilized as a substrate. Additionally, competence experiments indicate that a selective bond formation is favored at the α -position of boron and preliminary mechanistic studies indicate that the key step in this three-component reaction involves a 1,2-nickel migration.

Transition metal-catalyzed difunctionalization of alkenes has been developed into an essential strategy to expeditiously access valuable complex molecules. ^[1] The regioselectivity of addition to electronically unbiased olefins is a major challenging task in this area. ^[2] To address this problem, intramolecular systems are designed, ^[3] or coordination groups are introduced to the alkene substrate. ^[4] In contrast, fully catalyst-controlled, three-component transformations are still understudied.

Alkylboration of alkenes is of special interest owing to the construction of a C(sp3)-C(sp3) chemical bond, [5] with concurrent introduction of a boron group which provides enormous opportunities for downstream diversifications.^[6] Significant advances have been achieved particularly with copper catalysis (Figure 1a). For example, an intramolecular strategy was used by Sawamura^[7] and Ito^[8] independently, synthesizing strained small rings. The intermolecular studies were initiated by the Yoshida group with styrenes and electronically biased olefins.^[9] Recently, a new progress on regiodivergent 1,2- and 2,1-alkylborations of unactivated terminal olefins by the assistance of weak coordinating groups, was accomplished by the Fu group (Figure 1b). ^[10] However, the regioselective alkylboration of electronically unactivated olefins without a coordinating group is still a challenge. Herein, we report a coordinating-group-free, nickel-catalyzed 1,1alkylboration of electronically unbiased terminal alkenes, delivering difunctionalized products in an efficient and highly

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selective manner (Figure 1c). Accordingly, synthetically useful secondary aliphatic boronic esters ^[11,12] can be expected from readily available terminal alkenes and benzyl/allyl halides with a cheap boron reagent under very mild conditions.

a) Alkyboration of Alkenes [C(sp³)-C(sp³) & C(sp³)-B bond formation]:



b) 1,2- and 2,1-Alkylboration of Unactivated Alkenes (by the Fu group):



c) 1,1-AlkIboration of Unactivated Alkenes (this work):



Figure 1. Transition metal-catalyzed alkylboration of alkenes.

In copper-catalyzed alkylboration reactions, both the transient alkyl-Cu intermediate generated from alkene migratory insertion into a Cu-B bond, and following bond formation, mainly benefit from the difficult β -H elimination of the d¹⁰ metal.^[13] As a continuous interest in nickel catalysis,^[14] particularly after the success of nickel-catalyzed migratory arylboration of alkenes,^[15] we speculated that if the copper catalyst was replaced by nickel, rapid β -H elimination and migratory insertion ^[16] would lead to the formation of a stable R-CH(Bpin)Ni(II) species. The subsequent C(sp³)-C(sp³) bond formation, with an alkyl electrophile, would deliver the 1,1-alkylboration product. It should be pointed that, to the best of our knowledge, only a single example on nickel-catalyzed 1,1-difunctionalization of alkenes has been demonstrated to date by the Fu group.^[17]

Our initial effort focused on the three-component reaction with terminal alkene **1a**, benzylbromide **(2a)** and bis(pinacolato)diboron (B_2pin_2 , **3**). Anciliary ligands were thought to be the crucial factor for this 1,1-difunctionalization, therefore ligand screens were conducted under similar reaction conditions

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to our prior arylboration reaction.^[14] The ligand effects are illustrated in Table 1. It was surprising that many ligands commonly employed in nickel catalysis, including bipyridine (L1 and L3), 1,10-phenanthroline (L2 and L4), PyrBox (L5), tripyridine (L6) and pyrimine (L7) failed to gave rise to the desired product 4a in more than a trace amount. However, when an unusual pyridyl carboxamide^[18] L8 was employed, the 1,1alkylboration product 4a was obtained in 69% yield. Further optimization of this type of ligand improved the yield to 91% (L9). Comparing with L9 and L10, indicates that the methyl substituent adjacent to the nitrogen atom of the pyridine ring is very important. A user-friendly and air-stable nickel complex was prepared with L9, leading to a similar isolated yield. Notably, the excellent 1,1selectivity reveals that the reaction is initiated by the alkene insertion into a Ni-B bond, rather than the oxidative addition of the alkyl electrophile, despite utilizing a highly reactive one.

Table 1. Reaction Development [a]



[a] General conditions: NiBr₂-DME (5 mol %), Ligand (5 mol %), **1a** (0.4 mmol, 1.0 equiv), **2a** (0.6 mmol, 1.5 equiv), **3** (0.6 mmol, 1.5 equiv), LiOMe (0.8 mmol, 2.0 equiv), in Dioxane (2.5 mL), stirred at 30 °C for 12 h. GC yields against naphthalene. [b] Isolated yield at 0.4 mmol scale. DME = Dimethoxyl ethane.

Having identified the optimal reaction conditions, we next turned our attention to investigate the generality of this Nicatalyzed reaction. As illustrated in Table 2, the olefin partner was first studied. Unactivated terminal alkenes bearing a wide range of flexible functional groups including esters, ethers, ketones, amides, cyano, alcohols, tosylates, and epoxides, as well as functionalized thiophene, pyrrole and indoles were examined. All could successfully transform to the corresponding arylboration products in good to excellent yields with an extraordinary regioisomeric ratio (rr > 20:1). The 1,1-alkylboration product was obtained in a good yield from 1-heptene (4b), which indicates that the regioselectivity is governed by the catalyst not coordinating groups. It is noteworthy that homoallyl bromide was able to furnish the alkylboration product in a very good yield with the bromide intact (4e), and no cyclization products (5 or 6 member-ring) were detected in the reaction of 6-bromohexene (4n). Moreover, the substrates containing multiple double bonds, selectively reacted with the monosubstituted olefins (4s-4v), indicating this reaction exhibits good chemoselectivity among different types of double bonds. To further demonstrate the good compatibility of this method, biologically interesting, complex molecules (4w and 4x) were also synthesized. Interestingly, the α , β -unsaturated ketone was also well-tolerated in this nickel-catalyzed system (4w).

To further assess the generality of these catalytic conditions, we next investigated the reaction of terminal olefin 1a with a number of different alkyl electrophiles. A series of substituted benzyl bromides were examined. Both electron-rich and -deficient substituents did not greatly affect the reactivity. Remarkably, the aryl chloride, bromide and even iodide were all well-tolerated in this mild nickel-catalyzed condition, which open avenues for further downstream cross-couplings. Furthermore, heterocyclic benzyl bromides and benzyl chlorides were also suitable substrates (2m-2o). It should be noted that allyl bromides, while somewhat less reactive than the benzyl halides, were also able to generate the corresponding homoallyl boronic esters under the same reaction conditions, with extraordinary 1,1-regioselecitivity (2p-2r). Unfortunately, secondary benzyl bromides (2s) and unactivated alkyl bromides (2t) failed to yield the product under these reaction conditions.

In addition to aliphatic olefins, a diversity of vinylarenes, could also undergo alkylboration under the standard conditions (Table 3), but only 1,2-products were isolated in these reactions, consistent with Yoshida's copper-catalyzed system. ^[9] This is likely due to the stability of benzyl nickel intermediates. However, it is still difficult to get details on the selectivity between the benzylic position versus α -position of the boron group from the above results.

To get insight into the regioselectivity of this system, as illustrated in Scheme 1, allylbenzene and a couple of other allyl substituted functional groups were examined in the following studies. The 1,1-product **7** was still dominated in the reaction of allylbenzene with a regioisomeric ratio of 6:1, which exhibits a reversed selectivity with our previous arylboration reaction. Further competence of bond formation between α -position of an ester, amide and cyano group versus α -position of the boron group was explored. We were pleased to find that all three reactions afforded the 1,1-difunctionalized products in good yields with good selectivity. These results support the notion that the good regioselectivity is dictated by the new catalyst.

To further explore the potential scope of this 1,1-alkylboration, gaseous ethylene was utilized in this reaction. As shown in Scheme 2a, only with a balloon pressure, the desired product **11** could be obtained in 61% yield at a 10 mmol scale with 1 mol % catalyst loading.

Finally, a series of experiments were performed to shed light on the mechanism of this transformation (please see SI for more details and discussions). First of all, no signal was detected when the reaction was monitored by electron paramagnetic resonance (EPR) spectroscopy, which suggests that the catalyst resting states are Ni(0) or Ni(II) species.^[19] Therefore, the reaction is less likely involving a single Ni(I/III) catalytic cylce.^[20, 21] No Suzuki-Miyaura cross-coupling product was observed in the reaction of 1,1-diboron compound with **2a** under the optimal conditions (Scheme 2b), which rules out the possibility that the 1,1-diboron compound **12** serves as the intermediate in this alkylboration reaction.^[17] Furthermore, a terminal deuterium-labeled olefin, **[d]-1a**, was prepared and examined in the reaction (Scheme 2c). The product (**[d]-4a**) was isolated in 90% yield, with 53% D-atom migration to the β -position. Moreover, the addition of vinyl boronic

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[a] Standard conditions: [Ni]-1 (5 mol %), 1 (0.4 mmol, 1.0 equiv), 2 (0.6 mmol, 1.5 equiv), 3 (0.6 mmol, 1.5 equiv), LiOMe (0.8 mmol, 2.0 equiv), in Dioxane (2.5 mL), stirred at 30 °C for 12-15 h. Isolated yields. [b] Yield of the corresponding alcohol after oxidation.

Table 3. Reaction of vinylarenes.





Scheme 1. Regioselectivity studies.($Ar = 4-MeOC_6H_4$)

ester **13** into the reaction of **1a**, did not affect the efficiency and did not detect the formation of hydroalkylation products (**14**) (Scheme 2d). These results suggest a nickel migration is involved

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in this transformation and nickel-hydride is not dissociated from the intermediate during migration. Accordingly, a catalytic cycle involving a 1,2-nickel migration is proposed. As depicted in Scheme 2e, the reaction is initiated by a Ni(II) species (I), which undergoes transmetalation with B₂pin₂ to generate a Ni(II)-Bpin species (II). A following olefin migratory insertion leads to the formation of an alkylNi(II) intermediate (III). A β-H elimination delivers the nickel complex IV, and following rapid migratory insertion affords a new stable alkylNi(II) intermediate (V), which reacts with an activated alkyl halide (2) giving rise to the 1,1difunctionalized product (4). The reaction of intermediate V with the alkyl halides likely involves a radical chain process, ^[19, 22] but another possibility involving dual nickel transmetalation can not be ruled out at this stage.^[23] Further mechanistic investigations are currently underway in our laboratory.

a) Ethylene transformation:



Scheme 2. Ethylene transformation and mechanistic studies.

In summary, we have developed the first regioselective 1,1alkylboration of alkenes via nickel catalysis. Accordingly, a series of secondary alkyl boron compounds have been prepared effciently from readily accessible terminal alkenes, benzyl or allyl halides and B₂pin₂ under very mild conditions. The success of this transformation owes to the application of an unusual, pyridyl carboxamide ligand. Very importantly, this reaction displays extremely good regioselectivity and compatibility with a broad range of functional groups. We believe this development will greatly promote the alkene transformations and the synthesis of alkyl boron compounds.

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An unprecedented alkylboration of electronically unbiased terminal alkenes, featuring 1,1-regioselectivity, has been achieved by a novel nickel catalyst. The most appealing part of this reaction is the successful implementation of remarkable regioselectivity without the assistance of coordinating groups. Moreover, the reaction exhibits excellent functional group tolerance and chemoselectivity toward monosubstituted double bonds.

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