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Realization of *Anti*-S_N2' Selective Allylation of 4-Cyclopentene-1,3-diol Monoester with Aryl- and Alkenyl-Zinc Reagents

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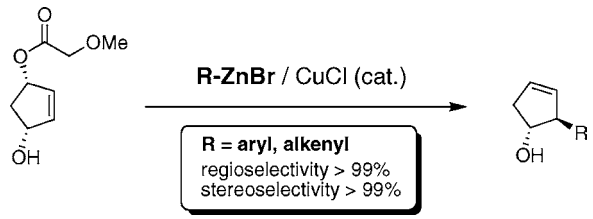
ABSTRACT



***Anti*-S_N2' mode of allylation of the monoester of 4-cyclopentene-1,3-diol with aryl and alkenyl anions was achieved, for the first time, with the $MeOCH_2CO_2$– group as a leaving group to which R-ZnBr and CuCl (as a catalyst) were best fitted. The aryl groups successfully installed were Ph, *o*- and *p*-MeC_6H_4, *o*-$MOMOC_6H_4$, *o*-$MeOC_6H_4$, and *p*-F–C_6H_4, while cis and trans alkenyl groups were attached with retention of the olefinic stereochemistries.**

The title monoester **1** is the complementary starting material to the well-established cyclopentenones in organic synthesis.[1] For installation of a side chain on it, allylic substitution is a convenient reaction in regard to accessibility of various types of reagents,[2] though the regio- and stereochemistries should be highly controlled. So far, this type of allylic substitution has partially been successful with certain types of reagents. In brief, the palladium-catalyzed allylation of monoacetate **1A** with soft carbon nucleophiles proceeds efficiently at α carbon with retention of configuration.[3,4] On the other hand, reactivity and the selectivity with hard carbon nucleophiles are dependent on the type of reagents and the conditions. The nickel-catalyzed reaction of **1A** with aryl and alkenyl borates takes place regioselectively at α site with inversion of configuration (S_N2 type),[5] while the palladium-catalyzed reaction with alkyl and aryl Grignard reagents does at γ site with retention (syn-S_N2' type)[6] though the regioselectivity

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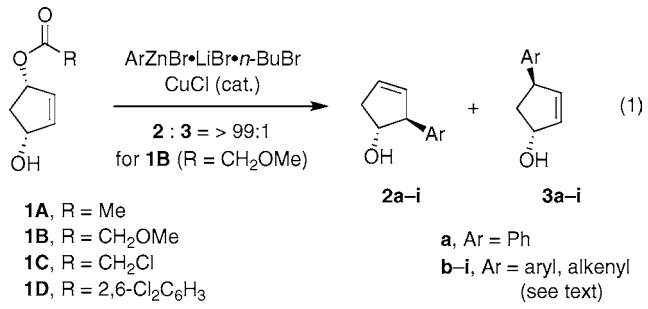
Table 1. CuX-Catalyzed Reaction of **1A**−**D** with PhZnX[a]

entry	substr.	R	reagent[c]	CuX	yields (%)[b] **2a**[d]	ester of **2a**	**3a**[d]	**4**	*anti*-S_N2':S_N2	convn (%)
1	**1A**	Me	PhZnBr·LiBr·*n*-BuBr	CuCl	24	1	0	0	> 99:1	−[e]
2	**1B**	CH_2OMe	PhZnBr·LiBr·*n*-BuBr	CuCl	88 (75)	6	0	0	> 99:1	100
3	**1C**	CH_2Cl	PhZnBr·LiBr·*n*-BuBr	CuCl	24	26	0	9	> 99:1	97[f]
4	**1D**	2,6-$Cl_2C_6H_3$	PhZnBr·LiBr·*n*-BuBr	CuCl	23	0	3	0	88:12	94[f]
5	**1B**	CH_2OMe	PhZnBr·LiBr	CuCl	86	7	0	3	> 99:1	100
6	**1B**	CH_2OMe	PhZnBr·LiBr·*n*-BuI	CuCl	93	4	0	0	> 99:1	100
7	**1B**	CH_2OMe	PhZnBr·LiBr·*n*-BuBr	CuBr	76	7	0	3	> 99:1	95
8	**1B**	CH_2OMe	PhZnBr·LiBr·*n*-BuBr	CuI	72	4	0	1	> 99:1	96
9	**1B**	CH_2OMe	PhZnBr·LiBr·*n*-BuBr	CuCN	9	13	0	5	> 99:1	91[f]
10	**1B**	CH_2OMe	PhZnBr·LiBr·*n*-BuBr	$(CuOTf)_2·C_6H_6$	44	14	0	3	> 99:1	86[f]
11	**1B**	CH_2OMe	PhZnBr·LiBr·*n*-BuBr	$Cu(OAc)_2$	16	17	0	7	> 99:1	81[f]
12	**1B**	CH_2OMe	PhZnCl·LiCl·*n*-BuBr	CuCl	6	22	0	12	> 99:1	−[e]
13	**1B**	CH_2OMe	PhZnI·LiI·*n*-BuBr	CuCl	17	13	4	0	81:19	89[f]

[a] Reactions were carried out with "PhZnX" (3 equiv) in the presence of a copper catalyst (30 mol %) in THF/Et_2O (2:1) at room temperature for 12 h. [b] Determined by ^1H NMR spectroscopy with 1-bromonaphtalene as an internal standard. [c] PhZnX·LiX·*n*-BuX′ were prepared from PhX′, *n*-BuLi, and ZnX_2, whereas PhZnBr·LiBr was derived from PhLi (purchased from a company) and $ZnBr_2$. [d] Ar = Ph. [e] Substrates **1A** and **1B** were recovered in 21 and 88% yields in entries 1 and 12, respectively. [f] Unidentified products were also produced.

is moderate. As for copper-mediated reaction with alkyl reagents, control at the α and γ sites with inversion (S_N2 and *anti*-S_N2' type) has been successful by properly choosing the ratio of alkyl-MgX/CuCN and the solvent among THF and Et_2O.[7,8] Later, the S_N2 type of the allylation was extended to aryl Grignard reagents.[9]

In contrast, application of the alkyl reagent system (RMgX/CuCN) developed for the *anti*-S_N2' allylation[7] to the phenyl reagent of several types produced a mixture of the regioisomers.[10,11] The low *anti*-S_N2' (high S_N2) selectivity of the aryl- and alkenyl reagents/CuX is also observed in the literatures with other cyclopentenyl esters[12] and epoxide.[13] The high *anti*-S_N2' selectivity has been reported with alkylmetal/CuX reagents.[14] Nevertheless, we continued investigation to realize *anti*-S_N2' selective allylation,[15] and eventually discovered a reaction system consisting of methoxyacetate **1B** (R = CH_2OMe), aryl- and alkenylzinc bromides (abbreviated as *sp*^{2}-RZnX), and a CuCl catalyst, for the first time (eq 1).



In general, *sp*^{2}-RZnX is the reagent used for the palladium- and nickel-catalyzed cross-coupling with aryl and alkenyl halides (known as the Negishi coupling),[16] whereas the use of *sp*^{2}-RZnX in palladium-catalyzed allylation of cyclic and acyclic allylic esters has been reported.[17] As for the copper-assisted allylation with *sp*^{2}-RZnX, the low regioselectivity and reactivity have been observed in the reaction with acyclic

(6) Hattori, H.; Abbas, A. A.; Kobayashi, Y. *Chem. Commun.* **2004**, 884−885.

(7) Ito, M.; Matsuumi, M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881−5889.

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(10) Reaction of **1A** in Et_2O with PhMgBr/CuCN (cat), $Ph_2Cu(CN)(MgBr)_2$, and PhCu(CN)(MgBr) gave **3a** (S_N2 product) in 10−60% yields with 70−60% regioselectivity, whereas that with PhCu(CN)(MgCl) and PhCu(CN)(MgBr) in THF afforded **2a** (*anti*-S_N2' product) in ca. 20% yields with ca. 70% regioselectivity.

(11) Low to moderate selectivities reported for allylation with *aryl*- and *alkenyl*-MgX/CuX: (a) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884−2891. (b) Torneiro, M.; Fall, Y.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1997**, *62*, 6344−6352. (c) Borthwick, S.; Dohle, W.; Hirst, P. R.; Booker-Milburn, K. I. *Tetrahedron Lett.* **2006**, *47*, 7205−7208.

(12) (a) Corey, E. J.; Mann, J. *J. Am. Chem. Soc.* **1973**, *95*, 6832−6833. (b) Finch, M. A. W.; Lee, T. V.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1979**, 677−678. (c) Mori, S.; Takechi, S. *Heterocycles* **1990**, *31*, 1195−1199. (d) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 234−236.

(13) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898−4913.

(14) (a) Curran, D. P.; Chen, M.-H.; Leszczweski, D.; Elliott, R. L.; Rakiewicz, D. M. *J. Org. Chem.* **1986**, *51*, 1612−1614. (b) Ernst, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4054−4056. (c) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059−1061. (d) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569−4572. (e) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021−1023.

(15) CuCl-catalyzed reactions of **1A** with PhMgBr and PhZnBr (from PhMgBr and $ZnBr_2$) both in THF and in Et_2O at room temperature for 12 h afforded a mixture of **2a** and **3a** in 39:61 and 64:36 ratios, respectively. Reaction with $Ph_2Cu(CN)Li_2$ (from PhLi and CuCN) in THF produced a 34:66 mixture. Knochel reagents derived from Ph_2Zn (from PhLi and $ZnBr_2$) and CuCN·2LiCl in 2:1 and 1:1 ratios in THF afforded a mixture of **2a** and **3a** with 54:46 and 77:23 ratios, respectively.

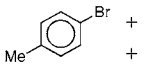
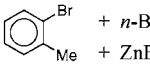
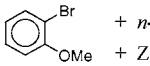
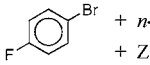
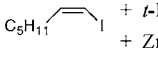
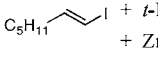
(16) (a) Negishi, E.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 1. (b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1; Wiley-VCH: Weinheim, 2002.

substrates[18] except for one cyclic case,[19] whereas high *anti*-S_N2' selectivity has been reported with *alkyl*-ZnX/CuX.[2b,14b,19,20] Recently, (sp^2-R)$_2$Zn was disclosed as the *anti*-S_N2' selective reagent in allylation with acyclic esters.[21]

The present investigation was initiated with a finding that reaction of allylic acetate **1A** (R = Me) with PhZnBr·LiBr·*n*-BuBr[22] (3 equiv), prepared from PhBr, *n*-BuLi, and $ZnBr_2$, in the presence of 30 mol % of CuCl at room temperature produced *anti*-S_N2' product **2a** (Ar = Ph) with high regioselectivity of >99% by ^{1}H NMR analysis, but only in 24% yield (Table 1, entry 1). Because the reaction proceeded incompletely, other leaving groups (RCO_2) with electron-withdrawing moieties in R were examined (entries 2−4). The best result was obtained with methoxyacetate **1B** to produce **2a** in high yield (75% isolated yield) with >99% regioselectivity (entry 2), whereas **1C** and **1D** afforded a mixture of products including **2a** in low yields (entries 3 and 4). We also examined reaction of **1B** with other "PhZnBr" prepared in different ways (PhLi + $ZnBr_2$ and PhI + *n*-BuLi + $ZnBr_2$) to expand reagent sources (entries 5 and 6 vs entry 2). A similar result observed with PhZnBr·LiBr[22] (entry 5) indicates no consumption of PhZnBr by perhaps conceivable copper-catalyzed coupling with *n*-BuBr that was coproduced with PhLi through the PhBr/*n*-BuLi exchange (entry 2). To our surprise, even *n*-BuI did not interfere the reaction nor produce any byproduct (entry 6). Examination of the reagent quantity revealed that 3 equiv is the minimum requirement for the high efficiency. Next, catalytic activity of copper salts other than CuCl and reactivity of reagents derived from ZnX_2 (X = Cl, I) were investigated. Among the copper salts used (entries 7−11), CuBr and CuI showed slightly lower efficiency in yield and in conversion. On the other hand, the reagents derived with ZnX_2 (X = Cl, I) were inferior than the $ZnBr_2$-based reagent (entries 12 and 13 vs entries 2, 5, and 6).

The procedure optimized above was applied to substituted phenyl zinc bromides to afford the *anti*-S_N2' products **2b**−**e** efficiently (Table 2, entries 1−4). Sterically congested reagents could be participants in the reaction (entries 2 and 3).

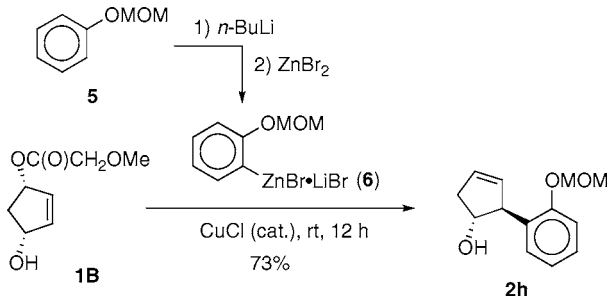
Table 2. CuCl-Catalyzed Reaction of **1B** (R = CH_2OMe) with Various Organozinc Bromides[a]

entry	reagent sources	yields (%)[b,c] **2**	ester[d]	**3**[e]	**2**:**3**[b]
1	 + *n*-BuLi + $ZnBr_2$	**2b**, 99 (77)	0	0	>99:1
2	 + *n*-BuLi + $ZnBr_2$	**2c**, 70 (58)	12	0	>99:1
3	 + *n*-BuLi + $ZnBr_2$	**2d**, 95 (78)	0	0	>99:1
4	 + *n*-BuLi + $ZnBr_2$	**2e**, (84)	*f*	0	>99:1
5	 + *t*-BuLi + $ZnBr_2$	**2f**, (67)	0	0	>99:1
6	 + *t*-BuLi + $ZnBr_2$	**2g**, (62)	0	0	>99:1

[a] Reactions were carried out with organozinc bromides (4 equiv) derived from chemicals indicated in "reagent sources" in the presence of CuCl (30 mol %) in THF/Et_2O (2:1) at room temperature for 12 h. [b] Determined by ^{1}H NMR spectroscopy with 1-bromonaphtalene as an internal standard. [c] Isolated yields are shown in parentheses. [d] Methoxyacetate of **2**. [e] ^{1}H NMR spectra of **3** for comparison, see refs 5 and 9. [f] **2e**/ester = 10:1 by ^{1}H NMR spectroscopy.

A zinc reagent **6** prepared by ortho lithiation[23] of methoxymethyl phenyl ether (**5**) followed by transmetallation with $ZnBr_2$ also furnished *anti*-S_N2' product **2h** with >99:1 regioselectivity in 73% isolated yield (Scheme 1).

Scheme 1. Synthesis of **2h**



The present reaction was successfully extended to alkenyl zinc reagents. As summarized in entries 5 and 6 of Table 2, the zinc reagents prepared from the cis and trans iodides by halogen-lithium exchange with *t*-BuLi followed by transmetallation with $ZnBr_2$ produced the *anti*-S_N2' products **2f** and **2g** in good yields without isomerization of the double bond. The *anti*-S_N2'/S_N2 selectivity was >99:1 by ^{1}H NMR analysis. The alkenyl zinc reagent derived from stannane **7** also furnished *anti*-S_N2' product **2i** in 55% isolated yield with >99% regioselectivity (Scheme 2). Compounds similar to

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(18) Ibuka, T.; Nakai, K.; Habashita, H.; Bessho, K.; Fujii, N. *Tetrahedron* **1993**, *49*, 9479−9488.

(19) 2-Iodo-cycloalkenyl esters: Soorukram, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3686−3689.

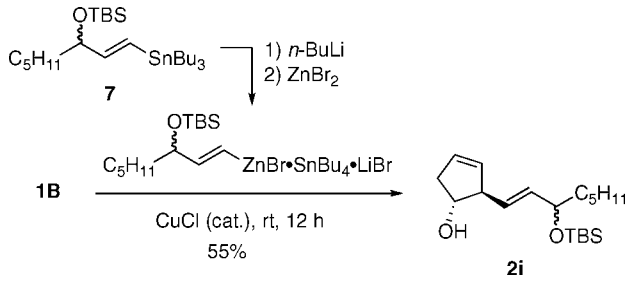
(20) (a) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091−3093. (b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445−1453. (c) Yamamoto, Y.; Chounan, Y.; Tanaka, M.; Ibuka, T. *J. Org. Chem.* **1992**, *57*, 1024−1026. (d) Fujii, N.; Nakai, K.; Habashita, H.; Yoshizawa, H.; Ibuka, T.; Garrido, F.; Mann, A.; Chounan, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 4227−4230.

(21) (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111−2114. (b) Perrone, S.; Knochel, P. *Org. Lett.* **2007**, *9*, 1041−1044.

(22) The phenylzinc reagents derived from PhX, *n*-BuLi, and ZnX_2 and from pure PhLi from ZnX_2 are drawn as PhZnX·LiX·*n*-BuBr and PhZnX·LiX, respectively. Other organometallic reagents used herein are indicated in a similar way.

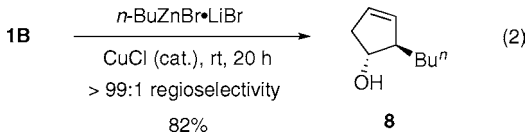
(23) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

Scheme 2. Synthesis of **2i**



2i were synthesized previously as prostaglandin intermediates with low to moderate yields.[24]

Finally, we applied the above reaction system to an alkyl reagent. As shown in eq 2, *n*-BuZnBr·LiBr, selected as a typical reagent of *alkyl* zinc bromides, proceeded with high regioselectivity to afford *anti*-S_N2' product **8** in 82% yield. No difference in regioselectivity and reactivity between sp^3-C (alkyl) and sp^2-C (aryl, alkenyl) reagents were thus established.



(2)

In conclusion, we have presented a new reagent system for delivering aryl, alkenyl, and alkyl groups in an *anti*-S_N2' manner with almost complete regioselectivity.[25] Application of the present method to the synthesis of biologically important molecules is now in progress.

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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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(25) Typical procedure: to an ice-cold solution of PhBr (0.126 mL, 1.20 mmol) in Et_2O (1.0 mL) was added *n*-BuLi (0.69 mL, 1.75 M in hexane, 1.20 mmol). After 30 min, a solution of $ZnBr_2$ (2.70 mL, 0.45 M in THF, 1.21 mmol) was added. The solution was stirred at 0 °C for 30 min, and CuCl (9 mg, 0.09 mmol) was added to it. After 20 min, a solution of methoxyacetate **1B** (52 mg, 0.30 mmol) in THF (1 mL) was added. The solution was stirred at room temperature for 12 h and diluted with saturated NH_4Cl with vigorous stirring. The resulting mixture was extracted with EtOAc four times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 4:1) to furnish **2a** (36 mg, 75%). The spectral data were identical with those reported: (a) Echavarren, A. M.; Tueting, D. R.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4039−4041. (b) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979−992.