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Hydroxyl-Directed Conjugate Additions of Carbon Nucleophiles to Cyclopentadienones

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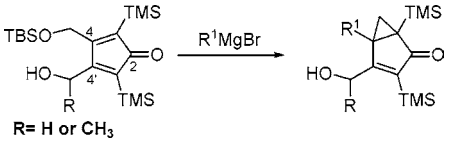
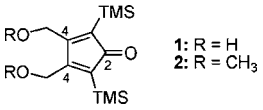
ABSTRACT

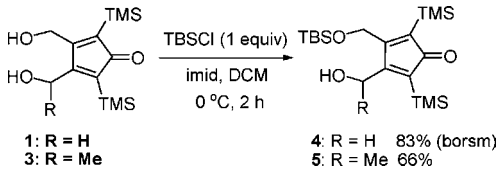


The conjugate additions of different carbon nucleophiles to cyclopentadienone substrates (1 and 2) with one free hydroxyl functional group were investigated to determine the role of the hydroxyl group in controlling regiochemistry. During this reaction an unexpected intramolecular displacement of OTBS by the enolate intermediate occurs, to afford cyclopropane derivatives.

We have previously reported the preparation of cyclopentadienone derivatives with two side-chain hydroxy groups, using a silicon-tethered $Fe(CO)_5$ promoted cyclocarbonylation followed by demetalation.[1] Conjugate additions of different Grignard reagents to 2,5-bis(trimethylsilyl)-3,4-bis(hydroxymethyl)cyclopentadienone (**1**) and the corresponding methyl ether (**2**) were investigated.[2] On the basis of the markedly different behavior observed for these two systems, we suggested that the hydroxyl groups probably play an important role in the conjugate addition process, such as transferring nucleophiles to the 4 position.



To test this proposition further, we have examined reactions of cyclopentadienones with only one free hydroxyl group. For this purpose, we chose two new cyclopentadienone substrates (**4** and **5**) with one free hydroxyl group and one TBS ether, since these are easily prepared in good yields from cyclopentadienones **1** and **3**.



The reactions of **4** and **5** with four Grignard reagents were investigated, and the results are shown in Tables 1 and 2. In the reactions of **4** with MeMgBr, VinylMgBr, and PhMgBr (entries 1, 3, and 6), nucleophiles were delivered to the 4 position remote from the hydroxyl group.

For the AllylMgBr system (entry 2), 1,2 adduct **9** was favored because the transition state corresponding to hydroxyl group participation would likely require at least a seven-member ring, as observed in our earlier work.[2] However, in the 1,4 addition products, cyclopropanes were formed by intramolecular displacement of the OTBS anion. Since the OTBS anion is not normally a good leaving group, this behavior was unexpected.

The structural assignment of the cyclopropanated 1,4 addition products was based on the disappearance of TBS peaks on the NMR spectra and the appearance of ABq at δ 1.50 and 1.10 ppm (**11b** as the example), corresponding to the cyclopropyl methylene group. Furthermore, the gHMQC spectra showed the proton peaks at δ 1.50 and 1.10 ppm

(1) Pearson, A. J.; Kim J. B. *Org. Lett.* **2002**, *4*, 2837.
(2) Pearson, A. J.; Kim J. B. *Org. Lett.* **2003**, *5*, 2457.

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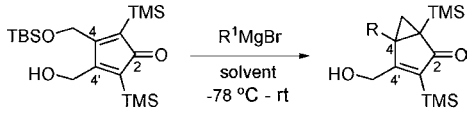
Table 1. Addition of Grignard Reagents to Cyclopentadienone **4**



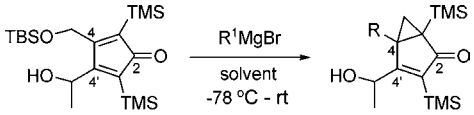
4

6a R = Me
6b R = Vinyl
6c R = Ph

entry	R^1	solvent	amount (equiv)	product/ yield (%)
1	Me	DCM	4	**6a**/34[a]
2	allyl	THF or DCM	2	*b*
3	vinyl	THF or DCM	2	**6b**/55
4	Ph	THF	2	*c*
5	Ph	DCM	2	*d*
6	Ph	DCM	10	**6c**/67

[a] 18% 1,2 adduct **7** and 13% 1,4′ adduct **8** were also isolated. [b] Only 1,2 adduct **9** was obtained in 49% yield. [c] SET product **10** was obtained in 52% yield. [d] Starting material was recovered.

Table 2. Addition of Grignard Reagents to Cyclopentadienone **5**



5

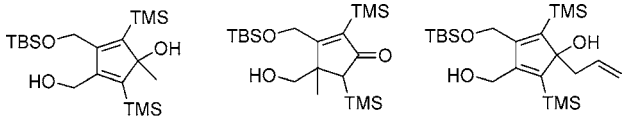
11a R = Me
11b R = Vinyl
11c R = Ph

entry	R^1	solvent	amount (equiv)	product/ yield (%)
1	Me	THF or DCM	2	*a*
2	Me	DCM	10	**11a**/28[b]
3	allyl	THF or DCM	2	*c*
4	vinyl	THF	2	**11b**/57
5	Ph	THF	2	**11c**/22[d]
6	Ph	THF	10	**11c**/76

[a] Starting material was recovered. [b] 5% 1,2 adduct **12** and 16% 1,4′ adduct **13** (TMS on sp^3 C was removed during workup) were also isolated. [c] Two diastereomers (1.7:1) of 1,2 adduct **14** were obtained in 53% yield. [d] Yield is based on 60% conversion.

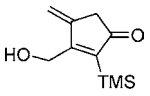
belong to one carbon. Further information on the NMR spectra for these compounds can be found in the Supporting Information.

Reaction of **4** with MeMgBr also gave 1,2 adduct **7** in 18% yield and 1,4′ adduct **8** in 13% yield. A possible explanation is that MeMgBr is more reactive than the other Grignard reagents, which leads to the poorer regioselectivity by competing intermolecular, non-hydroxyl directed addition.



7 **8** **9**

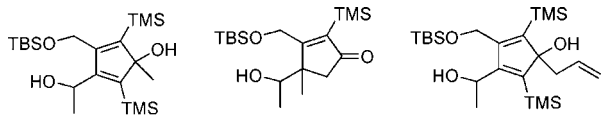
For most of the Grignard reagents, we did not observe any marked solvent effect. For entry 1, the yields were somewhat better in DCM than in THF. For entries 2 and 3, almost the same results were observed in either DCM or THF. However, from the reaction with PhMgBr, the elimination product **10** was obtained in 52% yield when THF was



10

the solvent, presumably via a two-step single electron transfer (SET) reduction to form an enolate that then ejects the OTBS anion. Since similar SET reactions of PhMgBr with different substrates have been reported,[3] the result for entry 4 was not surprising. The main challenge is how to prevent this reaction pathway. Birch and co-workers have reported that use of DCM as solvent could suppress SET reactions of alkylmagnesium and organolithium reagents.[4] When DCM was used for our reaction, no SET product was observed, and instead the cyclopropanated conjugate addition product **6c** was obtained in 67% yield.

Initially, we expected that conjugate additions to cyclopentadienone **5** would give several regio- and stereoisomers owing to the presence of one stereogenic center. However, as shown in Table 2, the results are very similar to those for cyclopentadienone **4**. Reaction of **5** with MeMgBr gave mainly the cyclopropanated 1,4 addition product, together with 5% 1,2 adduct **12** and 16% 1,4′ adduct **13**. For AllylMgBr addition, 1,2 adduct **14** was the only product.



12 **13** **14**

Both VinylMgBr and PhMgBr gave cyclopropanated 1,4 addition products in acceptable yields. Interestingly, all of the cyclopropanated 1,4 addition products in Table 2 are single diastereomers, though we have not yet determined their relative stereochemistry. Since 3-butyn-2-ol, the precursor for dienone **5**, is available as either enantiomer in optically pure form, this approach might provide a convenient method for accessing optically pure substituted cyclopentenone derivatives.

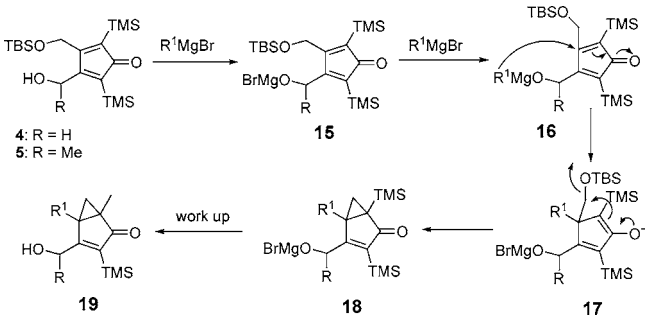
From these results it appears that a pendant hydroxyl group can play a critical role in controlling regiochemistry during

(3) For examples and mechanism for SET reactions of PhMgBr, see: Hendrickson, W. H., Jr.; MacDonald, W. D.; Howard, S. T.; Coligado, E. J. *Tetrahedron Lett.* **1985**, *26*, 2939. Giuseppe, B.; Marcella, B.; Gabriele, C.; Renato, D.; Francesco, C. *J. Chem. Soc., Perkin Trans. 2* **1985**, *6*, 773. Cornelis, B.; Grootveld, H. H.; Gerner, T. H.; Bickelhaupt, F. *J. Orgaomet. Chem.* **1970**, *24*, 549. Kharasch, M. S.; Fuchs, C. F. *J. Org. Chem.* **1945**, *10*, 292.

(4) Bandara, B. M.; Birch, A. J.; Khor, T. C. *Tetrahedron Lett.* **1980**, *21*, 3625.

Michael additions to cyclopentadienones. It is likely that the alkylmagnesium halide forms an alkoxymagnesium alkyl intermediate such as **16** (Scheme 1).[5] With Grignard reagents

Scheme 1



such as MeMgBr, VinylMgBr, or PhMgBr, the alkyl group is then delivered to the 4 position of the cyclopentadienone through a six-membered-ring transition state. Allylmagnesium reagents react with electrophiles at the carbon remote from Mg, and for intramolecular delivery to the 4 position would require an eight-membered ring, which is unfavorable. A seven-membered-ring structure, still unfavorable, would direct addition to the 4′ position. In this situation, it is likely that intermolecular 1,2-addition of AllylMgBr occurs more rapidly.

The enolate intermediate **17** undergoes rapid intramolecular reaction with the nearby TBS ether to afford the cyclopropane derivative. Although these products are intrinsically very interesting, their potential use for total synthesis of natural products is not reported.[6]

Acknowledgment. We thank the National Science Foundation and Case Western Reserve University for financial support.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H, gHMQC, and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061127H

(5) For examples of hydroxyl-directed nucleophilic addition reactions, see: Swiss, K. A.; Liotta, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 9393. Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta. *Synthesis* **1992**, 127. Fleming, F. F.; Guo, J.; Wang, Q.; Weaver, D. *J. Org. Chem.* **1999**, *64*, 8568. Csaky, A. G.; Mba, M.; Plumet, J. *J. Org. Chem.* **2001**, *66*, 9026.

(6) We are currently examining similar reactions of alkyl ether derivatives corresponding to **4** and **5** in an effort to circumvent this side reaction. Our progress will be reported in due course.