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Temporary Magnesium and Aluminum Connections in 4 + 2 Cycloadditions

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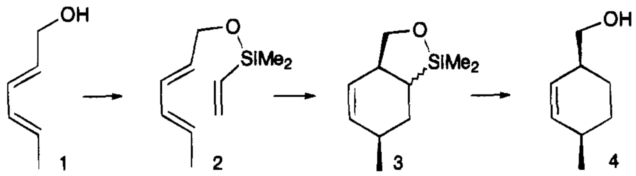
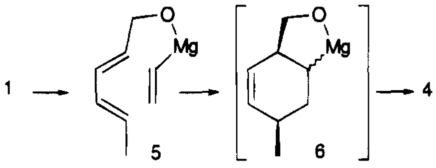
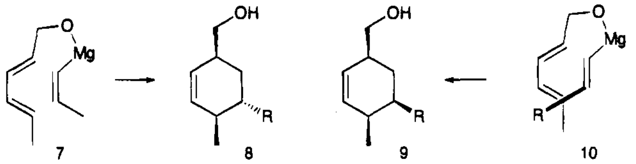
We have previously reported on the application of the process which we have termed the "temporary silicon connection" [1] to the construction of 4 + 2 cycloadducts,[2,3] as illustrated below:



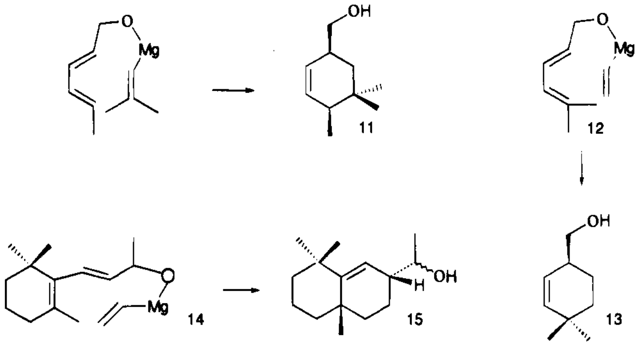
We now report the remarkable observation that a *magnesium* or an *aluminum* atom can serve as the temporary tether (cf. **5**; likely ligands on metal not shown). Not only does cycloaddition take place in spite of the fact that the "dienophile" is now formally a vinyl *carbanion*, but it is actually *greatly facilitated.* For example, the magnesium-tethered intermediate **5** (1 equiv of BuLi added at −78 °C to **1**, followed, at room temperature, by 1 equiv of 2 M vinylmagnesium bromide in THF) gave **4**[4] in ~70% yield after heating for *only 1 h at 80 °C.*[5] To place this result in context, we found that cycloaddition of the silicon-tethered **2** requires 3 h at 160 °C, and that of the allyl ether from **1** (**5**, CH_2 instead of Mg) takes 10 h at 160 °C.[6]



Substituted vinylmagnesium halides also appear to be suitable participants in the cycloaddition: the reaction product **7** of the lithium alkoxide of **1** with (*Z*)-1-propenylmagnesium bromide[7] gave (2 h heating at 130 °C; 60%), regiospecifically and stereoselectively, a mixture of the two 4,5-dimethyl-2-cyclohexenemethanols **8** and **9**, R = methyl,[2,8] in which **8** greatly predominated (9:1). The isomeric **10**, made from the (*E*)-propenyl Grignard reagent, gave (3 h, 130 °C; 60%) the same mixture of **8** and **9**, but the major isomer was now **9** (4:1). Similarly, the magnesium derivative from *β*-bromostyrene (*E*:*Z*, ~9:1) reacted with the lithium salt of **1** (160 °C, 8 h) to give a 70% yield of cycloadducts as a 2:1 exo:endo mixture of **9** and **8**, R = phenyl. The regiochemical results are consistent with an intramolecular 4 + 2 cycloaddition, while the stereochemistry of the adducts indicates a bias toward "exo" transition states.[9]



Disubstitution at the *β*-position of the vinyl "dienophile" still allows cycloaddition, as shown in the formation of **11** in ~60% yield (140 °C, 4 h). Even more remarkably, *terminal disubstitution of the diene* can be tolerated: the intermediate **12** from the lithium salt of 5-methyl-2,4-hexadienol and vinylmagnesium bromide gave (3 h, 130 °C) the cyclohexenemethanol **13** in 65% yield. Although we have prepared the same adduct from that same dienol by the silicon tether method,[2] this required 26 h at 200 °C and gave **13** in only ~30% yield. A somewhat more elaborate example of this type is the addition of the magnesio intermediate **14** from the lithium salt of *β*-ionol to vinylmagnesium bromide (140 °C, 14 h) to give adduct **15**[10] in 44% yield (60−70%, based on recovered ionol).



The assumed formation of cyclic magnesium alkoxides in the 4 + 2 magnesium-tethered cyclizations reported here is supported by the incorporation of deuterium[11] when D_2O was added before the usual workup of the putative intermediate **6**. Similarly, addition of CO_2 before workup gave lactone **16**.[12,13]

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(1) (a) For an overview of our work, see: Stork, G. 32nd National Organic Symposium, Minneapolis, 1991. (b) Application to radical reactions: Keitz, P. Ph.D. Thesis, Columbia, 1988. *Diss. Abstr. Int., B* **1991**, *52*, 838. (c) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (d) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826. (e) In photochemical processes: Lambert, P. Ph.D. Thesis, Columbia, 1991. *Diss. Abstr. Int., B* **1992**, *52*, 5828. (f) In C-glycoside construction: Stork, G.; Suk, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054. (g) In disaccharide synthesis: Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087.

(2) Stork, G.; Chan, T. Y.; Breault, G. *J. Am. Chem. Soc.* **1992**, *114*, 7578. This paper includes successful silicon-tethered 4 + 2 cycloadditions which were first achieved at Columbia by Dr. Breault in 1987, but as the referees pointed out, the first example of the process in print actually appears to be in a paper published in 1989.[3a]

(3) (a) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478. (b) Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885. (c) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, *31*, 6586. (d) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145. (e) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, *33*, 4073. (f) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279.

(4) This proved identical with the substance obtained previously (ref 2).

(5) Reactions were performed in sealed tubes. Purification was by flash chromatography with 1:1 ether−hexanes, after acidification with dilute hydrochloric acid. Unless otherwise noted, the structures and stereochemistries were assigned, inter alia, from results of NMR decoupling and NOE experiments. The Mg atom tethers shown in various structures are presumably coordinated to solvent molecules.

(6) A related all-carbon case is stated to give 45% conversion in 90 h at 160 °C: Lin, Y. T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2269. For a comprehensive survey of intramolecular Diels−Alder reactions, see: Ciganek, E. *Org. React.* (*N.Y.*) **1984**, *32*, 1.

(7) Prepared with Mg turnings in THF and the proper 1-bromopropene (*Z*:*E* = ~96:4; *E*:*Z* = ~87:13).

(8) These were transformed to the corresponding 1,2,4-trimethylcyclohexanes by sequential hydrogenation (Pd/H_2), tosylation, and LAH reduction. Stereochemistry was assigned by comparison (NMR; GLC, co-injection) with authentic samples from Wiley Organics, Coshocton, OH.

(9) "Exo" refers to the orientation of the metal tether. Such a mechanism is the most economical description of the processes reported here, but alternatives, such as sequential intramolecular carbanion−olefin additions (cf. ref 13a), can be imagined.

(10) The structure was proved by conversion to the known (Meyer, W. L.; Clemans, G. B.; Manning, R. A. *J. Org. Chem.* **1975**, *40*, 3686) 4a,8,8-trimethyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (i).

(11) From ^1H-decoupled ^{13}C NMR: *d* = 22.36 ppm (t, J_{C-D} = 19.4 Hz).

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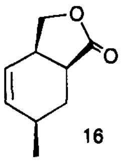
We have found that similar reactions can be carried out using *aluminum* as a connector: Addition (−78 °C) of 1 equiv of vinylmagnesium bromide in THF to diethylaluminum chloride in toluene and (room temperature) 1 equiv of the lithium alkoxide from **1**, followed by heating to 130 °C for 3 h, gave **4** in 70−75% yield. The formation of a species such as **17** is again suggested by the results of preworkup treatment with D_2O. Anhydrous oxygen gave a 2:1 mixture of diols **18**, presumably by a free radical pathway. As in the case of the magnesium connector, the concerted nature of the reaction was established by comparing the products of cycloaddition (70−75% yield), starting with either (*Z*)- or (*E*)-1-bromopropene. As was the case with the magnesium tether, carbinol **8**, R = methyl, was the major product (5.6:1) from the former (150 °C, 6 h), and carbinol **9**, R = methyl, was the major product (5:1) from the latter (160 °C, 10 h). The stereochemical results are, thus, quite similar with the magnesium and the aluminum tether, but they are the reverse of what was found[2] with the silicon connection, a result which may be of synthetic use.[14]



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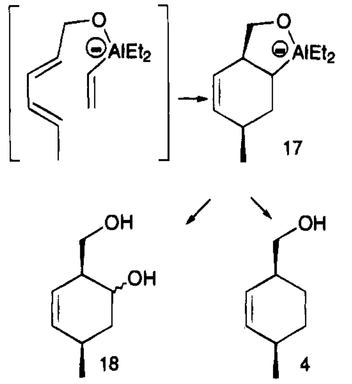

17

18

4

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[12] This lactone was formed in 34% yield, together with an equivalent quantity of the simple adduct **4**. It was correlated with the lactone made by cycloaddition of the silylation product from **1** with methyl 2-(chlorodimethylsilyl)acrylate, followed by desilylation (cf. ref 2).

[13] (a) Cherest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G. *Tetrahedron Lett.* **1966**, 875. (b) Blomberg, C.; Schat, G.; Grostveld, H. H.; Vrengdenhil, A. D.; Bickelhaupt, F. *Justus Liebigs Ann. Chem.* **1972**, *763*, 148. (c) Freijee, F.; Schat, G.; Mierop, R.; Blomberg, C.; Bickelhaupt, F. *Heterocycles* **1977**, *7*, 237.

[14] In contrast to the successful 4 + 2 cycloadditions of dienes with *alkenes* tethered via a magnesium or aluminum atom, we were unable to achieve cycloaddition with *alkynes*, even though these can be used with a silicon connector.