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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·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.

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.[1] 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.[2] To improve these negative situations, Breit[3,4] and Knochel[5] independently have introduced *o*-(Ph_2P)$C_6H_4CO_2$,[3] *o*-(Ph_2P=O)$C_6H_4CO_2$,[4] and $C_6F_5CO_2$[5] 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 picolinoxy leaving group for allylic substitution with aryl and simple alkenyl copper reagents derived from RMgX.[6] High performance including almost perfect anti S_N2' selectivity and a reasonable price of picolinic acid are synthetic advantages of this reaction.[7] 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)[8] and CuBr·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 picolinoxy group. However, we were delighted by the fact that the S_N2 product (*rac*-**3a**) was *not* detected by ^1H 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,[9] 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,[6] 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·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·Me_2S is recommended for high CT.[10]

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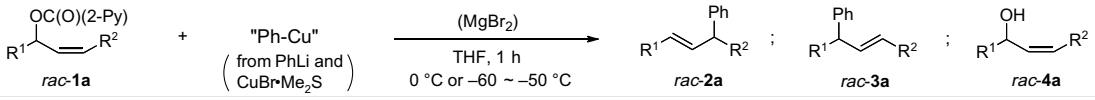
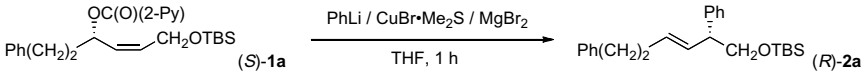
Table 1
Preliminary reaction of *rac*-**1a** (R^1 = $Ph(CH_2)_2$–, R^2 = CH_2OTBS) with 'Ph–Cu' derived from PhLi and CuBr-Me_2S



Entry	Ph–Li (equiv)	CuBr·Me_2S (equiv)	$MgBr_2$ (equiv)	Temp (°C)	Product ratio of *rac*-**2a**:-**3a**:-**4a**:-**1a**	Yield[a] (%)
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

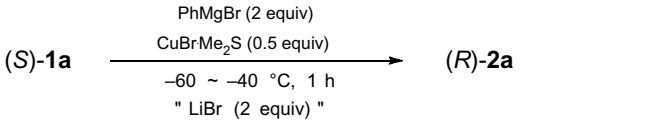
[a] nd: not determined.

Table 2
Allylic substitution of (*S*)-**1a**[a] with Ph copper reagents derived from various Ph lithiums



Entry	Source of PhLi (equiv)	CuBr·Me_2S (equiv)	$MgBr_2$ (equiv)	Temp (°C)	Product (*R*)-**2a**[b]	
					CT,[c,d] (%)	Yield (%)
1	Salt free PhLi[e] (2)	2	3	0	98	97
2	Salt free PhLi[e] (2)	2	3	−60 to −50	98	92
3	Salt free PhLi[e] (2)	1	3	0	98	92
4	Salt free PhLi[e] (2)	1	3	−60 to −50	98	92
5	Salt free PhLi[e] (2)	0.5	3	0	71	92
6	Salt free PhLi[e] (2)	0.5	3	−60 to −50	84	90
7	PhBr (2) + *n*-BuLi (2)	1	3	0	–	0[f]
8	PhBr (2) + *t*-BuLi (4)	1	5	0	98	93
9	PhI (2) + *n*-BuLi (2)	1	3	0	–	0[f]
10	PhI (2) + *t*-BuLi (4)	1	5	0	98	90

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



without LiBr 98% C.T., 83% yield
with LiBr 82% C.T., 76% yield

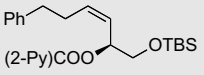
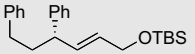
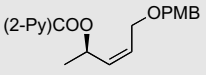
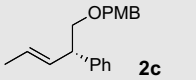
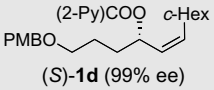
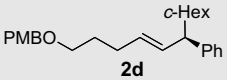
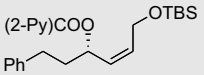
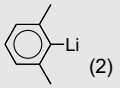
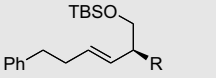
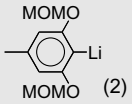
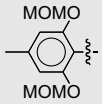
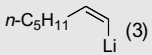
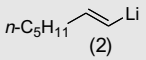
(1)

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_2O, and PhLi (2 equiv) produced with LiX (2 equiv; X = Br, I), $Me_2C{=}CH_2$ (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 $MgBr_2$ (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_N2' 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 $MgBr_2$ (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-$Me_2C_6H_3Br$ through lithium–halogen exchange with *t*-BuLi followed by complexation with CuBr·Me_2S. 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-$(MOMO)_2$-5-MeC_6H_3 by *ortho* lithiation[11] with *n*-BuLi followed by complexation with CuBr·Me_2S. This copper reagent upon reaction with (*S*)-**1a** furnished the expected product **2f** as well (entry 5).

Table 3
Allylic substitution of optically active picolinoates with copper reagents[a]

Entry	Allylic picolinoate (% ee)	RLi (equiv)	Method giving RLi	$CuBr{\cdot}Me_2S$ (equiv)	$MgBr_2$ (equiv)	Anti S_N2' product[b,c]		
						Structure	CT (%)	Yield (%)
1	 (*S*)-**1b** (99% ee)	PhLi (2)	—	1	3	 **2b**	99	87
2	 (*R*)-**1c** (99% ee)	PhLi (2)	—	1	3	 **2c**	98	84
3	 (*S*)-**1d** (99% ee)	PhLi (2)	—	1	3	 **2d**	98	94
4	 (*S*)-**1a** (97% ee)	 (2)	Li–Br exchange[d]	1	5	 **2e**, R = $2,6\text{-}Me_2C_6H_3$	97	88
5	(*S*)-**1a** (98% ee)	 (2)	*ortho* lithiation using *n*-BuLi	1	3	**2f**, R = 	>99	97
6	(*S*)-**1a** (98% ee)	 (3)	Li–I exchange[d]	1.5	7	**2g**, R = $n\text{-}C_5H_{11}$ 	98	75
7	(*S*)-**1a** (95% ee)	 (2)	Li–I exchange[d]	1	5	**2h**, R = 	98	93

[a] Reactions were carried out at 0 °C for 1 h.
[b] Regioselectivities for all of the reactions were >98% by ^1H NMR spectroscopy.
[c] The absolute configuration of **2b** was confirmed by converting to the known compounds. Those for other products **2c**–**j** were determined by analogy of **2a** and **2b**.
[d] Corresponding halide (3 or 2 equiv) and *t*-BuLi (6 or 4 equiv).

Note that the *ortho* lithiation is more convenient than the lithium–bromine exchange of the corresponding bromide in that additional steps are required for the preparation of bromide.

The present reaction is highlighted by reactions shown in entries 6 and 7. Usually, Grignard preparation from alkenyl halides suffers from isomerization of the double bond.[12] In contrast, the stereodefined alkenyllithiums generated from the corresponding cis and trans 1-heptenyl iodides were transformed to copper complexes, which furnished **2g** and **2h** without isomerization of the olefin geometry.

In summary, we have established an organolithium-based version of copper-assisted substitution of allylic picolinoates. The preparations of organolithiums such as lithium–halogen exchange and *ortho* lithiation were successfully coupled with the allylic substitution as delineated in Table 3, and thus providing another advantage for the allylic substitution using allylic picolinoates.

Acknowledgments

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7. Relative prices (Aldrich) of the major leaving groups as compared with picolinic acid (28 $/mol): $C_6F_5CO_2H$ 43 times; *o*-$(Ph_2P)C_6H_4CO_2H$ 330 times; *o*-$(Ph_2P{=}O)C_6H_4CO_2H$ available by oxidation of *o*-$(Ph_2P)C_6H_4CO_2H$.
8. Purchased from Kanto Chemical, Japan.
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10. To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (39.5 mg, 0.192 mmol) in THF (1.6 mL) were added PhLi (0.180 mL, 1.08 M in cyclohexane–Et_2O, 0.194 mmol) and $MgBr_2$ (1.40 mL, 0.20 M in THF, 0.280 mmol). After 30 min at 0 °C, a solution of (*S*)-**1a** (39.5 mg, 0.0960 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The resulting mixture was stirred at 0 °C for 1 h, and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*R*)-**2a** (34.0 mg, 97%). The ^1H NMR spectrum of (*R*)-**2a** was identical with that reported.[6] Enantiomeric information (96% ee, 98% CT) was determined by HPLC analysis of the corresponding alcohol: Chiralcel OD-H, hexane/*i*-PrOH = 98/2, 0.5 mL/min, t_R/min = 51.2 (*R*), 54.4 (*S*).
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