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Synthesis of the Active Form of Loxoprofen by Using Allylic Substitutions in Two Steps

Tomonori Hyodo, Yohei Kiyotsuka, and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

ykobayas@bio.titech.ac.jp

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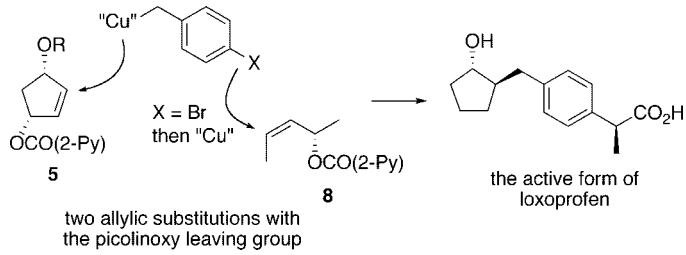
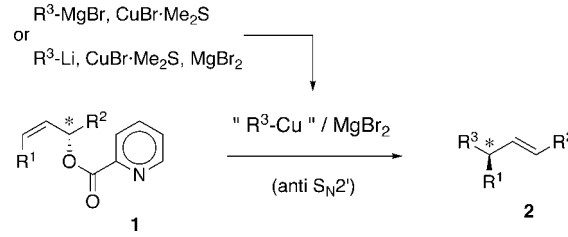
ABSTRACT



High regioselectivity for allylic substitution of the cyclopentenyl picolinate 5 with benzylcopper reagent was attained with $ZnBr_2$, and the finding was applied to the *p*-$BrC_6H_4CH_2$ reagent. The cyclopentene moiety in the product was reduced to the cyclopentane, and the *p*-BrC_6H_4 was converted to the "Cu"C_6H_4 for the second allylic substitution with picolinate 8 to furnish the title compound after oxidative cleavage of the resulting olefin moiety.

Copper-assisted substitution of secondary allylic esters with alkyl reagents usually produces anti S_N2' products with efficient regioselectivity and chirality transfer.[1] However, substitution with aryl and alkenyl anions has suffered from insufficient regioselectivity due to the low nucleophilicity. To improve the inconvenience, we have reported the picolinoxy leaving group (2-$PyCO_2$-), with which aryl and alkenyl copper reagents afforded the anti S_N2' products highly efficiently (Scheme 1).[2] The electron withdrawal by the pyridyl unit and the chelation of the group to $MgBr_2$ are responsible for the activation of the group. To demonstrate the new allylation system, we chose the active form of anti-inflammatory loxoprofen, i.e., **4**,[3] as a target,[4] for which we envisioned substitution of picolinate **8** and aryl copper reagent **9** as delineated in Scheme 2. In addition, we studied substitution of the picolinate **5** with benzylic copper reagent **6** for synthesis

Scheme 1. Allylic Substitution with the Picolinoxy Leaving Group



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(2) (a) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722. (b) Kiyotsuka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **2008**, *49*, 7256–7259.

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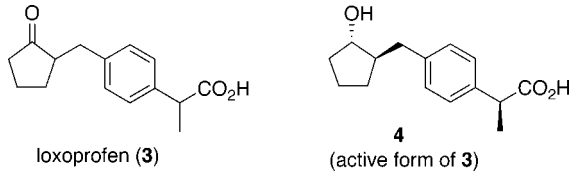
Table 1. Reaction of *rac*-**5a** with BnMgBr

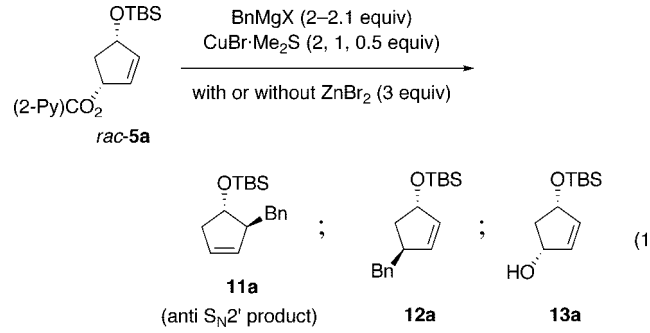
entry	equiv of BnMgX	equiv of $CuBr{\cdot}Me_2S$	equiv of $ZnBr_2$	temp, °C	time, h	ratio[a] of **11a**:**12a**:**13a**:*rac*-**5a**	combined yield, %[b]
1	BnMgBr,2.0	2.1	0	0 to rt	14	84:0:16:0	nd
2	BnMgBr,2.0	2.1	3.0	0 to rt	14	66:0:20:14	nd
3	BnMgBr,2.1	1.0	0	0	1	90:10:0:0	82
4	BnMgBr,2.1	1.0	3.0[c]	0	1	100:0:0:0	81
5	BnMgCl,2.1	1.0	0	0	1	95:5:0:0	97
6	BnMgCl,2.1	1.0	3.0	0	1	100:0:0:0	100
7	BnMgBr,2.0	0.5	0	0	1	88:12:0:0	nd
8	BnMgBr,2.0	0.5	3.0	0	1	100:0:0:0	nd

[a] Determined by ^{1}H NMR spectroscopy. Zero (0) indicates the case that signals were not seen in the expanded ^{1}H NMR spectra. [b] nd, not determined. [c] Complete regioselectivity was also obtained with 1.0 and 2.1 equiv of $ZnBr_2$, whereas use of 6.3 equiv of $ZnBr_2$ produced a mixture of **11a** and **13a** in a 84:16 ratio.

of the bromide **7**, a precursor of the reagent **9**, because the regioselectivity of the previous method to obtain alcohol **7** (R = H) is somewhat low.[5]

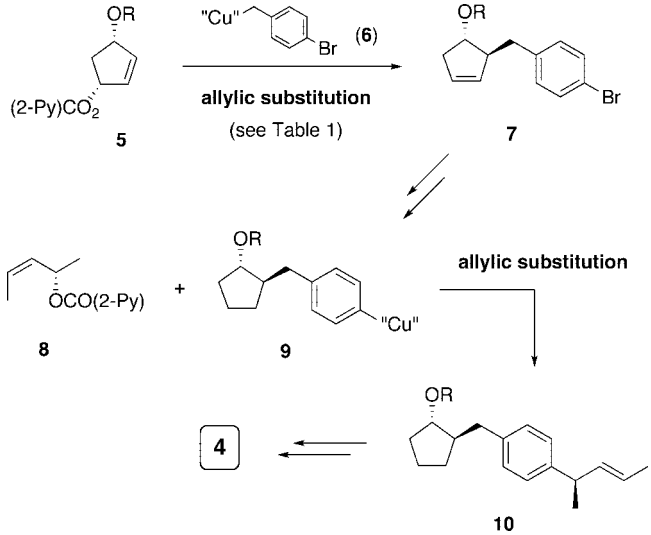


Since allylic picolinate **5** and *p*-bromobenzylcopper reagent **6** in the first substitution were new types that had not been studied in our early investigation with the acyclic picolinates and aryl coppers,[2] we first studied the reaction using a racemic picolinate *rac*-**5a** possessing the TBS group (R = TBS) and three benzylcopper reagents derived from BnMgBr (2.0−2.1 equiv) and varied quantities of $CuBr{\cdot}Me_2S$ (2.0, 1.0, and 0.5 equiv) according to the previous results with $ArMgBr/CuBr{\cdot}Me_2S$ (eq 1).



The reaction was carried out at 0 °C in THF/Et_2O (3−7:1). When reaction was not completed after 1 h, reaction was continued at higher temperature (rt) for 14 h. Ratios of the anti S_N2' product **11a**, regioisomer **12a**, alcohol **13a**, and/or $(Bn)_2$[6] were determined by ^{1}H NMR spectroscopy, and yield of product **11a** was calculated on the basis of the ^{1}H NMR ratio of the isolated (and weighted) mixture of **11a**, **12a**, and/or $(Bn)_2$.[7] As summarized in Table 1, copper reagents derived from BnMgBr (2.0−2.1 equiv) and $CuBr{\cdot}Me_2S$ (1.0 and 0.5 equiv), respectively, afforded **11a** as a major product (entries 3 and 7), whereas a copper reagent derived from BnMgBr/$CuBr{\cdot}Me_2S$ in 2.0/2.1 equiv was less reactive at 0 °C and produced alcohol **13a** competitively at rt (entry 1). Although the observed regioselectivities of **11a** in the former two entries were in good level (88−90%), separation of regioisomer **12a** by chromatography was unsuccessful. To improve the selectivity, we postulated an activation of the picolinoxy moiety by ZnX_2, which would be stronger than $MgBr_2$ generated in situ from the reagents. Indeed, addition of $ZnBr_2$ (3.0 equiv) brought the regioselectivity to a substantially complete level for $BnMgBr/CuBr{\cdot}Me_2S$ in 2/1

Scheme 2. Construction of **4**



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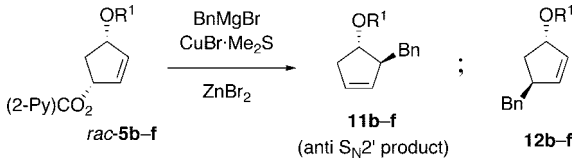
(4) Preparation by separation of the stereoisomers: (a) Naruto, S.; Terada, A. *Chem. Pharm. Bull.* **1983**, *31*, 4319–4323. (b) Mandai, T.; Yamakawa, T. *Synlett* **2000**, 862–864.
(5) Ito, M.; Matsuumi, M.; Murugeshi, M. G.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881–5889.
(6) Probably produced by the Wurtz-type coupling during the Grignard preparation from BnBr and Mg and/or by oxidative coupling of the remaining reagent during the workup.
(7) The trans stereochemistry of the products **11a** and **12a** was determined by correlation to the corresponding alcohols, which were synthesized by the previous CuCN-catalyzed substitution of the monoacetate of 4-cyclopenten-1,3-diol with BnMgBr.[5]

and 2/0.5 equiv (entries 4 and 8), though that in 2/2 equiv was not improved (entry 2). Among other molar ratios of $ZnBr_2$ examined, 1 and 2 equiv were similarly effective (cf., footnote c of Table 1).[8]

A copper reagent derived from BnMgCl (2.1 equiv) and $CuBr{\cdot}Me_2S$ (1.0 equiv) in the presence of $ZnBr_2$ (3.0 equiv) afforded **11a** as well (entry 6; see entry 5 for the result obtained in the absence of $ZnBr_2$). These results with BnMgCl are informative in a case where benzylic magnesium bromides are hardly accessible from $ArCH_2Br$ and Mg due to the rapid homocoupling reaction. In addition, $ZnCl_2$ in place of $ZnBr_2$ retarded the reaction with the copper reagents derived from BnMgCl/$CuBr{\cdot}Me_2S$ in 2.1/1.0 and 2.0/0.5 equiv at 0 °C, and further reaction at rt produced a mixture of **11a** and **13a**, though complete regioselectivity was observed (data not shown).

Next, the reaction conditions of entry 4 of Table 1 were applied to substrates *rac*-**5b**−**f**, which possess protective groups other than the TBS group (Table 2). In all cases $ZnBr_2$ assisted exclusive production of the anti S_N2' products **11b**−**f**. Interestingly, the native selectivity obtained without $ZnBr_2$ (ratios in parentheses) was dependent on the protective group: low selectivity with the electron-donating groups (TBDPS and Bn in entries 1 and 2) as in the case of the TBS group and high selectivity with the electron-withdrawing group (Ac and Piv in entries 4 and 5). In addition, entries 4 and 5 show a chemoselectivity indicating the picolinoxy group is the better leaving group compared to the AcO and PivO groups (see ref 8).

Table 2. Effect of Substituent on the Regioselectivity[a]

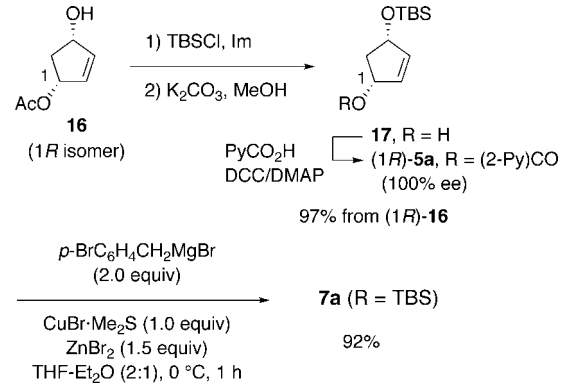


entry	substrate	R^1	ratio[b,c,d] of **11**:**12**	combined yield, %[e]
1	*rac*-**5b**	TBDPS	99:1	nd
			(60:40)	nd
2	*rac*-**5c**	Bn	99:1	nd
			(66:34)	nd
3	*rac*-**5d**	PMB	100:0	95
			(95:5)	83
4	*rac*-**5e**	Ac	100:0	82
			(99:1)	76
5	*rac*-**5f**	Piv	100:0	90
			(100:0)	82

[a] Reactions with BnMgBr (2.1 equiv) and $CuBr{\cdot}Me_2S$ (1.0 equiv) were carried out in the presence of $ZnBr_2$ (3.1 equiv) in THF/Et_2O (3−7:1) at 0 °C for 1 h. [b] Determined by ^1H NMR spectroscopy. Zero (0) indicates the case that signals for **12** were not seen in the expanded ^1H NMR spectra. [c] The corresponding alcohol and the starting compound were not obtained. [d] The ratios obtained without $ZnBr_2$ are shown in parentheses. [e] nd, not determined.

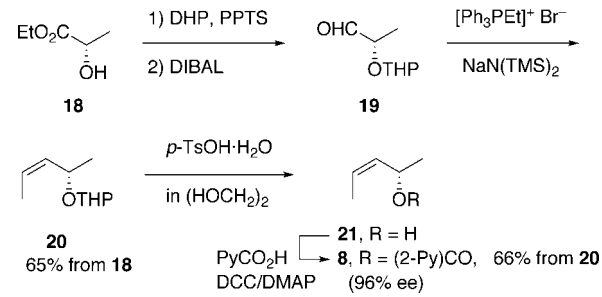
With the above results in mind, we chose (*R*)-**5a** (R = TBS) as a substrate in the first allylic substitution with *p*-$BrC_6H_4CH_2MgBr$/$CuBr{\cdot}Me_2S$. The substrate (∼100% ee by chiral HPLC) was synthesized by a method delineated in Scheme 3 starting with (1*R*)-monoacetate **16**, obtained by lipase-catalyzed hydrolysis of the corresponding diacetate followed by recrystallization.[9] Allylic substitution of (1*R*)-**5a** with the copper reagent derived from *p*-$BrC_6H_4CH_2MgBr$ (2.0 equiv) and $CuBr{\cdot}Me_2S$ (1.0 equiv) proceeded smoothly under the above conditions (0 °C, 1 h) to afford **7a** (R = TBS) regioselectively, which was isolated as a mixture with (*p*-$XC_6H_4CH_2)_2$ (X = Br and H). The mixture was treated with Bu_4NF, and the alcohol separated by chromatography was resilylated to **7a** for the further reaction (92% from (1*R*)-**5a**).

Scheme 3. Synthesis of the Key Intermediate **7a** through the Picolinate (1*R*)-**5a**

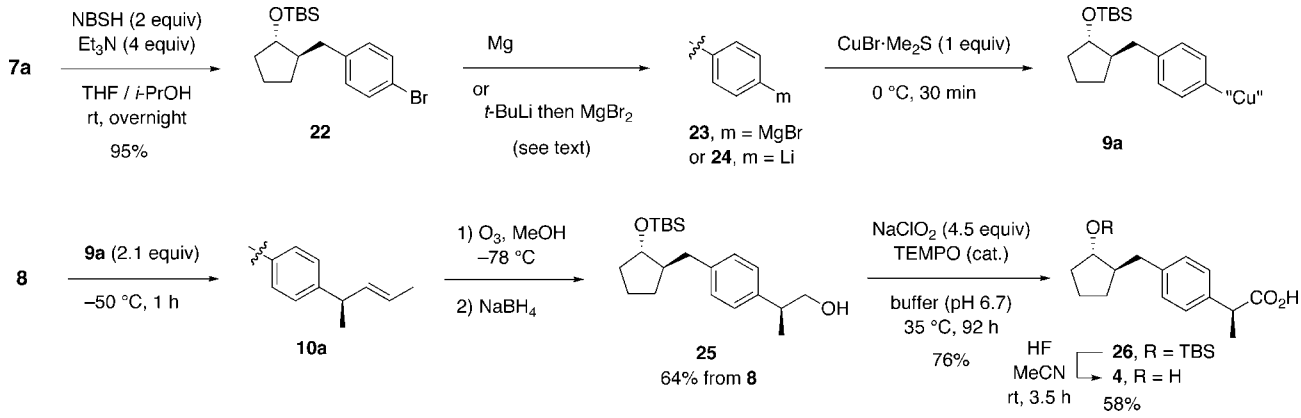


Allylic picolinate **8**, another key substrate, was prepared by a method shown in Scheme 4. Wittig reaction of aldehyde **19**, obtained from lactate **18** (natural form) in two steps, with an ylide derived from $[Ph_3PEt]^+Br^-$ and $NaN(TMS)_2$ afforded cis olefin **20** exclusively in 65% overall yield. Removal of the THP group in MeOH was successful. Unfortunately, removal of MeOH co-extracted with volatile **21** by evaporation resulted in substantial loss of **21**. To avoid the loss ethylene glycol was used as a solvent. The alcohol **21** extracted was free of the glycol for the next esterification with 2-$PyCO_2H$ to afford picolinate **8** (96% ee (by chiral HPLC)) in 66% yield from **20**.

Scheme 4. Synthesis of Picolinate **8**



Scheme 5. Latter Stage of the Synthesis Furnishing the Target Compound **4**



The cyclopentene part of **7a** was reduced with NBSH[10] to afford **22** in good yield (Scheme 5). Unfortunately, attempted preparation of the Grignard reagent **23** several times afforded varying concentrations of **23**. Alternatively, **22** was lithiataed with *t*-BuLi, and the resulting lithium anion **24** was converted to the copper reagent by transmetalation with $MgBr_2$ and then with $CuBr{\cdot}Me_2S$. The reagent thus prepared was subjected to reaction with picolinate **8** to produce **10a**, which underwent ozonolysis to afford, after in situ reduction, alcohol **25** in 64% yield from **8**. Oxidation of alcohol **25** to acid **26** was carried out successfully by using $NaClO_2$/TEMPO (cat.).[11,12] Finally, removal of the TBS group furnished **4** in 58% yield: $[\alpha]^{33}_D$ +77 (*c* 0.94, EtOH); cf. lit.[4b] $[\alpha]^{20}_D$ +72 (*c* 0.15, EtOH).

In summary, substitution of the cyclopentenyl picolinates and benzylic reagents was studied to find the substantial role of $ZnBr_2$ for the anti S_N2' preference, and the finding was applied to stereoselective synthesis of the active form of loxoprofen.

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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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(8) No substitution took place with the acetate corresponding to the picolinate *rac*-**5a** under the conditions of entry 4.

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(12) Jones reagent and $NaIO_4$ catalyzed by $RuCl_3$ afforded a mixture of acid **26** and the corresponding acetophenone as a byproduct.