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New Reagent System for Attaining High Regio- and Stereoselectivities in Allylic Displacement of 4-Cyclopentene-1,3-diol Monoacetate with Aryl- and Alkenylmagnesium Bromides

Yuichi Kobayashi,* Kenya Nakata, and Takayuki Ainai

Department of Biomolecular Engineering, Tokyo Institute of Technology, Box B-52, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

ykobayas@bio.titech.ac.jp

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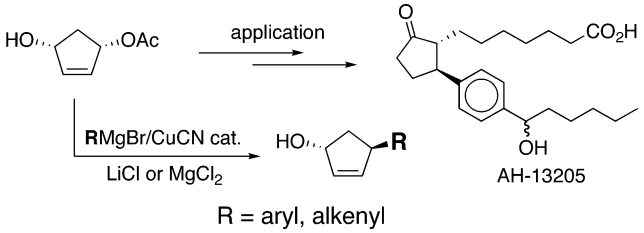
ABSTRACT



Low regioselectivity of RMgBr (R = aryl, alkenyl) in the CuCN-catalyzed reaction with 4-cyclopentene-1,3-diol monoacetate is improved by addition of LiCl or $MgCl_2$ to a similar extent as previously obtained with RMgCl (>90:10). The limitation encountered in the preparation of RMgCl no longer exists in the present method using RMgBr. The method is utilized in the synthesis of AH-13205, a selective EP_2-receptor agonist.

As part of our ongoing project to find a reagent that provides high regio- and stereoselectivities in allylic displacement of 4-cyclopentene-1,3-diol monoacetate (**1**),[1,2] we reported a CuCN-catalyzed S_N2-type reaction with arylmagnesium chlorides (ArMgCl) that affords **2** with high regioselectivity and complete stereoselectivity (eq 1).[3] The protocol was also successful with simple (vinyl)MgCl. Since then, we learned of the limited preparation of Grignard reagents from chlorides, and thus the method seemed far from being widely applicable. For example, functionalized aryl chloride **4** and alkenyl chlorides **6** and **7** shown in Figure 1 (X = Cl) did not afford the corresponding Grignard reagents even under forcing conditions of high temperatures and longer preparation times with Mg turnings preactivated in situ with Cl-$(CH_2)_2$Cl. Such difficulty associated with the Grignard preparation is also mentioned in the literature for aryl

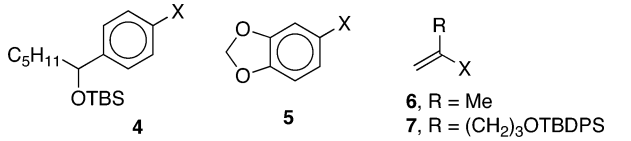


Figure 1. Examples of chlorides (X = Cl), which are marginally reactive to magnesium. In comparison, the corresponding bromides (X = Br) are easily transformed into the Grignard reagents.

(1) Kobayashi, Y. *Curr. Org. Chem.* **2003**, *7*, 133−147.
(2) (a) Hattori, H.; Abbas, A. A.; Kobayashi, Y. *Chem. Commun.* **2004**, 884−885. (b) Ito, M.; Matsuumi, M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881−5889.
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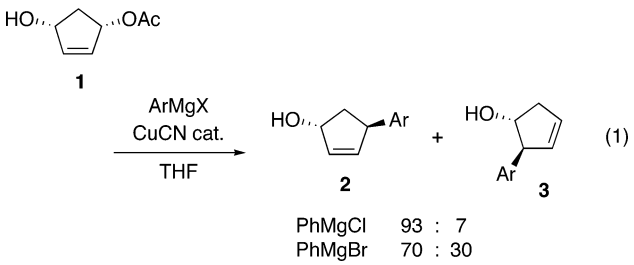
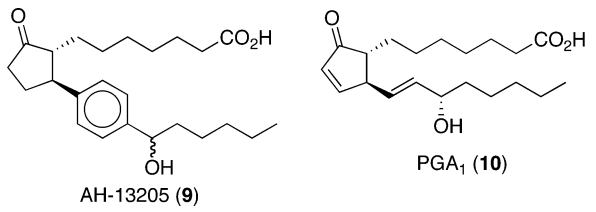
chlorides such as **5**, and the transition metal-catalyzed preparation of ArMgCl was developed instead.[4] The procedure is rather complicated, and the influence of the added catalyst on our copper-catalyzed reaction is unpredictable. Consequently, we turned our attention to aryl bromides (ArBr), which are, in general, easily convertible into ArMgBr (**8**) by routine operation.



The problem associated with the magnesium *bromide* **8**, however, is its low regioselectivity. For example, application of the protocol shown in eq 1 to PhMgBr (**8a**) afforded a 70:30 mixture of **2a** and **3a**. We postulated that an inorganic chloride would convert ArMgBr to ArMgCl by halide exchange, and thus contribute to higher regioselectivity. As presented herein, this idea was proved to be the case. Moreover, the new protocol was successfully utilized as the key reaction in the synthesis of AH-13205 (**9**),[5] which is an analogue of PGA_1 (**10**) with EP_2-receptor agonist activity.[6] Furthermore, we demonstrated that the protocol is applicable to alkenyl-magnesium bromides, thus showing a wider applicability of the present strategy using monoacetate **1** in organic synthesis.



To find effective inorganic chloride(s), LiCl, NaCl, KCl, $MgCl_2$, $CaCl_2$, and $AlCl_3$ were each added in the CuCN-catalyzed reaction of **1** with PhMgBr (**8a**) (3 equiv) in THF at 0 °C. Among them, LiCl and $MgCl_2$ did improve the native regioselectivity of **8a** (Table 1, entry 1). The best selectivity was recorded with ratios of LiCl/**8a** (entries 4 and 5) and of $MgCl_2$/**8a** (entries 7 and 8) equal to or slightly greater than one.[7] These selectivities as well as the yields of **2a** in these entries were almost equal to those obtained with PhMgCl (93:7, 90% NMR yield).[3]

Table 1. Effect of LiCl and $MgCl_2$ on the CuCN-Catalyzed Reaction of **1** with PhMgBr (**8a**)[a]

entry	additive	**2a**:**3a**	yield of **2a**, %[b,c]
1	–	70:30	63
2	LiCl (1 equiv)	86:14	80
3	LiCl (2 equiv)	90:10	75
4	LiCl (3 equiv)	92:8	84
5	LiCl (4 equiv)	93:7	94 (94)
6	$MgCl_2$ (1 equiv)	87:13	nd[d]
7	$MgCl_2$ (3 equiv)	93:7	90 (72)
8	$MgCl_2$ (4 equiv)	93:7	83 (73)

[a] Reactions were carried out with **8a** (3 equiv) and CuCN (0.3 equiv) in the presence of the additive (LiCl or $MgCl_2$) in THF at 0 °C for 1 h. [b] Yields were determined by ^{1}H NMR analysis. [c] Isolated yields are shown in parentheses. [d] Not determined.

High regioselectivity was also observed with other ArMgBr by using the protocol established above (Table 2). Thus,

Table 2. CuCN-Catalyzed Reaction with ArMgBr **8a**–**f**[a]

entry	**2**, **3**, **8** suffix	Ar	additive	**2**:**3**	yield of **2**, %[b,c]
1	**b**	2-MeC_6H_4	–	70:30	77
2	**b**	2-MeC_6H_4	LiCl	91:9	82 (80)
3	**b**	2-MeC_6H_4	$MgCl_2$	93:7	87
4	**c**	4-MeC_6H_4	–	75:25	80
5	**c**	4-MeC_6H_4	LiCl	91:9	94 (83)
6	**c**	4-MeC_6H_4	$MgCl_2$	94:6	86
7	**d**	2-$MeOC_6H_4$	LiCl	91:9	68
8	**d**	2-$MeOC_6H_4$	$MgCl_2$	94:6	77 (71)
9	**e**	4-$MeOC_6H_4$	LiCl	90:10	78
10	**e**	4-$MeOC_6H_4$	$MgCl_2$	91:9	91
11	**f**	3,4-OCH_2O–C_6H_3	–	75:25	75
12	**f**	3,4-OCH_2O–C_6H_3	LiCl	93:7	99 (92)
13	**f**	3,4-OCH_2O–C_6H_3	$MgCl_2$	93:7	98 (85)

[a] Reactions were carried out with ArMgBr (3 equiv) and CuCN (0.3 equiv) in the presence of LiCl or $MgCl_2$ (4 equiv) in THF at 0 °C for 1 h. [b] Yields were determined by ^{1}H NMR analysis. [c] Isolated yields are shown in parentheses.

the native selectivities of 2- and 4-Tol-MgBr (**8b** and **8c**, respectively) (entries 1 and 4) were improved by addition of LiCl or $MgCl_2$ (entries 2, 3 and 5, 6) to the levels (>90% selectivity) previously observed with 2- and 4-Tol-MgCl. Similarly, 2- and 4-(MeO)C_6H_4 groups were attached to **1** regioselectively in good yields (entries 7–10). Grignard reagent **8f**, prepared easily from **5** (X = Br) and Mg, also furnished high regioselectivity (entries 12 and 13). Note that the corresponding magnesium chloride is hardly prepared from 3,4-$OCH_2OC_6H_3Cl$ by the routine procedure as reported.[4]

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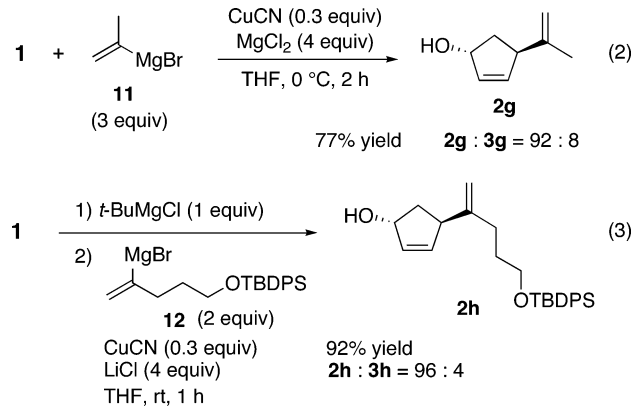
(5) A review: Nials, A. T.; Vardey, C. J.; Denyer, L. H.; Thomas, M.; Sparrow, S. J.; Shepherd, G. D.; Coleman, R. A. *Cardiovasc. Drug Rev.* **1993**, *11*, 165–179.

(6) (a) Spada, C. S.; Nieves, A. L.; Woodward, D. F. *Exp. Eye Res.* **2002**, *75*, 155–163. (b) Nials, A. T.; Coleman, R. A.; Hartley, D.; Sheldrick, R. L. G. *Br. J. Pharmacol.* **1991**, *102*, 24P. (c) Coleman, R. A.; Kennedy, I.; Sheldrick, R. L. G. *Br. J. Pharmacol.* **1987**, *91*, 323P.

(7) Since the 1–1.3 ratios of the chlorides (LiCl, $MgCl_2$) over PhMgBr seem to be insufficient for complete conversion of PhMgBr to PhMgCl, we presume that among two PhMgCl– and PhMgBr–CuCN complexes being in equilibrium with each other, the former complex of higher regioselectivity reacts faster than the latter. The following facts support this hypothesis: reaction with PhMgCl was completed at −18 °C for 1 h, while reaction with PhMgBr at −18 °C for 1 h was incomplete, affording a mixture of the starting monoacetate **1** and the products **2a** and **3a**.

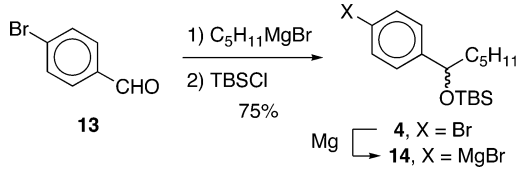
Next, we studied reaction of **1** with alkenyl Grignard reagents. Reaction with **11**[8] (3 equiv), CuCN catalyst, and $MgCl_2$ (4 equiv) proceeded with 92:8 regioselectivity favoring **2g** over regioisomer **3g** (eq 2). A similar ratio was also recorded with **11** and LiCl. Since the protocol requires 3 equiv of the Grignard reagents, effort was made to reduce the quantity of the reagents in reaction with **12**.[8] Thus, the hydroxyl group of **1** was quenched with 1 equiv of *t*-BuMgCl at 0 °C and the alkoxide thus formed was subjected to reaction with 2 equiv of **12** to afford **2h** with 96% regioselectivity in 92% isolated yield (eq 3). The product derived from *t*-BuMgCl was not detected by ^{1}H NMR spectroscopy or TLC analysis.



Previously, alkenyl compounds of type **2** have been synthesized from cyclopentadiene monoepoxide with (alkenyl)SnR_3/Pd cat.[9] and (alkenyl)Cu(CN)Li[10] in rather low regioselectivities of <2:1. Later, we developed two reagent systems to afford **2** regioselectively from monoacetate **1**, i.e., (alkenyl)borates having the 2,3-butanediol ligand (derived from the alkenyl boronate esters and BuLi) in combination with a nickel catalyst[11] and (alkenyl)MgCl with a CuCN catalyst.[3] However, the highly volatile nature of the boronate ester precursors having a small alkenyl group such as CH_2=CH− and CH_2=C(Me)− prevented their isolation, while preparation of (alkenyl)MgCl is limited to simple alkenyl chlorides. Consequently, the present reagent system is the only one that allows highly efficient installation of a wide range of alkenyl groups.

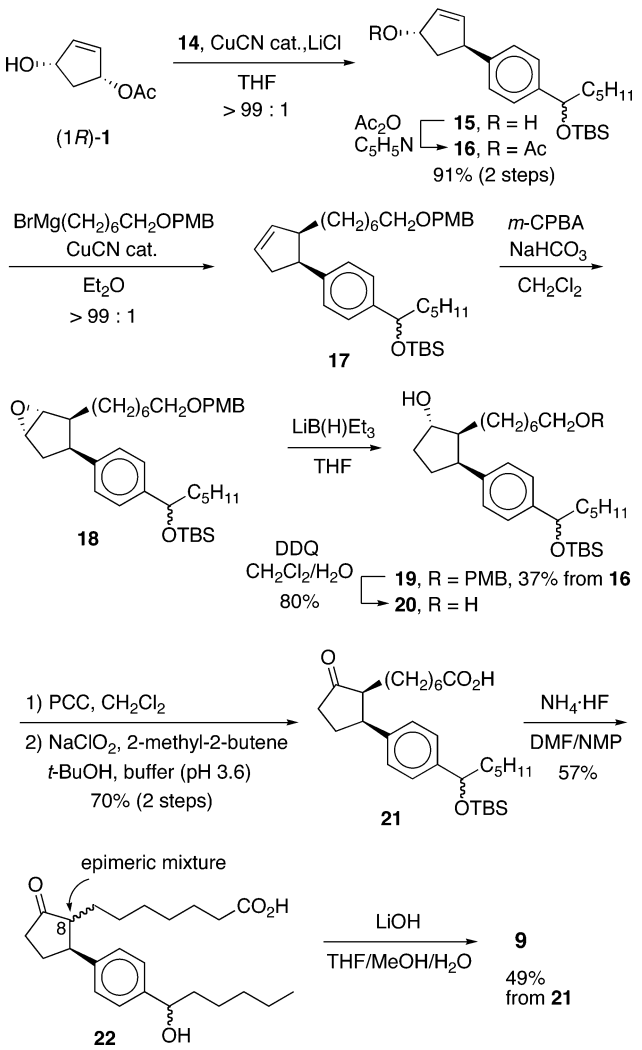
To demonstrate the advantage of the present reaction, we synthesized AH-13205 (**9**).[5,6] Since the target is a diastereomeric mixture at the benzylic chiral carbon, bromide **4** (X = Br) was prepared as a racemic mixture from aldehyde **13** in 75% yield by addition of $C_5H_{11}MgBr$ followed by silylation and converted easily into the Grignard reagent **14** with Mg turnings in THF (Scheme 1).[8] Reaction of (1*R*)-**1** with the Grignard reagent **14** under the conditions established

Scheme 1. Preparation of the Grignard Reagent **14**



above proceeded with an almost perfect regioselectivity of >99:1 favoring S_N2 product **15** over anti S_N2' product **23** (Scheme 2).[12] Product **15** isolated in 98% yield was

Scheme 2. Synthesis of AH-13205 (**9**)



transformed into acetate **16**, which was subjected to reaction with $BrMg(CH_2)_6CH_2OPMB$ under the conditions for the anti S_N2' reaction[13] (CuCN cat. in Et_2O) to afford **17** with more than 99% regioselectivity.

(8) Corresponding chloride did not undergo Grignard formation even at refluxing temperatures of THF for several hours with Mg turnings activated in situ by $Cl(CH_2)_2Cl$.

(9) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979−992.

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

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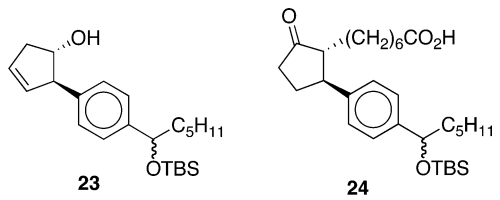
(12) CuCN-catalyzed reaction of (1*R*)-**1** with **14** without LiCl afforded an 80:20 mixture of **15** and **23**. The mixture was separated by chromatography, and both isomers were characterized by ^{1}H NMR spectoscopy (see Supporting Information).

To construct a carbonyl group at C(9), a hydroxyl group was introduced on **17** by epoxidation with *m*-CPBA followed by regioselective epoxide-ring opening with $LiB(H)Et_3$ to afford **19** in 37% yield from acetate **16**. After deprotection of the PMB group, the resulting diol **20** was converted into keto acid **21** in 70% yield by two-step oxidation. Deprotection of the TBS group with $NH_4F{\cdot}HF$ in DMF−NMP[14] for 72 h afforded a diastereomeric mixture **22** at C(8),[15] and, finally, exposure of **22** to LiOH effected epimerization to afford AH-13205 (**9**) in 49% yield from **21**. The ^1H NMR and ^{13}C NMR spectra support the structure of **9**.



23 **24**

In summary, we have established a new method to attain high regioselectivity in the allylic displacement of monoacetate **1** with Ar- and (alkenyl)MgBr. The limitation encountered in preparation of the corresponding magnesium chlorides no longer exists in the synthesis of cyclopentenes of type **2**.

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

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(15) C(8)-hydrogens for the cis and trans isomers in the ^1H NMR spectrum of **22** appeared at δ 3.59 (q, $J = 7$ Hz) and 2.95 (dt, $J = 6$, 12 Hz) ppm, respectively. The hydrogens at the same position in **21** and its trans isomer **24**, synthesized by epimerization with LiOH, showed similar chemical shifts.