Rapid Generation of Molecular Complexity: Synthesis of α-Hydroxyallenes Using Functionalized Grignard Reagents

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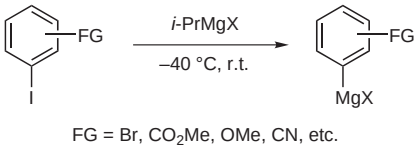
Abstract: The use of functionalized aryl-Grignard reagents in the copper-mediated S_N2' substitution of propargylic oxiranes leads to structurally complex α-hydroxyallenes, usually with high yield and diastereoselectivity. Further transformations, such as gold-catalyzed cycloisomerization to 2,5-dihydrofurans and palladium-catalyzed coupling reactions, demonstrate the high potential of these compounds for the rapid generation of molecular complexity.

Key words: allenes, chirality transfer, functionalized Grignard reagents, organocopper reagents, S_N2' substitution

Allenes in general and α-hydroxyallenes in particular are versatile building blocks for advanced organic synthesis because of the high reactivity inherent to their axially chiral backbone.[2] They are usually prepared by S_N2' substitution of propargylic electrophiles (esters, halides, oxiranes, sulfonates, etc.) with organocopper compounds.[2,3] Although the use of various organometallic precursors, which are transmetalated to the corresponding cuprates, is highly developed and well established, the scope of these nucleophiles was mostly limited to alkyl or simple aryl compounds. In our ongoing research dedicated to the synthesis and transformation of α-hydroxyallenes[3] and other functionalized allenes,[4] we became interested in the rapid formation of highly functionalized target molecules by using functionalized organometallic reagents.

Knochel and co-workers[5] have developed efficient protocols for the generation of arylmagnesium reagents bearing various functional groups which undergo trapping reactions with reactive electrophiles (including allylations) after transmetalation to copper. The key step is the halogen–magnesium exchange of an aryl bromide or iodide with isopropylmagnesium chloride or other Grignard reagents (Equation 1) which shows a high tolerance towards functional groups like halides, nitriles, esters and even nitro groups.[5,6] Aromatic iodides bearing electron-donating groups, like anisole derivatives, undergo the halogen–metal exchange as well, but higher temperatures and longer reaction times are required.[5] Thus, the application of these nucleophiles in the copper-mediated S_N2' substitution of propargylic oxiranes would open up a rapid access to highly complex α-hydroxyallenes bearing several functionalities for further transformations.



FG = Br, CO_2Me, OMe, CN, etc.

Equation 1 Synthesis of functionalized Grignard reagents by halogen–metal exchange

We began our study with the model substrates **1**[7] bearing a silyl or benzyl ether protecting group,[3,4] as well as the 4-trifluoromethylphenyl group, a well-known pharmacophore[8] (Table 1).

We were pleased to find that treatment of propargyl oxiranes **1** with various functionalized aryl cuprates consistently led to the exclusive formation of the desired S_N2'-substitution products **2a**–**j** which were mostly obtained with good to excellent chemical yield. Besides halides and methoxy groups, esters, nitro groups and even nitriles (which sometimes cause problems in copper-mediated reactions[9]) are tolerated. All reactions were performed in the presence of one equivalent of tri-*n*-butylphosphine or triethylphosphite in order to prevent the known[2,3,10] copper-promoted epimerization of the allene, so that the α-hydroxyallenes **2** were formed with high *anti* diastereoselectivity in most cases. Lower stereoselectivities were observed for the 2- and 3-methoxyphenyl cuprate (entries 6 and 7); in the latter case, use of triethylphosphite as additive gave a much higher diastereoselectivity, but a decreased chemical yield, compared to tri-*n*-butylphosphine (entry 8).

The dependence of allene epimerization on the nature of the cuprate and the additive is even more pronounced in the S_N2' substitution of the bicyclic epoxide **3** (Table 2). Here, the electron-deficient ester-substituted cuprate gave a dismal diastereoselectivity in the presence of *n*-Bu_3P, but a diastereomerically pure α-hydroxyallene with $(EtO)_3P$ (entries 1 and 2). In striking contrast, the substitution of the electron-rich anisol-derived cuprate hardly showed any dependence on the additive (entries 3–5); the highest diastereoselectivity (but the lowest chemical yield) was observed in the absence of an additive (entry 5).

Gratifyingly, the method is not restricted to terminal propargylic oxiranes. For steric and electronic reasons, the substrates **5** and **7** bearing an internal triple bond are expected to be less reactive towards nucleophiles than terminal alkynes; nevertheless, the reactivity of the

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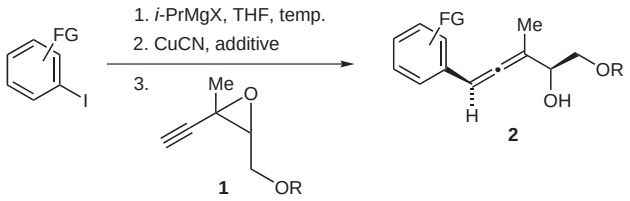
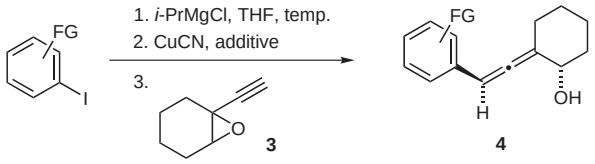
Table 1 Synthesis of the Functionalized α-Hydroxyallenes **2**



Entry	R	FG	Temp (°C)	Additive	Yield of **2** (%)	dr
1	TBS	4-F	–40	*n*-Bu_3P	**2a** (68)	94:6
2	TBS	2-F	–40	*n*-Bu_3P	**2b** (99)	85:15
3	TBS	4-Br	–40	*n*-Bu_3P	**2c** (77)	>95:5
4[a]	TBS	4-CO_2Me	–20	*n*-Bu_3P	**2d** (85)	15:85
5[a]	TBS	4-CN	–78	*n*-Bu_3P	**2e** (62)	10:90
6	TBS	2-OMe	r.t.	*n*-Bu_3P	**2f** (52)	75:25
7	TBS	3-OMe	r.t.	*n*-Bu_3P	**2g** (77)	75:25
8	TBS	3-OMe	r.t.	$(EtO)_3P$	**2g** (44)	>95:5
9	TBS	4-OMe	r.t.	*n*-Bu_3P	**2h** (71)	>95:5
10[b]	Bn	2-NO_2	–90	*n*-Bu_3P	**2i** (59)	>95:5
11	4-$CF_3C_6H_4$	4-CO_2Me	–40	*n*-Bu_3P	**2j** (66)	97:3

[a] The *trans*-oxirane was used instead of the *cis*-isomer.
[b] PhMgBr was used for the halogen–magnesium exchange.

Table 2 Synthesis of the Functionalized α-Hydroxyallenes **4**



Entry	FG	T (°C)	Additive	Yield of **4** (%)	dr
1	4-CO_2Me	–20	*n*-Bu_3P	**4a** (77)	60:40
2	4-CO_2Me	–20	$(EtO)_3P$	**4a** (85)	>95:5
3	4-OMe	r.t.	*n*-Bu_3P	**4b** (75)	85:15
4	4-OMe	r.t.	$(EtO)_3P$	**4b** (75)	88:12
5	4-OMe	r.t.	–	**4b** (41)	91:9
6	3-OMe	r.t.	*n*-Bu_3P	**4c** (85)	85:15

functionalized aryl cuprate obtained from methyl 4-iodobenzoate is sufficient to convert these electrophiles into the highly functionalized tetrasubstituted allenes **6** and **8** with good chemical yield and high *anti* diastereoselectivity (Scheme 1).

The functionalized α-hydroxyallenes described in this paper are highly useful synthetic intermediates (Scheme 2). For example, the bromo-substituted allene **2c** underwent a smooth gold-catalyzed cycloisomerization[3,4] to the 2,5-dihydrofuran **9** (72% yield) which was then subjected to a Sonogashira coupling with trimethylsilylacetylene in THF solution,[11] affording the functionalized heterocycle **10** in a highly stereoselective fashion. The reverse order of events gave the same product via allene **11** with a slightly lower chemical yield.

In conclusion, we have expanded the scope of the copper-promoted S_N2' substitution of propargylic oxiranes by using functionalized Grignard reagents formed by halogen–magnesium exchange.[12] We were able to obtain highly functionalized α-hydroxyallenes with high yield and excellent center-to-axis chirality transfer in most cases. The method can be applied to terminal and internal alkynes with similar efficiency. The utility of the products for further transformations was demonstrated in the gold-catalyzed cycloisomerization to 2,5-dihydrofurans, as well as in the palladium-catalyzed Sonogashira coupling, thereby taking advantage of the functionality introduced with the Grignard reagent.

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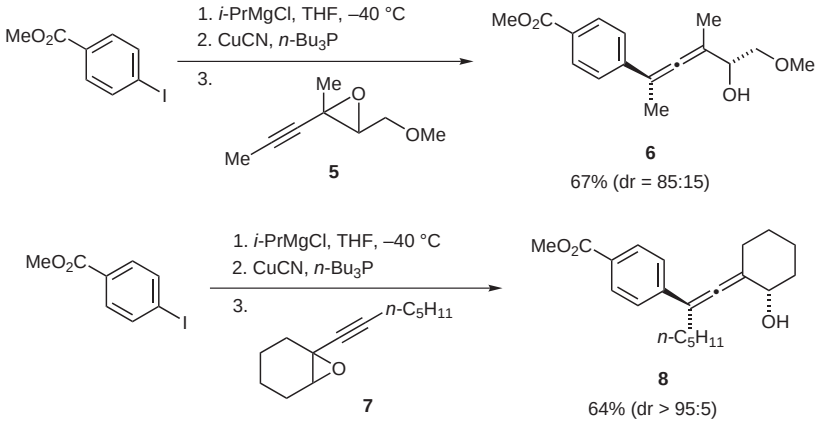
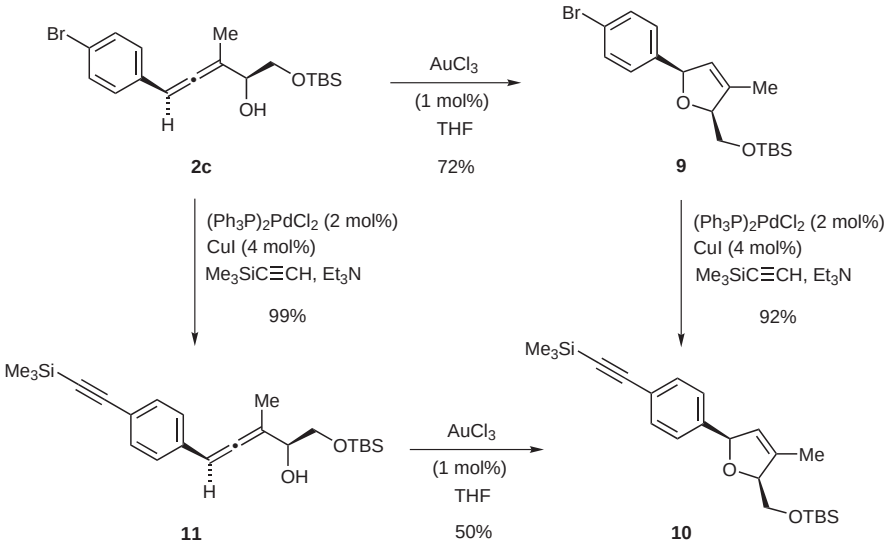


Scheme 1 Synthesis of the functionalized α-hydroxyallenes **6** and **8**



Scheme 2 Gold- and palladium-catalyzed transformations of α-hydroxyallene **2c**

References and Notes

(1) New address: Institute of Organic Chemistry, University of Mainz, Duesbergweg 10–14, 55128 Mainz, Germany.

(2) (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, **1984**. (b) *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, **2004**. (c) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (d) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (e) Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 2933; *Angew. Chem.* **2002**, *114*, 3057. (f) Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; *Angew. Chem.* **2004**, *116*, 1216. (g) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. (h) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

(3) (a) Krause, N.; Morita, N. In *Comprehensive Organometallic Chemistry III*, Vol. 9; Crabtree, R. H.; Mingos, D. M. P., Eds.; Elsevier: Oxford, **2006**, 501–586. (b) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (c) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759. (d) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (e) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995.

(4) (a) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (b) Morita, N.; Krause, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1897; *Angew. Chem.* **2006**, *118*, 1930. (c) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, 4634. (d) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.

(5) (a) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, **2005**. (b) Boudier, A.; Bromm, L. A.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; *Angew. Chem.* **2000**, *112*, 4584. (c) Knochel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, **2002**, 45–78. (d) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; *Angew. Chem.* **2003**, *115*, 4438.

(6) (a) Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; *Angew. Chem.* **2002**, *114*, 1680. (b) Sapountzis, I.; Dube, H.; Lewis, R.; Gommermann, N.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2445. (c) Krasovsky, A.; Straub, B. F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 159; *Angew. Chem.* **2006**, *118*, 165.

(7) Substrates **1a**,**b** and **3** have been synthesized previously: (a) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435. (b) Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1991**, *55*, 2225. (c) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677.
(8) Miko, T.; Ligeneau, X.; Pertz, H. H.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W.; Stark, H. *J. Med. Chem.* **2003**, *46*, 1523.
(9) (a) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779. (b) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153.
(10) Claesson, A.; Olsson, L. I. *J. Chem. Soc., Chem. Commun.* **1979**, 524.
(11) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551.
(12) **Representative Procedure and Spectroscopic Data – Synthesis of 1-(*tert*-Butyldimethylsilyloxy)-5-(4-fluorophenyl)-3-methylpenta-3,4-dien-2-ol (2a).**
To a stirred solution of 4-fluoroiodobenzene (706 mg, 3.2 mmol) in anhyd THF (15 mL) was added *i*-PrMgCl (2.1 mL, 3.4 mmol; 1.7 M in Et_2O) at –40 °C. After 1 h at this temperature, the Grignard reagent was added via cannula to a cold (–30 °C), freshly prepared solution of copper(I) cyanide (142 mg, 1.6 mmol) and tri-*n*-butylphosphine (322 mg, 1.6 mmol) in anhyd THF (20 mL). The resulting cuprate solution was stirred for 30 min at –30 °C, followed by addition of *cis*-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-3-methylpent-4-yne (**1**, 300 mg, 1.3 mmol) in anhyd THF (3 mL). After stirring for 16 h under warming to r.t., quenching with 3 mL of a sat. NH_4Cl solution, washing with 3 × 10 mL of a 2% H_2O_2 solution, filtration through a pad of Celite®, evaporation of the solvent and column chromatography (SiO_2, EtOAc–cyclohexane = 10:1) furnished 287 mg (68%) of **2a** as a yellow oil (dr = 94:6 according to NMR analysis). ^{1}H NMR (500 MHz, C_6D_6): δ = 7.14–7.09 (m, 2 H), 6.87–6.83 (m, 2 H), 6.10 (m, 1 H), 4.21 (m, 1 H), 3.73 (dd, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H), 3.66 (dd, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H), 2.41 (br s, 1 H), 1.88 (m, 3 H), 0.95 (s, 9 H), 0.04 and 0.03 (2 s, 6 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 202.0, 163.4 (d, $^1J_{CF}$ = 241 Hz), 132.3, 128.7 (d, $^3J_{CF}$ = 10 Hz), 115.9 (d, $^2J_{CF}$ = 21 Hz), 105.2, 95.6, 72.8, 66.2, 26.0, 18.4, 15.3, –5.3 ppm.
Spectroscopic Data of 2-(4-Methoxycarbonylphenylethenylidene)cyclohexan-1-ol (4a).
^{1}H NMR (400 MHz, C_6D_6): δ = 8.18 (d, $^3J_{HH}$ = 8.2 Hz, 2 H), 7.26 (d, $^3J_{HH}$ = 8.2 Hz, 2 H), 6.13 (s, 1 H), 4.04 (m, 2 H), 3.49 (s, 3 H), 2.43 (m, 1 H), 1.99 (m, 3 H), 1.65 (m, 1 H), 1.56 (m, 1 H), 1.44 (m, 1 H), 1.36 (m, 1 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 199.1, 166.6, 140.7, 130.5, 127.0, 112.3, 97.0, 69.2, 51.6, 36.3, 29.3, 27.0, 23.3 ppm.
Spectroscopic Data of *cis*-2-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-5-(4-trimethylsilylethynylphenyl)-2,5-dihydrofuran (10).
^{1}H NMR (400 MHz, C_6D_6): δ = 7.43 (d, $^3J_{HH}$ = 8.3 Hz, 2 H), 7.21 (d, $^3J_{HH}$ = 8.3 Hz, 2 H), 5.58 (br s, 1 H), 5.21 (s, 1 H), 4.68 (br s, 1 H), 3.79 (dd, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H), 3.66 (dd, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1 H), 1.62 (s, 3 H), 0.95 (s, 9 H), 0.10 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 142.2, 137.6, 131.4, 129.0, 125.7, 121.5, 88.7, 86.1, 65.1, 25.9, 18.3, 12.4, –0.8, –5.5 ppm.