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Copper-catalyzed cross-coupling reactions of epoxides with *gem*-diborylmethane: access to γ-hydroxyl boronic esters†

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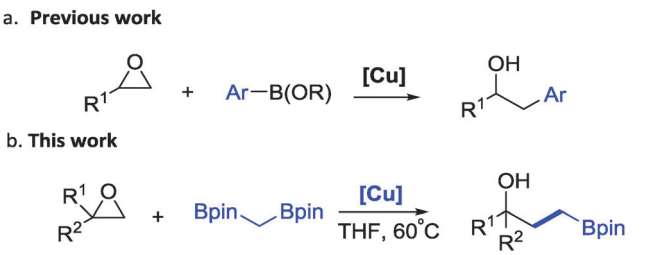
Herein, we describe a novel copper-catalyzed epoxide opening reaction with *gem*-diborylmethane. Aliphatic, aromatic epoxides as well as aziridines are converted to the corresponding γ-pinacolboronate alcohols or amines in moderate to excellent yields. This new reaction provides beneficial applications for classic epoxide substrates as well as interesting *gem*-diborylalkane reagents.

Transition metal catalyzed cross-coupling reactions towards the formation of C(sp^3)–C(sp^3) bonds play a significant role in organic synthesis,[1] whereas, in these reactions, alkyl halides and pseudo-halides were the common electrophiles.[2] As a class of functional electrophiles, epoxide compounds could undergo ring-opening cross-coupling and result in the corresponding β-substituted alcohols.[3] Compared to traditional organometallic reagents[4] (*e.g.* Grignard reagents, organozinc reagents or organolithium reagents), cross-coupling of epoxides with less reactive nucleophiles,[5] in particular organoborons,[6] has received increasing attention. For instance, Doyle has presented nickel-catalyzed Suzuki-type cross-coupling of epoxides with a variety of aryl boronic acids, generating rearranged products *via* a multicatalytic process.[6b] Very recently, our research group realized the copper-catalyzed terminal direct ring-opening coupling of epoxides with aryl boronic esters (Scheme 1a).[6c]

Regarding another research interest of our group, *gem*-diborylalkanes[7] emerged as a kind of valuable compounds due to their ability to introduce a boron group (*i.e.*, Bpin, pinacol boronic esters),[8] in C–C bond-forming reactions, which have more derived possibilities in further organic reactions. Herein, we report our efforts to expand the epoxide ring-opening reaction of our previously reported method to include the *gem*-diborylmethane derivative (Scheme 1b).

This study includes a series of aliphatic and aromatic epoxides which were converted to the corresponding secondary or tertiary γ-hydroxyl boronic esters. In addition, *N*-sulfonyl aziridines were also suitable for this transformation to afford the corresponding γ-amino boronic esters. Thus, this new reaction provides valuable applications for classic epoxide substrates as well as interesting *gem*-diborylalkane reagents.



Scheme 1 Previous studies on transition metal catalyzed Suzuki Miyaura cross-coupling reaction of epoxides.

To verify our initial copper catalyst hypothesis, we started the reaction by choosing 2-(phenoxymethyl)oxirane and diborylmethane as the model substrates at 60 °C in argon. On the basis of previous studies on Cu-catalyzed cross-coupling,[2c,6c,7g,9] various bases were subsequently screened in this reaction, such as NaO^{t}Bu, KO^{t}Bu, K_3PO_4, Cs_2CO_3, LiOMe and LiO^{t}Bu (Table 1, entries 1–8), among which LiO^{t}Bu was found to be the optimal one and afforded product **3a**, albeit in low yield (entry 9). The process occurred smoothly in 1,4-dioxane with CuI as catalyst, loading the expected product **3a** in moderate yield (entry 10). To our delight, in THF, CuI performed well with high effectivity delivering the deborylative alkylation alcohol product in high yield (88% GC yield and 85% isolated yield, entry 11). The decrease of copper catalyst loading to 10 mol% led to a slightly lower yield of 75% (entry 12). Next, a trace product was detected in the absence of CuI (entry 13). Furthermore, the use of CuCl in this transformation afforded lower yield (entry 14). Finally, considering our previously studies on using potassium iodide to promote the cross-coupling reaction,[6c] the iodide source (potassium iodide or Bu_4NI) was also examined, the results indicated that the addition of iodide salt did not accelerate this conversion.

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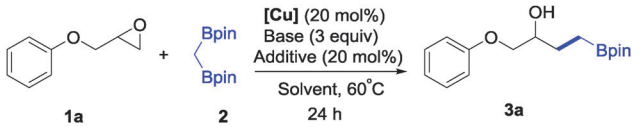
Table 1 Optimization of reaction conditions[a]

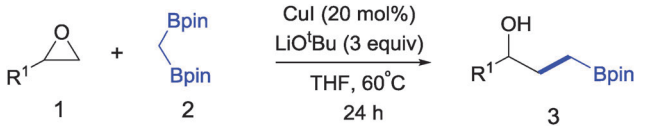


1a 2 3a

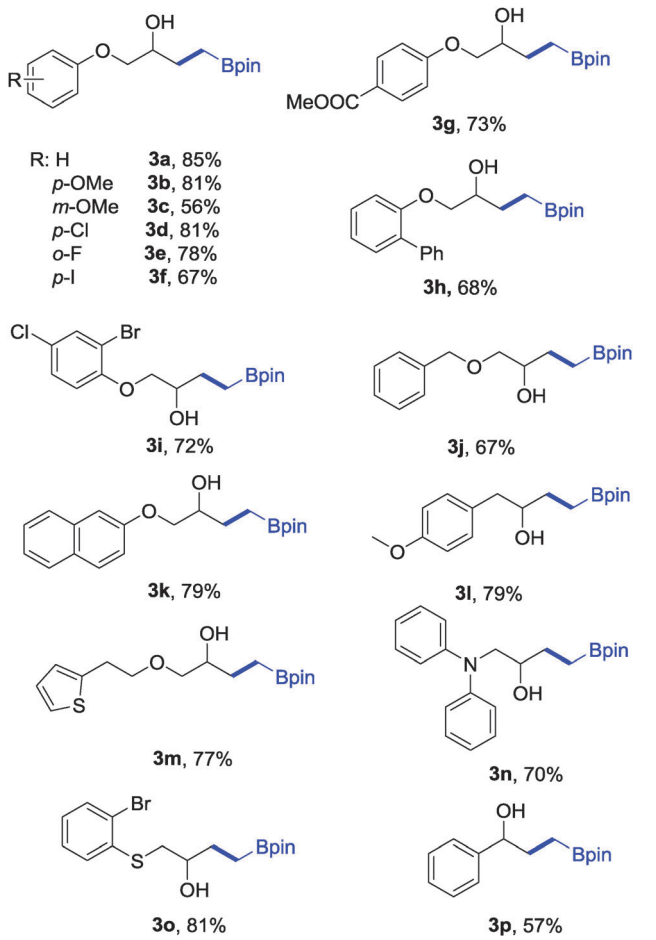
Entry	[Cu]	Base	Additive	Solvent	Yield[a] (%)
1	CuI	NaO^{t}Bu	—	THF	Trace
2	CuI	KO^{t}Bu	—	THF	n.r
3	CuI	NaO^{t}Am	—	THF	Trace
4	CuI	K_3PO_4	—	THF	n.r
5	CuI	Cs_2CO_3	—	THF	n.r
6	CuI	LiOMe	—	THF	Trace
7	CuI	LiO^{t}Bu	—	CH_3CN	Trace
8	CuI	LiO^{t}Bu	—	Toluene	Trace
9	CuI	LiO^{t}Bu	—	DMF	21
10	CuI	LiO^{t}Bu	—	Dioxane	57
11[b,c]	**CuI**	**LiO^{t}Bu**	—	**THF**	**88(85**[d]**)**
12[e]	CuI	LiO^{t}Bu	—	THF	75
13	—	LiO^{t}Bu	—	THF	Trace
14	CuCl	LiO^{t}Bu	—	THF	44
15[f]	CuCl	LiO^{t}Bu	Bu_4NI	THF	Trace
16[g]	CuCl	LiO^{t}Bu	KI	THF	75
17[h]	CuCl	LiO^{t}Bu	KI	THF	16

[a] Reaction conditions: epoxide (0.2 mmol), diborylmethane (2 equiv.), CuI (20 mol%), base (3 equiv.), in 0.5 mL of solvent at 60 °C for 24 h under an Ar atmosphere. The yield was determined by GC using benzophenone as internal standard (average of two GC runs). [b] At 80 °C, GC yield was 63%. [c] Reaction was performed for 18 h, yield = 69%. [d] Isolated yield. [e] CuI (10 mol%) was used. [f] Bu_4NI (20 mol%) was added. [g] KI (20 mol%) was added. [h] KI (1.5 equiv.) was used. DMF = *N*,*N*-dimethylformamide.

Table 2 Scope of epoxides[a,b]



1 2 3



[a] Reaction conditions: epoxides (0.2 mmol), diborylmethane (2 equiv.). CuI (0.04 mmol), LiO^{t}Bu (0.6 mmol), in 0.5 mL of THF at 60 °C for 24 h under an Ar atmosphere. [b] Isolated yield.

With the optimal reaction conditions in hand, various epoxides were subjected to examination of the generality of this new method (Table 2). First, as a series of analogues of **1a**, we continued our new reaction to other protected glycidyl substrates. A variety of aryl (**3a–i**, **k**), benzyl (**3j**) and other alkyl (**3m**) substrates effectively participated in the reaction and afforded the products in good yields. The aromatic ring with the functional groups substituted at the *ortho*-, *meta*-, *para*-position did not affect the reaction results. Next, it is worth noting that the substrates containing aryl chloride and bromide can be obtained smoothly; wherein, these halides are susceptible for further transformations by metal catalysis. Furthermore, this cross-coupling reaction was not limited to glycidyl substrates, and non-glycidyl substrates (**3l**, **3o**, **3n**, **3p**) were also suitable substrates. For instance, a heteroatom substituent on the side chain, such as sulfur (**3o**), and nitrogen (**3n**) were tolerable in this reaction. Finally, we found that the more active aromatic epoxide (**3p**) was the suitable substrate under our standard reaction conditions, which was not tolerated in our previous work on Cu-catalyzed cross-coupling of epoxides with arylboronates.[6c]

Furthermore, 1,1-disubstituted epoxides were also used in this reaction and converted to tertiary alcohol products (Table 3). Aromatic compounds with *para*-substituted (*e.g.* electron rich aromatic PMP **3ba**), naphthyl (**3bb**) and amide (**3bc**) groups were coupled well under standard conditions to give the desired products in moderate to good yields (59–74% yield). The ketal group survived in this transformation and afforded the corresponding product (**3bd**) in a yield of 60%, at a higher reaction temperature (*i.e.* 80 °C). The ring-opening cross-coupling of these compounds showed identical terminal-selectivity to our previous studies.[6c] However, 1,2-disubstituted epoxides did not afford the desired product.

The generation of alkylboronic ester derivatives, in particular γ-pinacolboronate amines, is important in organic synthesis, which have numerous transformations and pharmaceutical applications.[10] To our delight, under the standard reaction conditions, 2-butyl-1-tosylaziridine converted smoothly and provided the corresponding amine (**3ca**) in good yield (Scheme 2, 79% yield).

Due to the importance of chiral compounds in pharmaceutical chemistry, additional application of this reaction has been achieved for (*S*)-2-((benzyloxy)methyl)oxirane which reacted well with diborylmethane, followed by oxidation step with basic H_2O_2 at lower temperature,[11] to give the 1,3-diol product in high yield with fully maintained configuration as illustrated in Scheme 3.

In conclusion, we have developed the first copper-catalyzed ring opening coupling of epoxides with *gem*-diborylmethane

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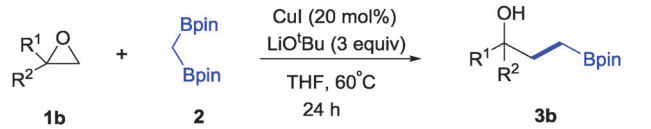
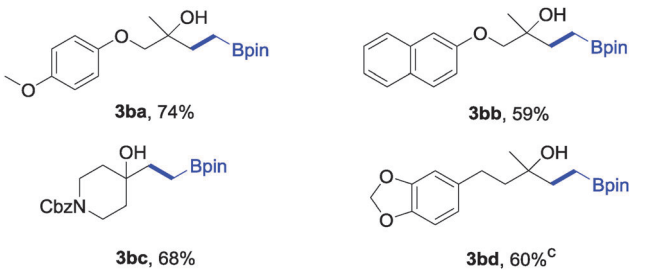
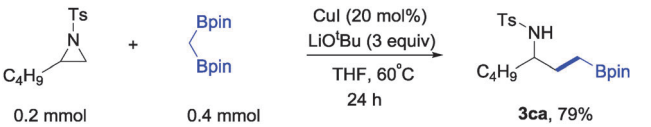
Table 3 Scope of 1,1-disubstituted epoxides[a,b]

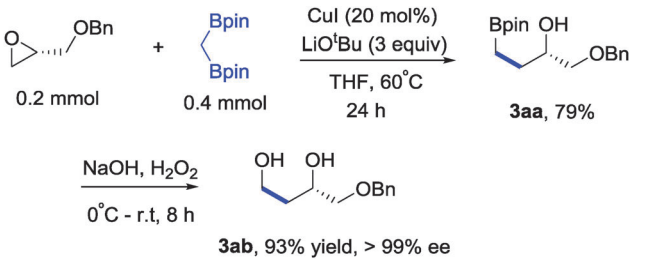




[a] Reaction conditions: epoxides (0.2 mmol), diborylmethane (2 equiv.). [b] Isolated yield. [c] The reaction was performed at 80 °C.



Scheme 2 Copper-catalyzed cross-coupling of aziridine derivatives.



Scheme 3 Copper-catalyzed cross-coupling of chiral epoxides.

reagents. In addition, *N*-sulfonyl aziridine could also been converted in this transformation. This newly developed reaction provided straightforward access to γ-hydroxyl boronic esters which are important synthetic intermediates in C–C bond-forming reactions. Furthermore, this strategy extended the applications of classic organic synthon epoxides as well as novel *gem*-diborylmethane reagents. The mechanism study for this reaction and transformation of more challenging substituted bis(boronates) are currently underway in our laboratory.

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