Carbenoid Homologation Reactions of Grignard Reagents: A Closer Look

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The carbenoid homologation reaction of α-haloalkyl Grignard reagents **3** with isopropylmagnesium chloride gives rise not only to the expected secondary Grignard reagents **5** but also to substantial amounts of the tertiary Grignard reagent **7**. The latter is postulated to arise by a carbenoid C−H insertion reaction within the mixed halide-bridged aggregate **14**.

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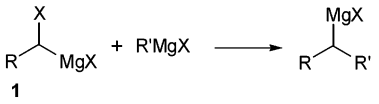
The carbenoid homologation of Grignard reagents[1] (cf. Scheme 1) opens the opportunity to generate secondary Grignard reagents in a process that avoids free radicals as intermediates.

Scheme 1

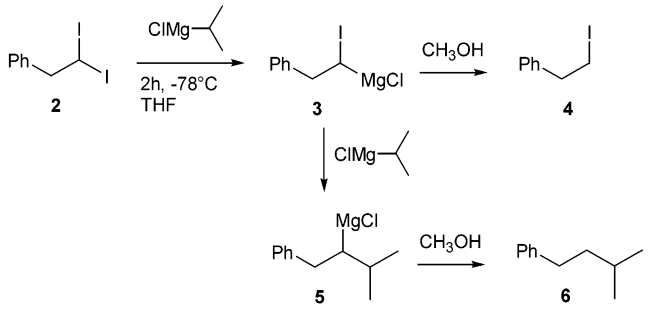


1

We became interested in this route to Grignard reagents when we set out to study the stereochemistry of the intramolecular carbomagnesiation of vinylsilanes[2] and to study enantiomerically enriched secondary Grignard reagents.[3] As a prelude to these studies, we took a closer look at the carbenoid homologation reaction. The partially unexpected results will be reported here in detail.[4]

The requisite magnesium carbenoid **3** was generated by an iodine/magnesium exchange reaction from the diiodoalkane **2** (Scheme 2). This exchange is complete after 2 h at −78 °C, as evidenced from protonation to give **4** in >90% yield.[5]

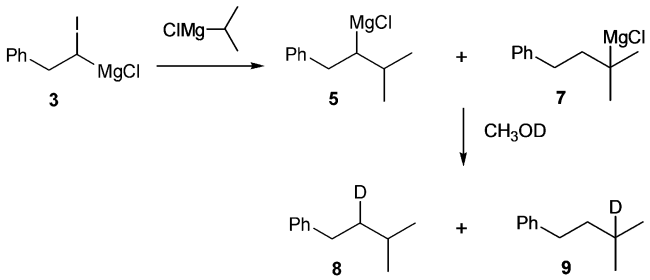
Scheme 2



When a total of 3 equiv of isopropylmagnesium chloride was applied and the reaction mixture was stirred at −20 °C before quenching, a >90% yield of the hydrocarbon **6** was obtained. This indicates a successful carbenoid homologation reaction from **3** to give **5**. The carbenoid homologation reaction is very slow at −78 °C in THF (10% conversion over 2 h in the case of (1-iodopentyl)magnesium chloride) but is quite rapid at −30 °C (83% conversion over 3 h).

However, the reaction turned out to be more complex than this simple result suggests: quenching of the reaction mixture with CH_3OD resulted in a mixture of the two isotopomeric hydrocarbons **8** and **9** (90:10) in 92% yield (Scheme 3).

Scheme 3



Quenching with ethyl α-(bromomethyl)acrylate gave rise to 91% of the two isomeric compounds **10** and **11** as an 87:13 mixture (Scheme 4).

This reveals that the reaction of **3** with isopropylmagnesium chloride furnished not only the secondary Grignard reagent **5** but also the tertiary Grignard reagent **7**. This unprecedented formation of the tertiary Grignard reagent **7** may become the major reaction pathway if the reaction is carried out in less polar solvents, as the data in Table 1 demonstrate. This holds for our standard substrate **2** and the related substrate 1,1-diiodopentane.

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(1) (a) Villiéras, J. *Bull. Soc. Chim. Fr.* **1967**, 1511−1520. (b) Hahn, R. C.; Tompkins, J. *Tetrahedron Lett.* **1990**, *31*, 937−940. (c) DeLima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133−134.

(2) Hoffmann, R. W.; Knopff, O.; Faber, T. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1785−1792.

(3) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225−230.

(4) For a preliminary communication see: Hoffmann, R. W.; Knopff, O.; Kusche, A. *Angew. Chem.* **2000**, *112*, 1521−1523; *Angew. Chem., Int. Ed.* **2000**, *39*, 1462−1464.

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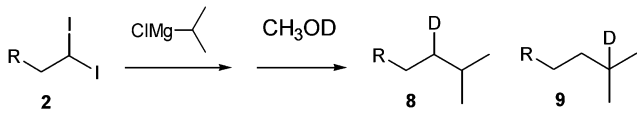
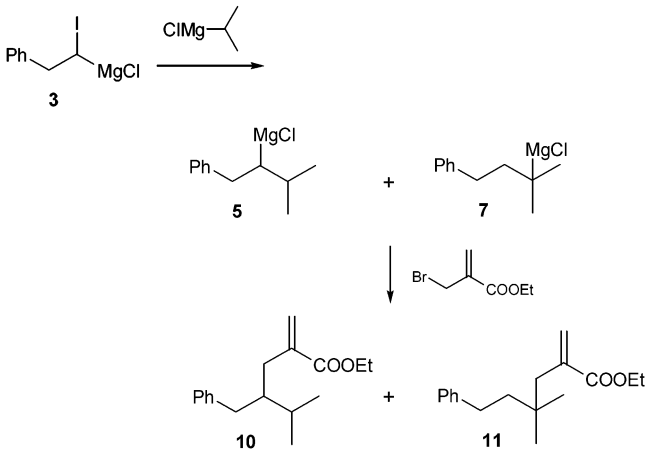
Table 1. Solvent Dependence of the Partitioning of the Reaction Pathways Leading to Secondary (5) and Tertiary (7) Grignard Reagents



2 **8** **9**

R	solvent	yield of **8** + **9** (%)	**8**:**9**
Ph	THF	92	90:10
Ph	^{t}BuOMe	82	31:69
Ph	Et_2O	91	25:75
Ph	$^{i}Pr_2O$	93	19:81
^{n}Pr	THF	92	87:13
^{n}Pr	^{t}BuOMe	92	14:86
^{n}Pr	Et_2O	85	26:74

Scheme 4



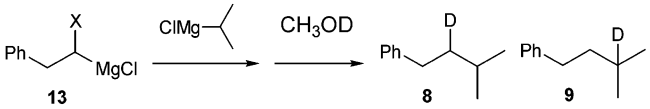
The Grignard reagents **5** and **7** are constitutionally stable under the reaction conditions. They do not equilibrate: for instance, when a solution of **5** and **7** generated in THF was concentrated and taken up in diethyl ether, quenching after 1 day at 20 °C provided **8** and **9** in a 90:10 ratio. When a solution of **5** and **7** generated in diethyl ether was concentrated and taken up in THF, quenching after 1 day at 20 °C provided **8** and **9** in a 20:80 ratio. Thus, the Grignard reagents **5** and **7** are generated in a kinetically controlled process.

A mechanistic scenario that leads to the desired homologation product **5** is readily drawn out. The two Grignard reagents **3** and isopropylmagnesium chloride may enter into a Schlenk equilibrium to generate the mixed dialkylmagnesium compound **12** (Scheme 5). Subsequent 1,2-migratory insertion[6] should give the secondary Grignard reagent **5**.

The dialkylmagnesium species **12** could also be generated from **2** and diisopropylmagnesium.[7] When this reaction was performed in THF (−78 to −20 °C) as usual, the conversion was low (26%) but the quenching product was pure **8**, whereas isomeric **9** could not be detected (<5%). Mixed dialkylmagnesium species such as **12** are usually generated from a Grignard reagent and an alkyllithium compound.[8] Hence, when **3** was reacted with isopropyllithium, this time in diethyl ether, the homologation reaction proceeded smoothly to give **5** and eventually 70% of **8**. Again, no isomeric product **9** was detected. We conclude that the mixed dialkyl Grignard reagent **12** is an intermediate on the route to the secondary Grignard reagent **5** but is not on the pathway that leads to the tertiary Grignard reagent **7**.

As a carbon−halogen bond has to be broken in the conversion of **3** to either **5** or **7**, we wondered how the nature of the halogen affects the partitioning between the two pathways. The results are compiled in Table 2 and reveal a marked halogen effect. The tendency to form the unexpected tertiary Grignard reagent **7** increased with increasing electronegativity of the halogen (I < Br < Cl); thus, with the (α-bromoalkyl)magnesium chloride the formation of the tertiary Grignard reagent was the dominant reaction, even in THF. However, this preference could be overruled by going to the more polar solvent dimethoxyethane. The electronegativity of the halogen atom in **13** affects the electrophilicity of the carbenoid and, as the data in Table 2 show, is more important for the formation of the tertiary Grignard reagent **7** than for the rearrangement of **12** to **5**. This

Table 2. Halogen Dependence of the Partitioning of the Reaction Pathways Leading to Secondary (5) and Tertiary (7) Grignard Reagents

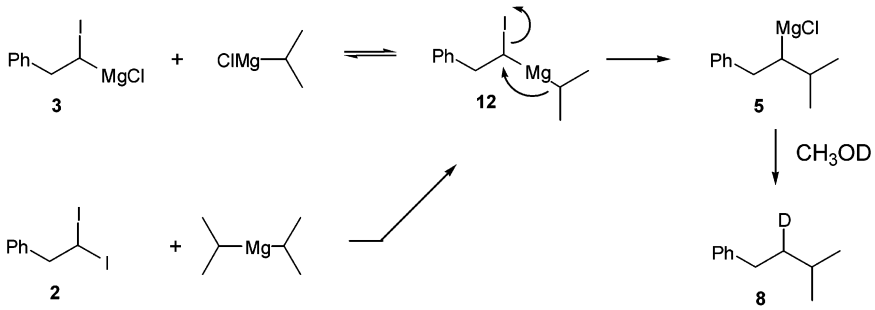


13 **8** **9**

R	solvent	yield of **8** + **9** (%)	**8**:**9**
I	THF	92	90:10
I	Et_2O	91	25:75
Br	THF	85	18:82
Br	Et_2O	65	34:66
Br	DME	92	100:0
Cl	THF	95	23:77
Cl	Et_2O	81	35:65

is an important hint to the mechanism of the formation of the tertiary Grignard reagent, as is the solvent dependence of the partitioning of the reaction pathways. Nonpolar solvents favor the formation of the tertiary Grignard reagent **7**! We take the latter effect as the starting point for the proposal of a mechanism: Grignard reagents form halide-bridged dimers in nonpolar

Scheme 5



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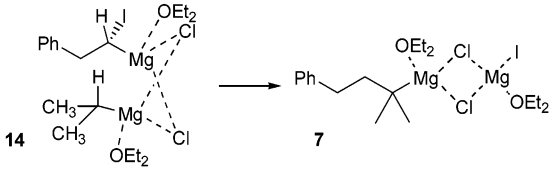
solvents.[9] This suggests that mixed aggregates (cf. **14**) between the Grignard reagent **13** and isopropylmagnesium chloride may prevail in nonpolar solvents (Scheme 6).

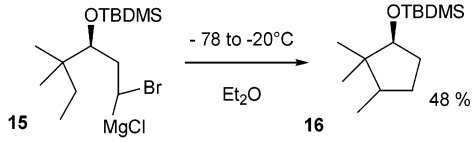
Scheme 6



In such an aggregate the α-CH bond of the isopropyl group may be positioned[10] at the rear lobe of the low-lying σ^* orbital of the C−X bond of the carbenoid moiety. This sets the stage for a (intraaggregate) carbenoid C−H insertion reaction, which leads directly to the tertiary Grignard reagent **7** as an aggregate with magnesium halide.

The ability to undergo C−H insertion reactions has generally been associated with reactive carbenes.[11] However, it has been shown that (α-haloalkyl)lithium compounds, i.e., carbenoids, may undergo intramolecular C−H insertion reactions as well.[12] It remains to be shown that the electrophilicity (i.e. the carbenoid character) of (α-haloalkyl)*magnesium* compounds is high enough to undergo C−H insertion reactions. Fortunately, we found an example of an intramolecular C−H insertion of the magnesium carbenoid **15** to give **16** in the context of a different project (Scheme 7).

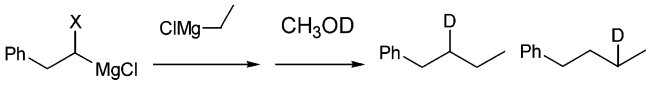
Scheme 7



The *gem*-dimethyl group in **15** favors conformations[13] in which the ethyl group and the carbenoid moiety can approach each other. The proximity of the C−H bond to the carbenoid moieties appears to be a necessary prerequisite to trigger such a C−H insertion reaction, as magnesium carbenoids in general are chemically stable for days at temperatures below −10 °C in a variety of solvents. We thus demonstrate that the formation of the aggregates **14** plays a key role in the reaction pathway leading to **7**. The tendency to form halide-bridged aggregates depends, among other factors, on the nature of the halide ion: chlorides have a high tendency and iodides a low tendency toward formation of halide-bridged aggregates.[9] Accordingly, we carried out an experiment with **2** and 3 equiv of isopropylmagnesium *iodide* in diethyl ether (−78 to −20 °C). Quenching with CH_3OD gave mainly (57%) deuterated **4**, indicating a low conversion to homologated products. Accordingly, only 5% of **8** was obtained. Significantly, there was no isotopomeric product **9** detected. This suggests that aggregate formation is indeed the key to the generation of the tertiary Grignard reagent **7**.

When the new carbon−carbon-bond is formed by a C−H insertion process in the generation of the tertiary Grignard reagent **7**, the tendency toward this reaction should depend on the bond strength of the particular C−Hbond.[14] It is a tertiary C−H bond in isopropylmagnesium chloride. We therefore tested whether the slightly stronger secondary C−H bond in ethylmagnesium chloride might be more resistant to such a C−H insertion to give **20**. The results of several experiments are compiled in Table 3.

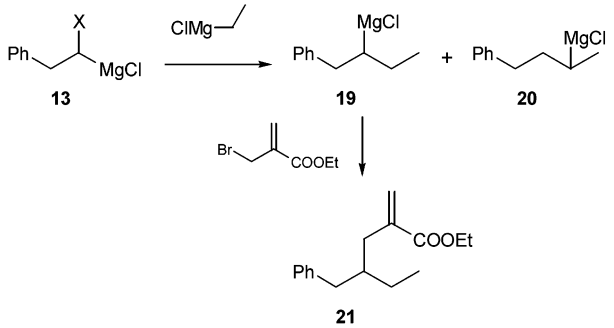
Table 3. Solvent and Halogen Dependence of the Partitioning of the Reaction Pathways Leading to Grignard Reagents 19 and 20



X	solvent	yield of **17** + **18** (%)	**17**:**18**
I	THF	72	100:0
I	Et_2O	71	100:0
Br	THF	74	89:11
Br	Et_2O	72	85:15
Cl	THF	76	97:3
Cl	Et_2O	81	94:6

The data in Table 3 (cf. also Table 2) show that, indeed, the tendency to undergo C−H insertion to give **20** and eventually **18** is clearly lower when *ethyl*magnesium chloride is applied compared to the reaction of *isopropyl*magnesium chloride. A clean homologation reaction toward **19** can be attained with ethylmagnesium chloride and an (α-iodoalkyl)magnesium chloride. The secondary Grignard reagent **19** could be trapped as well in good yield (82%) with (α-bromomethyl)-acrylate to give **21** (Scheme 8).

Scheme 8



Since an increased bond strength of the C−H bond α to magnesium in ethylmagnesium chloride leads to less C−H insertion, the lower bond strength in benzylmag-

(6) Cf.: (a) Kocienski, P.; Dixon, N. J. *Synlett* **1989**, 52−54. (b) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697−765.
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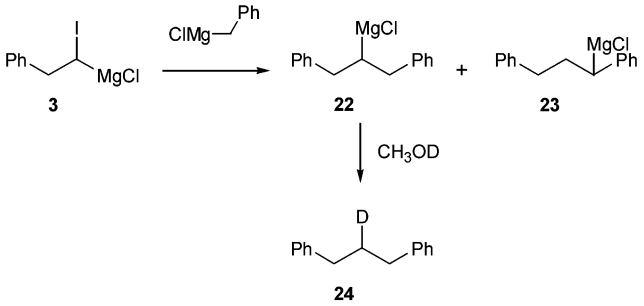
(14) (a) Benson, J. W. *J. Chem. Educ.* **1965**, *42*, 502−518. (b) Kerr, J. A. *Chem. Rev.* **1966**, *66*, 465−500. (c) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263.

nesium chloride should give rise to more of the product **23** (Scheme 9).

Scheme 9



Reaction of the (α-iodoalkyl)magnesium chloride with an excess of benzylmagnesium chloride in THF followed by quenching with CH_3OD gave 23% of 1,3-diphenylpropane. Contrary to expectation, the deuterium was exclusively located in the 2-position (cf. **24**). Thus, it appears that the partitioning between the two pathways is not controlled in a direct manner by the bond strength of the C−H bond in the α-position of the Grignard reagent. Perhaps other factors, such as the tendency to form mixed aggregates, are more important.

With this study we have delineated the conditions under which the carbenoid homologation reaction cleanly gives rise to a secondary Grignard reagent ((α-*iodo*-alkyl)magnesium chloride plus *primary* Grignard reagent in *THF or DME*) and the conditions under which a tertiary Grignard reagent can be obtained ((α-*chloro*-alkyl)magnesium chloride plus *secondary* Grignard reagent in *diethyl ether*).

Experimental Section

1. General Remarks. All temperatures quoted are uncorrected. All reactions with organometallic reagents were carried out in flame-dried glassware under an argon atmosphere. The concentration of Grignard solutions was determined after hydrolysis with 1 M hydrochloric acid by back-titration with 0.1 M NaOH.[15] Boiling range of petroleum ether: 40−60 °C. pH7 buffer: $NaH_2PO_4 \cdot 2H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 4H_2O$ (213.6 g) filled up to 1 L with water. ^{1}H NMR, ^{13}C NMR: Bruker ARX-200, AC-300, WH-400, DRX-400, AM-400, AMX-500. Analytical gas chromatography: Siemens Sichromat 3, 30 m × 0.3 mm quartz capillary column with DB 5, 1 bar of He. Flash chromatography: silica gel SI 60, E. Merck KGaA, Darmstadt, Germany, 40−63 μm. Starting 1,1-dihaloalkanes were prepared according to the literature.[16,17]

2. Reaction of 1,1-Diiodopentane with Isopropylmagnesium Chloride. A solution of 1,1-diiodopentane (284 mg, 0.88 mmol) in THF (1.7 mL) was added at −78 °C with stirring to a solution of isopropylmagnesium chloride (1.33 M in diethyl ether, 1.33 mL, 2.63 mmol) in THF (2 mL). The yellow color disappeared after 3 min. The temperature was allowed to reach −20 °C over 2 h. CH_3OD (0.14 mL, 3.5 mmol), saturated aqueous NH_4Cl solution (3 mL) and water (0.5 mL) were added. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated at 0 °C (20 min, 100−150 mbar, 1 min, 30 mbar), leaving 92 mg (92%) of 2-methylheptane. ^{2}H and ^{1}H NMR spectroscopy showed the ratio of 3-deuterio- to 2-deuterio-2-methylheptane to be 87:13. Data for 3-deuterio-2-methylheptane are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, J = 6.3 Hz, 6H, CH(−CH_3)$_2$), 0.86 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.08−1.40 (m, 7H), 1.41−1.49 (m, 1H, CH(−CH_3)$_2$). ^{2}H NMR (75 MHz, $CDCl_3$): δ 1.08 (bs). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.5 (2C), 22.7, 27.0, 27.9, 32.2, 38.6 (t, J = 19.0 Hz).

A similar reaction was carried out in *tert*-butyl methyl ether as principal solvent to give 92% of 2-methylheptane. ^{2}H and ^{1}H NMR spectroscopy showed the ratio of 3-deuterio- to 2-deuterio-2-methylheptane to be 14:86. Data for 2-deuterio-2-methylheptane are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (s, 6H, CH(−CH_3)$_2$), 0.86 (t, J = 7.2 Hz, 2H, CH_2CH_3), 1.08−1.40 (m, 7H). ^{2}H NMR (75 MHz, $CDCl_3$): δ 1.43 (bs). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5 (2C), 22.7, 26.9, 27.5 (t, J = 19.2 Hz), 32.1, 38.8.

3. Reaction of 1,1-Diiodo-2-phenylethane with Isopropylmagnesium Chloride. A solution of 1,1-diiodo-2-phenylethane (**2**; 150 mg, 0.42 mmol) in THF (0.5 mL) was added at −78 °C with stirring to a solution of isopropylmagnesium chloride (1.80 M in diethyl ether, 0.70 mL, 1.3 mmol) in THF (1 mL). The yellow color disappeared after 3 min. The temperature was allowed to reach −20 °C over 2 h. CH_3OD (0.14 mL, 3.5 mmol), saturated aqueous NH_4Cl solution (3 mL), and water (0.5 mL) were added. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated at 0 °C (20 min, 100−150 mbar, 1 min, 30 mbar), leaving 58 mg (92%) of monodeuterio-1-phenyl-3-methylbutane. ^{2}H and ^{1}H NMR spectroscopy showed the ratio of 2-deuterio- to 3-deuterio-1-phenyl-3-methylbutane to be 90:10. The crude product was purified by flash chromatography with pentane as eluent. Data for 2-deuterio-1-phenyl-3-methylbutane (**8**) are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, J = 6.6 Hz, 6H, CH(−CH_3)$_2$), 1.43−1.53 (m, 1H, PhCH_2-CHD), 1.53−1.63 (sept, J = 6.6 Hz, 1H, CH(−CH_3)$_2$), 2.59 (d, J = 8.0 Hz, 2H, PhCH_2), 7.14−7.20 (m, 3H, Ar H), 7.24−7.29 (m, 2H, Ar H). ^{2}H NMR (75 MHz, $CDCl_3$): δ 1.51 (bs). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.49 (2C), 27.58, 33.69, 40.40 (t, J = 19.3 Hz), 125.50, 128.22 (2C), 128.32 (2C), 143.08 (cf. the data in ref 18). Anal. Calcd for $C_{11}H_{15}D$ (149.13): C, 88.52; H + D, 10.81. Found: C, 88.54; H + D, 10.94.

A similar reaction was carried out in *tert*-butyl methyl ether as principal solvent to give 82% of 1-phenyl-3-methylbutane. ^{2}H and ^{1}H NMR spectroscopy showed the ratio of 2-deuterio- to 3-deuterio-1-phenyl-3-methylbutane to be 31:69. The crude product was purified by flash chromatography with pentane as eluent. Data for 3-deuterio-1-phenyl-3-methylbutane (**9**) are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 6H, CH-(CH_3)$_2$), 1.50 (t, J = 8.0 Hz, 2H, PhCH_2CH_2), 2.61 (t, J = 8.0 Hz, 2H, PhCH_2), 7.14−7.20 (m, 3H, Ar H), 7.24−7.29 (m, 2H, Ar H). ^{2}H NMR (75 MHz, $CDCl_3$): δ 1.62 (bs). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.39 (2C), 27.18 (t, J = 19.2 Hz), 33.75, 40.72, 125.50, 128.22 (2C), 128.32 (2C), 143.08 (cf. the data in ref 18). Anal. Calcd for $C_{11}H_{15}D$ (149.13): C, 88.52; H + D, 10.81. Found: C, 88.16; H + D, 11.13.

4. Ethyl 4-Benzyl-5-methyl-2-methylenehexanoate (10). A solution of ethyl 3-bromo-2-methylenepropanoate (254 mg, 1.32 mmol) in THF (0.7 mL) was cooled to −90 °C. At −20 °C a Grignard solution prepared as in section 3 in THF from 0.66 mmol of **2** was added via cannula. The flask of the Grignard reagent was rinsed twice with THF (0.5 mL). The washings were again transferred via cannula into the reagent solution. The latter was allowed to reach −78 °C over 30 min. Saturated aqueous NH_4Cl solution (2 mL) was added. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 4 mL). The combined organic layers were dried

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($MgSO_4$) and concentrated. Volatile coproducts were removed by bulb to bulb distillation at 4 Torr from a bath at 100 °C. The residue was then subjected to flash chromatography with pentane/*tert*-butyl methyl ether (30:1) to furnish the product **10** (136 mg, 79%) and **11** (21 mg, 12%). Data for ethyl 4-benzyl-5-methyl-2-methylenehexanoate (**10**) are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, J = 6.5 Hz, 3H, CHCH_3), 0.90 (d, J = 6.3 Hz, 3H, CHCH_3), 1.24 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.72 (qqd, J = 6.8 Hz, J = 6.8 Hz, J = 2.7 Hz, 1H, CH(CH$_3$)$_2$), 1.83 (ttd, J = 6.8 Hz, J = 6.8 Hz, J = 2.7 Hz, 1H, PhCH$_2$CH), 2.10 (dd, J = 13.9 Hz, J = 7.9 Hz, 1H, CHHCH=CH$_2$), 2.39 (dd, J = 13.9 Hz, J = 6.2 Hz, 1H, CHHCH=CH$_2$), 2.46 (dd, J = 13.9 Hz, J = 7.3 Hz, 1H, PhCHH), 2.58 (dd, J = 13.9 Hz, J = 7.4 Hz, 1H, PhCHH), 4.15 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 5.50 (dt, J = 1.2 Hz, J = 1.3 Hz, 1H, C=CHH), 6.19 (d, J = 1.7 Hz, 1H, C=CHH), 7.10−7.32 (m, 5H, Ar H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 18.0, 18.7, 27.7, 32.7, 36.3, 44.4, 60.4, 125.5, 125.8, 128.0 (2C), 129.0 (2C), 140.1, 141.5, 167.2. Anal. Calcd for $C_{17}H_{24}O_{20}$ (260.37): C, 78.42; H, 9.29. Found: C, 78.01; H, 9.05.

5. Ethyl 4,4-Dimethyl-2-methylene-6-phenylhexanoate (11). A Grignard solution was prepared from 1,1-dibromo-2-phenylethane (250 mg, 0.95 mmol) in THF as described in section 3. The reaction with ethyl 3-bromo-2-methylenepropanoate (367 mg, 1.90 mmol) and workup were conducted as described in section 4 to give after flash chromatography compound **10** (30 mg, 12%) and compound **11** (195 mg, 79%). Data for ethyl 4,4-dimethyl-2-methylene-6-phenylhexanoate (**11**) are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 6H, CCH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.45−1.55 (m, 2H, PhCH$_2$CH_2), 2.37 (s, 2H, CH_2C=CH$_2$), 2.53−2.65 (m, 2H, PhCH_2CH$_2$), 4.19 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 6.15 (d, J = 1.7 Hz, 1H, C=CHH_t), 6.19 (d, J = 1.7 Hz, 1H, C=CH_cH), 7.09−7.32 (m, 5H, Ar H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 27.0 (2C), 30.5, 33.9, 42.4, 44.2, 60.6, 125.4, 126.9, 128.1 (2C), 128.7 (2C), 139.8, 141.4, 167.2. Anal. Calcd for $C_{17}H_{24}O_2$ (260.37): C, 78.42; H, 9.29. Found: C, 78.36; H, 9.11.

6. Attempted Equilibration between the Grignard Reagents 5 and 7. A Grignard solution rich in **5** was prepared as described in section 3. The solution was allowed to reach 0 °C over 4 h. The THF solvent was removed in vacuo. Diethyl ether (3 mL) was added, and the solution was stirred for 1 day at room temperature. Workup as described in section 3 provided 62% of 1-phenyl-3-methylbutane. ^{2}H and ^{1}H NMR spectroscopy showed the ratio of 2-deuterio- to 3-deuterio-1-phenyl-3-methylbutane to be 90:10.

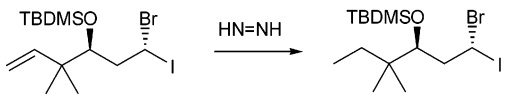
A Grignard solution rich in **7** was prepared in diethyl ether as described in section 3. The solution was allowed to reach 0 °C over 4 h. The ether solvent was removed in vacuo. THF (3 mL) was added, and the solution was stirred for 1 day at room temperature. Workup as described in section 3 provided 90% of 1-phenyl-3-methylbutane. ^{2}H and ^{1}H NMR spectroscopy showed the ratio of 2-deuterio- to 3-deuterio-1-phenyl-3-methylbutane to be 25:75.

7. Generation of the Grignard Reagents 19 and 20. 1-Bromo-1-iodo-2-phenylethane[17] (131 mg, 0.42 mmol) was treated with ethylmagnesium chloride in diethyl ether as described in section 3 to give 1-(2-deuteriobutyl)benzene (**17**) and 1-(3-deuteriobutyl)benzene (**18**) (41 mg, 72%) as a 85:15 mixture according to ^{2}H and ^{1}H NMR spectroscopy. Data for 1-(2-deuteriobutyl)benzene (**17**) are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.2 Hz, 3H, CH$_2$CH_3), 1.35 (pseudoq, J = 7.2 Hz, 2H, CH_2CH$_3$), 1.59 (pseudoq, J = 7.3 Hz, 1H, PhCH$_2$CHD), 2.60 (d, J = 7.5 Hz, 2H, PhCH_2), 7.12−7.21 (m, 3H, Ar H), 7.22−7.30 (m, 2H, Ar H). ^{2}H NMR (75 MHz, $CDCl_3$): δ 1.62 (bs). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.2, 33.2 (t, J = 19.3 Hz), 35.6, 125.5, 128.2 (2C), 128.4 (2C), 142.9.[19] Anal. Calcd for $C_{11}H_{15}D$ (135.22): C, 88.82; H + D, 10.44. Found: C, 89.00; H + D, 10.64.

8. Ethyl 4-Benzyl-2-methylenehexanoate (21). A solution of the Grignard reagent **19** in THF is generated as described in section 7 from 1,1-diiodo-2-phenylethane (301 mg, 0.84 mmol). The reaction with ethyl 3-bromo-2-methylenepropanoate followed the procedure described in section 4 to give the product **21** (170 mg, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.4 Hz, 3H, CH$_2$CH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3) overlaid with 1.28 (dq, J = 7.3 Hz, J = 6.9 Hz, 2H, CH_2CH$_3$), 1.84 (ttt, J = 6.5 Hz, J = 6.5 Hz, J = 6.5 Hz, 1H, PhCH$_2$CH), 2.22 (dd, J = 14.2 Hz, J = 6.6 Hz, 1H, CHHCH=CH$_2$), 2.32 (dd, J = 14.0 Hz, J = 7.4 Hz, 1H, CHHCH=CH$_2$), 2.51 (dd, J = 13.9 Hz, J = 7.3 Hz, 1H, PhCHH), 2.58 (dd, J = 13.9 Hz, J = 7.0 Hz, 1H, PhCHH), 4.18 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 5.50 (dt, J = 1.2 Hz, J = 1.3 Hz, 1H, C=CHH_t), 6.19 (d, J = 1.6 Hz, 1H, C=CH_cH), 7.10−7.32 (m, 5H, Ar H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.6, 14.2, 25.2, 36.1, 39.7, 40.0, 60.6, 125.7, 125.9, 128.1 (2C), 129.2 (2C), 139.9, 141.2, 167.4. Anal. Calcd for $C_{16}H_{22}O$ (246.34): C, 78.01; H, 9.00. Found: C, 77.83; H, 8.99.

9. 2-Deuterio-1,3-diphenylpropane (24). A solution of 1,1-diiodo-2-phenylethane (**2**; 150 mg, 0.42 mmol) in THF was added to 1 equiv of ethylmagnesium chloride as described in section 3. After the mixture was stirred for 2 h at −78 °C, a solution of benzylmagnesium chloride (1.00 M in diethyl ether, 0.84 mL, 0.84 mmol) was added dropwise. The temperature was allowed to reach −20 °C over 2 h. After quenching with methanol-*OD* and workup as described in section 3, the resulting product **24** (60 mg, 73%) displayed the following data. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88−2.04 (m, 1H, PhCH$_2$CHD), 2.64 (d, J = 7.5 Hz, 4H, PhCH_2), 7.12−7.34 (m, 10H, Ar H). ^{2}H NMR (75 MHz, $CDCl_3$): δ 2.06 (bs). ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.5 (t, J = 19.4 Hz), 35.3 (2C), 125.7 (2C), 128.2 (4C), 128.4 (4C), 142.2 (2C). Exact mass for $C_{15}H_{15}D$: calcd, m/z 197.1314; found (HRMS EI), m/z 197.1309.

10. Intramolecular Carbenoid CH Insertion in 15. The starting material was prepared from (1*R**,3*S**)-1-bromo-3-((*tert*-butyldimethylsilyl)oxy)-1-iodo-4,4-dimethyl-5-hexene[20] by diimide reduction:



To a solution of the alkene (365 mg, 0.82 mmol) and of potassium azodicarboxylate (652 mg, 3.4 mmol) in methanol (10 mL) was added at 0 °C pyridine (40 μL, 0.5 mmol). Acetic acid (0.34 mL, 5.9 mmol) was added dropwise over 1 h at 0 °C. After the mixture was stirred for 12 h at room temperature, GC indicated a conversion of ca. 40%. Therefore, another portion of potassium azodicarboxylate (605 mg, 3.2 mmol) was added, followed by dropwise addition of acetic acid (0.34 mL, 5.9 mmol) at −40 °C. After the mixture was stirred for 12 h at room temperature, conversion had reached 75%. Therefore, these steps were repeated with another amount of potassium azodicarboxylate (620 mg, 3.2 mmol) and acetic acid (0.30 mL, 5.2 mmol). After this mixture was stirred for 12 h at room temperature, *tert*-butyl methyl ether and petroleum ether (20 mL each) were added, the mixture was filtered. and the filtrate was concentrated at 0.5 Torr. The residue was taken up in THF (5 mL), and in order to remove residual alkene, a solution of borane in THF (0.4 M, 0.5 mL, 0.2 mmol) was added. After the mixture was stirred for 12 h, water (5 drops) was added. The solution was concentrated, diluted with petroleum ether (50 mL), and filtered through a small pad of silica gel. ^{1}H NMR still indicated the presence of residual alkene; therefore, again borane in THF (0.4 M, 1.0 mL, 0.4 mmol) was added and the above steps were repeated. Flash chromatography with petroleum ether furnished crude (1*R**,3*S**)-1-bromo-3-((*tert*-

(19) Cf.: Hendrickson, J. B.; Singer, M.; Sajjat Hussoin, M. *J. Org. Chem.* **1993**, *57*, 6913−6914.

(20) Stiasny, H. C.; Hoffmann, R. W. *Chem. Eur. J.* **1995**, *1*, 619−624.

butyldimethylsilyl)oxy)-1-iodo-4,4-dimethyl-5-hexane (175 mg, 48%) as a colorless oil, which was characterized by the spectroscopic data only. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.14 (s. 3H), 0.81 (s, 3H), 0.83 (s, 3H), 0.83 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 1.23 (dq, J = 13.8 and 7.3 Hz, 1H), 1.32 (dq, J = 13.9 and 7.5 Hz, 1H), 2.57−2.75 (m, 2H), 3.44 (dd, J = 7.0 and 2.9 Hz, 1H), 5.55 (dd, J = 9.8 and 4.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.8, −3.7, 8.2, 9.6, 18.7, 22.8, 23.5, 26.2 (3C), 31.1, 37.8, 52.3, 78.6.

A solution of isopropylmagnesium chloride (1.29 M in diethyl ether, 0.35 mL, 0.45 mmol) was added at −78 °C to a solution of the bromo iodo compound described above (130 mg, 0.29 mmol) in THF (1.5 mL). The yellow color faded over 5 min. The solution was stirred for 1 h at −78 °C, and the mixture was quenched by addition of allyl iodide (0.11 mL, 1.2 mmol). The solution was warmed to −20 °C over 4 h. After the mixture was stirred for 20 h at this temperature, saturated aqueous NH_4Cl solution (5 mL) was added, the layers were separated, and the aqueous layer was extracted with petroleum ether (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and concentrated. GC analysis showed the presence of **16** (48%, cis:trans = 1:3), 1-bromo-3-((*tert*-butyldimethylsilyl)-oxy)-4,4-dimethyl-5-hexane (10%), and 4-bromo-6-((*tert*-butyldimethylsilyl)oxy)-7,7-dimethyl-1-nonene (6%). Flash chromatography of the residue with petroleum ether furnished enriched **16**, which was identified by comparison of its spectroscopic data with a sample prepared as described below.

11. 1-((*tert*-Butyldimethylsilyl)oxy)-2,2,3-trimethylcyclopentane (16). A solution of *tert*-butyllithium (1.6 M in pentane, 0.55 mL, 0.88 mmol) was added at −78 °C to a solution of 3-((*tert*-butyldimethylsilyl)oxy)-1-iodo-4,4-dimethyl-5-hexene[20] (112 mg, 0.30 mmol) in diethyl ether (2 mL) and petroleum ether (2 mL). The mixture was allowed to reach −30 °C over 3 h. Methanol (0.2 mL) and pH 7 buffer solution (5 mL) were added, the layers were separated, and the aqueous layer was extracted with petroleum ether (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and concentrated. GC analysis showed the presence of **16** (cis:trans = 10:1). Flash chromatography of the residue with petroleum ether furnished **16** (61 mg, 84%) as a colorless oil. Anal. Calcd for $C_{14}H_{30}OSi$ (242.5): C, 69.35; H, 12.47. Found: C, 69.20; H, 12.33.

Data for *cis*-**16** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.01 (s, 3H), 0.61 (s, 3H), 0.83 (d, J = 6.7 Hz, 3H), 0.85 (s, 3H), 0.88 (s, 9H), 1.18−1.30 (m, 1H), 1.40 (dtd, J = 12.9, ∼8.6, and 5.0 Hz, 1H), 1.39−1.49 (m, 1H), 1.65 (dtd, J = 13.2, ∼8.9, and 5.1 Hz, 1H), 1.80 (dddd, J = 13.0, 9.6, 8.3, and 5.0 Hz, 1H), 3.57 (t, J = 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.4, 13.7, 14.4, 18.1, 25.3, 25.9 (3C), 28.4, 30.6, 40.5, 43.5, 81.7.

Data for *trans*-**16** are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.65 (s, 3H), 0.82 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.88 (s, 3H), 1.08−1.21 (m, 1H), 1.38−1.48 (m, 1H), 1.78−1.97 (m, 3H), 3.63 (dd, J = 5.3 and 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.5, 14.3, 18.1, 20.5, 22.1, 25.9 (3C), 30.1, 32.4, 39.9, 44.9, 82.4.

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