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Mercury-Free Preparation and Selective Reactions of Propargyl (and Propargylic) Grignard Reagents†

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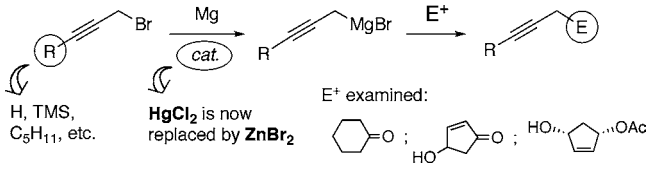
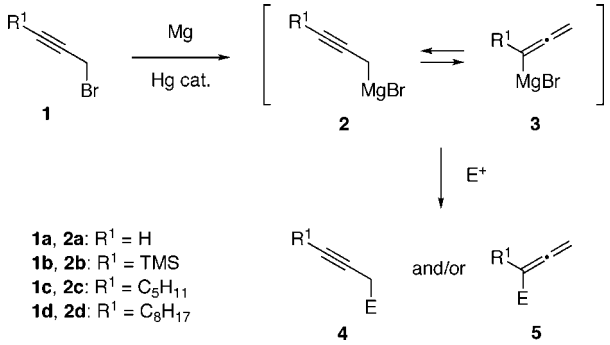
ABSTRACT



$ZnBr_2$ was found to catalyze formation of propargyl and propargylic Grignard reagents, and thus put an end to the standard method using a mercury catalyst. The Grignard reagents were submitted to addition reaction with carbonyl compounds and allylation with the cyclic monoacetate to afford the propargyl-type products selectively. Furthermore, the product from the monoacetate was transformed to an acetylene analogue of 2-(5,6-epoxyisoprostane A_2)phosphorylcholines.

As illustrated in Scheme 1, reaction of propargyl (HC≡CCH_2−) and propargylic (RC≡CCH_2−) Grignard reagents

Scheme 1. Standard Preparation of the Propargyl (and Propargylic) Grignard Reagents **2** and the Reaction Products with Electrophiles



2 with electrophiles (E^+) has produced **4** and/or **5** with low to high selectivity depending mainly on the steric factor and the reaction course in the transition state.[1] While the high level of native selectivity has found many applications in organic synthesis, study to improve the low selectivity was scarcely reported probably due to the use of a poisonous mercury catalyst such as $HgCl_2$ for the preparation of reagents **2** from halides **1** and magnesium in Et_2O.[2−4]

In the preparation of **2a** (R^1 = H), the mercury catalyst is understood to speed up the formation of **2a** over the unwanted consumption of **2a** via abstraction of the acetylenic

† Dedicated to the late Professor Yoshihiko Ito, Kyoto University.

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(4) Preparation of **2** ($R^1 \neq$ H): Yanagisawa, A.; Habaue, S.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 1969−1980.

proton from **1a** (R^1 = H) to produce HC≡CMe, which is ultimately changed to BrMgC≡CMe (**6**).[1] On the other hand, the role of the catalyst in the preparation of **2** ($R^1 \neq$ H) is not clearly stated to the best of our knowledge. To avoid the problem associated with recovery of the mercury catalyst, Rieke Mg was once used for the preparation of **2** (R^1 = TMS).[5] Use of zinc and lithium reagents similar to **2** (R = Si(alkyl)$_3$, alkyl)[4,6,7] and the dianion, LiC≡CCH$_2$Li,[8] has been an alternative choice. These anions have been synthesized by reaction of **1** with Zn,[4] by lithiation of 2-alkynes with *t*-BuLi,[6,7] and by lithiation of propyne and allene (CH_2=C=CH_2) with *n*BuLi,[8] respectively. On the other hand, several metals have been shown to assist generation of **2** in Barbier-type reactions.[9] These methods, however, seem less attractive because of the complicated operation to prepare Rieke Mg, inconvenience in handling gaseous propyne and allene for the preparation of 2-alkynes as well as for the direct lithiation, low reactivity and product selectivity, or the narrow range of electrophiles for Barbier-type reactions.

In contrast to the above method, two recent reports have described the preparation of **2a** (R^1 = H) in the usual way without a mercury catalyst.[10] Due to the significance, we reinvestigated the preparation and confirmed that the mercury catalyst is indeed necessary. Instead, we found an environmentally acceptable catalyst for the preparation of **2** (R^1 = H, TMS, alkyls). Herein, we describe the preparation of **2** and applications including the synthesis of 5,6-epoxyisoprostane phosphorylcholine and its acetylene derivative.

After confirmation of the successful preparation of **2a** in Et_2O (0.38 M by titration with methyl orange, 54% yield based on 0.70 M for 100% conversion) by adding propargyl bromide (**1a**) (1 mL scale) to Mg turnings (2 equiv) in the presence of $HgCl_2$ (0.2 mol %), the requirement of the solvent and the catalyst was briefly studied. In THF at 0−5 °C (ca. 2 h), Mg was consumed smoothly with formation of gray precipitates. Surprisingly, the concentration was almost 0 M by titration, which was consistent with the result that an attempted reaction of the mixture (supernatant and precipitates) with Ph(CH$_2$)$_2$CHO (**7**) did not afford any alcoholic products. These results indicate a pathway to quench anions **2a** and/or **6**. One possibility is a coupling of these anions with **1a** to afford $MgBr_2$ as precipitates. Pre-activation of Mg with Br(CH$_2$)$_2$Br in THF followed by reaction with **1a** produced similar precipitates. On the other hand, attempted preparation in Et_2O with and without the pre-activation of Mg (with Br(CH$_2$)$_2$Br) resulted in the complete recovery of Mg.

To identify effective catalysts, the preparation of **2a** in Et_2O was examined with a number of metal salts (2−5 mol %) from a stock room. While most of the common metal salts placed in group 1 of Table 1 were ineffective, consumption of Mg was observed with $TiCl_4$ (group 2), though concentration of **2a** by titration was almost 0 M. To our delight, production of **2a** was brought about with ZnX_2 (group 3, Table 1). Further investigation with other zinc salts was, however, unsuccessful (see the zinc salts listed in groups 1 and 2).

Table 1. Results of the Metal Salts Attempted for Preparation of **2a** in Et_2O[a]

group	metal salts		consumption of Mg[b]	concn of **2a** (M)[c]
1	$CuCl_2$	$HfCl_4$	no	
	$NiCl_2$	$ZrCl_4$	no	
	$CoCl_2$	Bu_3SnCl	no	
	$CeCl_3$	$Zn(OAc)_2$	no	
	$FeCl_3$	$Zn(acac)_2$	no	
	Cp_2TiCl_2		no	
2	$TiCl_4$	$Zn(OTs)_2$	yes	0
	$Zn(OTf)_2$	$ZnEt_2$	yes	0
3	ZnX_2 (X = Cl, Br, I)		yes	0−0.52

[a] Preparation was examined with **1a** (1.0 mL, 13 mmol), Mg (650 mg, 27 mg-atom), and a catalyst (2−5 mol %) in Et_2O (18 mL) at 0−5 °C for 1−2 h. [b] Mg turnings from Nacalai Tesque, Japan, were used for the investigation. [c] Determined by titration with methyl orange.

Concentrations of **2a** prepared with ZnX_2 of group 3 are summarized in Table 2. For the two catalyst quantities (2 and 4 mol %), the highest concentrations (0.41 and 0.52 M, respectively) were recorded with $ZnBr_2$ and were slightly better than that obtained above with $HgCl_2$ (0.38 M). A similar result was attained with Mg from a different company (see footnote a of Table 2). A somewhat lower concentration was recorded with 1 mol %. On the basis of these results,

Table 2. Concentration of **2a** vs Quantity of ZnX_2

mol % of ZnX_2	$ZnCl_2$	$ZnBr_2$	ZnI_2
1		0.39	
2	0.31	0.41	0
3		0.51	
4	0.29	0.52	0.35
5		0.49[a]	

[a] Mg turnings from Aldrich gave a similar result (0.48 M).

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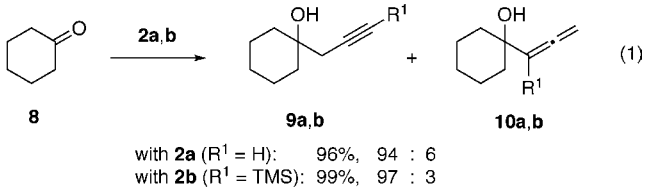
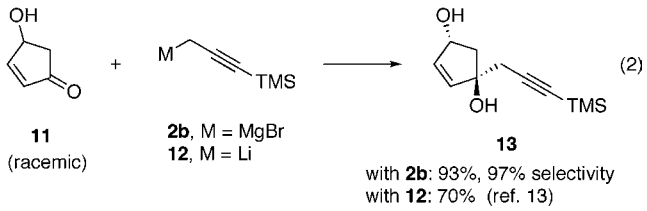
(10) (a) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141−145. (b) Schrock, R. R.; Duval-Lungulescu, M.; Tsang, W. C. P.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2004**, *126*, 1948−1949.

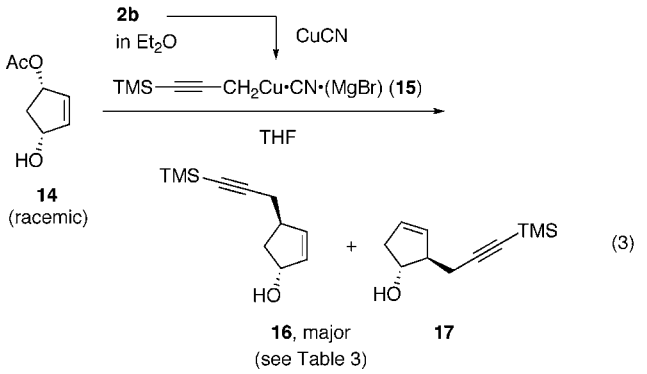
we recommend the use 2−5 mol % of $ZnBr_2$ in Et_2O for successful preparation of **2a**. Note that an attempted preparation of **2a** in THF with $ZnBr_2$ (4 mol %) produced the precipitates and a supernatant of 0 M concentration.

The $ZnBr_2$-assisted preparation established above was applied to **1b** (R^1 = TMS) successfully with 2 mol % of $ZnBr_2$. The yield of **2b** (75−86%, 0.49−0.56 M, 3 runs; cf. 0.65 M for 100% production) was a little higher than that obtained with $HgCl_2$ (65−77%, 3 runs). The preparation of **2b** with $ZnBr_2$ attempted in THF was also successful (0.43 M). The concentration was, however, substantially dropped to 0.21 M after 12 h at 0 °C, suggesting a similar process to quench **2b**. Bromides **1c** and **1d** (R = C_5H_{11}, C_8H_{17}) also produced **2c** and **2d** in 85% and 83% yields, respectively.

With the nontoxic preparation of the Grignard reagents **2** in hand, we turned our attention to reactions delineated in eqs 1−3. Addition of **2a** and **2b** to cyclohexanone **8** produced







the homopropargylic alcohols in good yields with a high product selectivity over the allenes (eq 1). The high selectivities observed are consistent with those reported for cyclic ketones[3a,7b,11,12] with **2a** and **2b** that were prepared with $HgCl_2$, thus concluding no influence of the zinc residue on yield and selectivity of the reaction. Likewise, 4-hydroxy-2-cyclopentenone (**11**) underwent reaction with **2b** to afford alcohol **13** with good yield and high selectivity (eq 2). Previously, lithium anion **12** was prepared by lithiation of TMSC≡CMe with *n*-BuLi for reaction with **11** (eq 2), and product **13** was transformed into clavulone II and its analogues.[13] Now, preparation of TMSC≡CMe[14] and its lithiation to **12** are no longer necessary.

Next investigated was allylic substitution of **14** with copper reagents[15] derived from **2b** (eq 3), in which the regioselection at the α or γ position of the allylic moiety should be controlled as well. According to the guideline established by us for alkyl and aryl reagents,[16] a 2:1 complex of **2b** and CuCN in THF was examined first, but produced the diol derivative of **14**. After unsuccessful attempts, we found that a 1:1 complex formulated as **15** (4 equiv) at 0 °C for 4 h afforded the propargyl type of the products, but with a low regioselectivity on the substrate **14** (Table 3, entry 1).

Table 3. Allylic Substitution of **14** with Propargylic Anion **15** Derived from **2b** and CuCN[a]

entry	method for preparation of **2b**	additive (equiv)	ratio of **16**:**17**[b]	combined yield (%)[c,d]
1	$HgCl_2$-catalyzed		68:32	83
2	$HgCl_2$-catalyzed	$MgCl_2$ (4)	85:15	81
3	$HgCl_2$-catalyzed	$MgCl_2$ (8)	94:6	76
4	$ZnBr_2$-catalyzed	$MgCl_2$ (8)	94:6	77
5	$ZnBr_2$-catalyzed	LiCl (8)	87:13	79

[a] Reactions were carried out with **2b** (4 equiv) and CuCN (4.2 equiv) in THF at 0 °C for 3−6 h. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield. [d] The products **16** and **17** were separable by chromatography on silica gel.

Fortunately, higher than the native selectivity was attained with 8 equiv of $MgCl_2$ (entry 3; cf. entry 2). Since **2b** examined in entries 1−3 was prepared by using the $HgCl_2$-catalyzed method, we also executed the reaction with **2b** prepared with $ZnBr_2$ to confirm almost the same selectivity and yield was obtained (entry 4), thus showing no interference to the allylation by the mercury and zinc residues remaining in the solutions of **2b**.

Finally, the allylation established above (eq 3) was applied to the synthesis of the acetylene analogue of 2-(5,6-epoxyisoprostane A_2)phosphorylcholine[17,18] (**18b** in Figure

(11) Quayle, P.; Rahman, S.; Ward, E. L. M. *Tetrahedron Lett.* **1994**, *35*, 3801−3804.

(12) A similar selectivity for the 2-bromo derivative: Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120−4122.

(13) Tanaka, H.; Hasegawa, T.; Iwashima, M.; Iguchi, K.; Takahashi, T. *Org. Lett.* **2004**, *6*, 1103−1106.

(14) While the authors of ref 13 did not mention the preparation, TMSC≡CMe has been synthesized by the methods: (a) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314−6319. (b) Wang, J.; Gurevich, Y.; Botoshansky, M.; Eisen, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 9350−9351. (c) See ref 6.

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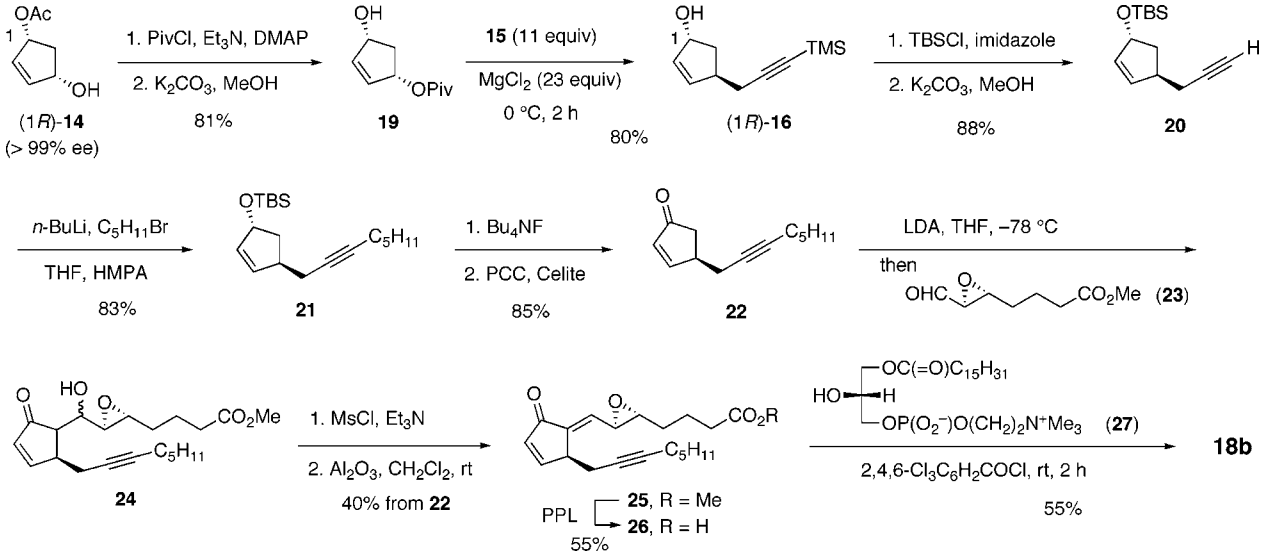
Scheme 2. Synthesis of the Acetylene Derivative and Natural 2-(5,6-Epoxyisoprostane A_2)phosphorylcholines **18b** and **18a**



1). Monoacetate (1*R*)-**14**[19] of >99% ee by HPLC was converted into pivaloate **19**[20] (Scheme 2). The reaction was somewhat slow with 4 equiv of **15** and hence an excess of the reagent was used to produce, after 2 h at 0 °C, a 93:7 mixture of (1*R*)-**16** and the regioisomer in good yield. After separation of the mixture by chromatography, (1*R*)-**16** obtained in 80% yield was converted to enone **22** through alkylation at the acetylenic carbon and subsequent oxidation of the hydroxyl group. Aldol reaction of **22** with the optically active epoxy aldehyde **23**[21] gave aldol adduct **24**, which was transformed to dienone **25** stereoselectively at the newly formed olefin through mesylation and Al_2O_3-assisted elimination of the mesyloxy group. Hydrolysis of methyl ester **25** by using PPL afforded acid **26**, which upon condensation with lyso-PC (**27**) using Yamaguchi reagent furnished **18b**.

To elucidate a step for tritium labeling, early intermediate **21**, ester **25**, and acid **26** were submitted to hydrogenation (H_2 instead of T_2, Pd/$BaSO_4$, quinoline). The former two afforded cis olefins (81% from **21**, 78% of **28** from **25** (Scheme 3)), while **26** gave a mixture of products. Previously, **28** was transformed to **18a** by us in two steps.[18a]

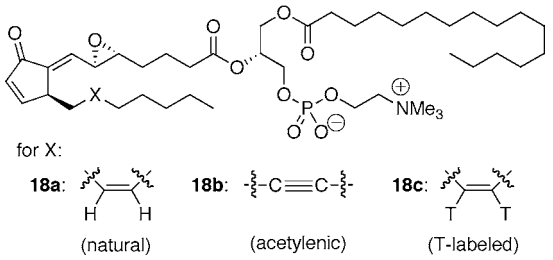
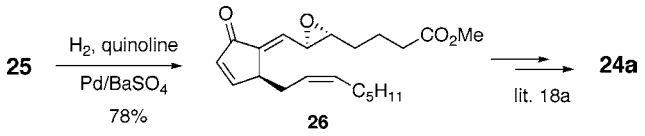


Figure 1. The 2-(5,6-epoxyisoprostane A_2)phosphorylcholine family (**18a**−**c**).

Scheme 3. Hydrogenation of Acetylene **25**



In summary, a new method for mercury-free preparation of **2** (R^1 = H, TMS, C_5H_{11}, C_8H_{17}) was established for the first time, facilitating investigation of reactions with **2**. We also studied reactions of **2** shown in eqs 1−3, which proceed regio- and/or stereoselectively. Furthermore, the reaction of eq 3 was applied to the synthesis of 2-(5,6-epoxyisoprostane A_2)phosphorylcholine **18a** and its acetylenic analogue **18b**.

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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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(20) Although (1*S*)-**14** is the direct substrate to give (1*R*)-**16**, synthesis of (1*S*)-**14** by the asymmetric hydrolysis of the diacetate by PLE of several lots was unsuccessful in our hand. The hydrolysis with PLE: (a) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695−3696. (b) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875−5878. Synthesis of **19**: (c) Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983−2004. (d) Myers, A. G.; Hammond, M.; Wu, Y. *Tetrahedron Lett.* **1996**, *37*, 3083−3086.

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