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Communications

Facile Formation of Substituted 2-Butene-1,4-diylmagnesium Using Highly Reactive Magnesium: A Simple Approach to Complex Carbocycles and Functionalized Ketones

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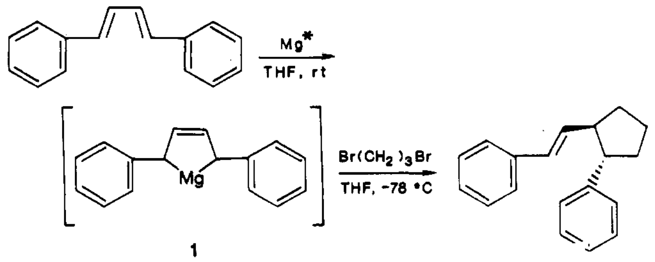
Summary: Substituted 2-butene-1,4-diylmagnesium compounds are readily prepared using highly reactive magnesium. Reactions with organodihalides yield 4-, 5-, and 6-membered carbocycles. In some cases, the initial monoalkylated intermediates can be reacted with other electrophiles. Polyfunctionalized ketones can be prepared in this manner. Depending on the initial 1,3-diene and by the proper choice of electrophiles, either 1,2-, 1,4-, or 2,1-additions may be observed.

Sir: Magnesium complexes of 1,3-dienes prepared using activated magnesium have received considerable attention in organometallic synthesis.[1] However, the utilization of these reagents in organic synthesis has been quite limited.[2] A primary cause for this limited use has been the difficulty of preparation of the complexes caused by the limited reactivity of magnesium.[3] Previous reports from our laboratory have demonstrated that highly reactive magnesium metal powders can be generated by the reduction of magnesium chloride with a variety of methods.[4] Recently, we found that the activated magnesium readily reacts with 1,3-dienes under mild conditions to generate high yields of substituted 2-butene-1,4-diylmagnesium complexes. In this paper, we report the reactions of the magnesium complexes with various electrophiles including dielectrophiles such as α,ω-alkylene and silylene dihalides (Table I).

Scheme I



The preparation of highly reactive magnesium (Mg*) is readily carried out by the reduction of anhydrous magnesium chloride with Li in THF using naphthalene as an electron carrier.[4b,5] The formation of 1,4-diphenyl-2-butene-1,4-diylmagnesium (**1**) was effected by stirring the mixture of newly generated magnesium and (*E,E*)-1,4-diphenyl-1,3-butadiene in THF at ambient temperature for 2 h. The resulting complex was deep red.[6] The addition of 1,3-dibromopropane to the complex at −78 °C caused an instantaneous disappearance of the red color. After being stirred at −78 °C for 30 min, the reaction mixture was allowed to warm to room temperature. Workup yielded a single cyclized product, *trans*-1-phenyl-2-*trans*-β-styrenylcyclopentane in 65% isolated yield (Scheme I).[7]

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[1] (a) Erker, G.; Kruger, C.; Muller, G. *Adv. Organomet. Chem.* **1985**, *24*, 1. (b) Yasuda, H.; Tasumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120. (c) Walther, D.; Pfuetrenreuter, C. *Naturwiss. Reihe.* **1985**, *34*, 789.

[2] (a) Baker, R.; Cookson, R. C.; Saunders, A. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1815. (b) Yasuda, H.; Kajihara, Y.; Ishikawa, T.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3035. (c) Yang, M.; Ando, M.; Takase, K. *Tetrahedron Lett.* **1971**, 3529.

[3] Yasuda, H.; Kajihara, Y.; Mashima, K.; Nagasuna, K.; Lee, K.; Nakamura, A. *Organometallics* **1982**, *1*, 388.

[4] (a) Rieke, R. D.; Burns, T. P.; Wehmeyer, R. M.; Kahn, B. E. *High Energy Processes in Organometallic Chemistry*; Suslick, K. S., Ed.; ACS Symposium Series 333; American Chemical Society: Washington, DC, 1987; pp 223–245. (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674.

[5] In a typical reaction, MgCl$_2$ (6.00 mmol), Li (12.60 mmol), and naphthalene (1.26 mmol) in freshly distilled THF (20 mL) were stirred at ambient temperature for 10 h under argon. The resulting magnesium surry was allowed to settle at least 3 h, and then the supernatant was drawn off via a cannula. Freshly distilled THF (20 mL) was added followed by the appropriate 1,3-diene.

[6] Crystal structure of (1,4-diphenyl-2-butene-1,4-diyl)magnesium has been reported: Kai, Y.; Kanehisa, N.; Miki, K.; Kasai, N.; Mashima, K.; Yasuda, H., Nakamura, A. *Chem. Lett.* **1982**, 1277.

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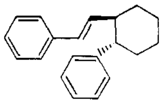
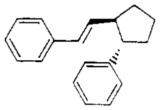
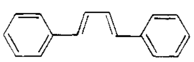
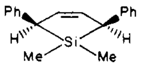
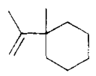
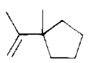
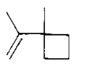
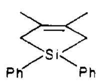
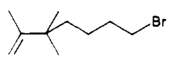
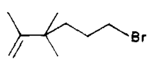
Table I. Reactions of Substituted 2-Butene-1,4-diylmagnesium Complexes with α,ω-Alkylene and Silylene Dihalides

entry	Mg diene[a]	dihalide	product[b,c]	% iso. yield[d]
1	1	$Br(CH_2)_4Br$		40[e]
2	1	$Br(CH_2)_3Br$		65[e]
3	1	$Br(CH_2)_2Br$		-
4	1	Me_2SiCl_2		66
5	2	$Br(CH_2)_4Br$		53[f] (69)
6	2	$Br(CH_2)_3Br$		- (75)
7	2	$Br(CH_2)_2Br$		- (49)
8	2	Ph_2SiCl_2		65
9	2	$Br(CH_2)_4Br$		79
10	2	$Br(CH_2)_3Br$		72[g]

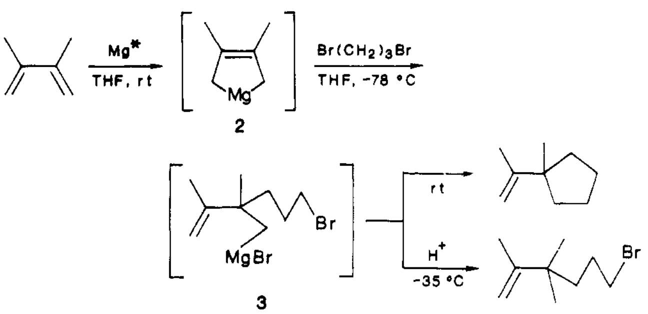
[a] 1 = THF solution of (1,4-diphenyl-2-butene-1,4-diyl)magnesium; 2 = THF solution of (2,3-dimethyl-2-butene-1,4-diyl)magnesium. [b] Reactions were typically done at −78 °C and then were warmed to room temperature prior to workup. [c] All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectra. [d] GC yields are given in parentheses. [e] Transconfigurations of two substituents on the ring of the products (entries 1 and 2) were determined by ozonolysis of the double bond followed by reduction with $NaBH_4$ at −78 °C, which gave (*trans*-2-phenylcyclohexyl)methanol[8] and (*trans*-2-phenylcyclopentyl)methanol,[9] respectively. [f] Cyclization completed after refluxing in THF for 5 h. [g] Uncyclized product was obtained by controlling the reaction temperature below −35 °C.

Similarly, reaction of 1,4-dibromobutane with 1 gave *trans*-1-phenyl-2-*trans*-β-styrenylcyclohexane as the only cyclized product (Table I).

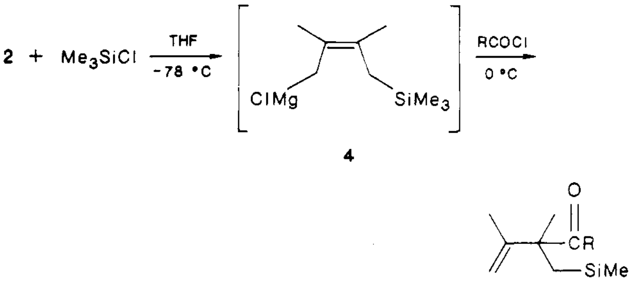
The initial attack of 1 by the α,ω-alkylene dibromides is believed to occur at the 1,4-positions, followed by intramolecular alkylation to give the cyclic products. Attempts to trap the initial adduct were unsuccessful. However, support for this mode of reaction comes from treatment of 1 with 1-bromobutane, which yielded exclusively 1,4-di-*n*-butyl-1,4-diphenylbut-2-ene.

Attempts to generate a 4-membered ring by reaction of 1 with 1,2-dibromoethane failed and only (*E*,*E*)-1,4-diphenyl-1,3-butadiene resulted. In this particular case 1 is acting as a two-electron reducing agent. This mode of reaction has been observed for the magnesium–anthracene complex.[10]

Scheme II



Scheme III



In contrast to the 1,2-cyclizations of 1 with α,ω-alkylene dibromides, dichlorodimethylsilane reacted with 1 to yield overall a 1,4-addition, producing *cis*-1,1-dimethyl-2,5-diphenylsilacyclopent-3-ene in 66% isolated yield.

The preparation of the magnesium complex of 2,3-dimethyl-1,3-butadiene has been reported to be very difficult.[3] However, it was prepared simply by reacting highly reactive magnesium[5] with an excess of freshly distilled 2,3-dimethyl-1,3-butadiene in THF. After the mixture was stirred for about 5 h at ambient temperature, the magnesium powders disappeared, forming a pale orange solution.[11] Reactions of the resulting complex with α,ω-alkylene dibromides appear to be more interesting. For example, the addition of 1,3-dibromopropane to the THF solution of 2,3-dimethyl-2-butene-1,4-diylmagnesium complex (**2**) at −78 °C gave an intermediate **3** which cyclized upon warming to room temperature to yield 1-methyl-1-isopropenylcyclopentane in good yield. On the other hand, an acidic workup of **3** at −35 °C yielded a single monoalkylated product, 2,3,3-trimethyl-6-bromohex-1-ene, in 72% isolated yield (Scheme II).[7] Similar chemistry was observed with 1,4-dibromobutane (Table I).

In sharp contrast to 1, the reaction of 2 with 1,2-dibromoethane generated a 4-membered ring to give 1-methyl-1-isopropenylcyclobutane in fair yield. In this case, the cyclization proceeded rapidly even at −78 °C, preventing the trapping of the intermediate.

Treatment of 2 with harder electrophiles resulted in initial attack at the 1,4-positions. Reaction of 2 with dichlorodiphenylsilane yielded exclusively 1,1-diphenyl-3,4-dimethylsilacyclopent-3-ene.

Significantly, the intermediate derived from the initial attack at the 2-position formed from reaction of 2 with α,ω-alkylene dibromides or alkyl bromides can be reacted

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(7) The molecular formula of 1 (see Scheme I) in the solid state is $Mg(THF)_3$(*s*-*cis*-PhCH=CHCH=CHPh) (see ref 6). The structure of 2 (see Scheme II) in THF probably is a polymer $(MgCH_2C(CH_3)=C(CH_3)CH_2 \cdot xTHF)_n$ and not the magnesium metallocycle (see ref 3). Fujita, K.; Ohnuma, Y.; Yasuda, H.; Tani, H. *J. Organomet. Chem.* **1976**, *113*, 201.

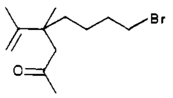
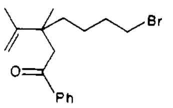
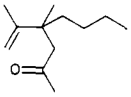
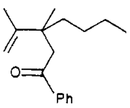
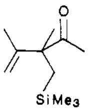
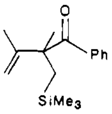
(8) (*trans*-2-Phenylcyclohexyl)methanol: mp 50–51 °C (lit. mp 50–51 °C. Baas, J. M. A.; Wepster, B. M. *Recl. Trav. Chim. Bays-Bas* **1972**, *91*, 285). The spectroscopic data are consistent with the structure.

(9) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980.

(10) Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. *J. Org. Chem.* **1988**, *53*, 3134.

(11) Generally, the THF solution of (2,3-dimethyl-2-butene-1,4-diyl)magnesium prepared in situ can be directly used. Occasionally, there is trace amount of magnesium residue left. In this case, separation of the THF solution of the complex from the magnesium residue is preferred.

Table II. Stepwise Electrophilic Addition to (2,3-Dimethyl-2-butene-1,4-diyl)magnesium with Two Different Electrophiles

entry	first electrophile[a]	second electrophile[b]	product[c]	% iso. yield
1	$Br(CH_2)_4Br$	MeCOCl		62
2	$Br(CH_2)_4Br$	PhCOCl		60
3	$Me(CH_2)_3Br$	MeCOCl		61
4	$Me(CH_2)_3Br$	PhCOCl		82
5	Me_3SiCl	MeCOCl		73
6	Me_3SiCl	PhCOCl		79

[a] The first electrophile was added to the THF solution of (2,3-dimethyl-2-butene-1,4-diyl)magnesium at −78 °C. The reaction mixture was then allowed to warm to room temperature prior to the addition of the second electrophile. [b] The second electrophile was added at 0 °C. [c] All new compounds have satisfactory spectroscopic data including ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data.

with other electrophiles. For example, the addition of alkyl or aryl acid chlorides results in high yields of the corresponding ketones (Table II). The overall scheme yields a net "2,1-addition". The overall high isolated yields indicate that Grignard addition to the initially formed ketone was minimal.

Utilizing the reverse regioselectivity of harder electrophiles, one can effectively secure overall "1,2-addition". Treatment of **2** with chlorotrimethylsilane resulted in initial attack at the 1-position, yielding an allylic Grignard. While the structure of the allylic Grignard reagent has not been verified by spectroscopic studies, the most logical structure is with the magnesium on the primary carbon (Scheme III). Treatment of **4** with acid chloride results in addition to the γ-carbon, generating a quaternary center. The overall reaction is a formal addition of R_3Si-COR′ across a terminal double bond with the generation of a quaternary center and introduction of two functional groups.

In summary, we have demonstrated that highly reactive magnesium can efficiently prepare substituted 2-butene-1,4-diylmagnesium complexes. Furthermore, we have shown that these halide-free bis-Grignard reagents can be used for the formation of 6-, 5-, and 4-membered rings containing a quaternary center. Formal 1,4-additions, "2,1-additions", and 1,2-additions can be effected by proper choice of electrophiles. Current efforts have shown that this approach can be extended to unsymmetrical 1,3-dienes. Utilization of this technique for the synthesis of natural products is also currently under investigation.

Acknowledgment. We gratefully acknowledge the support of this work by the National Institutes of Health (Grant GM35153). We would also like to thank Dr. T.-C. Wu and Dr. K. P. Daruwala for their helpful suggestions.

Registry No. **1**, 117527-70-5; **2**, 95251-09-5; $Br(CH_2)_4Br$, 110-52-1; $Br(CH_2)_3Br$, 109-64-8; $Br(CH_2)_2Br$, 106-93-4; Me_2SiCl_2, 75-78-5; $Me(CH_2)_3Br$, 109-65-9; $MgCl_2$, 7786-30-3; *trans*-1-phenyl-2-((*E*)-2-phenylethenyl)cyclohexane, 120853-48-7; *trans*-1-phenyl-2-((*E*)-2-phenylethenyl)cyclopentane, 120853-49-8; (*E*,*E*)-1,4-diphenyl-1,3-butadiene, 538-81-8; 1,1-dimethyl-2,5-diphenylsilacyclopent-3-ene, 120881-25-6; 1-methyl-1-(1-methylethenyl)cyclohexane, 16580-19-1; 1-methyl-1-(1-methylethenyl)cyclopentane, 120853-50-1; 1-methyl-1-(1-methylethenyl)cyclobutane, 120853-51-2; 3,4-dimethyl-1,1-diphenylsilacyclopent-3-ene, 29163-98-2; 7-bromo-2,3,3-trimethyl-1-heptane, 120853-52-3; 6-bromo-2,3,3-trimethyl-1-hexene, 120853-53-4; 7-bromo-2,3-dimethyl-3-methylcarbonylmethyl-1-heptene, 120853-54-5; 7-bromo-2,3-dimethyl-3-phenylcarbonylmethyl-1-heptane, 120853-55-6; 2,3-dimethyl-3-methylcarbonylmethyl-1-heptene, 120853-56-7; 2,3-dimethyl-3-phenylcarbonylmethyl-1-heptene, 120853-57-8; 3,4-dimethyl-3-trimethylsilylmethyl-4-penten-2-one, 31397-76-9; 3-benzoyl-2,3-dimethyl-4-trimethylsilyl-1-butene, 55532-01-9; 2,3-dimethyl-1,3-butadiene, 513-81-5; 1,4-di-*n*-butyl-1,4-diphenylbut-2-ene, 120853-58-9; dichlorophenylsilane, 80-10-4.

Cyclohexadienone Annulations of Aryl Carbene Complexes of Chromium: New Strategies for the Synthesis of Indole Alkaloids

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Summary: The first examples of the reactions of indolyl carbene complexes with acetylenes are reported. These reactions have potential for the development of a totally new approach to the synthesis of *aspidosperma* alkaloids.

Sir: The reactions of alkenyl- and arylchromium carbene complexes with acetylenes have become useful annulation processes for the construction of 4-alkoxyphenols and 4-alkoxynaphthols.[2] One of the synthetic advantages of

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