Synthesis of 1,1-diboronate esters by cobalt-catalyzed sequential hydroboration of terminal alkynes+

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A cobalt complex of iminopyridine-oxazoline catalyzes sequential hydroboration of alkyl and aryl alkynes with pinacolborane to form 1,1-diboronate esters. The reactions proceed under mild conditions with high yields, high regioselectivity, and wide functional group tolerance. The synthetic utility of 1,1-di(boronates) is demonstrated by chemoselective monoarylation and stepwise diarylation through palladium-catalyzed Suzuki–Miyaura coupling reactions.

1,1-Organodiboronate esters are valuable synthetic intermediates for preparation of multifunctionalized molecules. Such 1,1-diboryl compounds can be used as coupling reagents for C–C bond formations through Suzuki–Miyaura reactions. Advantages of 1,1-diborate esters over other 1,1-organodimetallic nucleophiles include their unique stability, operational simplicity, and non-toxicity. In addition, the boronate moiety can be readily converted into alcohol, amine, and other functional groups. Conventional, non-catalytic methods for synthesis of 1,1-diboronate esters involve reactions of lithiated reagents with bis(pinacolato)diboron or hydroboration of terminal alkynes with a mixture of trichloride and trialkylsilane, followed by treatment with a suitable diol reagent. However, these methods suffer from poor functional-group compatibility, formation of waste inorganic salts, and multiple synthetic sequences. Recently, transition-metal-catalyzed methods have gained attention. For example, copper-catalyzed diborylation of 1,1-dibromoethane with bis(pinacolato)diboron formed 1,1-diborylethane in moderate yield. Hall and Yun reported copper-catalyzed enantioselective hydroboration of alkenylboron compounds with a 1,8-naphthalenediaminatoboryl substituent, furnishing 1,1-diboronate esters with high optical purity. Hartwig reported iridium-catalyzed diborylation of benzylc–H bonds directed by a hydrosilyl group to form 1,1-benzyl(diboron esters. Platinum-catalyzed or metal-free carbene insertions into B–B bonds of diboron compounds have also been developed for preparation of 1,1-diboronate esters.

Due to high atom economy, ease of access of starting materials, and mild reaction conditions, the catalytic sequential hydroboration of terminal alkynes is a synthetically useful approach to 1,1-diboronates. However, the sequential, regioselective hydroboration of the alkenylboronate intermediates are rare, and most reactions generate a regioisomeric mixture. In 2009, Shibata reported a rhodium-catalyzed sequential hydroboration of alkynes with pinacolborane (HBpin) to afford 1,1-diboranes with high regioselectivity, but in low to moderate yields; monoborylalkanes are formed in noticeable yields (12–24%) as the side-products via reduction of the alkenylboronate intermediates (Scheme 1a). More recently, Yun reported a copper(i)-catalyzed selective sequential hydroboration of alkyll alkynes with HBpin to form...
1,1-diboronic esters, but reactions of aryl alkynes yield monoboryl and diboryl mixtures (Scheme 1b).16

Driven by our interest in developing base–metal catalyst systems for alkene hydrofunctionalizations,17 recently we and Lu independently reported iminopyridine-oxazoline (IPO) cobalt17e,18 and iron17e,19 complexes for asymmetric hydroboration/hydrosilylation of 1,1-disubstituted alkenes and ketones. Herein, we report that an IPO cobalt complex catalyzes regioselective sequential hydroboration of alkyl and aryl alkynes (Scheme 1c). Most reactions occur under mild conditions with high isolated yields. The method exhibits a broad substrate scope and wide functional group tolerance.

We commenced our studies by examining the reaction of 1-hexyne (1a) with HBpin (Table 1). When using 3 mol% of (IPO)FeBr2 (4a) as the catalyst precursor, NaBHEt3 as the activator, the reaction of 1a with 2 equiv. of HBpin in THF at room temperature after 12 h gave 23% of the desired dual hydroboration product 2a, 28% of trans-monoborylalkene (3α), and 42% of monoborylalkane (3β) (entry 1). However, using the cobalt analogue (IPO)CoCl2, 4b as the precatalyst led to the formation of 2a with very high selectivity and yield (96%) (entry 2). A control experiment with the catalyst activator, but without the precatalyst only gave 4% of 3α (entry 3). To evaluate the role of the ligand, reactions using the related cobalt complexes with bis(imino)pyridine (4c) and bis(oxazoline)pyridine (4d) ligands have been carried out. The former gave the desired product in low yield (11%), along with 39% of 3α and 43% of 3β (entry 5), whereas the latter gave 89% of 2a and 5% of 3β (entry 6). The addition of the catalyst activator is essential for the catalysis (entry 4), but it is not limited to NaBHEt3. The reaction using MeLi as the activator afforded the dual hydroboration product in a yield close to that using NaBHEt3. The reactions proceeded smoothly in other solvents, such as toluene, n-pentane, and diethyl ether, albeit with relatively low yield compared to that in THF (entries 7–10).

We next studied the scope and limitation of the protocol with (IPO)CoCl2, 4b as the catalyst precursor, NaBHEt3 as the activator, and THF as the solvent (Table 2). Terminal aliphatic alkynes all reacted with HBpin to form the diboryl products selectively. Simple alkynes with linear and branched alkyl groups were converted to the corresponding 1,1-diboronate esters in high yields (entries 1 and 2). Alkynes containing two different aliphatic terminal alkynes also occurred efficiently. Substrates containing both electron-donating and -withdrawing substituents, such as alkyl (2n and 2o), methoxy (2p), fluoro (2q), and dimethylamino (2r) groups, afforded the 1,1-diboryl products in high isolated yields. Naphthyl- (2s), thienyl- (2t), and ferrocenyl-substituted acetylenes (2u) are suitable substrates for sequential hydroboration with exclusive terminal selectivity.

Reactions of terminal aryl alkynes also occurred efficiently. In situ monitoring of the cobalt-catalyzed reaction of 1-hexyne (1a) with 2 equiv. of HBpin provided insight into the catalytic process. As shown in Fig. 1, the reaction at the early stage gave 2a in low yield, but a substantial amount of 3α (e.g., 15 min, 67% of 3α, 8% of 2a). The intermediate 3α was gradually converted to 2a over the course of the reaction. The transform-
ation was nearly complete in 3 h, furnishing 2a in 91% yield. Except for 2a, 3α, and a trace amount of 3β (<3%), no other products were detected by GC during the whole process. The results indicate that the reaction occurs via formation of trans-monoborylalkene (3α) as the intermediate, which undergoes subsequent hydroboration to give the 1,1-diboryl product.

The synthetic utility of 1,1-diborate esters was demonstrated by their applications to palladium-catalyzed Suzuki–Miyaura coupling reactions. Seminal work by Shibata showed that the adjacent boron atom in 1,1-diborylalkanes has a beneficial effect on the transmetallation step for coupling reactions. Using Pd[P(tBu)₃]₂ as the catalyst and KOH as the base, we found that 1,1-diboryl compound 2j coupled selectively with various aryl bromides at room temperature, giving the monoarylation products in high yields (Table 3). O- and S-containing benzoheterocyclic (5e–5g) and heterocyclic (5h) bromides are also favorable substrates under the reaction conditions. Noteworthily, while the reaction with a p-F-substituted aryl bromide gave the benzyl boronate 5b in 86% isolated yield, under otherwise identical conditions, the coupling with a p-CF₃-substituted aryl bromide afforded 80% of the proteodeborylation product 6a. Furthermore, with 4-bromo-2-methylpyridine as the substrate, a similar transformation involving the combination of cross coupling and proteodeborylation occurred to form 6b in 89% yield.

In addition, using a protocol developed by Crudden, the isolated secondary benzylic boronate esters could undergo

Table 2 Cobalt-catalyzed sequential hydroboration of various terminal alkynes with HBpin

| R     | HBpin | THF, rt | 3 h | 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2l, 2m, 2n, 2o, 2p, 2q, 2r, 2s, 2t, 2u, 2v | Yield (%) |
|-------|-------|---------|-----|--------------------------------------|-----------|
|       | 2 eqv |         |     |                                      |           |
| 1     | 2 eqv |          |     |                                      |           |
| 2a    | 2 eqv |          |     |                                      |           |
| 2b    | 2 eqv |          |     |                                      |           |
| 2c    | 2 eqv |          |     |                                      |           |
| 2d    | 2 eqv |          |     |                                      |           |
| 2e    | 2 eqv |          |     |                                      |           |
| 2f    | 2 eqv |          |     |                                      |           |
| 2g    | 2 eqv |          |     |                                      |           |
| 2h    | 2 eqv |          |     |                                      |           |
| 2i    | 2 eqv |          |     |                                      |           |
| 2j    | 2 eqv |          |     |                                      |           |
| 2k    | 2 eqv |          |     |                                      |           |
| 2l    | 2 eqv |          |     |                                      |           |
| 2m    | 2 eqv |          |     |                                      |           |
| 2n    | 2 eqv |          |     |                                      |           |
| 2o    | 2 eqv |          |     |                                      |           |
| 2p    | 2 eqv |          |     |                                      |           |
| 2q    | 2 eqv |          |     |                                      |           |
| 2r    | 2 eqv |          |     |                                      |           |
| 2s    | 2 eqv |          |     |                                      |           |
| 2t    | 2 eqv |          |     |                                      |           |
| 2u    | 2 eqv |          |     |                                      |           |
| 2v    | 2 eqv |          |     |                                      |           |

* Reaction conditions: 1 (0.5 mmol), HBPin (1.0 mmol), 4b (3 mol%), and NaBHEt₃ (6 mol%) in THF (2 mL) at rt. Isolated yields. With 3.0 mmol HBPin.

Fig. 1 Profile of sequential hydroboration of 1-hexyne (1a) with 2 equiv. of HBPin catalyzed by 3 mol% 4b and 6 mol% NaBHEt₃ in THF at room temperature.

Table 3 Coupling of 1,1-diborate 2j with aryl bromides and the subsequent coupling with aryl iodides

| ArBr | 1 ArBr | 5 mol % Pd[P(tBu)₃]₂ | 2 KOH | 3 PPh₃ | 1.5 Ag₂O | 1 ArI | 5 mol % Pd₂(dba)₃ | 2 KOH | 3 PPh₃ | 1.5 Ag₂O | 1 ArI' | 5 mol % Pd₂(dba)₃ | 2 KOH | 3 PPh₃ | 1.5 Ag₂O | 1 ArI' |
|------|--------|----------------------|-------|--------|----------|-------|------------------|-------|--------|----------|-------|------------------|-------|--------|----------|-------|
| Ph   | Ph     | 90%                  |       |       |          |       | Ph               |       |       |          |       | Ph                |       |       |          |       |
| 5a   | 90%    |                      |       |       |          |       | 5c               | 91%   |       |          |       | 5c               | 91%   |       |          |       |
| 5b   | 80%    |                      |       |       |          |       | 5e               | 86%   |       |          |       | 5e               | 86%   |       |          |       |
| 5d   | 89%    |                      |       |       |          |       | 5f               | 89%   |       |          |       | 5f               | 89%   |       |          |       |
| 5g   | 86%    |                      |       |       |          |       | 5h               | 56%   |       |          |       | 5h               | 56%   |       |          |       |
| 5h   | 56%    |                      |       |       |          |       | 6a               | 80%   |       |          |       | 6a               | 80%   |       |          |       |
| 5b   | 80%    |                      |       |       |          |       | 6b               | 89%   |       |          |       | 6b               | 89%   |       |          |       |
| 7a   | 74%    |                      |       |       |          |       | 7b               | 75%   |       |          |       | 7b               | 75%   |       |          |       |
| 7c   | 49%    |                      |       |       |          |       | 7c               | 49%   |       |          |       | 7c               | 49%   |       |          |       |

* Reaction conditions: 2j (0.22 mmol), ArBr (0.2 mmol), Pd[P(tBu)₃]₂ (5 mol%), and KOH aq. (40 µL, 10 M in H₂O) in dioxane (1 mL) at RT. Isolated yields. * Reaction conditions: 5a (0.2 mmol), ArI (0.24 mmol), Pd₂(dba)₃ (5 mol%), PPh₃ (0.2 mmol), and Ag₂O (0.3 mmol) in dioxane (1 mL) at 90 °C. Isolated yields. * Carried out on 0.5 mmol scale.
subsequent cross couplings. For example, the reactions of 5a with aryl iodides catalyzed by Pd2(dbal)2/PPh3 in the presence of Ag2O afforded the diarylation products (7a–c) in useful yields. Thus, the sequence of dual hydroboration and two-step cross coupling reactions provides a synthetically efficient approach to diarylmethane derivatives from simple alkynes.

In summary, we have developed a cobalt catalyst system for selective synthesis of 1,1-diboronates from terminal alkyl and aryl alkenes. Featuring the use of low-cost base–metal catalyst, 100% atom economy, mild reaction conditions, high conversion, wide substrate scope, and broad functional group compatibility, the cobalt-catalyzed alkyne sequential hydroboration could be an attractive route to 1,1-organodiborate esters. We have also demonstrated that the dual hydroboration products are useful synthetic intermediates for chemoselective Suzuki–Miyaura coupling reactions.

Conflict of Interest The authors declare no competing financial interest.

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20 Using aryl iodides as the electrophiles, NaOH as the base, THF/H2O as the solvent, Hartwig and co-workers showed that cross coupling with 1,1-benzyldiboronate esters was accompanied by protodeborylation. Also see ref. 10.

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