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Cross-Coupling Reaction of *tert*-Alkyl Halides with Grignard Reagents in Dichloromethane as a Non-Lewis Basic Medium

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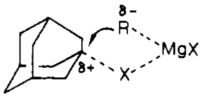
In dichloromethane as a non-Lewis basic solvent, 1-haloadamantane **1** underwent a cross-coupling reaction with Grignard reagents to give bridgehead-substituted products **3–16** in moderate yields. In this case the same kind of halogen in both **1** and a Grignard reagent was favored; if not, functional exchange (i.e., **1a** to **1c**) occurred first. The reaction using 5-hexenylmagnesium bromide as a radical probe afforded uncyclized/cyclized coupling products in a 6/4 ratio. These facts suggested the significant participation of the single-electron-transfer process in these reactions. The present method could be extended to *tert*-butylation with some Grignard reagents. Interestingly, 1,3-dichloro-3-methylbutane coupled with butylmagnesium chloride selectively at the tertiary position. For the above displacement reaction of **1**, an organozinc was also found to be effective.

The carbon–carbon bond formation involving the use of organometallics proceeds via nucleophile–electrophile interactions that may conveniently be classified into several types according to the reactant structure. Among them, the cross-coupling reaction is a process of a single carbon–carbon bond formation between two unlike carbon groups, specifically between organometals, lithium and magnesium, in particular, and organic halides or their equivalents (eq 1).

$$R^1X + R^2M \rightarrow R^1R^2 + MX \qquad (1)$$

The scope and mechanism for this reaction have been reviewed concisely by Negishi.[1] In general, an S_N2 mechanism (two-electron-transfer process) plays a significant role, and, thus, a primary group for R^1 is essentially favored. On the other hand, a radical recombination mechanism (single-electron-transfer process) is involved in some cases. It may also be possible that more than one mechanism operates concurrently.[2] While, in the past decade, this type of coupling procedure has been considerably broadened by the cooperation of transition metals such as copper, nickel, and palladium,[3] the displacement of *tert*-alkyl halides with organoalkali metals has not yet been achieved efficiently, due to the intrinsic structure; an S_N2 mechanism is incompatible with the *tert*-alkyl group and side reactions (e.g., elimination) often dominate.[4] In our continuous interest in the synthesis of adamantane derivatives, the substitution at its bridgehead has been desired using any given organometallics. In the preceding papers, organosilanes have been demonstrated to be useful,[5] since the moderately electropositive silicon is rather suited to the mode of this substitution (electrophilic conditions). On the other hand, strong nucleophiles such as organoalkali metals were not so effective, and, so far, the successful substitution reactions were limited to the cases where a triflate as an excellent leaving group[6] or forced conditions such as heating in a sealed tube at 100 °C[7] were employed. We envisioned a possibility for the Grignard reagent to act both as a nucleophile and as a Lewis acid;[8,9] complexation of the Lewis acidic magnesium center with a bridgehead halide might be followed by the attack of an organic group bound on the magnesium to the weakly positive adamantane bridgehead carbon center (S_Ni-like substitution). In order to maximize the complex formation, the solvent nature must be changed from a Lewis basic ether to a non-Lewis basic medium. To this end, we have chosen dichloromethane as a suitable solvent, which is often used for Friedel–Crafts-type substitution reactions.[10] As a matter of fact, the reaction of 1-haloadamantane with alkylmagnesium halide carried out in dichloromethane proceeded smoothly, and the cross-coupling product, 1-alkyladamantane, was obtained in a reasonable yield. However, the mode of the bond formation was different from the envisaged one via an ionic pathway; actually, the radical-natured intermediate appeared to participate to a large extent. Nevertheless, by this method *tert*-butyl halides underwent cross-coupling reactions with some Grignard reagents, and interestingly, 1,3-dichloro-3-methylbutane was alkylated selectively at the tertiary position. Here we describe these results in detail.



Results and Discussion

The Grignard reagents were prepared first in ether by the standard procedure[11] and then the solvent was exchanged from ether to dichloromethane. To the resulted cloudy mixture (the reagent precipitated but yet dissolved partly) was added 1-haloadamantane **1** and the reaction mixture was stirred at room or reflux temperature under

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(1) Negishi, E. **Organometallics in Organic Synthesis**; Wiley: New York, 1980; p 105.

(2) For Grignard case: (a) Kharasch, M. S.; Reinmuth, O. **Grignard Reactions of Nonmetallic Substances**; Prentice-Hall: New York, 1954; p 1046. (b) Muraoka, K.; Nojima, M.; Kusabayashi, S. **J. Chem. Soc., Perkin Trans. 2** *1986*, 76 and references cited therein.

(3) (a) Carruthers, W. In **Comprehensive Organometallic Chemistry**; Wilkinson, G., Ed.; Pergamon Press; Oxford, 1982; Vol. 7, p 721. (b) Jolly, P. W., ref 3a, Vol. 8, p 713. (c) Trost, B. W.; Verhoeven, T. R., ref 3a, Vol. 8, p 910.

(4) Several examples for the preceding coupling reactions of *tert*-alkyl halides with Grignard reagents are listed in the table of ref 2a (pp 1067–1125).

(5) (a) Sasaki, T.; Usuki, A.; Ohno, M. *J. Org. Chem.* **1980**, *45*, 3559. (b) Sasaki, T.; Nakanishi, A.; Ohno, M. *Chem. Pharm. Bull.* **1982**, *30*, 2051; (c) *J. Org. Chem.* **1982**, *47*, 3219.

(6) Takeuchi, K.; Moriyama, T.; Kinoshita, T.; Tachino, H.; Okamoto, K. *Chem. Lett.* **1980**, 1395.

(7) Osawa, E.; Majerski, Z.; Schleyer, P. v. R. *J. Org. Chem.* **1971**, *30*, 2051.

(8) Along this line, the alkynylaluminum reagent was report to undergo a substitution reaction at the adamantane bridgehead via a carbocation intermediate: Negishi, E.; Baba, S. *J. Am. Chem. Soc.* **1975**, *97*, 7386.

(9) For the titanium case, see: Reetz, M. T.; Westermann, T.; Steinbach, R. *Angew. Chem.* **1980**, *92*, 931, 933.

(10) Dichloromethane is scarcely reactive with the Grignard reagent under the normal conditions. No appreciable exothermic reaction took place on adding this solvent to the reagent at least in a small scale experiment: Hattori, K.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982**, *23*, 3395.

(11) Reference 2a, p 5.

0022-3263/88/1953-0729$01.50/0

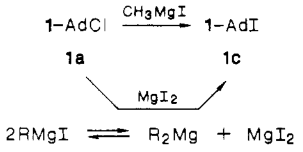
Table I. Cross-Coupling Reactions of *tert*-Alkyl Halides 1, 18, and 22 with Grignard Reagents in Dichloromethane

entry	RX	RMgX, R =	time^{a} (h)	product^{b}	yield (%)	mp (°C) [lit. mp]
1	**1a**	$CH_2CH_2CH_2CH_3$	5	**3**^{c}	60 (30)^{d}	
2		$CH_2CH_2C_6H_5$	5	**4**	65	61–62
3		$CH_2C_5H_9$	8	**5**	50	
4		$C(CH_3)_3$	9	**8**^{e}	11	
5		$CH_2CH{=}CH_2$	5	**9**^{f}	57	
6		$CH_2CH{=}CHCH_3$	8	**10**/**11** (5/9)	53	
7	**1b**	$CH_2CH_2CH_2CH_3$	5	**3**^{c}	56	
8		CH_2CH_3	5	**6**^{g}	61^{h}	
9		C_6H_5	8	**12**^{i}	57	86–88 [87–88]^{i}
10		$3\text{-}CH_3C_6H_4$	8	**13**^{j}	57	76–77 [77]^{j}
11		$4\text{-}BrC_6H_4$	50	**14**^{j}	24	102–103 [101–101.5]^{j}
12		$C_{10}H_7$	6	**15**^{k}	2	200–202 [196–198]^{k}
13		3-indolyl	4	**16**	22	167–168
14	**1c**	$CH_2CH_2CH_2CH_3$	5	**3**^{c}	56	
15		CH_3	5	**7**^{h}	58	100–101 [102–103]^{h}
16	**18a**	$CH_2CH_2C_6H_5$	3	**19**^{l}	54	
17		$CH_2CH{=}CHC_6H_5$	3	**20**/**21**^{m} (1/3)	64	
18	**18b**	$CH_2CH_2C_6H_5$	3	**19**^{l}	37	
19	**22**	$CH_2CH_2CH_2CH_3$	6	**23**	70^{n}	

[a] At room temperature for entries 11, 13, 16, 17, and 18 and at reflux temperature for all others. [b] Usually **2** was formed in 15–25% yield in addition to the coupling product, and in some cases, **1** was recovered in more or less 10%. In entry 4, nearly 50% of **2** was produced. In entry 12, 69% of **2b** was recovered. [c] Reference 6. [d] In hexane at reflux temperature. [e] Reference 32. [f] Reference 5a. [g] Reference 7. [h] Estimated on GLC for a distilled mixture of **6** contaminated with **2**. [i] Reference 33. [j] Reference 34. [k] Reference 35. [l] Reference 30. [m] Reference 2b. [n] Yield based on GLC.

an atmosphere of nitrogen, while inorganic precipitates appeared gradually. After the conventional workup, the products were purified by a combination of chromatography and trap-to-trap distillation or recrystallization.

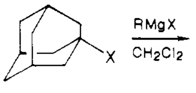
When 1-chloroadamantane (**1a**) was treated as above with methylmagnesium iodide, 1-iodoadamantane (**1c**) was produced as the result of functional exchange (eq 2).[12]



(2)

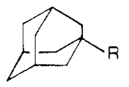
(3)

This Finkelstein-type product might arise by the action of equilibrated MgI_2 (eq 3);[13] in a comparative experiment MgI_2 was shown to react with **1a** to give also **1c**. This halogen exchange could be avoided by using the same kind of halogen in both **1** and the Grignard reagent. Typically, the reactions of **1a**, **1b**, and **1c** with the corresponding butylmagnesium chloride, bromide, and iodide gave bridgehead-butylated adamantane **3** in 55–60% isolated yield. No appreciable differences in reactivity among them were observed. In these cases adamantane (**2**), a reduction product, was formed as a major byproduct (15–25%), which could be removed by sublimation. While the reduction as seen above is one of the side reactions featured in a radical process, biadamantyl, a homocoupling product, was not detected. The reactions with the other Grignard reagents were also carried out in the same manner, and these results are summarized in Table I.



(1-Ad)

1a, X = Cl
b, X = Br
c, X = I



3–16

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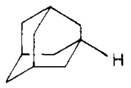

2

3, R = $CH_2CH_2CH_2CH_3$
4, R = $CH_2CH_2C_6H_5$
5, R = $CH_2C_5H_9$
6, R = CH_2CH_3
7, R = CH_3
8, R = $C(CH_3)_3$
9, R = $CH_2CH{=}CH_2$
10, R = $CH_2CH{=}CHCH_3$
11, R = $CH(CH_3)CH{=}CH_2$
12, R = C_6H_5
13, R = $3\text{-}CH_3C_6H_4$
14, R = $4\text{-}BrC_6H_4$
15, R = $1\text{-}C_{10}H_7$
16, R = 1-indolyl

Because of steric hindrance, the reaction with a bulky Grignard reagent resulted in a much lower yield accompanied by the increased formation of **2** (entry 4). In the reaction with an allylic Grignard reagent (entry 6), no site-selectivity was attained; crotylmagnesium chloride coupled with **1a** at the α- and γ-positions in a ratio of 5/9 (GLC), although S_N2-reactive butoxymethyl chloride was reported to be completely γ-selective.[14] Aryl Grignard reagents were also reactive with **1** (entries 9–13); the reactions of **1b** with (*m*-tolyl- and (*p*-bromophenyl)magnesium bromides afforded 1-(*m*-tolyl- (**13**) and 1-(*p*-bromophenyl)adamantane (**14**) in 57% and 24% yields, respectively, as the ipso-substituted product. However, the reaction with 1-naphthylmagnesium bromide afforded only a 2% yield of 1-(1-naphthyl)adamantane (*15*), also due to steric hindrance. For one particular case, the substitution occurred on nitrogen rather than on carbon in the reaction of **1b** with 3-indolylmagnesium bromide, giving 1-(1-adamantyl)indole (**16**) in 22% yield. In contrast to the above successful results, 1-heptynylmagnesium bromide (sp carbanion) did not react with **1**.[15]

Related to the mechanistic aspect, several experiments were attempted. First, the solvent effect was examined in the butylation; in hexane as an alternative non-Lewis basic solvent, the coupling product **3** was obtainable but in a lower yield than in dichloromethane (entry 1).[16] Second, in the Schlenk equilibrium between alkyl-

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[12] Reference 2a, p 1060. This was also reported as a minor reaction between **1b** and methylmagnesium iodide in ether (100 °C); see ref 6.

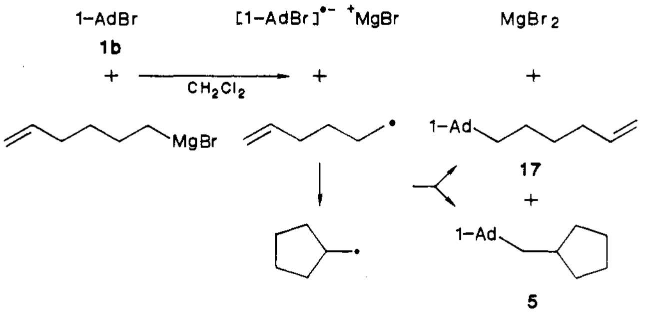
[13] Reference 2a, p 102.

[14] Benkeser, R. A. *Synthesis* **1971**, 347.

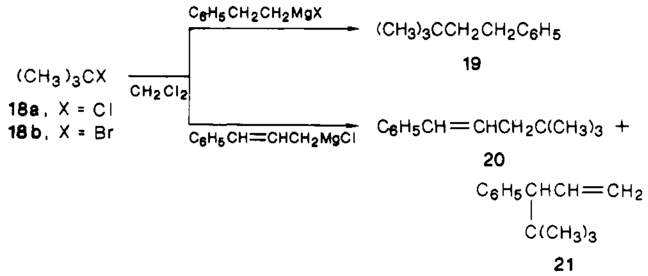
[15] Reference 2a, p 1053.

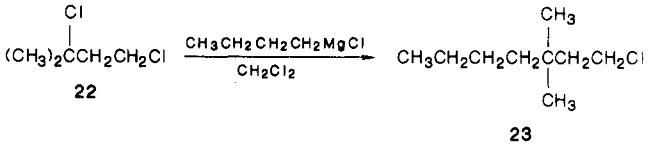
[16] The solvent effect observed may be explained in terms of the relative solubility of a Grignard reagent. After exchange of the solvent, alkylmagnesium halide is still associated with one to two molecules of ether (our ^1H NMR inspection; see also ref 2a, p 99), and this complex was found to be partly soluble in dichloromethane. In contrast, it was not soluble in hexane. This heterogeneous conditions might lead to the difference in the reactivity.

magnesium halide and dialkylmagnesium (eq 3), it is unclear which was a reactive species. Experimentally, the reaction using the discretely prepared dibutylmagnesium[17] gave no coupling product **3**, suggesting that dialkylmagnesium was not an important form. Then, the problem is the nature of the reaction intermediate. In the beginning of this study, we visualized the S_Ni-like mechanism for the present reaction. However, the reduction product **2** was usually formed as a byproduct. Further, only trace of **6** was obtained in the reaction of **1a** with ethylaluminum dichloride in dichloromethane; this product should be formed if S_Ni mechanism were operative, since this organoaluminum chloride has stronger Lewis acidity than an organomagnesium chloride. All these observations suggested that not a carbocation but a radical intermediate was involved in the above coupling reaction. Consequently, this was verified by the representative testimony for the radical intermediacy: cyclization aptitude of the 5-hexenyl moiety.[18,19] As a blank test, the Grignard reagent prepared from 5-hexenyl bromide and Mg in ether was stirred for 5 h after exchange of the solvent from ether to dichloromethane and was quenched with water. In the products methylcyclopentane was negligibly included (GLC), indicating that 5-hexenylmagnesium bromide did not cyclize to (cyclopentylmethyl)magnesium bromide before the coupling reaction.[20] With this fact in mind, 5-hexenylmagnesium bromide was treated with **1b** in dichloromethane as before. The GLC analysis and spectroscopic analyses (see Experimental Section) indicated that the products were isomeric alkylated adamantanes in a 6/4 ratio, which were revealed as 1-(5-hexenyl)adamantane (**17**) and 1-(cyclopentylmethyl)adamantane (**5**, entry 3)), respectively. Considering that the previously observed uncyclized/cyclized ratio of the 5-hexenyl radical ranges from 1/4 to 2/1,[18] these facts supported the conclusion that the single-electron-transfer mechanism was involved in the displacement reaction of **1** with a Grignard reagent.[21]



Irrespective of the mechanism, the cross-coupling reaction of 1-haloadamantane **1** with a Grignard reagent proceeded best in dichloromethane. This method could be extended to normal *tert*-alkyl halides. Typically, *tert*-butyl chloride (**18a**) and bromide (**18b**) underwent cross-coupling reactions with phenethylmagnesium chloride and bromide to give (3,3-dimethylbutyl)benzene (**19**) in 54% and 37% yields, respectively (entries 16 and 18). Compared with the adamantyl case (entry 2), the yield was modest; presumably, the elimination reaction might take place in addition to the reduction; the elimination is prohibited by Bredt's rule in the adamantyl case.[22] The same reaction with cinnamylmagnesium chloride afforded α- and γ-*tert*-butylated products **20** and **21** in a 1/3 ratio (GLC)[23] (entry 17). Interestingly, 1,3-dichloro-3-methylbutane (**22**) reacted with butylmagnesium chloride in a similar manner, and the tertiary chloride was selectively displaced to give 1-chloro-3,3-dimethylheptane (**23**) in 70% yield based on GLC (entry 19).[24]





For the above-mentioned cross-coupling reaction, an organozinc may be applicable instead of an organomagnesium. This is indeed the case. When **1a** was treated in dichloromethane with butylzinc chloride prepared from 1:1 $ZnCl_2$ and butylmagnesium chloride,[25] **3** was obtained in 49% yield. Moreover, the reagent prepared from 1:1 zinc halide and organolithium worked as well. For example, after butyllithium was treated with $ZnCl_2$ in ether, the same procedure as employed for a Grignard reagent afforded **3** in 45% yield. Likewise, **12** was obtained in 30% yield starting from phenyllithium. Thus, this route constitutes a method for the coupling reaction with an organolithium in a one-pot procedure.[26]

$$\begin{array}{lcc} \text{RLi} & \xrightarrow[\text{2. 1a}]{\text{1. ZnCl}_2} & \text{1-AdR} \\ R = C_4H_9 & & \mathbf{3} \\ R = C_6H_5 & & \mathbf{12} \end{array}$$

It should be noted, however, that similar treatment using CuCl and $FeCl_3$ with organolithium or -magnesium resulted in the formation of only reduced adamantane or recovery of the starting material. This is the same tendency as observed previously in organocopper chemistry.[27]

All of the compounds obtained above were characterized on the basis of spectral and elemental analyses, and, if

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(17) Noller, C. R.; White, W. R. *J. Am. Chem. Soc.* **1937**, *59*, 1354.

(18) For example, the electron-transfer process by 5-hexenylmagnesium halide was proven in the reactions with (a) α,β-unsaturated sulfone, (b) 3-chloro-1-phenyl-1-butene, (c) air, (d) 3-iminoindole. (a) Eisch, J. J.; Behrooz, M.; Galle, J. E. *Tetrahedron Lett.* **1984**, *25*, 4851. (b) Muraoka, K.; Nojima, M.; Kusabayashi, S. *Abstract of Papers*, the 35th Symposium on Organic Reaction Mechanisms Tokyo, 1984, p 173. (c) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1970**, *92*, 6609. (d) Eberson, L.; Greci, L. *J. Org. Chem.* **1984**, *49*, 2135. Very recently, remarkable differences between S_N and SET mechanisms were reported in the reactions of cinnamyllithium with *tert*-butyl and adamantyl bromides: (e) Tanaka, J.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1987**, *109*, 3391.

(19) For general discussion, see: (a) Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press; New York, 1982; Vol. 2, p 121. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

(20) References 14a (footnote 8) and 14c. See also: Bodewitz, H. W. H. J.; Bickelhaupt, F. *Tetrahedron* **1975**, *31*, 1053.

(21) The spectroscopic evidence for a radical intermediate in the reaction of a Grignard reagent and *tert*-butyl halide was reported: Ward, H. R.; Lawler, R. G.; Marzilli, T. A. *Tetrahedron Lett.* **1970**, 521. Nevertheless, this observation does not rule out the possible participation of S_N2' and $S_{RN}1$ mechanisms in the cases of allyl and aryl Grignard reagents.

(22) However, no attempts were made to detect byproducts arising from a *tert*-butyl radical.

(23) According to ref 16e, an S_N2' process might predominate.

(24) For the similar selective alkylation, see ref 9.

(25) Boersm, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 2, p 837.

(26) Similarly, the well-known transmetalation between organolithium and magnesium halide allows this type of coupling procedure.

(27) Whitesides, G. M.; Fischer, W. F.; San Filippo, J., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

required, comparison was made with the sample synthesized independently.

In conclusion, the cross-coupling reactions of *tert*-alkyl halides including 1-adamantyl halide with Grignard reagents were found to proceed in dichloromethane. This reaction provides a novel synthetically useful method for construction of a quartenary carbon by direct combination using readily available Grignard reagents.

Experimental Section

Infrared spectra were determined on a JASCO A-100 spectrophotometer, and all of the crystalline products were scanned in KBr disks except for the oily products (neat). ^{1}H NMR spectra were determined at 60 MHz in CCl_4 with a JEOL 60-HL spectrometer, and chemical shifts were recorded in δ with tetramethylsilane as an internal standard. ^{13}C NMR spectra were determined in $CDCl_3$ on a JEOL JNM-FX60 spectrometer. Spectral patterns are designated as follows: s, singlet, d, doublet; t, triplet; m, multiplet, br, broad. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. GLC analyses were performed on Varian Gas Chromatograph 1400 series (silicon SE-30). The chromatographic separations were carried out on a silica gel column (Mallinckrodt, 100 mesh) eluted with hexane, unless otherwise noted. The typical Grignard reagents were prepared according to the standard method[11] and titrated before use ((*p*-bromophenyl)magnesium bromide, ref 28; 3-indolylmagnesium bromide, ref 29). Dichloromethane used as a reaction solvent was dried over $CaCl_2$, distilled, and kept over 4-Å molecular sieves. *Caution*: laboratory operations involving organic halides and dichloromethane in particular should be performed in a good hood due to the carcinogenicity of these compounds.

General Procedure for the Coupling Reaction of 1 with a Grignard Reagent. A flask fitted with a two-way stopcock which was connected to a nitrogen balloon at the side arm and a vacuum pump to the top arm (a rubber septum was attached here when a reagent was introduced into a flask) was well-dried under vacuum and filled with nitrogen gas. To this was introduced by a syringe 1.5–2.0 equiv of Grignard reagent prepared in ether, the ether was evaporated under reduced pressure, and lastly, slight warming was applied to complete the removal of the ether (note: incomplete removal of ether occasionally caused a lower yield). After covering with nitrogen gas again, dichloromethane (3 mL) and **1** (1 mmol) were added to the residue, successively. This mixture was stirred at room or reflux temperature (in the latter case the stopcock was replaced by a reflux condenser fitted with a bubbler) under an atmosphere of nitrogen for a period as indicated in the table. The reaction mixture was poured into ice–water and the products were extracted with dichloromethane. The organic layer was washed with aqueous NH_4Cl and water successively and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a silica gel column to give a fairly separated product. This was further subjected to fractional trap-to-trap distillation to give reduced **2** and recovered **1** at an oven temperature of 60 °C (5 mmHg) and the product at higher temperatures (120–200 °C) and more reduced pressure (2 mmHg). Otherwise, solid products (**4**, **7**, **12–15**) were recrystallized from methanol after chromatography. Only for **16**, purification was achieved by preparative TLC developed with 5/1 (v/v) hexane/ethyl acetate. The spectral data for the new compounds obtained are as follows.

4: IR 690, 710, 740, 1490, 1600, 2840, 2900, 3000 cm^{-1}; ^{1}H NMR δ 1.33 and 2.52 (A_2B_2, each 2 H, J = 8 and 5 Hz), 1.50–2.20 (m, 15 H), 7.10 (s, 5 H). Anal. Calcd for $C_{18}H_{24}$: C, 89.94; H, 10.06. Found: C, 89.88; H, 10.21.

5: IR 1450, 2840, 2900 cm^{-1}; ^{1}H NMR δ 0.66–2.50 (m, 26 H); ^{13}C NMR δ 25.2 (t), 28.9 (d), 35.0 (s), 35.3 (t), 37.3 (t), 43.1 (d), 43.2 (t), 51.7 (t). Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 88.28; H, 11.72.

10 and 11 (as a mixture): IR 905, 960, 990, 1640, 2840, 2900 cm^{-1}; ^{1}H NMR δ 0.90 (d, J = 7 Hz), 1.30–2.15 (m), 4.85 (dd, J = 16 and 3 Hz), 4.91 (dd, J = 10 and 3 Hz), 5.20–6.00 (m), in a ratio of 3:26:2:2, from which the ratio **10**/**11** was estimated to be 1:2, paralleling the GLC ratio. Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.23, H, 11.72.

16: IR 705, 725, 1450, 1510, 2840, 2900 cm^{-1}; ^{1}H NMR δ 1.62–2.48 (m, 15 H), 6.30 (d, J = 3 Hz), 6.87–7.03 (m, 2 H), 7.14 (d, J = 3 Hz), 7.39–7.67 (m, 2 H).

The reaction in hexane was carried out in the same manner except for replacing with hexane, in which **3** was obtained in 30% yield (at reflux temperature for 10 h).

Functional Exchange between 1a and Methylmagnesium Iodide. The reaction of **1a** with 1 equiv of methylmagnesium iodide was conducted at room temperature for 18 h as above, and **1c** was obtained in 51% yield by recrystallization from methanol. Separately, **1c** was obtained in 47% yield by stirring a mixture of **1a** (255 mg, 1.5 mmol) and MgI_2 (460 mg, 1.7 mmol) in dichloromethane (4 mL) at room temperature for 92 h followed by the usual workup and recrystallization.

Reaction of 1b with 5-Hexenylmagnesium Bromide. After exchange of the solvent as described above, a mixture of **1b** (430 mg, 1 mmol) and 1.2 equiv of 5-hexenylmagnesium bromide in dichloromethane (8 mL) was refluxed for 5 h, and the same workup and purification as in the general procedure gave 70 mg of oil. This was shown to be a 6:4 mixture of the coupling product by GLC and MS (M^+ 218) analyses, coupled with elemental analysis. (Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 87.95; H, 12.05). The minor product was identical with independently synthesized **5** (entry 3). The major product was assigned as **17**, which was supported by the remaining IR and ^{1}H NMR spectra [IR 910, 990, 1640, 2840, 2910 cm^{-1}; ^{1}H NMR δ 0.80–1.30 (m), 4.85 (dd, J = 16 and 2 Hz), 4.88 (dd, J = 12 and 2 Hz), 5.73 (m)] in which the peak area ratio (49:3) of aliphatic and olefinic protons indicated the ratio of **5**/**17** to be ca. 1:1, paralleling the GLC ratio.

Coupling Reactions of *tert*-Alkyl Halides with Grignard Reagents. According to the same procedure employed for **1**, a mixture of *tert*-butyl halide (2 mmol) and 1.1–1.2 equiv of Grignard reagent in dichloromethane (8 mL) was stirred at room temperature for 3 h, followed by the usual workup. The oily product **19**[30] was obtained, after chromatography and trap-to-trap distillation (oven temperature 120 °C/5 mmHg). The products **20** and **21**[2b] were obtained and analyzed as a mixture after chromatography and trap-to-trap distillation (oven temperature 150 °C/5 mmHg). In ^{1}H NMR the peak area ratio at δ 0.88 and 0.92 (s, $C(CH_3)_3$ in **20** and **19**, respectively) indicated the ratio **20**/**21** to be 1:3, coinciding with the GLC ratio.

Selective Butylation of 22. After exchange of the solvent, a mixture of **22** (141 mg, 1 mmol) and 1.2 equiv of butylmagnesium chloride in dichloromethane (4 mL) was refluxed for 6 h, followed by the usual workup. The GLC analysis exhibited that a single product was obtained in 70% yield, and its structure was tentatively elucidated as **23** by spectral analysis: IR 710, 2850, 2920, 2950 cm^{-1}; ^{1}H NMR δ 0.90 (s, 6 H), 0.80–1.40 (m, 9 H), 1.70 (t, 2 H, J = 8 Hz), 3.45 (t, 2 H, J = 8 Hz). It was finally confirmed by the following independent synthesis: to a suspension of lithium aluminum hydride (57 mg, 1.5 mmol) in ether (5 mL) was added a solution of ethyl 3,3-dimethylheptanoate[31] (248 mg, 1.3 mmol) in ether (2 mL) at 0 °C, and the mixture was stirred under reflux for 1.5 h. The reaction mixture was decomposed with ice–water and the organic layer was separated by decantation and dried over Na_2SO_4. After evaporation of the solvent the residue was chromatographed on a silica gel column (hexane/ethyl acetate, 5/1) to give 90 mg (47% yield) of 3,3-dimethylheptanol as an oil: IR 3300 cm^{-1}; ^{1}H NMR δ 0.89 (s, 6 H), 0.80–1.58 (m, 10 H), 1.44 (t, 2 H, J = 8 Hz), 3.60 (t, 2 H, J = 8 Hz). Anal. Calcd for $C_9H_{20}O$: C, 74.94; H, 13.97. Found: C, 75.12; H, 13.79. This alcohol was converted by the standard pyridine–thionyl chloride method to

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the corresponding chloride, which was identical with the cross-coupling product obtained above in GLC and ^1H NMR.

Coupling Reaction of 1 with an Organozinc. To a flask containing $ZnCl_2$ (137 mg, 1 mmol) in dry ether (4 mL) was added butyllithium (0.62 mL of a 15% hexane solution, 1 mmol) at 0 °C under an atmosphere of nitrogen, and the mixture was stirred for 30 min. After exchange of the solvent from ether to dichloromethane (4 mL) as before, **1a** (170 mg, 1 mmol) was added and this mixture was stirred for 21 h at room temperature. The same workup and purification as in the Grignard case gave **3** in 45% yield. Similarly, **12** was obtained in 30% yield from **1b** and phenyllithium.

Registry No. **1a**, 935-56-8; **1b**, 768-90-1; **1c**, 768-93-4; **2**, 281-23-2; **3**, 14449-41-3; **4**, 88458-84-8; **5**, 112298-59-6; **6**, 770-69-4; **7**, 768-91-2; **8**, 20440-81-7; **9**, 22922-62-9; **10**, 112298-60-9; **11**, 112298-61-0; **12**, 780-68-7; **13**, 1974-86-3; **14**, 2245-43-4; **15**, 57822-52-3; **16**, 112298-62-1; **17**, 112298-63-2; **18a**, 507-20-0; **18b**, 507-19-7; **19**, 17314-92-0; **20**, 63238-62-0; **21**, 63213-06-9; **22**, 624-96-4; **23**, 112319-77-4; $CH_3(CH_2)_3MgCl$, 693-04-9; $Ph(CH_2)_2MgCl$, 90878-19-6; $C_5H_9CH_2MgCl$, 108697-83-2; CH_3CH_2MgBr, 925-90-6; CH_3MgI, 917-64-6; $C(CH_3)_3MgCl$, 677-22-5; $CH_2{=}CHCH_2MgCl$, 2622-05-1; $CH_3CH{=}CHCH_2MgCl$, 6088-88-6; $CH_3(CH_2)_3MgBr$, 693-03-8; C_6H_5MgBr, 100-58-3; 3-$CH_3C_6H_4MgBr$, 28987-79-3; 4-BrC_6H_4MgBr, 18620-02-5; $C_{10}H_7MgBr$, 703-55-9; $CH_3(CH_2)_3MgI$, 1889-20-9; $C_6H_5(CH_2)_2MgBr$, 3277-89-2; 1-heptynylmagnesium bromide, 61307-38-8; 5-hexenylmagnesium bromide, 30043-41-5; cinnamylmagnesium chloride, 51800-74-9; butylzinc chloride, 42930-39-2; butyllithium, 109-72-8; 3-indolylmagnesium bromide, 7058-69-7; phenyllithium, 591-51-5.

Geometry of Porphyrin–Porphyrin Interactions

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NMR, UV/visible absorption, and fluorescence studies on two free base porphyrin cofacial dimers and on their dizinc derivatives are reported. In the free-base molecules, characteristic upfield chemical shifts induced at the protons and carbons of one porphyrin moiety by the ring current of the other porphyrin moiety are interpreted in terms of an offset stacked geometry; this geometry is virtually unchanged by insertion of zinc. It is suggested that the observed offset geometry is a fundamental property of the porphyrin–porphyrin interaction, being found in solution and solid state, in restrained porphyrin dimers, and in aggregates of unrestrained monomers. It is further suggested that these cofacial dimers are good models for the study of porphyrin–porphyrin aggregation.

It has been known for many years that porphyrins in solution tend to aggregate,[1-3] but we understand remarkably little of the nature or geometry of porphyrin–porphyrin interactions. There is a substantial amount of evidence to suggest that porphyrins prefer to stack in an offset manner rather than with one molecule directly over another,[3-7] but this evidence is too fragmentary to enable any firm conclusions to be drawn either about the fundamental geometry of the porphyrin–porphyrin interaction or about the role (if any) of a central metal ion. Three types of interaction have been previously proposed in connection with porphyrin aggregation:[3] (i) free-base porphyrins aggregate via a weak π–π interaction; (ii) some metalloporphyrins exhibit a stronger metal–π interaction that can be abolished by ligand binding to the metal; and (iii) a strong metal–side chain binding. The latter is particularly marked in magnesium-containing porphyrins and is not considered further in this paper.

We now present NMR, UV/visible absorption, and fluorescence results for a series of free base and metalated porphyrin cofacial dimers that elucidate several aspects of porphyrin aggregation chemistry. In particular, we demonstrate (a) that these dimers exhibit a preferred offset geometry in solution, (b) that this geometry is accompanied by strong electronic interaction, and (c) that the *geometry* of the interaction is not necessarily or significantly affected by the presence of a central metal ion but that the *strength* of the interaction may be affected. Finally, we suggest, on the basis of published results on other compounds, that these geometries and conclusions are a general property of the porphyrin–porphyrin interaction.

Most of the results described here have been obtained by using the meso form of the dimer **1** and its dizinc derivative Zn_2-**1**; some less detailed, but corroborative, results are also reported for **2** and Zn_2-**2**. These molecules have been designed such that they are adequately constrained to encourage intramolecular interaction and sufficiently flexible to be able to fold into a favorable conformation for porphyrin–porphyrin interaction. In addition, Zn_2-**1** is sufficiently loose that the two faces can be pried apart by manipulation of its coordination chemistry.

Our approach in this work has been described in detail very recently[8] so we summarize it here only briefly. The geometrical dependence of the ring-current shifts induced by porphyrins is well-known; it is therefore a relatively simple matter to interpret the shifts observed in a porphyrin cofacial dimer in terms of the relative disposition of the two component macrocycles. Similarly, the ap-

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