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## COMMUNICATION

## Cu-Catalyzed Cross-Coupling Reactions of Epoxides with Organoboron Compounds

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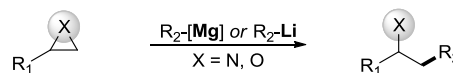
A copper-catalyzed cross-coupling reaction of epoxides with arylboronates is described. The reaction is not limited to aromatic epoxides, because aliphatic epoxides are also suitable substrates. In addition, N-sulfonyl aziridines can be successfully converted into the products. The reaction provides convenient access to  $\beta$ -phenethylalcohols, which are valuable synthetic intermediates.

Transition metal catalyzed C-C bonds cross-coupling reactions play an important role in modern organic synthesis,<sup>1</sup> which usually use carbon-halogen or carbon-OSO<sub>2</sub>R as electrophiles.<sup>2</sup> Compared with the traditional electrophiles, epoxides and aziridines possess ring strain that make them susceptible to nucleophilic ring opening,<sup>3</sup> and various carbon-based nucleophiles have been investigated over the past several years.<sup>4</sup> After the ring-opening reaction, epoxides can be easily converted to  $\beta$ -substituent alcohol.<sup>5</sup> Traditional methods of the ring-opening reaction used strong nucleophilic organometallics,<sup>6</sup> such as Grignard reagents or organolithium reagents (Scheme 1a). The drawback of these reactions is the functional-group tolerance. In this context, Doyle and Jamison have reported nickel-catalyzed Negishi-type cross-coupling of aziridines (Scheme 1b).<sup>7</sup> It is recognized that organoboron compounds show excellent stability and commercial availability. Thus, Takeda and Minakata, as well as Michael have achieved the Suzuki-type coupling reaction of organoboron and aziridines (Scheme 1c).<sup>8</sup>

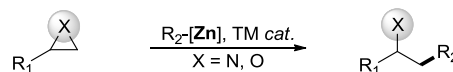
As a continuation of our previous work about Cu-catalyzed cross-coupling reactions,<sup>2b,11</sup> we report the first example Cu-catalyzed of epoxides with arylboronates ring-opening cross-coupling reaction (Scheme 1c). It's worth pointing out that Doyle reported nickel-catalyzed cross-coupling of styrenyl epoxides with arylboronic acids.<sup>9</sup> In the reaction nickel was inserted into the C-O bond, followed by  $\beta$ -hydride elimination and isomerized to aldehyde, generating rearranged products. In contrast with this research, our work realized the direct ring-opening reaction, and the configuration of C-O can be retained. This methodology allows access to synthetically valuable secondary alcohols and tertiary alcohols from readily available and inexpensive terminal epoxides, which are

valuable synthetic intermediates in a variety of C-C bond-forming manifolds.<sup>2e, 10</sup>

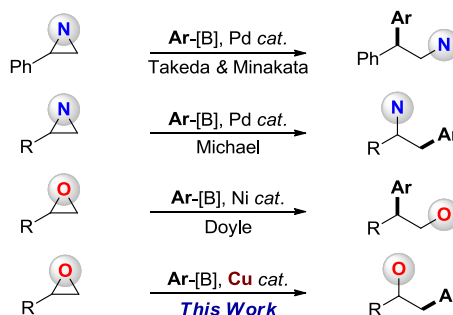
## a. Nucleophilic Ring-opening



## b. Negishi-type

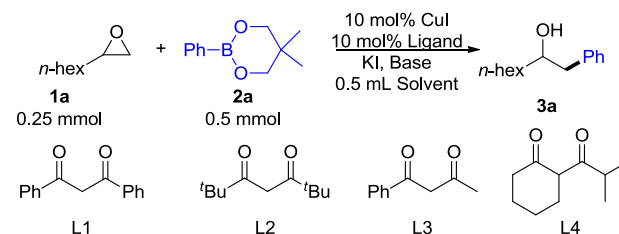


## c. Suzuki-type



**Scheme 1** Previously Reported Cross-Couplings Reactions of Epoxides and Aziridines. Neop = (OCH<sub>2</sub>CMe<sub>2</sub>CH<sub>2</sub>O).

**Table 1** Optimization of the reaction conditions.



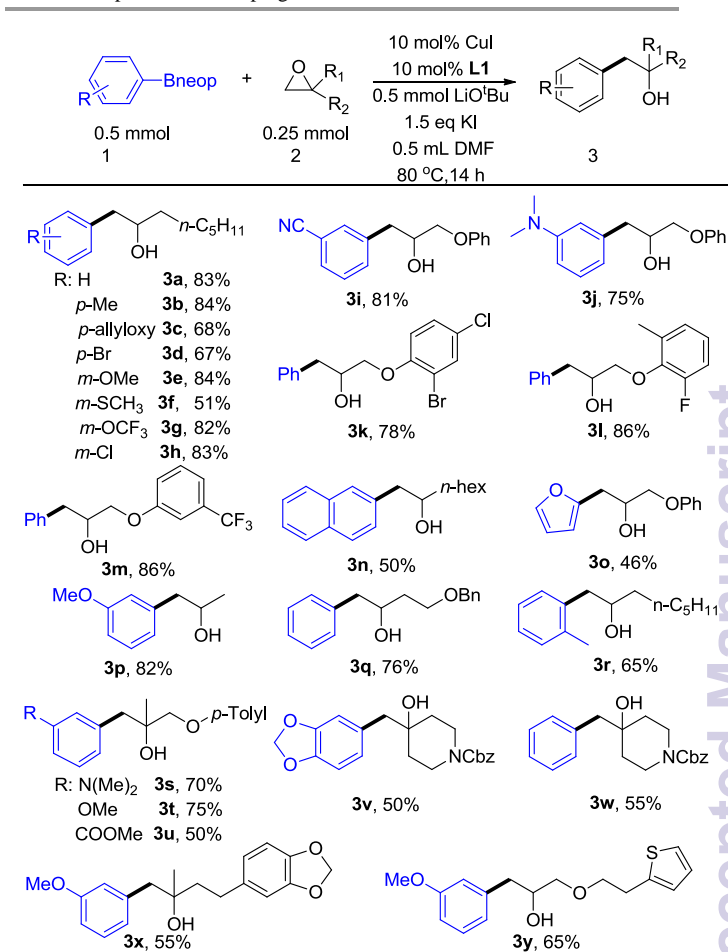
Entry	Ligand	Base	Solvent	KI	Yield <sup>a</sup>
1	-	LiO <sup>t</sup> Bu	DMF	-	6
2	PPh <sub>3</sub>	LiO <sup>t</sup> Bu	DMF	-	5
3	Johnphos	LiO <sup>t</sup> Bu	DMF	-	15 <sup>c</sup>
4	TMEDA	LiO <sup>t</sup> Bu	DMF	-	8 <sup>c</sup>
5	xantphos	LiO <sup>t</sup> Bu	DMF	-	40
6	xantphos	LiO <sup>t</sup> Bu	DMF	1.0 eq	48 <sup>b</sup>
7	L1	LiO <sup>t</sup> Bu	DMF	1.0 eq	75 <sup>b</sup>
8	L2	LiO <sup>t</sup> Bu	DMF	1.0 eq	35 <sup>b</sup>
9	L2	LiOtBu	NMP	0.5eq	trace
10	L3	LiO <sup>t</sup> Bu	DMF	0.5 eq	30 <sup>b</sup>
11	L4	LiO <sup>t</sup> Bu	DMF	0.5 eq	trace <sup>b</sup>
12	<b>L1</b>	<b>LiO<sup>t</sup>Bu</b>	<b>DMF</b>	<b>1.5 eq</b>	<b>88<sup>b</sup>(83<sup>e</sup>)</b>
13	L1	LiO <sup>t</sup> Bu	DMF	-	36
14	L1	LiO <sup>t</sup> Bu	DMF	1.5 eq	0 <sup>d</sup>
15	L1	LiO <sup>t</sup> Bu	DMF	1.5 eq	61 <sup>f</sup>
16	L1	LiO <sup>t</sup> Bu	DMF	1.5eq	44 <sup>g</sup>

<sup>a</sup> Reaction conditions: CuI (10 mol%), Base (2 equiv), ligand (10 mol%) in 0.5 mL solvent at 80 °C for 14h under Ar atmosphere. <sup>b</sup> KI was added. <sup>c</sup> 60 °C for 14h. <sup>d</sup> no CuI. The yield was determined by GC using dodecyl alcohol as internal standard (average of two GC runs). <sup>e</sup> Isolated yield. <sup>f</sup> aryl-Bpin was used in the coupling. <sup>g</sup> Boronic acid was used in the coupling. DMF = N,N-dimethylformamide. DMSO = dimethyl sulfoxide.

We began our study by choosing commercial availability 1-octene epoxide (**1a**) and phenylboronate (**2a**) as the model substrates (Table 1). On the basis of recent studies on Cu-catalyzed cross-coupling reaction of alkyl electrophilic reagents with arylboronates,<sup>2b,11</sup> we first examined previously reported catalytic systems for the coupling of 1-octene epoxide and arylboronates. Gratifyingly, we observed the product, albeit in low yield (entry 1). The result indicated that the conditions previously reported for the coupling were not suitable. To assess the role of various nitrogen and phosphine ligands, CuI was next evaluated as a copper source (entry 2-5). With PPh<sub>3</sub>, Johnphos and TMEDA reaction efficiencies remained poor (entry 2-4). Unexpectedly, the use of xantphos as the ligand improved reaction efficiency (entry 5), but the yield was not high even after screening of a series of bases and solvents with the xantphos ligand (see Supporting Information). Next we examined the role of iodide for the opening-ring cross-coupling, but the effect was not good (entry 6 vs entry 5). In consideration of our previous work utilizing the diketone as ligands in catalytic cross-coupling reactions,<sup>11</sup> we tested the diketone family ligands to see whether they can accelerate the reaction (entry 7-12). Excitedly, we obtained a good result (88% GC yield and 83% isolated yield, entry 12) in a further evaluation of these reaction parameters. However, once we took out KI in the optimal conditions we only obtained 36% yield (entry 13). In the absence of copper source, no product formation was observed (entry 14). Compared with other organoboron compounds, using neopentyl boranes as substrate, the yield is the highest (entry 15-16).

With the optimized conditions in hand, we decided to examine the substrate scope (Table 2). First, for the simple 2-monosubstituted epoxides, electron-rich and electron-poor substrates provided good yields (**3a-3r**, **3y**). A series of relevant functional groups including olefin (**3c**), ether (**3e**), methylthio (**3f**), trifluoromethoxy (**3g**), cyano (**3i**), amino (**3j**), trifluoromethyl (**3m**) can be well tolerated to give the products in yields of 68-84%. Aryl-X (X= F, Cl, Br) bond (**3d**, **3h**, **3k**, **3l**) did not hinder the transformation, so that it was possible to conduct additional cross-coupling reactions at the halogenated positions. The epoxides with different chain lengths (**3p**, **3q**) did not interfere the reaction. Steric hindrance (**3r**) was tolerated to a certain

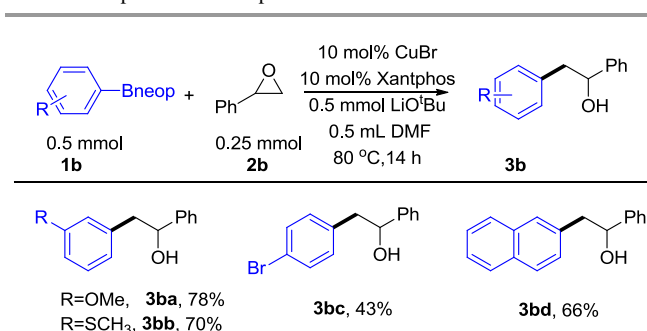
Table 2 Scope of cross-coupling<sup>a,b</sup>.



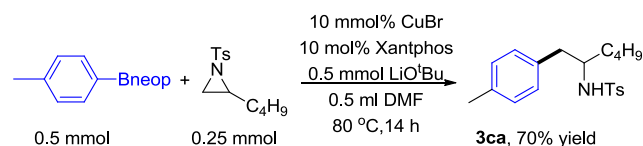
<sup>a</sup> Reaction conditions: Epoxides (0.25 mmol), Arylboronic esters (2 equiv), LiO<sup>t</sup>Bu(2 equiv). <sup>b</sup> Isolated yields. *p*-Tolyl = 4-methylphenyl.

extent. Naphthyl (**3n**), furan (**3o**) and thiophene (**3y**) can also be present in the reaction. Second, we smoothly obtained tertiary alcohols, when we utilized 2,2-disubstituted epoxides as substrates (**3s-3x**). Electron-rich or electron-poor arylboronates, for instance amino (**3s**), methoxyl (**3t**) and ketal (**3v**), can also be well tolerated. In particular ester (**3u**) and amide (**3v**, **3w**), which were sensitive to metallic reagents, can also be used in the reaction. Unfortunately, when both carbons of the epoxide are substituted, the yield is very low.

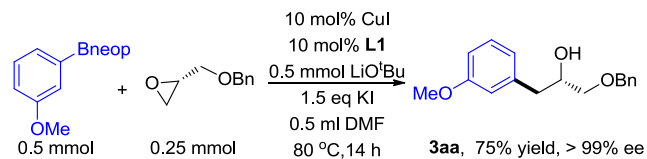
Next, we examined whether more highly active aromatic epoxides could involve in the reaction. Under the present conditions aromatic epoxides were not viable substrates. Fortunately, after a variety of screening experiments, the desired products were obtained in high yield (Table 3). Arylboronate bearing methoxy (**3ba**), sulphur (**3bb**) atom or bromine (**3bc**) groups reacted under these conditions to afford the desired products in moderate to good yields (43-78 yield). Naphthalene substrate (**3bd**) was also reacted in 66% yield. The selectivity of aromatic epoxides was different from the Doyle and Weix's work.<sup>9,12</sup> Moreover, in Weix's study a mixture of products were obtained.

**Table 3.** Scope of aromatic epoxides<sup>a,b</sup>.

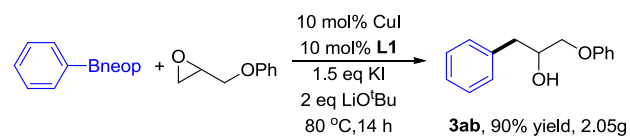
<sup>a</sup> Reaction conditions: Epoxides (0.25 mmol), arylboronic esters (2 equiv), LiO<sup>t</sup>Bu (2 equiv). <sup>b</sup> Isolated yields.

**Scheme 2** Cross-coupling of N-sulfonyl aziridine.

The β-phenethylamine fragment exists in many important neurotransmitters and often be used in syntheses of drug targets. The condition for aromatic epoxides is also applied to N-sulfonyl aziridines. As illustrated in Scheme 2, it provides a method in synthesis of such compounds (eg. **3ca**, 70% yield).

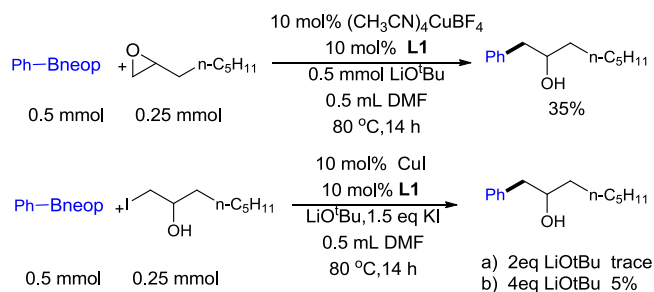
**Scheme 3** Cross-coupling of chiral epoxide.

Chiral compounds play a leading role in many applications, particularly for the production of active pharmaceutical ingredients. As expected, the ring-opening of (S)-configuration epoxide with arylboronate afforded product (**3aa**) with high enantiospecificity (Scheme 3, 75% yield, > 99% ee).

**Scheme 4.** A gram-scale cross-coupling reaction.

To demonstrate the scalability of this reaction, we also performed this copper-catalyzed opening-ring reaction on a gram scale and gained **3ab** in 90% yield (Scheme 4).

To illustrate the mechanism of the reaction, we chose (CH<sub>3</sub>CN)<sub>4</sub>CuBF<sub>4</sub> as the copper source, and didn't add any iodide. Fortunately, we also obtained 35% yield. A preformed iodohydrin substrate only yielded little product, even though we increased the LiO<sup>t</sup>Bu to 4 equivalent (Scheme 5). The exact reaction process is not clear, but the preformed iodohydrin substrates can not replace our epoxides. Further investigations on the possible mechanism were underway.

**Scheme 5** Support experiments for the proposed mechanism of the opening cross-coupling reaction reaction.

In summary, for the first time, we have developed a Cu-catalyzed ring-opening reaction of epoxides with arylboronates. A series of aromatic and aliphatic epoxides could be smoothly converted into the products. The reaction is also applicable to N-Ts aziridines. Additionally, this reaction expands the scope of electrophilic reagents in copper-catalyzed cross-coupling. The reaction provides effective methods for the synthesis of secondary alcohols and tertiary alcohols, which are valuable synthetic intermediates in C-C bond-forming reactions. In contrast to traditional nucleophilic epoxides and aziridines ring-opening chemistry, the mild conditions of this methodology tolerate a wide variety of functional groups.

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## Notes and references

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- F. Diederich and P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 1998.
- (a) S. L. Zultanski and G. C. Fu, *J. Am. Chem. Soc.*, 2011, **133**, 15362; (b) C. T. Yang, Z. Q. Zhang, Y. C. Liu and L. Liu, *Angew. Chem. Int. Ed.*, 2011, **50**, 3904; (c) A. Wilsily, F. Tramutola, N. A. Owston and G. C. Fu, *J. Am. Chem. Soc.*, 2012, **134**, 5794; (d) Z. Lu and G. C. Fu, *Angew. Chem. Int. Ed.*, 2010, **49**, 6676; (e) C.-T. Yang, Z.-Q. Zhang, J. Liang, J.-H. Liu, X.-Y. Lu, H.-H. Chen and L. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 11124. (f) T. Hatakeyama, T. Hashimoto, K. K. A. D. S. Kathirarachchi, T. Zenmyo, H. Seike and M. Nakamura, *Angew. Chem. Int. Ed.*, 2012, **51**, 8834. (h) M. Kuriyama, M. Shinozawa, N. Hamaguchi, S. Matsuo and O. Onomura, *J. Org. Chem.*, 2014, **79**, 5921.
- R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.
- (a) J. He, J. Ling and P. Chiu, *Chem. Rev.*, 2014, **114**, 8037; (b) N. Jiang, Q. Hu, C. S. Reid, Y. Lu and C.-J. Li, *Chem. Commun.*, 2003, 2318; (c) U. K. Roy and S. Roy, *Tetrahedron*, 2006, **62**, 678; (d) J. Muzart, *Eur. J. Org. Chem.*, 2011, **2011**, 4717; (e) A. Gansäuer, M. Behlendorf, D. von Laufenberg, A. Fleckhaus, C. Kube, D. V. Sadasivam and R. A. Flowers, *Angew. Chem. Int. Ed.*, 2012, **51**, 4739. (f) J. Kjellgren, J. Aydin, O. A. Wallner, I. V. Saltanova and K. J. Szabó, *Chem. Eur. J.*, 2005, **11**, 5260; (g) B. Olofsson and P. Somfai, in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 315-347. (h) H. Ohno, in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 37-71; (i) J. He, J. Ling and P. Chiu, *Chem. Rev.*, 2014, **114**, 8037.
- (a) P. Crotti and M. Pineschi, in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 271-313;

- (b) V. V. Fokin and P. Wu, in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 443-477; (c) P. A. S. Lowden, in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 399-442; (d) H. Ohno, in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 37-71; (e) B. Olofsson and P. Somfai, in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006, pp. 315-347. (f) C.-Y. Huang and A. G. Doyle, *Chem. Rev.*, 2014, **114**, 8153; (g) J. A. Kalow, D. E. Schmitt and A. G. Doyle, *J. Org. Chem.*, 2012, **77**, 4177; (h) J. A. Kalow and A. G. Doyle, *J. Am. Chem. Soc.*, 2011, **133**, 16001; (i) *J. Am. Chem. Soc.*, 2010, **132**, 3268; (j) T. J. A. Graham, R. F. Lambert, K. Ploessl, H. F. Kung and A. G. Doyle, *J. Am. Chem. Soc.*, 2014, **136**, 5291.
- 6 (a) M. Alam, C. Wise, C. A. Baxter, E. Cleator and A. Walkinshaw, *Org. Process Res. Dev.*, 2012, **16**, 435; (b) C. Bonini, L. Chiummiento, M. T. Lopardo, M. Pullez, F. Colobert and G. Solladié *Tetrahedron Lett.*, 2003, **44**, 2695.
- 7 (a) C. Y. Huang and A. G. Doyle, *J. Am. Chem. Soc.*, 2012, **134**, 9541; (b) K. L. Jensen, E. A. Standley and T. F. Jamison, *J. Am. Chem. Soc.*, 2014, **136**, 11145; (c) D. K. Nielsen, C. Y. Huang and A. G. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 13605.
- 8 (a) M. L. Duda and F. E. Michael, *J. Am. Chem. Soc.*, 2013, **135**, 18347; (b) Y. Takeda, Y. Ikeda, A. Kuroda, S. Tanaka and S. Minakata, *J. Am. Chem. Soc.*, 2014, **136**, 8544.
- 9 D. K. Nielsen and A. G. Doyle, *Angew. Chem. Int. Ed.*, 2011, **50**, 6056.
- 10 (a) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417; (b) J. E. Steves and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 15742.
- 11 Y.-Y. Sun, J. Yi, X. Lu, Z.-Q. Zhang, B. Xiao and Y. Fu, *Chem. Commun.*, 2014, **50**, 11060.
- 12 Y. Zhao and D. J. Weix, *J. Am. Chem. Soc.*, 2014, **136**, 48.