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Picolinoxy Group, a New Leaving Group for anti S_N2' Selective Allylic Substitution with Aryl Anions Based on Grignard Reagents

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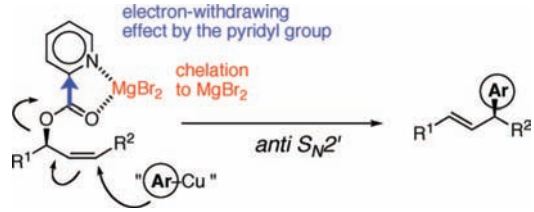
ABSTRACT



The picolinoxy group was found to be an extremely powerful leaving group for allylic substitution with aryl nucleophiles derived from ArMgBr and CuBr•Me_2S. The substitution proceeds with anti S_N2' pathway and with high chirality transfer. The electron-withdrawing effect of the pyridyl group and chelation to $MgBr_2$ are likely the origin of success. Results suggesting these effects were obtained.

Copper-promoted allylic substitution of optically enriched secondary allylic alcohol derivatives with hard nucleophiles is a potentially useful method for construction of an asymmetric C−C bond.[1] Since the α and γ positions of the allylic moiety are susceptible, regio-(α vs γ) and stereoselections should be highly controlled. Furthermore, stoichiometric use of reagent and low cost for obtaining the leaving group are desirable. Thus far, good to excellent levels of the selectivities have been attained with the following leaving group/reagent systems: $C_6F_5CO_2$-,[2] 2,6-$F_2C_6H_3CO_2$- (in one occasion),[2f] and *o*-$(Ph)_2P(=O)C_6H_4CO_2$-(*o*-DPPB oxide group)[3] with R_2Zn/CuCN•2LiCl; $(RO)_2P(O)O$-[4] with R_2Zn/CuCN•2LiCl; MsO in γ-mesyloxy-α,β-unsaturated esters[5] with $R_2Cu(CN)Li_2$•BF_3 or $RCu(CN)Li$•BF_3; *o*-$(Ph)_2PC_6H_4CO_2$-

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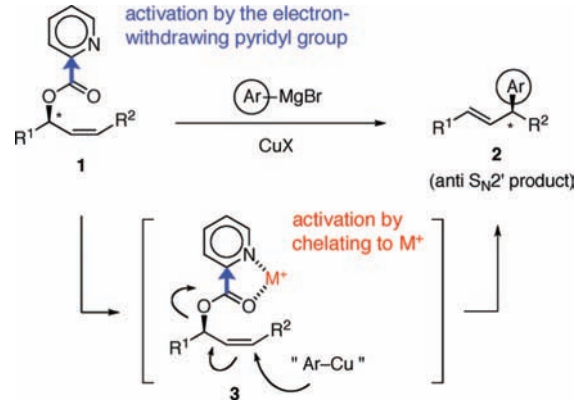
(*o*-DPPB group)[6] with RMgX/CuBr•Me_2S, etc.[7] Among these leaving groups, the *o*-DPPB group meets the requirement for the reagent stoichiometry, and thus the stereoselective synthesis of certain polyketides of deoxy-type and tocopherol has been concisely attained.[8–10] However, the *o*-DPPB group is quite expensive, while the other leaving groups generally require a large quantity of the reagents.

It should be noted that these reaction systems have been developed for alkyl reagents (sp^3-C reagents). Unfortunately, application of the systems to aryl and alkenyl reagents (sp^2-C reagents) has been unsuccessful[4b,11] except for certain types of reactive or sterically biased substrates.[2a,f,12–14] The lower nucleophilicity of the sp^2-C reagents is responsible for the unsuccessful results. Recently, the regioselectivity in the reaction of a racemic allylic *o*-DPPB ester with copper reagents derived from PhMgBr and CH_2═C(Me)MgBr was improved (use of CH_2Cl_2 in place of Et_2O or slow addition),[6b] but the scope of substrates to be covered by the improved conditions and the chirality transfer (C/T, (% ee of product)/(% ee of substrate) × 100) thereof are uncertain.

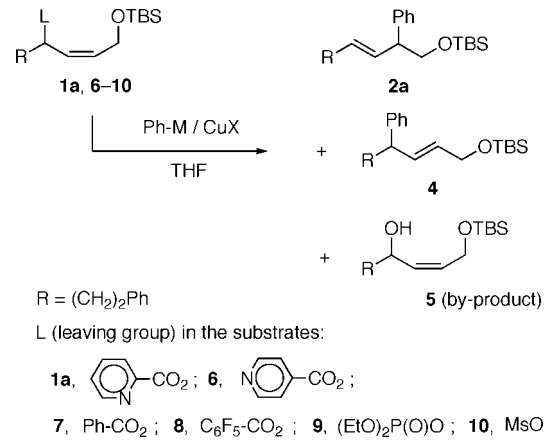
To overcome the above limitation associated with the sp^2-C reagents, we directed our attention to the picolinoxy group (2-pyridyl-CO_2-),[15] for which we expected two types of activations (Scheme 1). One is electrostatic activation by the electron-withdrawing pyridyl group as the C_6F_5 group in the $C_6F_5CO_2$ moiety. The other is dynamic activation induced by chelating the carbonyl oxygen and the pyridyl nitrogen to a metal cation (M^+) as illustrated in **3**, Scheme 1. In addition, picolinic acid is quite inexpensive.[16] Herein, we

Scheme 1. Expected Activations of the Picolinoxy Group in the Allylic Substitution



describe successful results of this idea with aryl reagents of an ArMgBr/CuX type.

A phenyl reagent derived from PhMgBr (2 equiv) and CuBr•Me_2S (1 equiv) was first submitted to the allylic substitution with the racemic allylic picolinate **1a** that was selected as a typical substrate (eq 1).



The reaction at 0 °C in THF completed within 1 h to afford the desired S_N2' product **2a** with high regioselectivity (99:1) over the S_N2 product **4**[17] by ^1H NMR spectroscopy (Table 1, entry 2); in contrast, the trans isomer of **1a** showed low regioselectivity.[18] The free alcohol **5** was not detected. Even with 1.2 equiv of PhMgBr the reaction was completed (entry 4).[19] In contrast to **1a**, isonicotinate **6** underwent incomplete reaction even at somewhat higher temperatures (0 °C to rt) (entry 10), while no reaction took place with benzoate **7** (entry 11). The high reactivity observed for the picolinoxy group could be understandable by the dual effect we have postulated in the above paragraph.

Reagents with different Ph/Cu ratios of 2:0.5 and 2:2 provided similarly high reactivity and regioselectivity (entries

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(12) (a) Yamazaki, T.; Umetani, H.; Kitazume, T. *Tetrahedron Lett.* **1997**, *38*, 6705–6708. (b) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832–11833. (c) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3000–3006.

(13) In contrast to the *o*-DPPB ester, the *o*-DPPB oxide ester[3b] requires 2 equiv of Ph_2Zn/Cu(CN)•2LiCl, which is equal to 4 equiv of the Ph anion.

(14) Another solution is PPh_2 directed nickel-catalyzed substitution of allylic ethers possessing the PPh_2 ligand in substrates. However, removal of the PPh_2 group in the products is the another problem of this approach: Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117* , 727–7274.

(15) (a) On the other hand, allylic substitution of 2-alkenyl-1-ol derivatives with a pyridyloxy group as a leaving group was reported to show similar reactivity and regioselectivity to the corresponding acetates: Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585–5588. (b) Okamoto, S.; Tominaga, S.; Saino, N.; Kase, K.; Shimoda, K. *J. Organomet. Chem.* **2005**, *690*, 6001–6007.

(16) Relative prices (Aldrich) of the major leaving groups as compared with picolinic acid (28 $/mol): $C_6F_5CO_2H$ 43 times; *o*-$(Ph)_2PC_6H_4CO_2H$ 330 times; $(Ph)_2P(=O)C_6H_4CO_2H$ available by oxidation of $(Ph)_2PC_6H_4$-CO_2H; $(EtO)_2P(O)Cl$ 4 times; cf. DCC 2.1 times.

(17) Authentic **4** possessing the trans olefin in it was synthesized unambiguously (see entry 8 of Table 2 for the enantiomerically enriched version of **4** as (*S*)-**2e**).

(18) A mixture of **2a** and **4** in a 60:40 ratio was obtained from the trans isomer of **1a**.

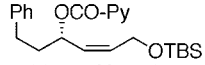
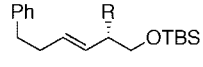
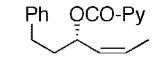
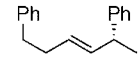
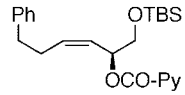
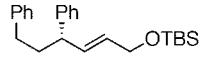
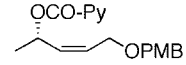
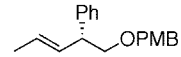
(19) Two equivalents of ArMgBr were used in most cases to avoid any technical error.

Table 1. Exploration of Leaving Groups and Reagents in an Allylic Substitution

entry	substrate	reagent (equiv)	temp (°C)	time (h)	ratio of **2a/4/5/1a**[a]	Yield [%][b,c]
1	**1a**	PhMgBr (2)/CuBr•Me_2S (0.5)	0	1	99:1:0:0	85
2	**1a**	PhMgBr (2)/CuBr•Me_2S (1)	0	1	99:1:0:0	91
3	**1a**	PhMgBr (2)/CuBr•Me_2S (2)	0	1.5	98:2:0:0	84
4	**1a**	PhMgBr (1.2)/CuBr•Me_2S (0.5)	0	1	98:0:1:1	92
5	**1a**	PhMgBr (2)/CuCN (0.5)[d]	0	1	96:0:2:2	88
6	**1a**	Ph_2Zn•2LiBr (3)/CuBr•Me_2S (1.5)	−15 to 0	4	31:0:46:23	ND
7	**1a**	Ph_2Zn•2LiBr (3)/CuCN•2LiCl (1.5)	−15 to 0	4	25:0:60:15	ND
8	**1a**	Ph_2Zn•2$MgBr_2$ (2)/CuBr•Me_2S (1)	−15 to 0	1	99:1:0:0	91
9	**1a**	Ph_2Zn•2$MgBr_2$ (2)/CuCN•2LiCl (1)	−15 to 0	1.5	84:1:5:10	ND
10	**6**	PhMgBr (2)/CuBr•Me_2S (1)	0 to rt	13	46:0:0:54	ND
11	**7**	PhMgBr (2)/CuBr•Me_2S (1)	0 to rt	20	0:0:0:100	-
12	**8**	PhMgBr (2)/CuBr•Me_2S (2)	0 to rt	18	60:0:40:0	ND
13	**9**	PhMgBr (3)/CuBr•Me_2S (1)	0[e]	3	99[f]:1:0:0	90

[a] Zero (0) is given in the case the product signal(s) was not detected by ^{1}H NMR spectroscopy. [b] Isolated yield of **2a** (and **4**, if produced). [c] ND: not determined. [d] Other CuX (X = Cl, Br, I) showed similar results to CuCN. [e] Almost no reaction took place at −50 to −30 °C for 4 h. [f] An olefinic impurity was seen in the ^{1}H NMR spectrum.

Table 2. Allylic Substitution of Enantiomerically Enriched Allylic Picolinates

entry	substrate (% ee)	reagent (equiv)	CuBr•Me_2S (equiv)	temp (°C)	time (h)	product[a,b]	yield (%)	% ee	C/T[c] (%)
1	 (*S*)-**1a** (90% ee)	PhMgBr (2)	0.5	0	1	 (*R*)-**2a**, R = Ph	85	48	53
2	(*S*)-**1a** (90% ee)	PhMgBr (2)	0.5	–20 to –15	1	(*R*)-**2a**	84	64	71
3	(*S*)-**1a** (90% ee)	PhMgBr (2)	0.5	–60 to –40	1	(*R*)-**2a**	83	88	98
4	(*S*)-**1a** (90% ee)	PhMgBr (2)	1	–60 to –40	1	(*R*)-**2a**	89	88	98
5	(*S*)-**1a** (90% ee)	*o*-MeC_6H_4MgBr (2)	1	–60 to –40	1	(*R*)-**2b**, R = *o*-MeC_6H_4	81	89	99
6	(*S*)-**1a** (90% ee)	*o*-$MeOC_6H_4MgBr$ (2)	1	–60 to –40	1	(*R*)-**2c**, R = *o*-$MeOC_6H_4$	85	88	98
7	 (*S*)-**1b** (89% ee)	PhMgBr (2)	1	–60 to –40	1	 (*R*)-**2d**	86	89	99
8	 (*S*)-**1c** (95% ee)	PhMgBr (2)	1	–40	1	 (*S*)-**2e**	93	92	97
9	 (*S*)-**1d** (97% ee)	PhMgBr (2)	1	–60 to –40	1	 (*R*)-**2f**	83	97	99

[a] Absolute configurations of **2a**, **2d**, and **2e** were determined unambiguously, while that of the products **2b**, **2c**, and **2f** were determined by analogy. [b] Regioselectivities of >98:2 were determined by ^{1}H NMR spectroscopy. [c] Chirality transfers were determined by chiral HPLC of the derivatives.

1, 3). The independence of the results from the Ph/Cu composition (entries 1−3) is unusual in the allylic substitution. From the synthetic point of view, the independence is welcome since the precise measurement of the source reagents is no longer necessary. Other copper salts (CuCl, CuBr, CuI, CuCN) were equally effective (entry 5 for CuCN). However, except for CuCN, the other reagents derived with CuX (X = Cl, Br, I) showed slightly decreased reactivity when reactions were carried out at lower temperatures (ca. 10% recovery of **1a**) (data not shown).

Although we have attained full success using PhMgBr as a reagent source, phenylzinc reagents derived from PhM (M = Li, MgBr) and $ZnBr_2$ (therefore one more step of the transmetalation is required) were briefly examined. Surprisingly, Ph_2Zn derived from PhLi and $ZnBr_2$ with CuBr•Me_2S and that with CuCN•2LiCl (Knochel reagent)[2a,c–f,4c,d,20] were ill-suited to **1a** (entries 6, 7). On the other hand, Ph_2Zn derived from PhMgBr with CuBr•Me_2S (entry 8) afforded the S_N2' product **2a** efficiently. These results suggest that the metal cation to be chelated effectively

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to the picolinoxy group is $MgBr_2$produced in situ from PhMgBr and CuBr•Me_2S.

To compare reactivity of the picolinoxy group with the others, pentafluorobenzoate **8** and phosphonate **9** were submitted to reaction with PhMgBr/CuBr•Me_2S (entries 12 and 13). The former produced alcohol **5** competitively and the latter provided a mixture of **2a** and an olefinic isomer (footnote f). On the other hand, an attempted mesylation gave a mixture of products.

We then studied the reaction course and the chirality transfer (C/T) using (*S*)-**1a** of 90% ee, which was prepared through the Sharpless asymmetric epoxidation[21] (see Supporting Information). The anti S_N2' pathway with the Ph/Cu reagent of 2:0.5 ratio was proven by establishing the absolute configuration of the product **2a** as *R* (Table 2, entries 1–3).[22] Unexpectedly, the C/T for the reaction at 0 °C was unacceptable (entry 1). However, we were pleased to attain high level of C/T (98%) at −60 to −40 °C (entry 3, cf. entry 2). High efficiency was also recorded with the Ph/Cu reagent of 2:1 ratio (entry 4).

To clarify the range of substrates the present reaction system covers, the following reactions were examined. The substituent (Me and MeO groups) at the ortho position of the phenyl ring neither retarded the reaction nor lowered the C/T (entries 5 and 6). Substrates (*S*)-**1b** and (*S*)-**1c** produced (*R*)-**2d** and (*S*)-**2e**, respectively, with the almost same efficiency as (*S*)-**1a** (entries 7 and 8).[23] These results clearly indicate that anti S_N2' selectivity and the reactivity are not affected by any methylene substituents at the α and γ positions. An additional result supporting this conclusion is presented in entry 9.

In summary, we have developed anti S_N2' selective allylic substitution for the aryl reagents, for the first time, using the picolinoxy group as the powerful leaving group. The reaction proceeded with the efficient chirality transfer (C/T). Additionally, picolinic acid/DCC and RMgBr/CuBr•Me_2S are inexpensive, while both enantiomers of the starting allylic alcohols are easily available by asymmetric reactions and from natural sources (condensation using DCC and the Mitsunobu inversion). The concept of the chelation-induced activation of the picolinoxy leaving group seems applicable to other types of coupling reactions. We are continuing investigation along this line.

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Supporting Information Available: Experimental procedures and spectral data of compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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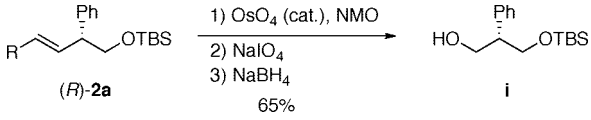
(22) Transformed into the known compound **i** (*S* configuration): $[\alpha]^{25}_D$−13 (*c* 0.12, $CHCl_3$); cf. lit. $[\alpha]^{23}_D$ +14.6 (*c* 0.12, $CHCl_3$) for the (*R*)-enantiomer. Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983–6998.



(23) The absolute configurations of (*R*)-**2d** and (*S*)-**2e** in Table 2 were determined by transformation into the known compounds (see Supporting Information). Other products of the allylic substitution were assigned by analogy.