<u>LETTERS</u>

Copper-Catalyzed $S_N 2'$ -Selective Allylic Substitution Reaction of gem-Diborylalkanes

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Supporting Information



ABSTRACT: A Cu/(NHC)-catalyzed S_N2' -selective substitution reaction of allylic electrophiles with *gem*-diborylalkanes is reported. Different substituted *gem*-diborylalkanes and allylic electrophiles can be employed in this reaction, and various synthetic valuable functional groups can be tolerated. The asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands.

• opper-catalyzed cross-coupling reactions of allylic electro-✓ philes are powerful methods for constructing C−C bonds, especially for the formation of saturated C-C bonds.¹ In the past few decades, a variety of organometallic reagents have been used in these reactions, such as Grignard, alkyllithium, alkylaluminum, alkylzirconium, and dialkylzinc.² Despite their high activity, their air and moisture sensitivity have limited their application in synthesis. In contrast, organoboronic acid derivatives are widely used because of their stability, availability, and good functional group tolerance.³ To date, many studies in the field of coupling between allylic electrophiles with organoboron compounds have been reported,⁴ which often employ aryl,⁵ alkenyl,⁶ and allyl boron reagents⁷ and alkyl-9-BBN.⁸ Among of them, allylboron reagents and alkyl-9-BBN applied in these methods can realize the alkylation of allylic electrophiles.

Recently, a series of novel alkylboron compounds, namely gem-diboryalkanes, attracted attention from chemists. In the field of construction of C-C bonds with gem-diboryalkanes, Shibata et al. reported the pioneering work.¹⁰ More and more attention focused on these interesting synthons due to their special activity and structure. Thereafter, Morken and coworkers developed the first Pd-catalyzed stereoselective Suzuki cross-coupling of 1,1-diborylalkanes,¹¹ and then Morken's¹² and our group¹³ independently reported the coupling of alkyl (pseudo)halides with gem-diborylalkanes. Recently, Meek's group also reported the addition reaction of aldehydes and 1,1-diborylalkanes.¹⁴ Despite many reaction types, allylic substitution reactions of allylic electrophiles with 1,1-diborylalkanes have rarely been reported (Scheme 1a).^{10c,12,13} Furthermore, the γ -selective reaction of gem-diborylalkanes remains challenging. Herein, we describe copper-catalyzed S_N2'-selective alkylation reactions of allylic electrophiles with

Scheme 1. Regioselective Allylic Substitution Reactions of Allylic Electrophiles with *gem*-Diborylalkanes



1,1-diborylalkanes (Scheme 1b).¹⁵ Through this method, we can obtain the branched γ -substitution products through the Cu/(NHC)-catalyzed system successfully. Various synthetic valuable functional groups could be tolerated with mild reaction conditions. Different side-chain-substituted *gem*-diborylalkanes and allylic electrophiles can be employed. Finally, the asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands.

Recently, we reported Cu-catalyzed/promoted alkylation of *gem*-diborylalkanes. We found that diborylmethane could react with cinnamyl phosphate to afford the linear α -substitution product.¹³ On the basis of this finding, we attempted to achieve the synthesis of branched products by governing the catalyst system. Subsequently, we examined the allylic substitution of 1,1-diborylalkanes with allylic electrophiles. Diborylmethane (1) and cinnamyl electrophiles were selected as the model substrates (Table 1). At first, we repeated our previous conditions with cinnamyl phosphate (1b) (entry 1 and 2) and obtained major product 2a. Then we tried THF and dioxane (entry 3 and 4) and found that 1a was the major product and the selectivity of 1a and 2a was reversed. We next examined the ligand effect with SIMes, IMes, IPr, and L1

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Table 1. Optimization of the Reaction Conditions^a



entry	Х	solvent	ligand	yield (%)	1a/2a
1 ^b	$OPO(OEt)_2$	DMF	-	88	8:92
2	$OPO(OEt)_2$	DMF	-	87	4:96
3	$OPO(OEt)_2$	THF	-	66	83:17
4	$OPO(OEt)_2$	dioxane	_	68	87:13
5	$OPO(OEt)_2$	dioxane	SIMesHCl	72	85:15
6	$OPO(OEt)_2$	dioxane	IMesHCl	67	80:20
7	$OPO(OEt)_2$	dioxane	IPrHCl	23	82:18
8	$OPO(OEt)_2$	dioxane	L1	89	97:3
9 ^b	$OPO(OEt)_2$	dioxane	L1	64	96:4
10	Cl	dioxane	L1	79	90:10
11	OAc	dioxane	L1	trace	-
12	OCOOMe	dioxane	L1	22	75:25
13 ^c	$OPO(OEt)_2$	dioxane	L1	0	-

^{*a*}All reactions were carried out at 60 °C on a 0.15 mmol scale, and 10 mol % of CuCl, 3 equiv of LiOMe, 2 equiv of diborylmethane (1), and 1 mL of solvent were used. The yields and the ratios of 1a/2a were determined by GC (average of two GC runs). ^{*b*}t-BuOLi was used instead of LiOMe. ^{*c*}The reaction was carried out without CuCl.

(entries 5–8; for details, see the Supporting Information). Significantly, ligand L1 not only improved the yield to 89% but also gave excellent regioselectivity (entry 8, 1a/2a = 98:2). In addition to cinnamyl phosphate, we also tried some other cinnamyl electrophiles (Cl, OAc, OCOOMe); however, all these attempts failed to give better regioselectivity or yield. With control experiments, we found that this reaction could not be processed without copper catalysts (entry 13).

With the optimized conditions in hand, we investigated the scope of this newly developed reaction. As shown in Table 2, diborylmethane can react with both aromatic and aliphatic allylic phosphates. A variety of halogen-substituted cinnamyl phosphates can successfully afford the corresponding products in good yields and $S_N 2'$ selectivity. Different substituted positions on the cinnamyl phosphates posed no problem with these reaction conditions (2c-6c and 8c). Many important functional groups were also compatible, such as NO₂ (7c), CF_3 (9c), CN (10c), and vinyl (13c). Both (Z)- and (E)-allylic phosphates (12b and 11b) have similar reactivity and afforded the same product (11c). Substrates with commonly used hydroxyl protecting groups can also be employed and give γ selective product in high yields (14c, 17c, and 18c). The heterocyclic compounds (15c and 16c) survived under our reaction conditions with good yields. In addition to primary allylic phosphates, the secondary ones also can be used in this reaction (19c). Finally, we examined the allylic phosphates which can afford quaternary carbon center (20b). The desired product (20c) was obtained with moderate yield and regioselectivity.

Meanwhile, we also investigated the substituted *gem*diborylalkanes under the reaction conditions. Unfortunately, the yield (52%, $S_N 2'/S_N 2 = 82:18$) and dr value (1.2:1) were very low when 1,1-diborylalkane (2) was used. Modifications to lead to improvements were carried out, and we determined

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R	O P OEt +	Bpin Bpin LiOMe 3 1 dioxane,	<u>nol %</u> ₀ol % R [^] equiv 60 °C	Bpin 1c			
entry	substrates	product	yield (%)	$S_N2':S_N2^{\ b}$			
Y	OPO(OEt) ₂	Y II					
1	Y = 2-Br 2b	2c	77	96:4			
2	Y = 4-Br 3b	3c	83	97:3			
3	Y = 2-Cl 4b	4c	79	95:5			
4	Y = 3-Cl 5b	5c	77	97:3			
5	Y = 4-Cl 6b	6c	76	96:4			
6	$Y = 4-NO_2 7\mathbf{b}$	7c	82	93:7			
7	Y = 4-F 8b	8c	88	98:2			
8	$Y = 3 - CF_3 9b$	9c	85	97:3			
9	Y = 4-CN 10b	10c	66	92:8			
OPO(OEt) ₂							
10	(E)- 11b	11c	58	98:2			
11	(Z)- 12b	12c	52	97:3			
	OPO(OEt)2	Bpin					
12	13b	13c	57	98:2			
	PGO-GPO(OEt)2	PGO					
13	PG = Benzoyl 14b	14c	45	96:4			
14	PG = 2-Thenoyl 15b	15c	75	98:2			
15	PG = 2-furoyl 16b	16c	54	93:7			
16	PG = Bn 17b	17c	77	95:5			
17	PG = TBS 18b	18c	62	98:2			
BzO							
18	19b	19c	68	97:3			
	OPO(OEt) ₂	Bpin					
10 ^c	206	200	72	85.15			

"Reactions were carried out under the conditions shown, using allylic phosphates as substrates, and all yields are isolated yields. ^bThe ratios of $S_N 2'/S_N 2$ were determined by ¹H NMR analysis of the reaction mixture. "When L1 was used as ligand, the $S_N 2'/S_N 2$ was low (68:32). When L2 was used, the regioselectivity ratio was improved to 85:15.

newly optimized conditions. We examined several allylic phosphates to afford the corresponding products (1d-4d) with good yield, S_N2' -selectivity, and moderate diastereose-lectivity. (Scheme 2; for details, see the Supporting Information).

Allylic epoxide could be recognized as a special allylic electrophile; thus, we also tried to employ it in this reaction and found it can indeed react with different *gem*-diborylalkanes to generate $S_N 2'$ -selective products (Scheme 3).

The asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands.

Scheme 2. Substrate Scope for the Reaction of Allylic Phosphates with Substituted *gem*-Diborylalkanes^a



^{*a*}Reactions were carried out under the conditions shown, all yields were isolated yields, and the ratios of $S_N 2'/S_N 2$ were determined by ¹H NMR analysis of the reaction mixture.

Scheme 3. Reaction of Allylic Epoxide with Substituted gem-Diborylalkanes^a



"Reactions were carried out under the conditions shown, all yields are isolated yields, and the ratios of $S_N 2'/S_N 2$ were determined by ¹H NMR analysis of the reaction mixture.

We found that the ee value can be governed when diborylmethanes are used with different steric hindrance (X = pinacol, 40% ee, X = pinanediol, 64% ee) (Scheme 4; for details, see the Supporting Information).

Scheme 4. Asymmetric Selectivity of the Reaction of Allylic Phosphates with Diborylmethanea



"Reactions were carried out under the conditions shown, all yields are isolated yields, and the ee value were determined by HPLC analysis.

In summary, we have reported a copper-catalyzed $S_N 2'$ -selective allylic alkylation reaction of allylic electrophiles with substituted *gem*-diborylalkanes.¹⁶ A variety of synthetically important functional groups can be compatible under these conditions. The asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands,

and further efforts to improve the enantio- and diastereoselectivity of this reaction are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b03692.

Detailed experimental procedures and spectra data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(15) While our manuscript was in preparation, Cho et al. described a Cu-catalyzed $S_N 2'$ -selective substitution reaction of 1,1-diborylalkanes. In their work, *gem*-diborylalkanes can react with allyl chlorides smoothly by IMesCuCl catalysis. However, the reaction was mainly applied to allyl chlorides, and the diastereoselectivity of substituted 1,1-diborylalkyanes is very low. The asymmetric version of this reaction was not investigated. See: Kim, J.; Park, S.; Park, J.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1498.

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