



## New protocol for allylic substitution with aryl and alkenyl copper reagents derived from organolithiums

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### ABSTRACT

Substitution of allylic picolinoates with copper reagents derived from  $sp^2$ -carbon-lithiums and  $CuBr \cdot Me_2S$  was established to furnish anti  $S_N2'$  products with almost perfect regioselectivity and chirality transfer. The preparations of organolithiums such as lithium-halogen exchange and *ortho* lithiation were coupled to the substitution to install various  $sp^2$ -carbon groups, which include Ph, 2,6- $Me_2C_6H_3$ , 4-Me-2,6-(MOMO) $C_6H_2$ , and *cis* and *trans* 1-heptenyl groups.

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Among the copper-assisted allylic substitution with hard nucleophiles, a method using optically active secondary allylic esters has been a potentially useful asymmetric C–C bond forming reaction.<sup>1</sup> However, regio- and stereoselectivities have been much affected by bulkiness of reagents and substituents on the allylic moiety, reactivity of reagents, and/or an electronic bias.<sup>2</sup> To improve these negative situations, Breit<sup>3,4</sup> and Knochel<sup>5</sup> independently have introduced *o*-( $Ph_2P$ ) $C_6H_4CO_2$ ,<sup>3</sup> *o*-( $Ph_2P=O$ ) $C_6H_4CO_2$ ,<sup>4</sup> and  $C_6F_5CO_2$ <sup>5</sup> as leaving groups. These leaving groups appear quite powerful and compensate steric obstacles to attain excellent regio- and stereoselectivities constantly with alkylcoppers derived from alkyl metals such as  $RMgX$ ,  $RZnX$ , and  $R_2Zn$ . However, the power of these leaving groups seems still insufficient for less reactive aryl and alkenyl anions. In addition, these leaving groups are expensive. Quite recently, we reported the picolinoxyl leaving group for allylic substitution with aryl and simple alkenyl copper reagents derived from  $RMgX$ .<sup>6</sup> High performance including almost perfect anti  $S_N2'$  selectivity and a reasonable price of picolinic acid are synthetic advantages of this reaction.<sup>7</sup> We then turned our attention to copper reagents derived from organolithiums and a copper salt in expectation that the various preparations of lithium reagents would add another advantage to the allylic substitution. In practice, halogen–lithium exchange and *ortho* lithiation were examined successfully as presented in this Letter.

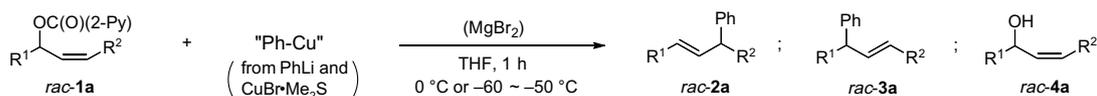
First, phenylcopper reagents derived from salt free  $PhLi$  (2 equiv)<sup>8</sup> and  $CuBr \cdot Me_2S$  (2, 1, and 0.5 equiv) (defined as 2/2, 2/1, and 2/0.5  $Ph/Cu$  reagents, respectively) were subjected to reaction with racemic picolinoate *rac*-**1a** ( $R^1 = Ph(CH_2)_2-$ ,  $R^2 = CH_2OTBS$ ) in THF at 0 °C for 1 h to afford a mixture of *rac*-**2a** ( $S_N2'$  product), *rac*-**4a** (alcohol, byproduct), and *rac*-**1a** (substrate) as summarized in Table 1 (entries 1, 4, and 9), indicating competition with an attack to the carbonyl carbon of the picolinoxyl group.

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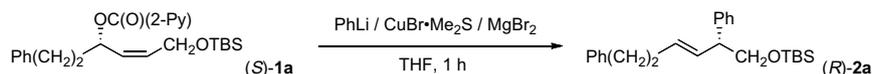
E-mail address: [ykobayas@bio.titech.ac.jp](mailto:ykobayas@bio.titech.ac.jp) (Y. Kobayashi).

However, we were delighted by the fact that the  $S_N2$  product (*rac*-**3a**) was not detected by <sup>1</sup>H NMR spectroscopy. To improve the product selectivity, reactions with the 2/1  $Ph/Cu$  reagent were carried out in the presence of  $MgBr_2$  (2, 3, and 4 equiv). Among these quantities, *rac*-**2a** was produced almost exclusively with 3 and 4 equiv of  $MgBr_2$  (entries 6 and 8 vs entry 5). Furthermore,  $MgBr_2$  was found to accelerate the reaction to be completed within 1 h. No retardation was observed even at –60 to –50 °C (entry 7). Addition of  $MgBr_2$  was similarly effective on the reactions with the 2/2 and 2/0.5  $Ph/Cu$  reagents (entries 2, 3, 10, and 11).

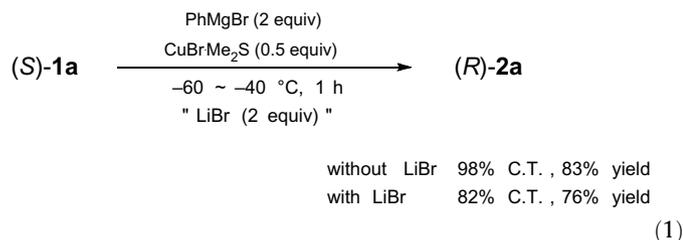
We then applied the  $PhLi/CuBr/MgBr_2$  reagent system to the enantiomerically enriched (*S*)-**1a** (95–98% ee), prepared via asymmetric reduction of the corresponding ynone,<sup>9</sup> and the results are summarized in Table 2. Reactions of (*S*)-**1a** with 2/2, 2/1, and 2/0.5  $Ph/Cu$  reagents were carried out in the presence of  $MgBr_2$  (3 equiv) at 0 °C and at –60 to –50 °C for 1 h. The *R* configuration of the product **2a** was determined by comparison of retention time on a chiral HPLC with an authentic sample of the known configuration,<sup>6</sup> unambiguously establishing the anti  $S_N2'$  mode of the reaction. Next, chirality transfer (CT), defined as % ratio of enantiomeric excesses of (*R*)-**2a** over (*S*)-**1a**, was calculated from the data of chiral HPLC analysis to find excellent CTs with the 2/2 and 2/1  $Ph/Cu$  reagents (entries 1–4). Furthermore, the CTs were independent of the reaction temperatures, indicating that temperature control in a narrow range is not necessary for obtaining efficient CT. On the other hand, the 2/0.5 reagent gave somewhat low CT (entries 5 and 6). An unwanted effect of LiBr formed in situ on the Cu(I) species was elucidated to be a reason by an experimentation shown in Eq. 1, in which addition of 2 equiv of LiBr resulted in lowering the native CT. On the other hand, the reactions with the 2/2 and 2/1 reagents (derived from 2 equiv of  $PhLi$  and 2 or 1 equiv of  $CuBr \cdot Me_2S$  as defined above) and  $MgBr_2$  (3 equiv) were not affected by LiBr (2 equiv) formed with the  $Ph/Cu$  preparations (entries 1–4). Consequently, use of more than 1 equiv of  $CuBr \cdot Me_2S$  is recommended for high CT.<sup>10</sup>

**Table 1**Preliminary reaction of *rac*-**1a** ( $R^1 = \text{Ph}(\text{CH}_2)_2$ ,  $R^2 = \text{CH}_2\text{OTBS}$ ) with 'Ph-Cu' derived from PhLi and CuBr·Me<sub>2</sub>S

Entry	Ph-Li (equiv)	CuBr·Me <sub>2</sub> S (equiv)	MgBr <sub>2</sub> (equiv)	Temp (°C)	Product ratio of <i>rac</i> - <b>2a</b> :- <b>3a</b> :- <b>4a</b> :- <b>1a</b>	Yield <sup>a</sup> (%)
1	2	2	0	0	9:0:69:22	nd
2	2	2	3	0	100:0:0:0	97
3	2	2	3	-60 to -50	100:0:0:0	93
4	2	1	0	0	11:0:47:42	nd
5	2	1	2	0	84:0:15:1	nd
6	2	1	3	0	100:0:0:0	94
7	2	1	3	-60 to -50	100:0:0:0	nd
8	2	1	4	0	98:0:2:0	92
9	2	0.5	0	0	48:0:44:8	nd
10	2	0.5	3	0	98:2:0:0	95
11	2	0.5	3	-60 to -50	99:1:0:0	nd

<sup>a</sup> nd: not determined.**Table 2**Allylic substitution of (*S*)-**1a**<sup>a</sup> with Ph copper reagents derived from various Ph lithiums

Entry	Source of PhLi (equiv)	CuBr·Me <sub>2</sub> S (equiv)	MgBr <sub>2</sub> (equiv)	Temp (°C)	Product ( <i>R</i> )- <b>2a</b> <sup>b</sup>	
					CT, <sup>c,d</sup> (%)	Yield (%)
1	Salt free PhLi <sup>e</sup> (2)	2	3	0	98	97
2	Salt free PhLi <sup>e</sup> (2)	2	3	-60 to -50	98	92
3	Salt free PhLi <sup>e</sup> (2)	1	3	0	98	92
4	Salt free PhLi <sup>e</sup> (2)	1	3	-60 to -50	98	92
5	Salt free PhLi <sup>e</sup> (2)	0.5	3	0	71	92
6	Salt free PhLi <sup>e</sup> (2)	0.5	3	-60 to -50	84	90
7	PhBr (2) + <i>n</i> -BuLi (2)	1	3	0	—	0 <sup>f</sup>
8	PhBr (2) + <i>t</i> -BuLi (4)	1	5	0	98	93
9	PhI (2) + <i>n</i> -BuLi (2)	1	3	0	—	0 <sup>f</sup>
10	PhI (2) + <i>t</i> -BuLi (4)	1	5	0	98	90

<sup>a</sup> 95–98% ee.<sup>b</sup> The absolute configuration was determined by chiral HPLC analysis.<sup>c</sup> Chirality transfer (CT) defined by (% ee of (*R*)-**2a** / % ee of (*S*)-**1a**) × 100.<sup>d</sup> Determined by chiral HPLC analysis.<sup>e</sup> Obtained from a company.<sup>f</sup> Unidentified compound(s) was produced.

Next, PhLi prepared in situ by Li-halogen exchange was investigated to clarify any effect by the residue(s) coproduced with PhLi. First, lithiation of PhX (X = Br, I; 2 equiv) was carried out using *t*-BuLi (4 equiv) at 0 °C for 30 min in Et<sub>2</sub>O, and PhLi (2 equiv) produced with LiX (2 equiv; X = Br, I), Me<sub>2</sub>C=CH<sub>2</sub> (2 equiv), and *t*-BuH (2 equiv) was converted to the 2/1 Ph/Cu reagent. Reaction of (*S*)-**1a** with the Ph/Cu reagent was carried out in THF in the presence of MgBr<sub>2</sub> (5 equiv) was used to prevent the negative effect of LiBr) to produce (*R*)-**2a** with excellent product selectivity and reactivity as presented in entries 8 and 10 of Table 2 (cf. entry 3). In contrast to *t*-BuLi, preparation of PhLi from PhX (X = Br, I; 2 equiv) and *n*-BuLi (2 equiv) was not compatible with the allylation (entries 7 and 9).

The anti S<sub>N</sub>2' allylic substitution established above for (*S*)-**1a** and Ph/Cu reagent was applied to several picolinoates with different substituents. The substrates shown in entries 1–3 of Table 3 were subjected to reaction with the 2/1 Ph/Cu reagent in the presence of MgBr<sub>2</sub> (3 equiv) at 0 °C for 1 h. Reaction of (*S*)-**1b** possessing an opposite array of the substituents to (*S*)-**1a** produced the regioisomer of **2a** (i.e., **2b**) with excellent regioselectivity, CT, and yield similar to those of **2a** (entry 1, cf. Table 2, entry 3). This result suggests that various substituents of the size of methylene on picolinoates do not affect performance of the substitution. Indeed, substrates (*R*)-**1c** and (*S*)-**1d** were converted to **2c** and **2d**, respectively, without any event (entries 2 and 3).

To demonstrate high potency of the present reaction system, a bulky copper reagent was prepared from 2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>Br through lithium-halogen exchange with *t*-BuLi followed by complexation with CuBr·Me<sub>2</sub>S. This reagent was subjected to reaction with (*S*)-**1a** under the conditions established. No retardation of the reaction nor lower selectivity was observed, thus producing **2e** efficiently (entry 4). Another bulky copper reagent was prepared from 1,3-(MOMO)<sub>2</sub>-5-MeC<sub>6</sub>H<sub>3</sub> by *ortho* lithiation<sup>11</sup> with *n*-BuLi followed by complexation with CuBr·Me<sub>2</sub>S. This copper reagent upon reaction with (*S*)-**1a** furnished the expected product **2f** as well (entry 5).

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