Copper-Catalyzed Cross-Coupling Reactions of Epoxides with gem-Diborylmethane: Access to γ-hydroxyl Boronic Esters

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Copper-Catalyzed Cross-Coupling Reactions of Epoxides with *gem*-Diborylmethane: Access to γ-Hydroxyl Boronic Esters

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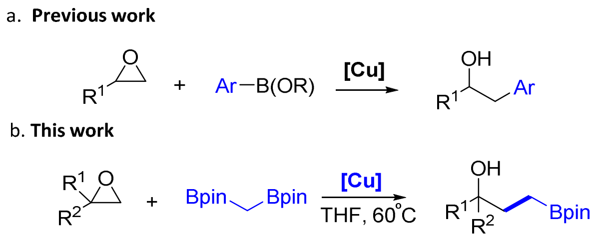
Herein, we describe a novel copper-catalyzed epoxides opening reaction with *gem*-diborylmethane. Aliphatic, aromatic epoxides as well as aziridines are converted to corresponding γ-pinacolboronate alcohols or amines in moderate to excellent yields. This new reaction provides beneficial application for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

Transition metal catalyzed cross-coupling reactions towards C(sp^3)–C(sp^3) bonds formation play a significant role in organic synthesis,[1] whereas, in these reactions, alkyl halides and pseudohalides were the common electrophiles.[2] As a class of functional electrophiles, epoxide compounds could undergo ring-opening cross-coupling and result to 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 variety of aryl boronic acids, generating rearranged product via 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 to another research interest of our group, *gem*-diborylalkanes[7] are emerged as a kind of valuable compounds due to their ability of introducing a boron group (i.e., Bpin, pinacol boronic esters),[8] while C-C bond-forming, which have more derived possibilities in further organic reaction. Herein, we report our efforts to expand the epoxides ring-opening reaction of our previously reported method to include *gem*-diborylmethane derivative (Scheme 1b).

This study includes a series of aliphatic and aromatic epoxides which were converted to secondary or tertiary corresponding 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 application for classic epoxide substrates as well as interesting *gem*-diborylalkane reagents.



Scheme 1 Previous works 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 under argon. On the basis of previous works about 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 the 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 highly effective delivered the deborylative alkylation alcohol product in high yield (88% GC yield and 85% isolated yield, entry 11). The decreasing of copper catalyst loading to 10 mol % leaded to a slightly lower yield of 75% (entry 12). Next, 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 of our previously studies 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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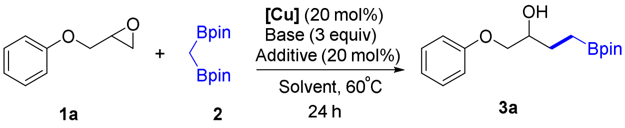
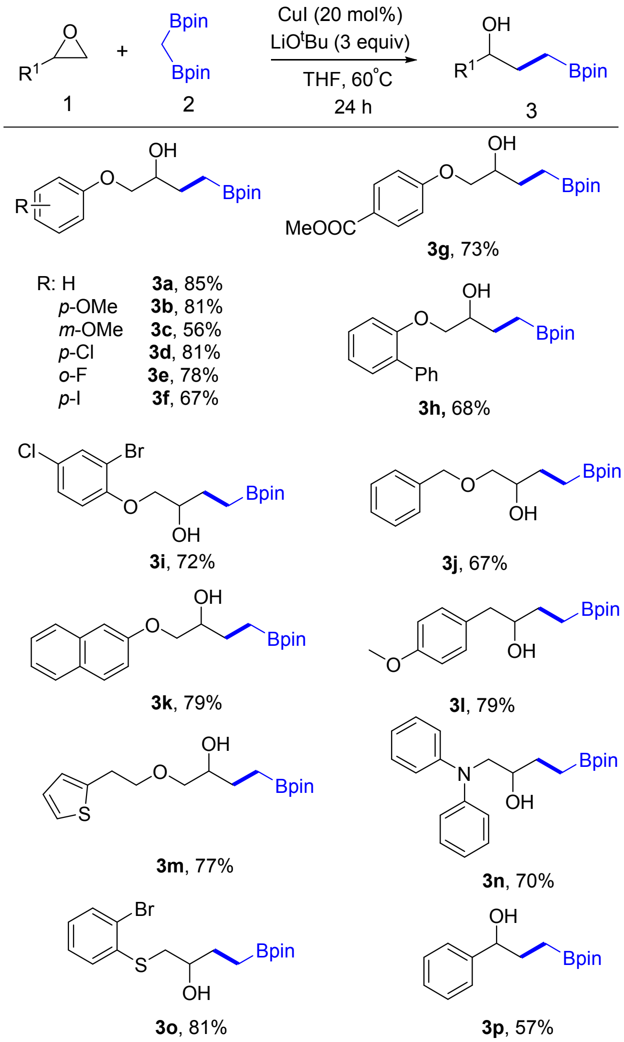
Table 1 Optimization of Reaction Conditions [a]



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 Ar atmosphere. The yield was determined by GC using benzophenone as internal standard (average of two GC runs). [b] At 80 °C GC yield obtained 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 substrates cross coupling [a, b]



[a] Reaction conditions: epoxides (0.2 mmol), diborylmethane (2 equiv.). CuI (0.2 mmol), LiO^{t}Bu (0.3 mmol), in 0.5 mL of THF at 60 °C for 24 h under Ar atmosphere. [b] Isolated yield.

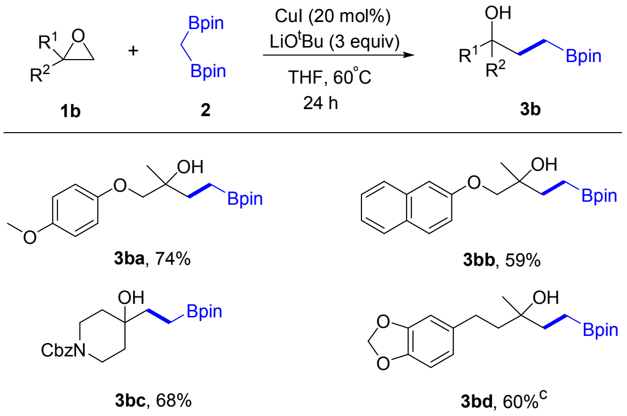
With the optimal reaction conditions in hand, various epoxides were subjected to examine the generality of this new method (table 2). First, as a series of analogues of **1a**, we continued our new reaction to other protected glycidyl substrates. A variety of aryl (**3a**-**i**, **k**), benzyl (**3j**) and other alkyl (**3m**) substrates were 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, non-glycidyl substrates (**3l**, **3o**, **3n**, **3p**) were also suitable substrates. For instance, heteroatom substituent on the side chain, such as sulfur (**3o**), and nitrogen (**3n**) were tolerable in this reaction. Finally, we found the more active aromatic epoxide (**3p**) was suitable substrate in our standard reaction condition, which was not tolerated in our previous work about Cu-catalyzed cross-coupling of epoxides with arylboronates.[6c]

Furthermore, 1,1-disubstituted epoxides were also conducted 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**) group were coupled well under standard condition 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 yield of 60%, with 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.

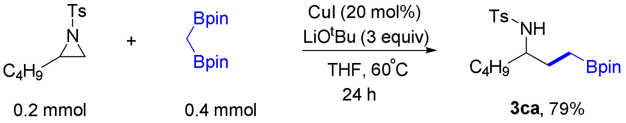
The generation of alkylboronic ester derivatives, in particular γ-pinacolboronate amines is important in organic synthesis, which have numerous transformations and pharmaceutical applications.[10] To our delight, under the standard reaction condition, 2-butyl-1-tosylaziridine converted smoothly and provided 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 achieved for (S)-2-((benzyloxy)methyl)oxirane which reacted well with diborylmethane, followed by oxidation step with basic H_2O_2 at

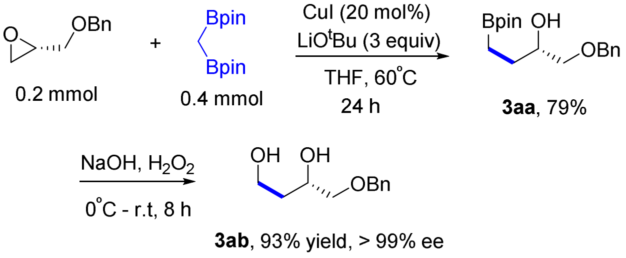
Table 3 Scope of 1, 1-disubstituted epoxides [a, b]



[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 epoxide.

lower temperature,[11] to give the 1,3-diol product in high yield with fully maintained of configuration as illustrated in Scheme 3.

In conclusion, we have developed the first copper-catalyzed ring opening coupling of epoxides with *gem*-diborylmethane 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. Mechanism study for this reaction and transformation of more challenging substituted bis(boronates) are currently underway in our laboratory.

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