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Copper-catalyzed/mediated borylation reactions of epoxides with diboron reagents: access to β-hydroxyl boronic esters†

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We report the first copper-catalyzed/mediated borylative ring opening reaction of epoxides. This process represents a direct borylative $C(sp^3)$ -O bond cleavage of terminal epoxide substrates with commercially available diboron reagents. A wide range of epoxides with different functional

able diboron reagents. A wide range of epoxides with different functional groups are involved, and were subsequently converted to the corresponding β -hydroxyl boronic esters smoothly. Moreover, the ring opening product β -pinacol boronate alcohol provided a more beneficial approach for the formation of C–C and C–N bonds.

Alkylboronates are versatile synthetic intermediates in organic synthesis and have exhibited useful applications in materials science and medicinal chemistry.1 Due to the stability and availability of diboron reagents, numerous methods have been developed for utilizing them as efficient borylative reagents.² On the other hand, the ring opening reaction of epoxides, as a classic reaction, provided efficient access to the corresponding β -substituted alcohols.³ The combination of the epoxide ring opening reaction with diboron reagents would be beneficial for the synthesis of alcohols containing boron atoms. To date, transition-metal-catalyzed borylative ring opening of vinyl substituted epoxides with diboron reagents has been reported.⁴ As a pioneer work, Pineschi realized nickel-catalyzed borylative ring opening of vinyl epoxides.^{4c} Tortosa reported the first Cu(1)-catalyzed borylation with allylic epoxides, generating allylboronate intermediates, followed by an oxidation step to give 1,4-diols (Scheme 1a).^{4d} However, the borylation of epoxides has not been well studied.

Our research group recently reported a copper-catalyzed epoxide ring opening cross-coupling reaction with a *gem*-diborylmethane reagent (Scheme 1b).⁵ In light of our continued interest in copper-catalyzed ring opening reactions of epoxides,⁶ we herein describe

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Previous works



Scheme 1 Previous studies on transition-metal-catalyzed borylation and cross-coupling reaction of vinyl- and classic epoxides.

the first copper-catalyzed ring opening C–B forming reaction⁷ of epoxides with diboron reagents (Scheme 1c). Through this method, a series of epoxide substrates were successfully converted to the corresponding β -hydroxyl boronic esters. In addition, chiral epoxides were employed in this reaction, which were then converted to 1,2-diols *via* an additional oxidation step. Furthermore, the Suzuki–Miyaura cross-coupling of β -hydroxyl boronic esters with aryl halides was conducted to generate a variety of aryl-substituted secondary alcohols. Regardless of the achievements mentioned above, a Chan–Lam–Evans cross-coupling reaction was performed with our product to give arylated amine alcohols as well.

We started the reaction with 2-(phenylmethyl)oxirane (1a) and bis(pinacolato)diboron B_2pin_2 (2a) as model substrates (as shown in Table 1). The initial experiments were inspired by our previous studies.^{5,6,8} This reaction was performed with several copper catalysts, using LiO^tBu as the base and THF as the solvent. The utilization of CuCl and CuBr led to slight improvement of this reaction, respectively (entries 1 and 2). For the screen of bases, we found that MO^tBu (M = Na or K) and

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Table 1 Optimization of reaction conditions^a



1	2a	CuCl	LiO ^t Bu	THF	Trace
2	2a	CuBr	LiO ^t Bu	THF	10
3	2a	CuI	NaO ^t Bu	THF	n.r
4	2a	CuI	KO ^t Bu	THF	n.r
5	2a	CuI	LiOMe	THF	Trace
6	2a	CuI	LiO ^t Bu	DMF	Trace
7	2a	CuI	LiO ^t Bu	DME	70
8	2a	CuI	LiO ^t Bu	1,3-Dioxane	52
9	2a	CuI	LiO ^t Bu	EtOAc	34
10	2a	CuI	LiO ^t Bu	Diglyme	55
11	2a	CuI	LiO ^t Bu	THF	85 (82^b)
12^c	2a	CuI	LiO ^t Bu	THF	54
13	2a	—	LiO ^t Bu	THF	n.r
$14^{d,e}$	2a	CuI	LiO ^t Bu	THF	60
15	2b	CuI	LiO ^t Bu	THF	65^{f}
16	2c	CuI	LiO ^t Bu	THF	n.r
17	2d	CuI	LiO ^t Bu	THF	n.r

^{*a*} Standard reaction conditions: epoxide (0.2 mmol), diborane reagent (3 equiv.), CuI (15 mol%), base (3 equiv.), in 1 mL of solvent at 60 °C for 20 h under an Ar atmosphere. The yield was determined by GC (average of two GC runs) using diphenyl methanol as the internal standard. ^{*b*} Yield represents isolated yield after purification by silica gel chromatography. ^{*c*} **2a** (2 eq.) was used with 2 eq. of LiO^{*t*}Bu. ^{*d*} CuI (10 mol%) was used. ^{*e*} CuI (5 mol%) afforded 26%. ^{*f*} Isolated yield. DMF = *N*,*N*-dimethylformamide; DME = 1,2-dimethoxy ethane.

LiOMe afforded unsatisfactory results (entries 3-5). Subsequently, several solvents were screened (entries 6-11). For example, DME gave the desired product in good yield, and among all the solvents THF was found to be the best. Under optimal conditions (CuI and LiO^tBu) (entry 11), the GC yield was found to be 85% with an 82% isolated yield of β-hydroxyl boronic esters (3a). Further experiments were carried out to test the required amount of reagent 2a, and lower yield was obtained when 2.0 equivalents were used (entry 12, see the ESI† for details). With the control experiment (entry 13), it was proven that the copper catalyst was necessary for this reaction. Finally, the loading of the copper catalyst remained the effective factor, wherein decreasing of CuI to 10 and 5 mol% led to 60% and 26% of yield respectively (entry 14). Under our optimal conditions, other diboron reagents were also tested for this reaction (entries 15-17). For instance, neopentylglycolatediboron B₂neop₂ (2b) was used instead of B₂pin₂, and afforded good result, whereas $B_2 \operatorname{cat}_2(2\mathbf{c})$ (Bcat: benzo[d][1,3,2]dioxaborolane) and pinB-Bdan (2d) (Bdan: 2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine) were not suitable for this transformation. The reactivity of these diboron reagents was similar to that involved in the previous studies of borylation of aryl-fluorides, ethers,9 and 2-arylaziridines.7

Table 2 Scope of borylation^{a,b}



^{*a*} Standard reaction conditions: epoxides (0.2 mmol), diborane reagent (3 equiv.), CuI (0.03 mmol), LiO^{*t*}Bu (0.6 mmol), in 1 mL of THF at 60 °C for 20 h under an Ar atmosphere. ^{*b*} Results are an average of two experiments and yield represents isolated yield after purification by silica gel chromatography.

With the optimized conditions in hand, we proceeded to investigate the scope of the borylative opening reaction using a variety of terminal epoxides (Table 2). A series of protected glycidyl epoxides could be converted smoothly in this reaction (Table 2, 3a-3o). The aryl (3c-3g) epoxides can successfully afford the corresponding products in moderate to good yields. This reaction was compatible with various functional groups, including the relatively electron-donating methoxy groups (both at meta- and para-positions), electron neutral (Ph) and electronwithdrawing (CF₃) groups. Besides, heterocyclics such as 3h were tolerated in this reaction. Moreover, substrates (3i-3l) bearing halogen atoms on the aromatic ring can participate in this reaction and afford good yields in this transformation. Other functional groups such as ester (3m, 3n) and secondary terminal alcohol (30) were also compatible under our mild conditions. Meanwhile, non-glycidyl substrates were also included in this reaction, and resulted in the formation of 3p and 3g. Moreover, switching the aryl substituents to amine does not affect the reaction and 3r was obtained in 89% isolated yield. However, styrene oxide and 1,1-disubstituted epoxides were not applicable in this transformation.

Next, we tested the conversion of our product (β -hydroxyl boronic ester) in the Suzuki–Miyaura cross-coupling reaction.¹⁰ To our delight, the arylation reaction of **3a** with aryl halides proceeded to yield products **4a–4d** successfully. Both aryl chloride



Scheme 2 Suzuki–Miyaura cross-coupling of β -hydroxyl boronic ester with arylhalides.

and aryl bromide were suitable substrates for this $C(sp^2)-C(sp^3)$ cross-coupling (as illustrated in Scheme 2).

Several experiments were carried out to confirm the optical purity of our products. For instance, the obtained products of β -hydroxyl boronic esters (**3bb**) of (*S*)-2-((benzyloxy)methyl) oxirane can be converted to 1,2-diols (**3bd**) in 80% yield under basic conditions with H₂O₂ (Scheme 3).⁵ In addition, the arylation reaction was also conducted for borylated alcohol (**3bd**) to give **5b** in 57% yield in a stereospecific manner (see the ESI† for details of HPLC).

We also tested the transformation of our products in Chan–Evans–Lam cross–coupling reactions.¹¹ A catalytic amount of $Cu(OAc)_2$ was employed to promote the amination reaction of β -hydroxyl boronic ester with *N*-methylaniline. We found that **3a** was converted to the corresponding phenyl-amino alcohol derivative (**6a**) in 49% yield (Scheme 4).

To evaluate the efficiency of this novel synthetic strategy (as copper-catalyzed borylative opening of epoxides), a gramscale reaction of 2-(phenylmethyl)oxirane (**1a**) with B_2pin_2 was carried out, and the corresponding product **3a** was given in 85% isolated yield (Scheme 5).

In summary, we reported the first copper-catalyzed ring opening C–B forming reaction of epoxides with diboron reagents.



Scheme 3 Copper-catalyzed borylation reaction of racemic and chiral epoxides, and palladium-catalyzed arylation reaction of β -hydroxyl boronic esters.



Scheme 4 Chan-Lam C-N cross-coupling of β -hydroxyl boronic ester with N-methylaniline.



Our method presents a straightforward catalytic method for the preparation of β -hydroxyl boronic esters, which have the potential for further transformations in organic syntheses. Moreover, the versatility of the β -hydroxyl boronic ester products toward the synthesis of the corresponding aryl-substituted alcohols is underlined. The amination reaction of β -hydroxyl boronic ester is also described. Expanding of the scope of epoxides, as well as the investigation of the mechanism for this reaction, is currently underway in our lab.

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