Pd/Cu-Catalyzed amide-enabled selectivity-reversed borocarbonylation of unactivated alkenes†

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The addition reaction between CuBpin and alkenes to give a terminal boron substituted intermediate is usually fast and facile. In this communication, a selectivity-reversed procedure has been designed and established. This selectivity-reversed borocarbonylation reaction is enabled by a cooperative action between palladium and copper catalysts and proceeds with complete regioselectivity. The key to the success of this transformation is the coordination of the amide group and slower CuBpin formation by using KHCO₃ as the base. A wide range of β-boryl ketones were produced from terminal unactivated aliphatic alkenes and aryl iodides. Further synthetic transformations of the obtained β-boryl ketones have been developed as well.

The catalytic borocarbonylation of alkenes represents a novel synthetic tool for the simultaneous installation of boron and carbonyl groups across alkenes, enabling rapid construction of molecules with high complexity from abundant alkenes. In particular, the obtained organoboron compounds are versatile synthetic intermediates that can be readily converted into a wide range of functional groups with complete stereospecificity. Consequently, several catalytic systems have been developed to diversify the molecular frameworks through carbonylative borofunctionalization. In general, carbonylative borofunctionalization of alkenes proceeds via an alkyl-copper intermediate, which was produced by the addition of CuBpin to the terminal position of the alkene starting material, followed by CO insertion and other related steps. A new C-B bond is formed at the terminal position of the alkene and a carbonyl group has been installed at the β-position simultaneously (Scheme 1a). However, in contrast to the progress in the borocarbonylation, a selectivity-reversed procedure (the boryl group is installed at the internal position) to give β-boryl ketone products is still unprecedented.

Recently, several attractive strategies have emerged for the borofunctionalization of unactivated alkenes to give β-boryl products. In 2015, Fu, Xiao and their co-workers established a copper-catalyzed regiodivergent alkylboration of alkenes. In the same year, Miura and Hirano’s group reported a copper-catalyzed aminoboration of terminal alkenes. In these two attractive procedures, the regioselectivity was controlled by the ligand applied. More recently, an intermolecular 1,2-alkylboration of alkenes was described by Ito’s research group. A radical-relay strategy was used to achieve the targeted regioselective addition. Furthermore, Engle and co-workers explored a palladium-catalyzed 1,2-carboboration and -silylation reaction of alkenes. Stereocontrol can be achieved in this new procedure with the assistance of a chiral auxiliary which is a coordinating group in this case.

Inspired by these pioneering studies, we assumed that if the reaction could be initiated by the insertion of an acylpalladium...
complex into alkenes, followed by transmetalation with CuBpin before reductive elimination, β-boryl ketones can finally be produced (Scheme 1b). However, due to the inherent reactivity of the palladium species toward alkenes, olefin substrates were usually restricted to styrenes and a large excess of them is typically required (>6 equivalents). Therefore, the critical part of the reaction design is to promote the reaction of the acyl-palladium intermediate with alkenes faster than the insertion of CuBpin into olefins. One of the ideas is taking advantage of the coordinating group to transform the reaction from intermolecular to intramolecular. Among the developed directing groups, 8-aminoquinoline (AQ) is interesting and has been relatively well studied by various groups in a number of novel transformations. Although the AQ directing group contains a NH group which can participate in intramolecular C–N bond formation, we believe that the selectivity-reversed borocarbonylation of alkenes can potentially be achieved through cooperative Pd/Cu catalysis. Then, valuable β-boryl ketones can be produced from readily available substrates directly and effectively.

To test the viability of our design on selectivity-reversed borocarbonylation of alkenes, N-(quinolin-8-yl)pent-4-enamide (1a), iodobenzene (2a), and bis(pinacolato)diboron (B$_2$pin$_2$) were chosen as model substrates for systematic studies. As shown in Table 1, by using IMesCuCl and Pd(TFA)$_2$ as the co-catalyst system, xantphos L1 as the ligand and K$_2$CO$_3$ as the base, the desired product 3a was obtained in 29% yield. Other ligands and bases were also investigated, and the results are summarized in Table 1. The optimization of the reaction conditions is shown in Table 1.

**Table 1** Optimization of the reaction conditions

| Entry | [Pd] | Ligand | Cu | Base | Yield of 3a (%) |
|-------|------|--------|----|------|----------------|
| 1     | Pd(TFA)$_2$ | L1 | IMesCuCl | K$_2$CO$_3$ | 29 |
| 2     | Pd(OAc)$_2$ | L1 | IMesCuCl | K$_2$CO$_3$ | 34 |
| 3     | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | IMesCuCl | K$_2$CO$_3$ | 41 |
| 4     | [Pd(cinnamyl)Cl]$_2$ | L1 | IMesCuCl | K$_2$CO$_3$ | 36 |
| 5     | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | IPrCuCl | K$_2$CO$_3$ | 0 |
| 6     | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | CuCl | K$_2$CO$_3$ | 33 |
| 7     | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | CuBr | K$_2$CO$_3$ | 41 |
| 8     | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | Cu | K$_2$CO$_3$ | 50 |
| 9     | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L2 | Cu | K$_2$CO$_3$ | 38 |
| 10    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L3 | Cu | K$_2$CO$_3$ | 47 |
| 11    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L4 | Cu | K$_2$CO$_3$ | 0 |
| 12    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L5 | Cu | K$_2$CO$_3$ | 0 |
| 13    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L6 | Cu | K$_2$CO$_3$ | <2 |
| 14    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L7 | Cu | K$_2$CO$_3$ | 10 |
| 15    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L8 | Cu | K$_2$CO$_3$ | 12 |
| 16    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | Cu | KHCO$_3$ | 58 (51)$^b$ |
| 17    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | Cu | K$_2$HPO$_4$ | 26 |
| 18    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | Cu | NaHCO$_3$ | 0 |
| 19    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | Cu | NaO$_2$Bu | 11 |
| 20$^c$| [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L1 | Cu | KHCO$_3$ | <5 |
| 21    | [Pd($\eta^5$-C$_3$H$_5$)Cl]$_2$ | L7 | Cu | KHCO$_3$ | 40 |

$^a$ All reactions were carried out on a 0.1 mmol scale with alkene (0.1 mmol) and aryl iodide (2.0 equiv.). Yields were determined by $^1$H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. $^b$ Isolated yield. $^c$ Xantphos (10 mol%).
base at 70 °C under 10 bar of CO for 18 h, the desired product 3a can be successfully obtained in 29% yield (Table 1, entry 1). In the reaction mixture, a small amount of N-phenyl- N-(quinolin-8-yl)pent-4-enamide can be detected due to copper promoted C–N bond coupling. In the testing of palladium precursors, allylpalladium chloride dimer proved to be the best palladium

Table 2  Substrate scope for the synthesis of β-boryl ketones

| Substrate | Yield (%) | Scope of aryl iodides
|-----------|-----------|----------------------|
| Ar        |           |                      |
| Me        | 51%       | 3a                   |
| Me        | 66%       | 3b                   |
| Me        | 53%       | 3c                   |
| Me        | 70%       | 3d                   |
| Bu        | 73%       | 3e                   |
| Me        | 56%       | 3f                   |
| Me        | 41%       | 3g                   |
| Me        | 57%       | 3h                   |
| Bu        | 61%       | 3i                   |
| Me        | 69%       | 3j                   |
| Me        | 42%       | 3k                   |
| Me        | 60%       | 3l                   |
| Me        | 81%       | 3m                   |
| Me        | 75%       | 3n                   |
| Me        | 49%       | 3o                   |

| Substrate | Yield (%) | Scope of olefins
|-----------|-----------|---------------------|
| Ar        |           |                      |
| Ph        | 73% (dr = 1:1) | 4a                  |
| Ph        | 62% (dr = 1:1) | 4b                  |
| Ph        | 54% (dr = 3:2) | 4c                  |
| Pr        | 73% (dr = 1:1) | 4d                  |
| Pr        | 65% (dr = 1:1) | 4e                  |
| Pr        | 60% (dr = 1:1) | 4f                  |
| Pr        | 57% (dr = 1:1) | 4g                  |
| Pr        | 42% (dr = 1:1) | 4h                  |
| Ph        | 64% (dr = 1:1) | 4i                  |
| Ph        | 48% (dr > 20:1)| 4j                  |

| Substrate | Yield (%) | Scope of complexed molecules
|-----------|-----------|-------------------|
| Ar        |           |                    |
| Ar        | 67%       | 5a                 |
| Ar        | 45%       | 5b                 |
| Ar        | 51%       | 5c                 |
| Ar        | 57%       | 5d                 |
| Ar        | 43%       | 5e                 |
| Ar        |            |                    |

All reactions were carried out on a 0.1 mmol scale. Alkenes (0.1 mmol), aryl iodides (2.0 equiv.), B2pin2 (1.5 equiv.), CuI (10 mol%), [Pd(η⁵-C₅H₅)Cl]₂ (2.5 mol%), xantphos (5 mol%), KHCO₃ (2.0 equiv.), CO (10 bar), and DMSO (0.2 M) were stirred at 70 °C for 18 h. The dr value given was determined by ¹H NMR.
catalyst for this reaction, affording 3a in 41% yield (Table 1, entries 1–4). Subsequently, we evaluated the influence of copper precursors. The NHC ligand is proved to be unnecessary as copper iodide can give the target product in 50% yield (Table 1, entries 5–8). Various phosphine ligands were studied to examine ligand effects. Monodentate phosphine ligands failed to deliver the desired product 3a (for details, see the ESI†) and tend to generate the by-product β-aminoketone. Xantphos was found to be superior to the other tested bidentate ligands (Table 1, entries 9 and 10). Commonly used chiral ligands failed to exert any chiral induction (Table 1, entries 11–15). One possibility is that the AQ group was coordinated to palladium at the beginning of the reaction. In the testing of bases, to our delight, weaker base KHCO3 can provide 58% yield of the final product (Table 1, entries 16–19). Increasing the loading of xantphos to 10 mol% inhibited the reaction, indicating that xantphos only coordinates with palladium (Table 1, entry 20). Notably, other directing groups DG2–DG7 had no positive effect on the reaction outcome. Using N-phenyl-N-(quinolin-8-yl)pent-4-enamide as the substrate could not give any carbonylation product.

With the optimized reaction conditions in hand, we examined the scope of this selectivity-reversed borocarbonylation with various unactivated alkenes and aryl iodides toward the synthesis of β-boryl ketones (Table 2). Aryl iodides spanning a range of electronic properties were tested for this transformation (3a–3h). Functional groups such as ether (3i and 3j), pyrrole (3l), thiophene (3m and 3n), indole (3o), morpholine (3p), Bpin (3q) and highly lipophilic group OCF3 (3k) were all compatible with the reaction conditions to produce the target products in moderate to excellent yields. Bromobenzene and 4-bromobenzotrifluoride were also tested in place of iodo-benzene, and no desired product could be detected even at increased reaction temperature. Phenyl triflate and alkenyl halides and triflate were tested with the model alkenes as well, and no reaction occurred. However, 87% yield of cinnamic acid was obtained when (E)-(2-bromovinyl)benzene was tested under our standard conditions. Subsequently, we evaluated a series of aliphatic alkenes in the reaction with 2-iodothiophene as a representative electrophile. When α-monosubstituted 4-ene-noic amides with alkyl, cyclopropyl, benzyl or phenyl substitution were tested, the borocarbonylation reaction occurred smoothly and gave the desired product (4a–4h) in moderate to excellent yields, albeit with low diastereoselectivity. Notably, monocarbonylative coupling occurred selectively at the γ,δ-C=C bond even when there are two C=C bonds in the amide substrates (4i and 4j).

To demonstrate the synthetic utilities of the obtained borocarbonylation products, a series of further synthetic transformations of the β-boryl ketones were performed (Scheme 2).
From a practical point of view, the reaction can be easily performed on the gram-scale and gave the target product 3m in 67% yield. β-Hydroxyl ketone 6a (CCDC: 2079475;† determined by X-ray crystallography and the ORTEP drawing with 50% thermal ellipsoids) was produced in 95% yield by oxidation of the parent β-boryl ketone 3a. Furthermore, the C–B bond can be easily converted into a C–N bond, affording β-aminoketone 6b in 60% yield. Upon the reduction reaction of 3m with NaBH₄, the corresponding reduced oxaborole amide 6c could be isolated in 70% yield. Finally, a two-step transamination process was performed to remove the AQ group.16

To gain some insight into the mechanism of this selectivity-reversed borocarbonylation of alkenes, several control experiments were performed. The target product 3a was not formed, instead byproduct 6b was obtained in 40% yield, in the case without xantphos. Possible explanations for this result are: (i) the bidentate directing group AQ increases the stability of Pd(ii) species and promotes the carbonylation step; (ii) the role of xantphos is to coordinate to C(sp³) species and promotes the carbonylation step; (iii) the role of Pd(II) species a er the CO insertion step, the acyl-PdII species a er its α–H elimination followed by hydroboration could be involved as well. However, we believe the direct reaction between palladium and copper intermediates is the main one for this procedure due to the proven importance of the AQ group and the known achievements of copper-catalyzed hydroboration of enones, even with enantioselective versions.17

On the basis of the above results and related literature studies,5,11–14 a possible reaction pathway is proposed (Scheme 4). Initially, the AQ directing group coordinates with Pd⁰, which produces the active AQ-Pd⁰ catalyst I. This is followed by oxidative addition to aryl iodides to generate PdII species II, and then by base promoted iodine dissociation to form complex III. After the CO insertion step, the acyl-PdIII species IV coordinates with the alkene and undergoes migratory insertion to generate C(sp³)–PdIII intermediate V, which is stabilized by the xantphos ligand and AQ directing group. Subsequently, C(sp³)–PdIII complex V reacts especially with CuBpin to give the desired product β-boryl ketone and regenerate the Pd⁰ complex. Finally, ligand exchange of Pd⁰Lₐ regenerate AQ-Pd⁰ I for the next catalytic cycle. Additionally, another minor pathway that involves the carbonylative Heck reaction to give an enone derivative, followed by its hydroboration to give the final product could be included as well.

In summary, a novel Pd/Cu catalyzed amide-directed selectivity-reversed borocarbonylation for the selective synthesis of β-boryl ketones from terminal alkenes has been developed. Various aryl iodides and aliphatic alkenes were transformed into the desired β-boryl ketones in moderate to excellent yields. In this catalyst system, the assistance from the AQ directing group is essential for successful reaction design.

Author contributions

XFW supervised this project and revised the manuscript. FPW performed all the experiments and prepared this draft.

Conflicts of interest

There are no conflicts to declare.

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