Two Efficient Routes to *m*-Terphenyls from 1,3-Dichlorobenzenes

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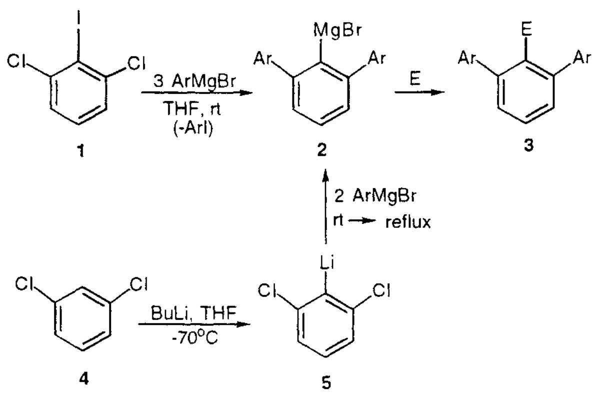
Received 14 March 1996; revised 10 June 1996

In the first route 2,6-dichlorophenyllithium (**5**), prepared by direct lithiation of 1,3-dichlorobenzene, reacted with aryl Grignard reagents to give *m*-terphenyls in 57–93 % yields (Table 1); the methodology was extended to substituted 1,3-dichlorobenzenes (i.e. **8** → **10**). Also, reaction of **5** with $MgCl_2$ gave 2,6-dichlorophenylmagnesium chloride which, on warming, produced the self-capture product tetrachloro-*m*-terphenyl **7** in moderate yield. In the second route, reaction of 1,3-dichlorobenzene with excess of aryllithium in diethyl ether at room temperature gave the corresponding *m*-terphenyls in 59–94 % yields (Table 2). Examples are given in which the aryllithium was prepared by three different routes (ArX + Li, ArX + *t*-BuLi, ArH + BuLi).

Because of their shape, *m*-terphenyls are useful intermediates for constructing cyclophanes and related compounds with cavities that can specifically bind small molecules.[1–4] New general methods for synthesizing *m*-terphenyls are therefore important.[5] We previously described one such method, by treating 2,6-dichloroiodobenzene (**1**) with three or more equivalents of an aryl Grignard reagent.[5–9]



The mechanism involves selective metal-halogen exchange at iodine (loss of ArI) followed by two successive elimination-regioselective nucleophilic additions via aryne intermediates. The method, which is general and gives good yields of **3**, has certain disadvantages that we address in this paper. The starting material **1** is not commercially available and must be synthesized. Also, one equivalent of aryl Grignard is consumed unproductively in the initial metal-halogen exchange, although this disadvantage can be overcome by using one equivalent of vinylmagnesium bromide prior to reaction with the aryl Grignard reagent.[10, 11] We describe here two general routes to *m*-terphenyls from 1,3-dichlorobenzenes.

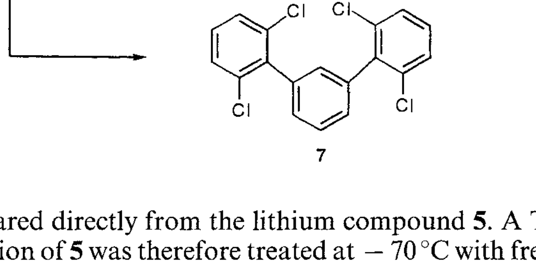
Route I: *m*-Terphenyls via 2,6-Dichlorophenyllithium (5)

In 1988 Kress reported[12] that **5** can be prepared by regioselective lithiation of **4** with BuLi in THF at −70 °C, and that such solutions are stable below −50 °C. We found that such solutions react with aryl Grignard reagents at room temperature or reflux to give *m*-terphenyls in yields of 57–93 % (Table 1).

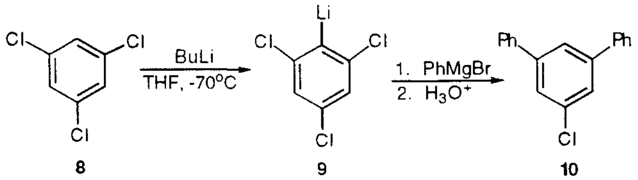
Two general procedures were used. In procedure A, the Grignard solution (THF) was added rapidly, via a cannula, to the slurry of **5** at −84 °C (ethyl acetate/liquid N_2 slush), after which the mixture was allowed to warm to room temperature and/or was heated at reflux. In procedure B the addition was reversed. Method A is preferred unless the aryl Grignard is rare or expensive and an excess is to be avoided. Although only two equivalents of the Grignard reagent are required by the stoichiometry (**5** → **2**), the yield is improved somewhat (15–20 %) if three equivalents are used.

All of the terphenyls listed in Table 1 are known;[6] melting points agreed with those in the literature. Yields are comparable to those reported earlier starting with **1**, except for the tetramethoxyterphenyl, which is much improved (82 % vs 25 %).

In a study of the thermal stability of THF solutions of **5**, Kress observed[12] that darkening began at −45 °C, and at −20 °C a highly exothermic reaction occurred yielding a black sludge from which **7** was isolated (22 %). We thought that the corresponding Grignard reagent **6** would be considerably more stable, and that it could be prepared directly from the lithium compound **5**. A THF solution of **5** was therefore treated at −70 °C with freshly prepared $MgCl_2$ (from 1,2-dichloroethane and Mg powder in THF). When this solution was warmed to 0 °C no darkening occurred; an iodine quench gave **1** (95 %; no **7** was formed). However, warming solutions of **6** to room temperature or above gave **7** in higher yield (44 %) and a cleaner reaction than could be obtained from **5**.



Other 1,3-dichlorobenzenes besides **4** can also serve as starting points in this *m*-terphenyl synthesis. For example, 1,3,5-trichlorobenzene (**8**) gave **10**[13] in 54 % yield, through the intermediacy of trichlorophenyllithium (**9**).



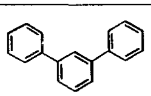
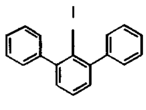
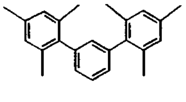
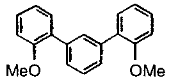
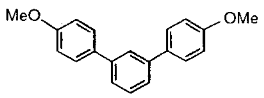
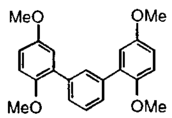
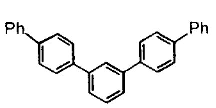
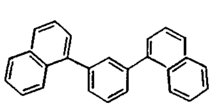
In summary, this methodology provides a two-step one-pot general route to *m*-terphenyls from 1,3-dichlorobenzenes in moderate to good yields.

Route II: *m*-Terphenyls from 1,3-Dichlorobenzenes and Aryllithiums

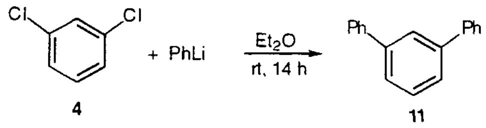
In route I, the intermediate 2,6-dichlorophenyllithium (**5**) was obtained by lithiation of **4** in THF. We found that by changing the solvent to diethyl ether one can obtain *m*-terphenyls directly from 1,3-dichlorobenzene (**4**) and and excess (3–5 equiv) of an aryllithium at room temperature.

In 1942 Wittig and Merkle described[14] the low-yield (18 %) synthesis of *m*-terphenyl **11** from **4** and two equivalents of PhLi in diethyl ether. This result was not discussed in the main body of the paper, which described Wittig's now classic study showing that PhF reacts much faster than do the other halobenzenes with PhLi to produce biphenyls by a mechanism that involves, as a first step, removal of a proton ortho to the fluorine atom. Eventually, but not in this paper, these experiments led to Wittig's proposal of dehydrobenzene (benzyne) as a reactive intermediate. One can only speculate why only two equivalents of PhLi were used by Wittig and Merkle in the reaction with 1,3-dichlorobenzene; most probably it was because the displacement of chlorine (but not fluorine) was viewed as a direct nucleophilic substitution by the conventional addition-elimination mechanism. If,

Table 1. *m*-Terphenyls Prepared from ArMgBr and **5** by Route I

Entry	ArMgBr (equiv)	Method	Reaction Conditions	Product	Yield (%)	mp (°C)	
						found	reported
1	PhMgBr (2)	B	r.t., 24 h		73	89–90	89[16]
2	PhMgBr (2)	B	r.t., 24 h; reflux, 3 h; I_2 quench		57	114–115	113.5–115[6]
3	2,4,6-$Me_3C_6H_2$MgBr (3)	A	r.t., 13 h; reflux, 3 h		74	132–133	133–134[6]
4	2-$MeOC_6H_4$MgBr (3)	A	r.t., 13 h; reflux, 3 h		93	99–100	97–98.5[6]
5	4-$MeOC_6H_4$MgBr (2) (3)	B B	reflux, 12 h; r.t., 48 h		60 80	198	196–198[6]
6	2,5-$(MeO)_2C_6H_3$MgBr (3)	A	r.t., 14 h; reflux, 4 h		82	123–124	122–124[6]
7	4-$C_6H_5C_6H_4$MgBr (2)	B	r.t., 24 h; reflux, 3 h		65	269–270	268–270[6]
8	1-naphthylmagnesium bromide (2)	B	r.t., 24 h; reflux, 3 h		63	130–131	130–132[6]

however, **11** was formed by metallation at the 2-position of **4**,[12] elimination to an aryne (3-chlorobenzyne) and regioselective nucleophilic addition to the aryne, followed by repetition of the sequence, then at least three equivalents of PhLi would be required. Accordingly, we repeated the Wittig-Merkle experiment using 3 equiv of PhLi; the yield of **11** nearly tripled, and by using excess PhLi (5 equiv) to favor capture of the aryne, the yield of **11** was further enhanced to 85%.



Equiv. of PhLi	Yield (%) of **11**
2	18[14]
3	51 (this work)
5	85 (this work)

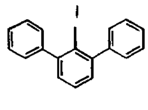
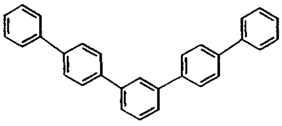
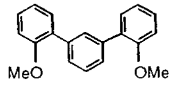
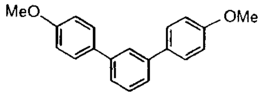
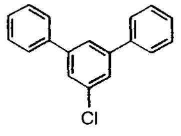
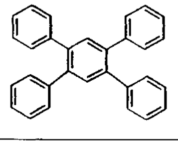
The method is general (Table 2); substituted aryllithiums and/or substituted 1,3-dichlorobenzenes can be used. Three different methods were used to prepare the aryllithiums: direct metallation of the aryl bromide with metallic lithium (entries 1–3, 5, 6), metal-halogen exchange using an aryl bromide and *t*-BuLi (entry 3), and ortho metallation of an activated arene with BuLi (anisole, entry 4). All of the products in Table 2 were previously known, and their identity was established by comparison (mp, spectra) with authentic samples.

In summary, two short efficient routes to *m*-terphenyls from 1,3-dichlorobenzenes are described. In the first, lithiation in THF at – 70 °C is followed by treatment with excess arylmagnesium halide; in the second, the 1,3-dichlorobenzene is treated in diethyl ether at room temperature with excess aryllithium. Yields are comparable for the two methods, and a choice between them may be based on whether the aryl Grignard or aryllithium reagent is the more readily available.

All reactions were performed under dry argon using reaction vessels previously dried at 120 °C. THF and Et_2O were distilled from benzophenone sodium ketyl prior to use. Melting points were determined with an Electrothermal Model 9100 apparatus and are uncorrected. The drying agent was anhyd $MgSO_4$ and silica gel for chromatography was 230–400 mesh.

2,6-Dichlorophenyllithium (5):[12]
To a stirred solution of 1,3-dichlorobenzene (**4**; 1.47 g, 10 mmol) in THF (25 mL) at – 70 °C was slowly added (20 min) from a dropping

Table 2. *m*-Terphenyls Prepared by Route II

Entry	1,3-Dichlorobenzene	ArLi (equiv)	Reaction Conditions	Product	Yield (%)	mp (°C)	
						found	reported
1	**4**	PhLi (4)	r.t., 15 h; I_2 quench		55	114–115	113.5–115[6]
2	**4**	4-$C_6H_5C_6H_4$Li (4)	r.t., 24 h		63	269–270	268–270[6]
3	**4**	2-$MeOC_6H_4$Li (3) 2-$MeOC_6H_4$Li (5) 2-$MeOC_6H_4$Li (3)[a]	r.t., 48 h r.t., 15 h r.t., 48 h		73 94 76	99–100	97–98.5[6]
4	**4**	4-$MeOC_6H_4$Li (3)[b]	r.t., 7 h		52	197–198	196–198[6]
5	1,3,5-trichlorobenzene	PhLi (5)	r.t., 12 h		78	93–94	
6	1,2,4,5-tetrachlorobenzene	PhLi (8)	r.t., 24 h reflux, 1 h		22	268–269	267–268[17]

[a] Prepared from PhOMe and BuLi.
[b] Prepared from 4-$MeOC_6H_4$Br and *t*-BuLi.

funnel BuLi (10 mmol, 1.6 M in hexanes). The reaction mixture was stirred at – 70 °C for 1.5 h, after which the resulting white slurry was ready for use.

Route I: *m*-Terphenyls via 2,6-Dichlorophenyllithium (5); General Procedures (Table 1):

Method A: The slurry of **5** (10 mmol) was cooled to – 84 °C (EtOAc/liquid N_2 slush) and a solution containing the arylmagnesium bromide [prepared from aryl bromide (20 or 30 mmol) and Mg (20 or 30 mmol) in THF (30 mL)] was added with stirring via cannula or syringe. The mixture was allowed to warm to r.t. and was stirred or heated at reflux for the times mentioned in Table 1. It was then cooled in an ice-salt bath and quenched with dil HCl or NH_4Cl (40 mL). THF was removed under reduced pressure and the aqueous mixture was extracted several times with CH_2Cl_2. Combined organic layers were washed with water, dried, and the residue obtained after solvent removal was either chromatographed or recrystallized to give the products in isolated yields shown in Table 1.

Method B: The arylmagnesium solution (prepared as in Method A) was warmed to just below the boiling point and the slurry of **5**, cooled to – 84 °C, was added via cannula over 10 min under a positive argon pressure. At first the tip of the cannula may become red due to decomposition of **5**, but this color change stops as soon as the cannula is sufficiently cooled. The mixture was stirred at r.t. and/or reflux for the times indicated in Table 1 and was worked up as in Method A.

2,6-Dichloroiodobenzene (1):

To a stirred slurry of **5** (10 mmol) at – 70 °C was added a solution of I_2 (2.54 g, 10 mmol) in THF (15 mL), and the mixture was allowed to warm to r.t. Ice water (30 mL) was added and the mixture was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with dil Na_2SO_3 (20 mL), water (20 mL), brine (20 mL) and dried. TLC (silica gel plate, hexanes) showed only one spot (no **7**). Removal of the solvent and recrystallization of the residue from EtOH gave 2.57 g (94 %) of **1**; mp 67–68 °C (Lit.[15] mp 67.2–67.6 °C).

2′-Iodo-1,1′:3′,1″-terphenyl (Table 1, Entry 2):

General procedure B was followed, but instead of the usual quench the reaction mixture was cooled (ice bath) and a solution of I_2 (1.1 equiv) in THF (10 mL) was added. The mixture was stirred vigorously, warmed to r.t., washed with aq Na_2SO_3 and extracted with Et_2O (3 × 30 mL). Combined organic layers were washed with water, brine and dried. The residue after solvent removal was flash chromatographed (silica gel, hexanes) and recrystallized from petroleum ether (bp 50–70 °C) to give 2.03 g (57 %) of the iodoterphenyl; mp 114–115 °C.

2,6,2″,6″-Tetrachloro-1,1′:3′,1″-terphenyl (7):

To a slurry of **5** [prepared from **4** (15 mmol) and BuLi (15 mmol) in THF (30 mL)] cooled to – 84 °C was added via syringe a solution of $MgCl_2$ in THF [freshly prepared from 1,2-dichloroethane (495 mg, 5 mmol) and Mg powder (122 mg, 5 mmol) in THF (10 mL)]. The mixture was allowed to slowly warm to r.t., then refluxed for 1 h. The mixture was cooled to 0 °C, quenched with 10 % NH_4Cl (30 mL), extracted with Et_2O (3 × 40 mL) and the combined Et_2O extracts were dried. Removal of the solvent and chromatography of the residue (silica gel, hexanes) gave 0.81 g (44 %) of **7**; mp 127–128 °C (Lit.[12] mp 128–129 °C).

5-Chloro-1,1′:3′,1″-terphenyl (10):

To a slurry of **9** [prepared from 1,3,5-trichlorobenzene (**8**; 1.81 g, 10 mmol) and BuLi (1.6 M in hexane, 10 mmol) in THF (25 mL), at – 70 °C] cooled to – 84 °C (EtOAc/liquid N_2 slush) was added via a cannula under positive argon pressure a solution of PhMgBr [prepared from PhBr (30 mmol) and Mg (30 mmol) in THF (30 mL)]. The mixture was allowed to warm to r.t., stirred for 13 h, then refluxed for 3 h. It was then cooled (ice-salt bath), quenched with 3M HCl (20 mL) and extracted with Et_2O (3 × 40 mL). The combined extracts were washed with water, brine and dried. Removal of the solvent, flash chromatography (silica gel, hexanes) and recrystallization from EtOH gave 1.43 g (54 %) of **10**; mp 93–94 °C.

^1H NMR ($CDCl_3$/TMS): δ = 7.42–7.57 (m, 6 H), 7.61–7.76 (m, 7 H).

^{13}C NMR ($CDCl_3$/TMS) δ = 124.3, 125.9, 127.1, 127.9, 128.9, 135.0, 139.8, 143.3.

MS: m/z (%) = 266 (32), 265 (19), 264 (100), 228 (26), 227 (12), 226 (19), 113 (17), 101 (12).

Anal. Calcd for $C_{18}H_{13}Cl$: C, 81.66; H, 4.95. Found: C, 81.58; H, 4.91.

Route II: *m*-Terphenyls from 1,3-Dichlorobenzenes and Aryllithium; General Procedure (Table 2, Entries 1–3, 5, 6):

To the aryllithium, prepared from aryl bromide (30–50 mmol) and lithium chips (60–100 mmol) cut from wire in anhyd Et_2O (30–40 mL) was added very slowly the appropriate 1,3-dichlorobenzene (10 mmol) in Et_2O (10 mL). The heat of reaction usually caused the Et_2O to reflux. The mixture was stirred at r.t. for the times indicated, then cooled (dry ice) and carefully hydrolyzed with dil aq NH_4Cl or HCl (25 mL), extracted with Et_2O or CH_2Cl_2 (3 × 50 mL) and dried. The solvent was removed and the residue was recrystallized or chromatographed using hexane or EtOAc/hexane. For entries 2 and 6, the product is only slightly soluble in Et_2O and, after hydrolysis, can be filtered directly, washed with water, Et_2O, and dried.

2,2″-Dimethoxy-1,1′:3′,1″-terphenyl; Alternative Procedure (Table 2, Entry 3):

To a stirred solution of redistilled anisole (3.24 g, 30 mmol) in anhyd Et_2O (30 mL) was added BuLi (30 mL, 1.1M hexane solution) and the mixture was refluxed for 20 h. To the resulting 2-methoxyphenyllithium solution was added slowly (1 h) at r.t. a solution of **4** (10 mmol) in Et_2O (10 mL). After stirring 48 h at r.t., the mixture was worked up as above. The product was chromatographed over 9:1 hexane/EtOAc.

4,4″-Dimethoxy-1,1′:3′,1″-terphenyl (Table 2, Entry 4):

To a solution of 4-bromoanisole (30 mmol) in Et_2O (30 mL) was added at – 78 °C over 10 min a solution of *t*-BuLi (60 mmol, 1.1 M pentane solution). The mixture was stirred for 45 min, the temperature raised to – 30 °C and a solution of **4** (10 mmol) in Et_2O (10 mL) was added slowly without external cooling. The mixture was stirred at r.t. for 7 h and worked up as above, except that product recovery required several extractions with CH_2Cl_2.

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(13) Compound **10** has been reported among the photoproducts obtained by irradiating benzene solutions of 3,5-dibromochlorobenzene (Nakada, M.; Miura, C.; Nishiyama, H.; Higashi, F.; Mori, T.; Hirota, M.; Ishii, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3122) but no physical constants or characterization has, as far as we are aware, been described. The 4′-Cl isomer has been characterized (Cook, W.A.; Cook, K.H. *J. Am. Chem. Soc.* **1933**, *55*, 1212).
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