ORGANIC LETTERS

2005
Vol. 7, No. 7
1319−1322

Aryl- and Alkenyllithium Preparations and Copper-Catalyzed Reaction between the Derived Magnesium Reagents and the Monoacetate of 4-Cyclopentene-1,3-diol

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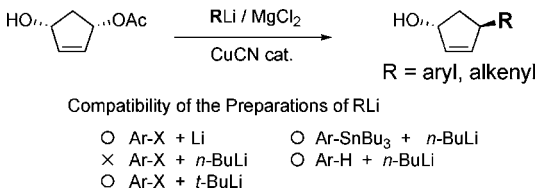
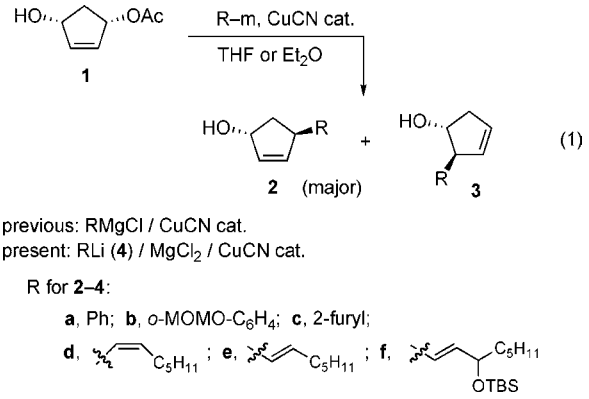
Received January 18, 2005

ABSTRACT



Aryl- and alkenyllithiums, prepared by halogen–lithium exchange with lithium, exchange with *n*-(or *t*-)BuLi, stannane–lithium exchange with *n*-BuLi, and direct lithiation with *n*-BuLi, were transformed into magnesium reagents with $MgCl_2$ and subjected to CuCN-catalyzed reaction with the title monoacetate. Except for the halogen–lithium exchange with *n*-BuLi, the other preparations of the lithium anions were found to be compatible with the CuCN-catalyzed reaction to afford S_N2-type products efficiently.

Although preparation of the monoacetate of 4-cyclopentene-1,3-diol (**1**) was established in the late 1980s,[1] this compound had not actively been used as a starting compound in organic synthesis before we started our investigation[2] due to the lack of an efficient reaction for installation of a carbon moiety onto the cyclopentene ring. Recently, we have developed a reagent system for arylation of **1** consisting of a chlorine-based Grignard reagent (ArMgCl) and a CuCN catalyst, which proceeds in S_N2 fashion to produce **2** (eq 1).[2b,3] The S_N2 preference is unusual among copper-assisted reactions.[4] Later, the reaction was expanded to bromine-based Grignard reagents (ArMgBr) of low regioselectivity by adding $MgCl_2$ or LiCl in the ArMgBr/CuCN catalyst system.[5]



In connection with this research project, we targeted organomagnesium chlorides derived from RLi (**4**) and $MgCl_2$.

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10.1021/ol0501065 CCC: $30.25
Published on Web 03/08/2005

Since **4** is accessible by several methods[6] such as halogen−lithium exchange with lithium, exchange with *n*-(or *t*-)BuLi, stannane−lithium exchange, and direct lithiation, these preparations were expected to raise the synthetic potential of the CuCN-catalyzed reaction of **1**. For example, the organolithium alternation serves sterically defined alkenyl anions without loss of the stereochemical integrity of the precursors. In this regard, partial loss of the olefin geometry in Grignard preparation from the alkenyl halides and Mg seems difficult to suppress.[7] Herein, we present in situ preparations of aryl- and alkenyllithiums (**4**) according to the methods mentioned above and the CuCN-catalyzed reaction of **1** with the derived magnesium reagents. Except for the halogen−lithium exchange of ArX with *n*-BuLi, the preparations of **4** were compatible with the subsequent reaction. Furthermore, we elucidated a reason for the different results among the preparations and established a guideline for the successful installation using **4**.

With RMgCl in mind as a necessary source for performing the S_N2-type reaction with the CuCN catalyst, PhLi (**4a**) (3 equiv of monoacetate **1**) in cyclohexanes−Et_2O (2:1), which was prepared by halogen−lithium exchange with lithium,[8] was added to an ice-cold mixture of $MgCl_2$ (2−5 equiv)[9] in THF. After 15 min, CuCN (0.3 equiv) and, again after 20−30 min, monoacetate **1** (1 equiv) were added to the mixture, and the reaction was carried out at 0 °C for 1 h to obtain the results summarized in Table 1. For comparison, the native

Table 1. Phenylation of Monoacetate **1**[a]

entry	additive	equiv	ratio of **2a**:**3a**	yield of **2a**, %[b]	conversion of **1**, %[b]
1	–	–	65:35	22	100[c]
2	$MgCl_2$	2	75:25	26	55[d]
3	$MgCl_2$	3	86:14	51	64[d]
4	$MgCl_2$	4	>95:<5	78 (75)	100
5	$MgCl_2$	5	>95:<5	85 (72)	100

[a] Reaction was conducted with PhLi (**4a**) (3 equiv) in the presence or absence of the additive and CuCN (0.3 equiv) in THF at 0 °C for 1 h. [b] Yield and conversion were determined by ^{1}H NMR analysis. Isolated yields are indicated in parentheses. [c] Major products were $Ph_2C(OH)Me$ and the corresponding diol. [d] Starting **1** was recovered.

property of the **4a**/CuCN catalyst was also examined (entry 1).[10] As can be seen, $MgCl_2$ not only altered the native low regioselectivity but also suppressed the nucleophilic attack to the Ac carbon (entries 2−5 vs entry 1). Among the entries, 4−5 equiv of $MgCl_2$ provided the best results in terms of the yield of **2a** and the regioselectivity (**2a** over **3a**) as shown in entries 4 and 5.

The best reaction conditions found above were applied to PhLi (**4a**) prepared in situ from PhX (X = I, Br, $SnBu_3$) by several methods. First, **4a** was prepared in the usual manner from PhI by halogen−lithium exchange with *n*-BuLi and subjected to the reaction with **1**. Surprisingly, the expected product **2a** was not produced (Table 2, entry 1); instead,

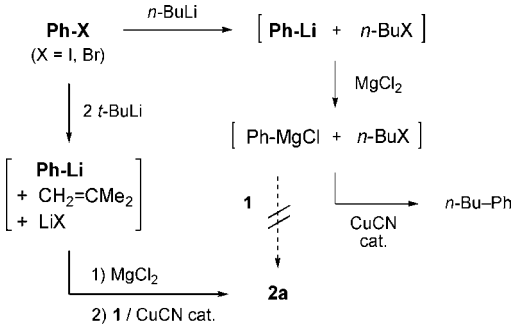
Table 2. Phenylation of Monoacetate **1** Using PhLi Derived from PhX or $PhSnBu_3$ and BuLi[a]

entry	source of PhLi[b] (equiv)	ratio of **2**:**3**	yield of **2**, %[c]	conversion of **1**, %[c]
1	PhI (3), *n*-BuLi (3.3)	–	0	<10[d]
2	PhBr (3), *n*-BuLi (3.3)	–	0	<10[d]
3	PhI (3), *t*-BuLi (6.0)	92:8	94 (91)	100
4	PhBr (3), *t*-BuLi (6.0)	92:8	90 (85)	100
5	$PhSnBu_3$ (3.6), *n*-BuLi (3.6)	>95:<5	86 (74)	100

[a] CuCN-catalyzed reactions were carried out with PhMgCl·LiCl (3−3.6 equiv) prepared from PhLi (**4a**) (3−3.6 equiv) and $MgCl_2$ (4 equiv) (THF, 0 °C, 1 h). [b] PhLi (**4a**) was prepared in situ from the source indicated in the table. [c] Yield and conversion were determined by ^{1}H NMR analysis. Isolated yields are indicated in parentheses. [d] Instead, starting **1** and butylbenzene were confirmed by ^{1}H NMR spectroscopy.

butylbenzene (*n*-Bu−Ph), though volatile, was detected in the crude reaction mixture with recovered monoacetate **1** by ^{1}H NMR spectroscopy. A similar result was also observed in entry 2 using the anion derived from PhBr and *n*-BuLi. We postulated that *n*-BuX (X = I, Br), coproduced with **4a** by the halogen−lithium exchange, substantially consumed PhMgCl by the CuCN-catalyzed coupling reaction before addition of **1** even within 30 min (Scheme 1).[11]

Scheme 1. Reaction Courses of PhLi Generated by Halogen−Lithium Exchanges[a]



[a] Results are summarized in Table 2.

To support this hypothesis, *n*-BuX (X = I, Br) (3 equiv of **1**) was added externally to the solution of PhLi (3 equiv)

(3) Compounds **2** (R = aryl, alkenyl) have been synthesized from cyclopentene monoepoxide, but in low regioselectivities: (a) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898−4913. (b) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979−992. (c) Tucci, F. C.; Chieffi, A.; Comasseto, J. V.; Marino, J. P. *J. Org. Chem.* **1996**, *61*, 4975−4989.

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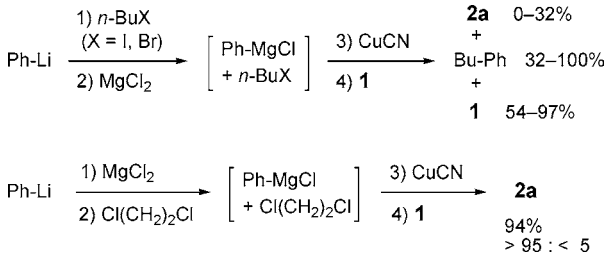
(7) Ref 5 in: Sapountzis, I.; Dohle, W.; Knochel, P. *Chem. Commun.* **2001**, 2068−2069.

(8) We thank Kanto Kagaku, Japan for providing us this information.

(9) Prepared freshly from Mg and $Cl(CH_2)_2Cl$ in a ratio of 1:3.

in cyclohexanes−Et_2O, which was prepared by the halogen−lithium exchange with Li, and the resulting solution was mixed first with $MgCl_2$ (4 equiv) for 15 min and then with CuCN (30 mol %) for 20−30 min. The mixture thus prepared upon reaction with **1** afforded **2a** in 0−32% yields with *n*-Bu−Ph (32−100%) and **1** (54−97%) (Scheme 2).

Scheme 2. Results Supporting the Side Reaction of PhMgCl with *n*-BuX by Using PhLi (3 equiv to **1**), *n*-BuX or $Cl(CH_2)_2Cl$ (3 equiv), CuCN (30 mol %), and **1** (1 equiv)



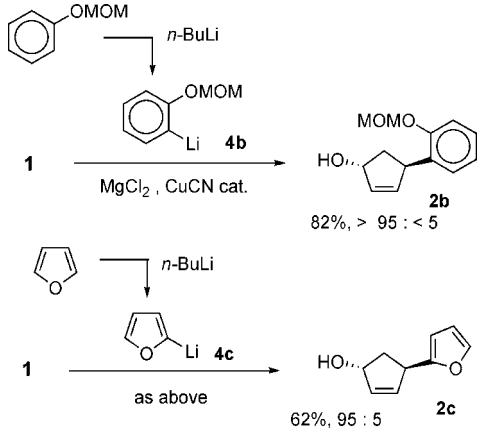
Since *n*-BuX was confirmed to consume PhMgCl, one might expect a similar interference by $Cl(CH_2)_2Cl$, which was used for the preparation of $MgCl_2$ from Mg. Although the successful results of Table 1, entries 4 and 5, precluded such an interference, additional evidence was provided by external addition of $Cl(CH_2)_2Cl$ to the pure PhMgCl and subsequent reaction with **1**, which afforded the normal coupling product **2a** in good yield (Scheme 2, the lower equation).

The above results suggested successful phenylation of **1** with PhLi (**4a**) prepared from PhX by halogen−lithium exchange with *t*-BuLi, since LiX and isobutene, coproduced with PhLi, would be inert in the desired reaction (see Scheme 1). In practice, the *t*-BuLi alternation was proved to be the case. Thus, **4a** (3 equiv of **1**), produced from PhX (X = I, Br) and *t*-BuLi, was combined with $MgCl_2$ (4 equiv), and the subsequent CuCN-catalyzed reaction with **1** produced **2a** in good yields and high regioselectivity (Table 2, entries 3 and 4). The efficiency thus observed was comparable to that obtained with the PhLi/$MgCl_2$/CuCN catalyst (Table 1, entries 4 and 5).

Preparation of PhLi (**4a**) by the stannane−lithium exchange of $PhSnBu_3$ and *n*-BuLi was also expected to be compatible with the CuCN-catalyzed reaction of **1**. Thus, **4a** was produced from $PhSnBu_3$ and *n*-BuLi in THF at 0 °C for 30 min, and subsequent reaction with **1** after transformation into PhMgCl produced **2a** with good efficiency (Table 2, entry 5), which is as high as that of entry 4 in Table 1.

Another compatible preparation of ArLi would be direct lithiation of aromatic compounds with *n*-BuLi, which was proven by using the aryl anion **4b** derived from the MOM ether of phenol by ortho lithiation with *n*-BuLi.[12] After conversion into the magnesium species, **4b** afforded the S_N2-type product **2b** in 82% isolated yield with >95% regioselectivity (Scheme 3). In a similar way, 2-furyllithium **4c**[13]

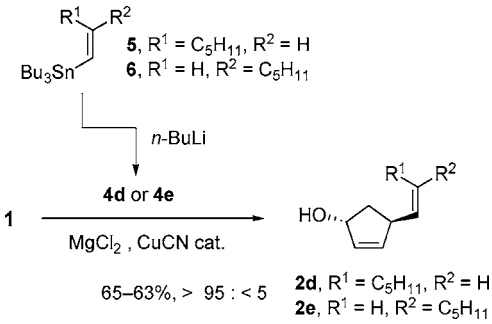
Scheme 3. Reaction of **1** with Reagents Derived from **4b** or **4c** (3 equiv), $MgCl_2$ (4 equiv), and CuCN (30 mol %)



derived from furan and *n*-BuLi furnished **2c** efficiently.

The synthetic advantage of using an organostannane as a source of alkenyllithium was highlighted by alkenylation of **1**. Thus, *cis*-alkenyllithium **4d** was prepared from *cis*-alkenylstannane **5** and *n*-BuLi and subjected to the CuCN-catalyzed reaction with **1** after in situ conversion into the organomagnesium chloride to afford **2d** in 65% yield with >95% regioselectivity (Scheme 4). Similarly, *trans*-alkenyl-

Scheme 4. Reaction of **1** with Reagents Derived from **4d** or **4e** (3 equiv), $MgCl_2$ (4 equiv), and CuCN (30 mol %)



stannane **6** produced **2e** as well. No product crossover by **2e** was observed in the ^1H NMR spectra of **2d** and vice versa. In comparison with the previous alkenylation with lithium alkenylborates/nickel catalyst[2d] (85−89% yield, 83−86% regioselectivity), the present method is more efficient and the reagent preparation is simpler than that of the borates, which took three steps from the alkenyllithiums.

The alkenyl protocol was applied to prostaglandin synthesis (Scheme 5). Alkenyl stannane **7** was prepared by

(10) Reactions with $Ph_2Cu(CN)Li_2$ (3 equiv) and PhCu(CN)Li (3 equiv) in THF at 0 °C to room temperature afforded a mixture of products among which the corresponding diol was the major component.

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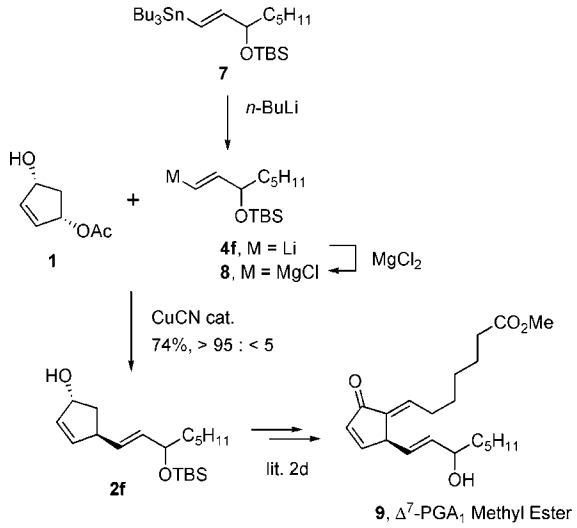
Scheme 5. Synthesis of Prostaglandin Intermediate **2f**



hydrostannation of the corresponding acetylene[14] and converted into the magnesium reagent **8** by the stannane−lithium exchange with *n*-BuLi followed by transmetalation of the resulting **4f** with $MgCl_2$. Reaction of **1** and **8** thus prepared proceeded cleanly with the CuCN catalyst to produce **2f** exclusively in 74% yield. Previously, **2f** was synthesized by the nickel-catalyzed alkenylation[2d] in 76% yield with >95% regioselectivity, and transformed into Δ^7-PGA_1 methyl ester (**9**), which is an antitumor agent found by Suzuki and Noyori.[15] Although the efficiency of the respective methods is comparable, the present reaction is advantageous in terms of the reagent preparation (vide ante).

In summary, the CuCN-catalyzed arylation of **1** with aryl-MgCl to afford the S_N2 product **2** was expanded to aryl and alkenyllithium anions, which were prepared through halogen−lithium exchange with lithium, exchange with *t*-BuLi, stannane−lithium exchange with *n*-BuLi, and direct lithiation with *n*-BuLi. However, the lithium anion prepared by the usual halogen−lithium exchange with *n*-BuLi was not compatible with the CuCN-catalyzed reaction. The reason for the failure was elucidated and is informative for other Cu-catalyzed reactions.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Typical experimental procedures, compound characterization, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0501065

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