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New Methods For Aryl-Carbon Bond Formation

presented by

Chi-Jen Frank Du

has been accepted towards fulfillment of the requirements for

Ph. D. degree in Chemistry

Harold Hart
Major professor

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NEW METHODS FOR ARYL-CARBON BOND FORMATION

By

Chi-Jen Frank Du

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ABSTRACT

NEW METHODS FOR ARYL-CARBON BOND FORMATION

By

Chi-Jen Frank Du

Nucleophilic addition of organometallics to an aryne is a potentially useful method for constructing an aryl-carbon bond. The reactions of polyhaloarenes with organomagnesium halide (Grignard reagent), which belong mechanistically in this category, are the subject of this thesis. The mechanisms of these reactions consist of three steps, (1) halogen-metal exchange to form a polyhalogenated aryl Grignard reagent, (2) elimination of magnesium bromide to form an aryne intermediate, and (3) nucleophilic addition of the Grignard reagent to the aryne. For multiple bond formation, the last two steps are repeated.

A new one-pot route to p-terphenyls is described in chapter A. Addition of 1,4-dibromo-2,5-diiodobenzene to an excess of an aryl Grignard reagent gives, prior to quenching, a 1,1';4',1"-terphenyl-2',5'-di-Grignard reagent. After aqueous quench, p-terphenyls are isolated in 30% to 50% yield.

In chapter B, the reaction of o-dihalobenzenes with aryl Grignard reagents, followed by electrophilic quench, has been developed into a useful synthesis of unsymmetric biaryls.

Hexabromobenzene or 1,2,4,5-tetrabromo-3,6-dichlorobenzene reacts with an excess of an aryl Grignard reagent in THF to give 1,2,4,5-tetraarylphenyl-3,6-di-Grignard reagent, which can then be quenched with various electrophiles (H_2O, D_2O, Br_2 and I_2). Twenty new 1,2,4,5-tetraarylbenzenes were prepared in this way. A mechanism that involves a sequence of organometallic aryne intermediates is proposed.

The reaction of an aryl Grignard reagent with 2,6-dibromoiodobenzene or other 1,2,3-trihalobenzenes gives 2,6-diarylphenylmagnesium halide. The mechanism involves Grignard exchange at the central halogen, followed by two cycles of magnesium halide loss and regioselective capture of the resulting aryne by the aryl Grignard reagent. Quenching with an electrophile then gives a m-terphenyl in which the outer rings are identical and in which the 2' position in the central ring is substituted with the electrophile.

Some preliminary results on the reaction of selected vinyl, alkyl, acetylenic and heteroaryl Grignard reagents with polyhaloarenes are presented in chapter E. Vinyl and alkyl Grignards behave similar to aryl Grignards, and successful examples of p, m and 1,2,4,5 aryl-vinyl or aryl-

alkyl bond formation are described. For selected acetylenic and heteroaryl Grignards, the necessary initial halogen-metal exchange step did not take place, preventing the desired reaction. this difficulty was overcome by using one equivalent of alkyl Grignard for the exchange and stoichiometric amounts of acetylenic or heteroaryl Grignards to trap the aryne intermediates.

Two unusual examples of the Diels-Alder reaction are described in the final section of this thesis. In both cases, the diene component appeared to be an aryl or heteroaryl Grignard reagent. Reaction of mesitylmagnesium bromide with hexabromobenzene gave after aqueous quench, in addition to 1,2,4,5-tetramesitylbenzene, a mixture of two biscycloadducts in a 20% yield, 9,10-dibromo-1,3,5,7,11,13-hexamethyl-[1,4,5,8]-bisetheno-1,4,5,8-tetrahydroanthracene and 9,10-dibromo-1,3,6,8,11,14-hexamethyl-[1,4,5,8]-bisetheno-1,4,5,8-tetrahydroanthracene. Quenching with deuterium oxide or with methyl iodide showed that these bis-adducts, prior to quench, possess two organometallic functionalities in vinyl positions. In the reaction of 2-thienylmagnesium bromide with 2,6-dichlorophenylmagnesium bromide, there was obtained after aqueous quench, in addition to the expected major product 1,3-bis[2-thienyl]benzene, a low yield of 1-chloronaphthalene. The latter product is thought to arise from the cycloaddition of 3-chlorobenzyne to 2-thienylmagnesium bromide, followed by extrusion of sulfur. Quenching with D_2O support this

conclusion. These two examples suggest that a carbanion on a diene may enhance its reactivity toward dienophiles in the Diels-Alder reaction.

ACKNOWLEDGEMENTS

The author wishes to express special gratitude to Professor Harold Hart for his continual guidance and encouragement. Professors W. H. Reusch, G. E. Leroi and D. Nocera are also acknowledged for their serving on my committee.

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INTRODUCTION

The formation of aryl-aryl bonds is an important manipulation in organic synthesis. A number of methods have been developed to effect the homo-condensation of two aromatic rings, including the direct oxidative dehydrodimerization by Pd,[1] V[2] or Tl[3] (eq. 1) and the reductive coupling with loss of a substituent group as in the classical[4a-d] and modified[4e-l] Ullmann reaction (eq. 2). Recently, the coupling of organometallic compounds catalyzed by transition metals[5] has also served as a method of choice (eq. 3).

$$2\ ArH \xrightarrow{Pd,\ V,\ Tl} Ar-Ar \qquad \text{(eq. 1)}$$

$$2\ Ar\text{-}X \xrightarrow[X = I,\ Br,\ Cl]{Cu,\ Ni,\ Pd} Ar-Ar \qquad \text{(eq. 2)}$$

$$2\ Ar\text{-}M \xrightarrow[M = Tl(OTf)_2,\ HgCl,\ MgBr]{Cat.} Ar-Ar \qquad \text{(eq. 3)}$$

Cat. = Pd, Rh, Tl

However, extention of these methods to the cross-coupling of two unlike aromatic moieties has been limited by their unavoidable homo-coupling side reaction. Therefore, a wide variety of approaches, either modified procedures or new

pathways, for the unsymmetric condensation of two different aryl rings either inter- or intramolecularly have been explored to address this problem. Here we have attempted to classify and briefly review these literature methods into several categories based on their reaction features.

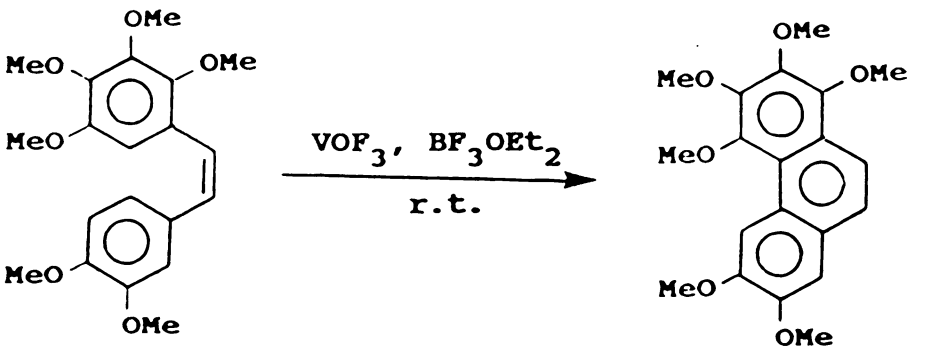
A. Electrophilic Aromatic Substitutions

Reactions that involve the formation of an aryl cation, which then acts as an electrophile to attack another aromatic ring, thus constructing a new aryl-aryl bond, fall into this category. Historically, metal salt induced oxidative dehydrodimerizations of aromatic compounds (eg. 4) have been known for many years and are refered to as the Scholl[6] reaction. Such processes have little synthetic

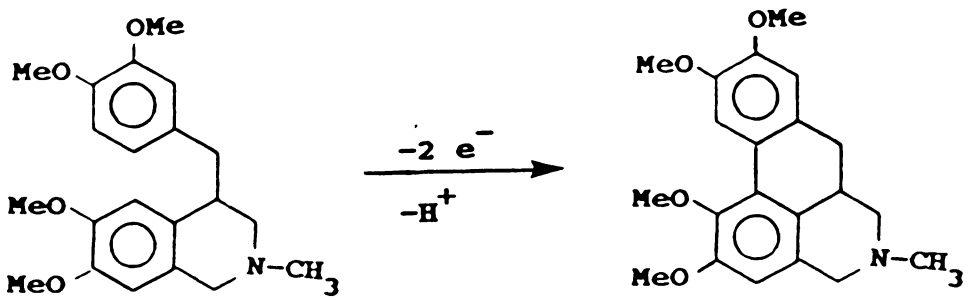
$$ArH + Ar'H \xrightarrow{MX_n} Ar-Ar' \quad \text{(eq. 4)}$$

utility, however, primarily because of low reaction yields and complex mixtures of products. They appear to proceed most readily (a) with relatively electron rich aromatic subtrates and (b) when a metal salt is used which can function as a one electron oxidant. For example, electron-rich substrates such as phenols and phenol ethers can be effectively coupled intramolecularly by using vanadium oxytrihalide as an oxidant (eq. 5).[7] Recently, several different metal salts including $Tl(OTf)_3$[8] and $Pb(OAc)_4$[9] were

found to give better yields. Alternatively, controlled potential electrochemical oxidation[10] of phenolic and phenol ether substrates has been developed as a method of choice for the synthesis of certain natural products (eq. 6).

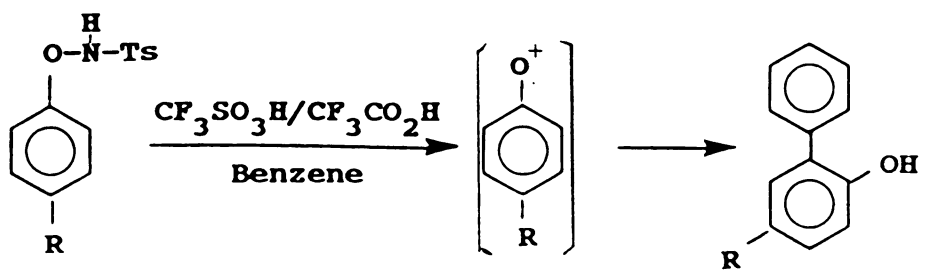


(eq. 5)

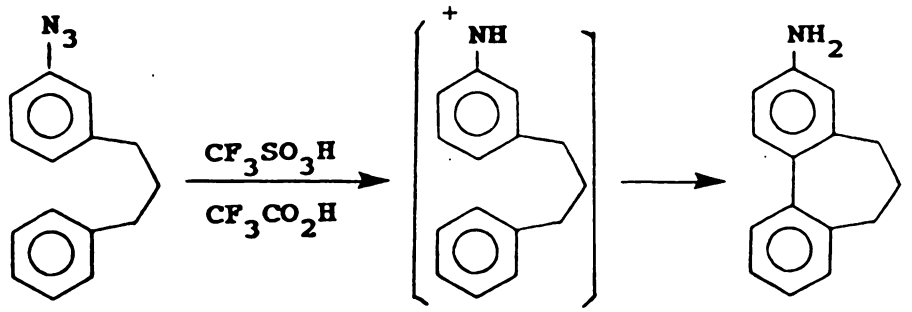


(eq. 6)

Another facet of electrophilic substitution reactions is seen in some recent examples which utilize either the phenoxenium[11] or arylnitrenium[12] ion as the electrophile to form the corresponding hydroxy- or amino-biphenyl (eq. 7 and 8). Recently, Okamoto[13] and coworkers reported a case of

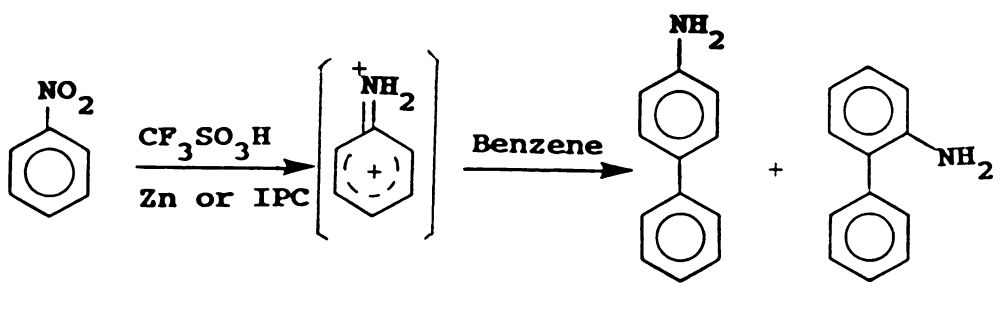


(eq. 7)

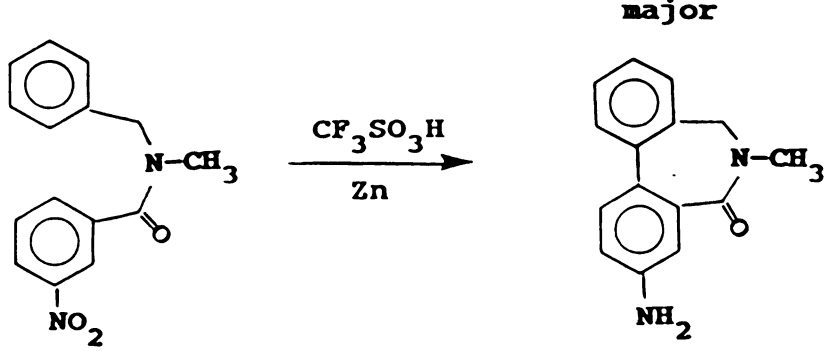


(eq. 8)

reductive phenylation which involves an iminium-benzenium dication intermediate (eq. 9). The intermediate was generated by the reduction of a nitro aromatic compound with zinc or iron pentacarbonyl in the presence of trifluoromethansulfonic acid. Reaction with benzene gives mainly 4-amino-biphenyl and the method has general utility for aminobiphenyl synthesis. An intramolecular example of the reductive phenylation is shown in (eq. 10).



(eq. 9)

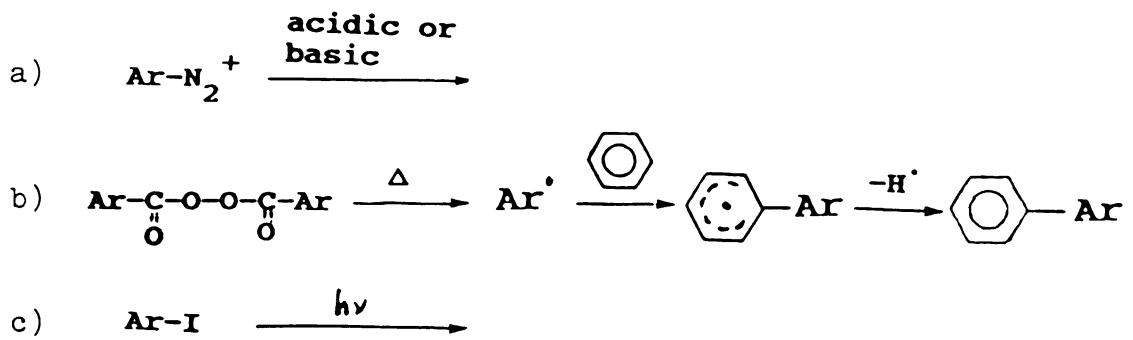


(eq. 10)

B. Radical-mediated Reactions

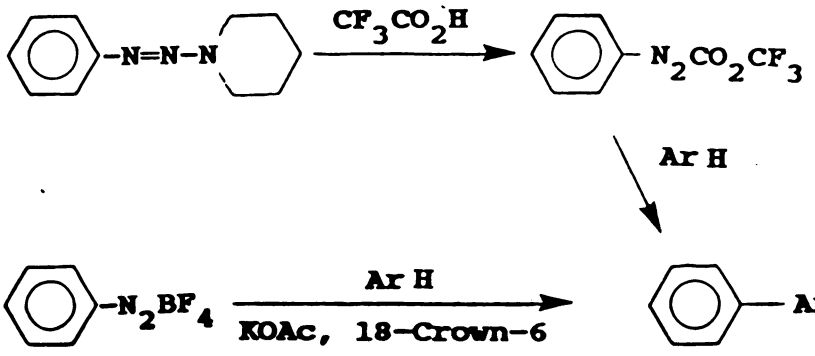
Radical-mediated reactions[14] involve the initial formation of aryl radicals, followed by reaction with the other aromatic ring and termination by hydrogen atom abstraction. In the first step, the aryl radicals can be generated by several methods (Scheme 1) including (a) the thermal decomposition of diazonium salts under alkaline conditions (Gomberg-Bachman-Hey reaction) or under acidic conditions (Pschorr reaction), (b) the thermal decomposition of arenecarbonyl peroxides and (c) the photolysis of aryl halides. Next, the aryl radicals attack the aromatic subtrates in much the same way as in the electrophilic substitution, and the subsequent loss of a hydrogen atom results in the formation of unsymmetric biaryls.

Scheme 1



Although radical-mediated reactions are widely used for intramolecular cyclizations in natural product synthesis,[15] in general, the intermolecular condensation is not as effective. Lately, however, there have been several

modifications and new developments. For example, for those reactions involving the aryldiazonium intermediate, higher yields can be obtained either by generating a stable aryldiazonium salt from an aryltriazene in CF_3CO_2H[16] or by introducing the phase transfer reagent 18-crown-6 to catalyze the reaction (eq. 11).[17] In the Pschorr



(eq. 11)

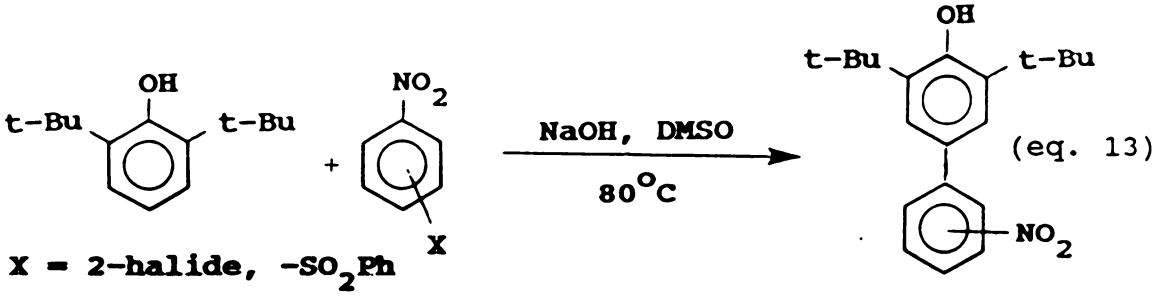
phenanthrene synthesis (eq. 12), the presence of sodium iodide and a phenylsulfonyloxy group on the acceptor ring also improves the reaction yield significantly.[18]

(eq. 12)

		Yield
R = $CH_2C_6H_5$	i-$C_5H_{11}CNO$	20%
	1) i-$C_5H_{11}CNO$ 2) NaI	45%
R = $SO_2C_6H_5$	1) i-$C_5H_{11}CNO$ 2) NaI	64%

C. Nucleophilic Aromatic Substitutions

Nucleophilic substitutions rely on electron-withdrawing substituents in the substrates to stabilize the electron-rich intermediates. For example, the reaction under alkaline conditions of 2,6-di-t-butylphenol with nitrobenzenes bearing a leaving group leads to the formation of unsymmetric biaryls in good yields via nucleophilic aromatic substitution (eq. 13).[19] A. I. Meyers reported an aromatic

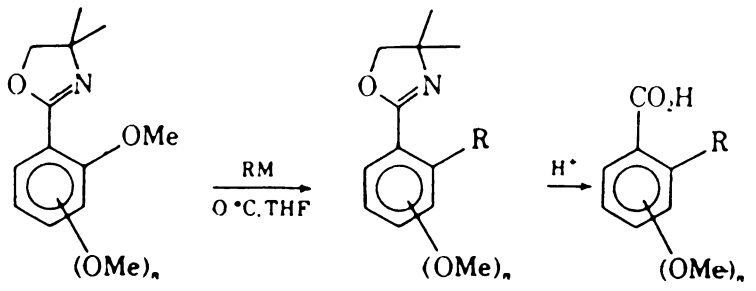


(eq. 13)

X = 2-halide, $-SO_2Ph$

4-NO_2, $-SO_2Ph$

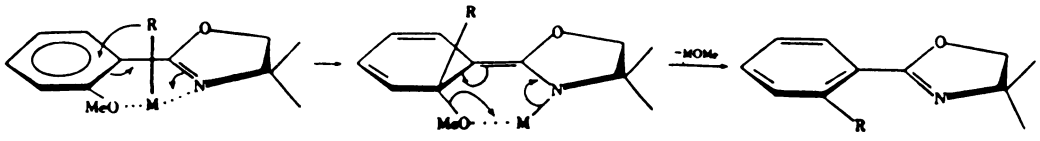
substitution process which involves an oxazoline function as the activating group.[20] It activates only organometallics capable of chelation and transfer of the nucleophile from a tight ion pair to the electrophilic site. For example, the reaction of an (o-methoxy)aryloxazoline with aryllithium or aryl Grignard reagent results in methoxy displacement to give o-(aryl)aryloxazolines, which can be



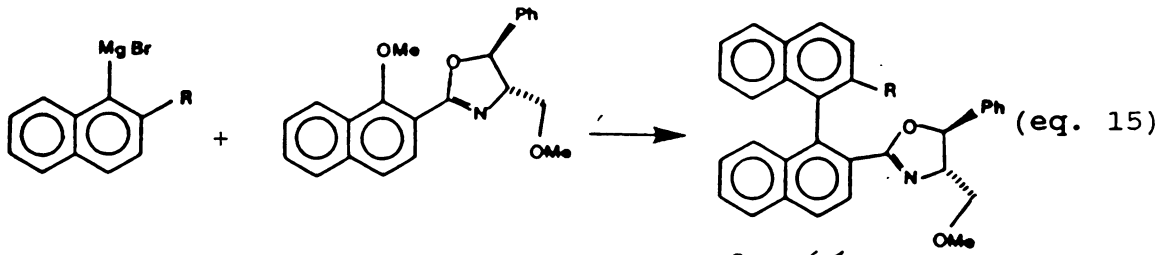
(eq. 14)

further hydrolysed to the corresponding benzoic acid derivatives (eq. 14). The reaction probably proceeds via an addition-elimination sequence (Scheme 2).

Scheme 2

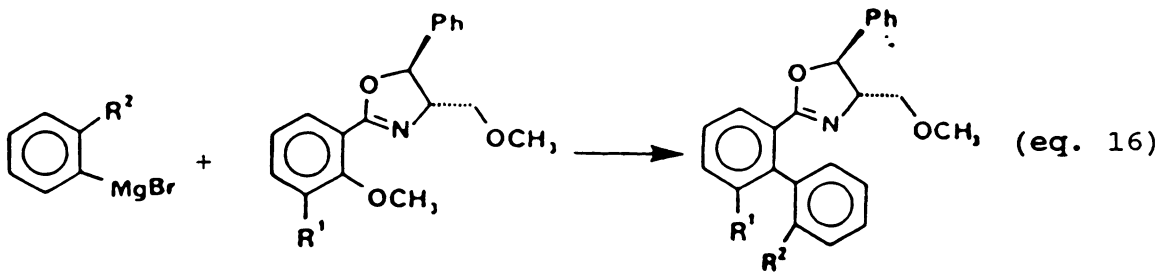


With chiral oxazolines, the aryl-organometallics can be directed to add enantioselectively to the o-methoxy-aryloxazolines to generate optically active products. For instance, the chiral 1,1'-binaphthyls[21] and the optically stable 2,2',6-trisubstituted biphenyls[22] are prepared in high enantiomeric excess (eq. 15 and 16). D. J. Cram[23]



(eq. 15)

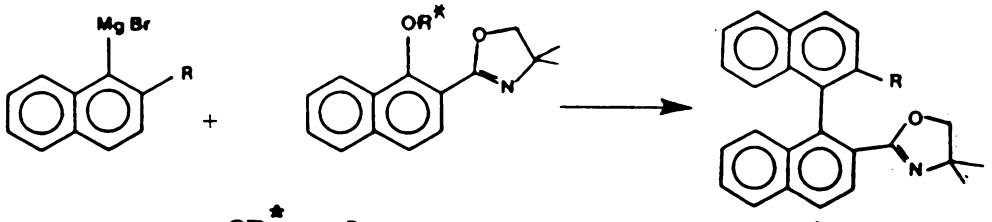
87-96% ee



(eq. 16)

developed a different methodology for introducing chirality via nucleophilic aromatic substitution, by utilizing naturally occuring chiral alcohol leaving groups. For

example, using the 1-menthoxy group as a chiral leaving group, chiral 1,1'-biphenyls are generated in good optical yields (eq. 17).



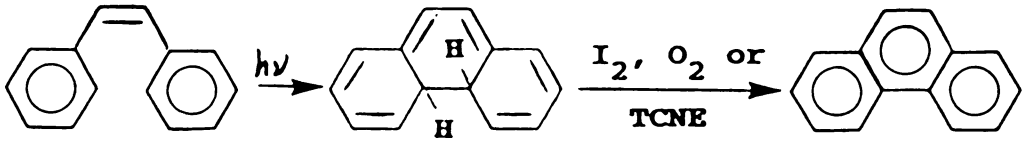
(eq. 17)

OR^* = 1-menthoxy

95% ee

D. Photocyclizations

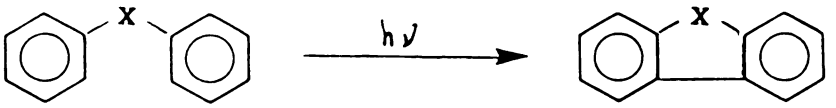
On UV irradiation in solution, cis-stilbene undergoes reversible photocyclization to give trans-4a,4b-dihydrophenanthrene. This intermediate that can be trapped oxidatively with hydrogen acceptors such as iodine, oxygen or tetracyanoethylene to give phenanthrene in high yield (eg 18).[24] This type of photocyclization occurs with a wide range of substituted stilbenes and related molecules, including various polycyclic and heterocyclic analogs. In



(eq. 18)

addition, certain systems with a single heteroatom (N, O or S) in place of the central carbon-carbon double bond also

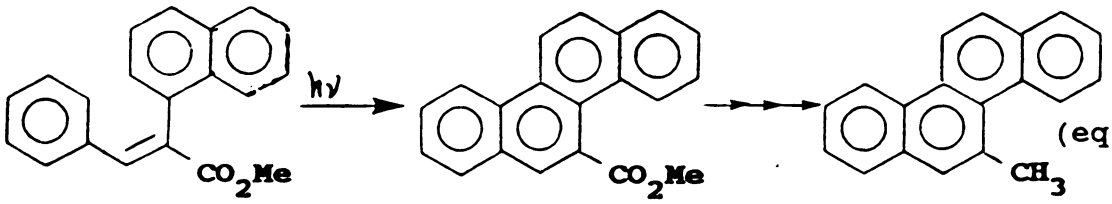
undergo photocyclization, creating a new five membered heterocyclic ring (eq 19).



(eq. 19)

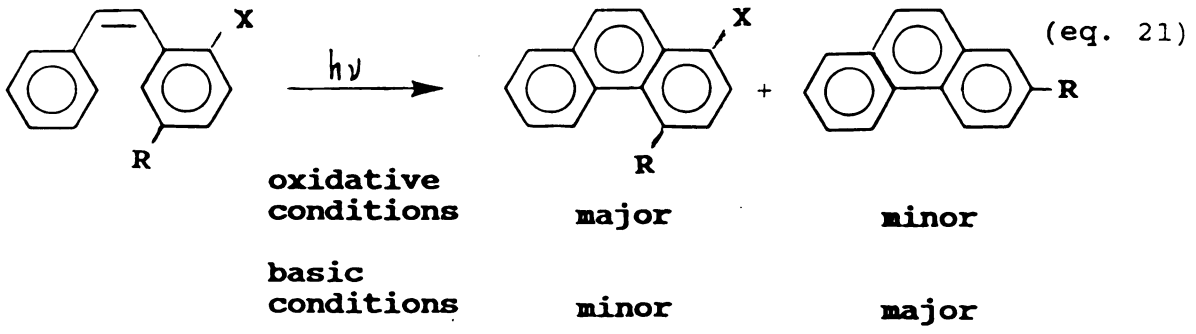
X = S, O, NH, $-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-$, $-N=N-$, $-\overset{\overset{H}{|}}{C}=N-$

Photocyclization is the preferred method for the synthesis of many different polynuclear aromatic systems. For example, in the synthesis of the biologically interesting 5-methylchrysene,[25] the photocyclization of methyl 3-phenyl-2-(1-naphthyl)propenoate to 5-carbomethoxychrysene is the key step in the synthetic sequence (eq. 20). In some cases, the regiochemistry of the photocycli-



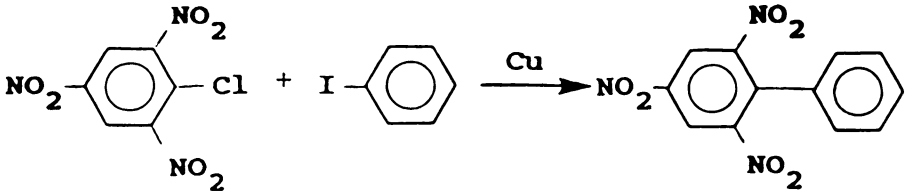
(eq. 20)

zation may be controlled by placing a halogen substituent in an ortho position, and by carrying out the reaction under the appropriate conditions. For instance, when an o-halostilbene[26] is photolyzed under oxidative conditions, the products are derived mainly from cyclodehydrogenation, whereas under basic conditions, the major products arise from cyclodehydrohalogenation (eq. 21).



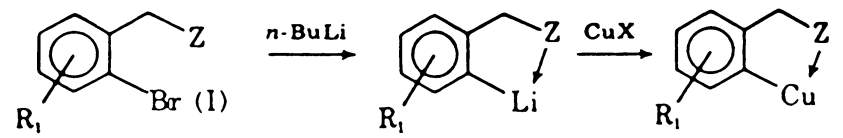
E. Transition-Metal Catalysed Coupling Reactions

The catalysis of coupling reactions with transition metals has received a great deal of attention in organic synthesis during last decade. One of the traditional reactions used to effect aryl-aryl bond construction is the Ullmann reaction, in which copper or copper oxide is employed as a catalyst to combine two aryl halides. In the case of cross-couplings, the yield of the Ullmann reaction is determined by the difference in reactivity between the two aryl halides. In general, electronegative groups such as nitro and methoxycarbonyl in the ortho position strongly activate the aryl halides; on the other hand, the reaction is greatly inhibited by substituents such as amino, hydroxyl and free carboxyl group. An optimum yield is usually obtained when one aryl halide is activated and the other is relatively unreactive. For example, the activated 2,4,6-trinitrochlorobenzene is condensed with iodobenzene to give the cross-coupled product in 80% yield (eq. 22).

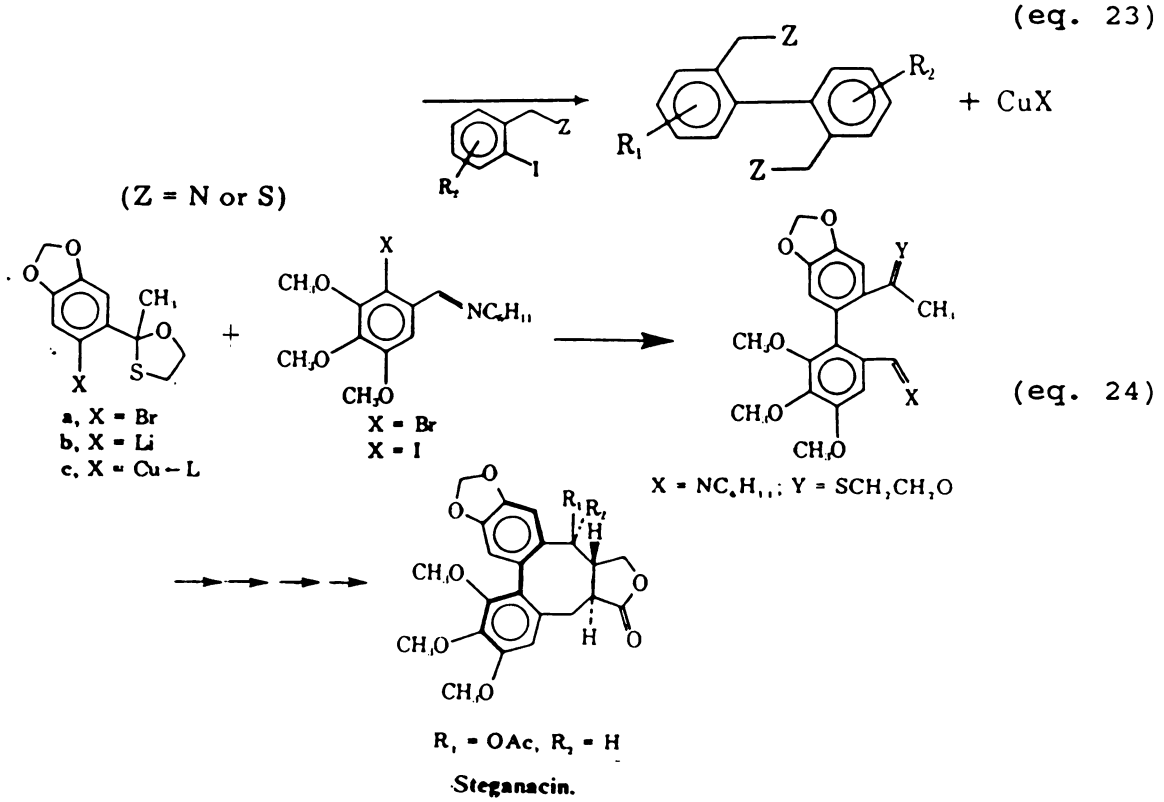


(eq. 22)

A recent modification[27] proceeding through an arylcopper intermediate requires a two-step sequence (eq. 23). A copper(I) aryl species stabilized intramolecularly by a heteroatom is generated from one aryl halide. It is then reacted with another aryl halide bearing an ortho substituent which may also function as a ligand. This modified pathway was successfully applied to the total synthesis of steganacin (eq. 24).[27]



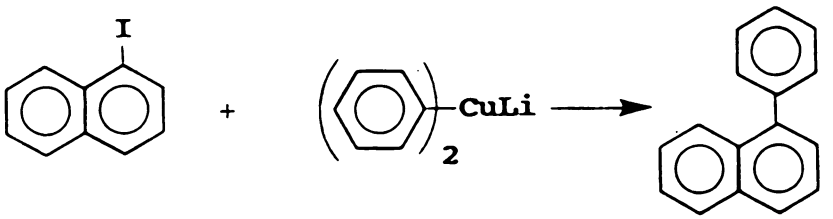
(eq. 23)



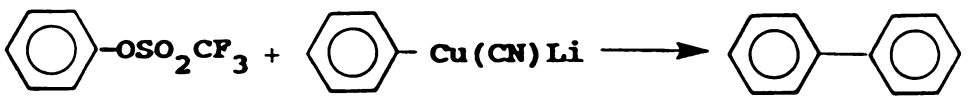
(eq. 24)

Another rapidly developing method for aryl-aryl bond formation is the coupling between an arylorganometallic and an aryl derivative catalyzed by a transition metal complex. In 1972, Kumada[28] and Corriu[29] reported that the cross-coupling of Grignard reagents with aryl and alkenyl halides could be catalyzed by nickel complexes. Since then a great deal of coupling methods[30] involving various organometallics and various organoderivatives have been developed, and some of them have been successfully adapted to the construction of aryl-aryl bonds. These include the reaction of lithium diphenylcuprate and aryl halides (eq. 25),[31] the condensation of a higher order mixed cuprate and the aryltriflate derived from phenol (eq. 26),[32] the reaction of aryl Grignard reagents and aryl halides catalyzed by nickel complexes (eq. 27),[33] the cross coupling of an arylzinc reagent and an aryl halide in the presence of a palladium or nickel catalyst (eq. 28),[34] the reaction of arylboronic acids and aryl halides catalyzed by palladium complexes (eq. 29),[35] the condensation of an aryl phosphate with an aryl Grignard reagent in presence of nickel (eq. 30),[36] the palladium-catalyzed electro-inductive coupling of aryl halides (eq. 31),[37] the nickel-induced reaction between an aryl ether and an arylmagnesium bromide (eq. 32),[38] aryl demetallation of aryltin reagents in the presence of palladium complexes (eq. 33),[39] the selective arylation of a bis(alkylthio)benzene with an aryl Grignard reagent catalyzed by nickel complexes (eq. 34),[40] the reaction of an

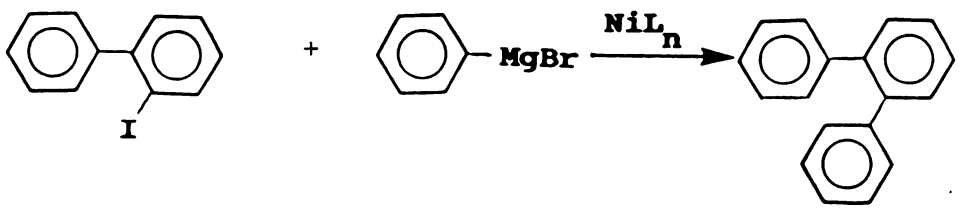
arylcopper and an aryl halide with a palladium catalyst (eq. 35),[41] and the arylation of a triphenylaluminum with an aryl halide using a palladium complex (eq. 36).[42]



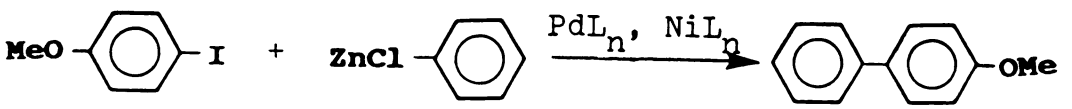
(eq. 25)



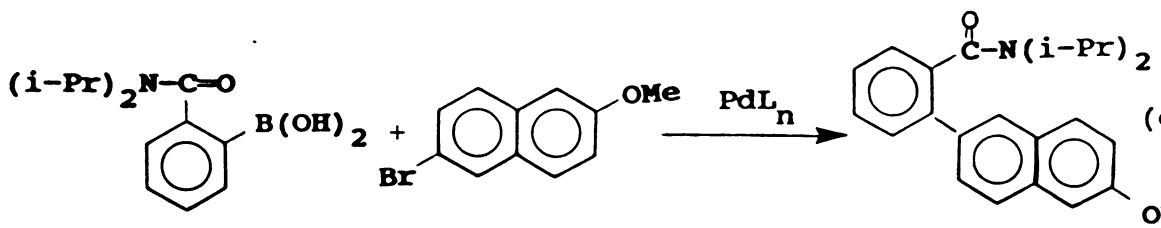
(eq. 26)



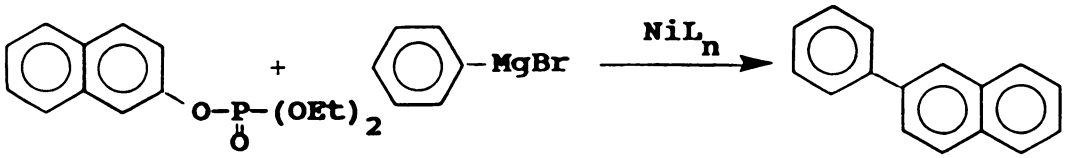
(eq. 27)



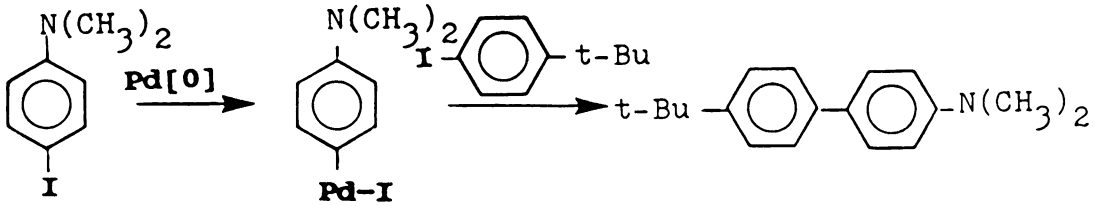
(eq. 28)



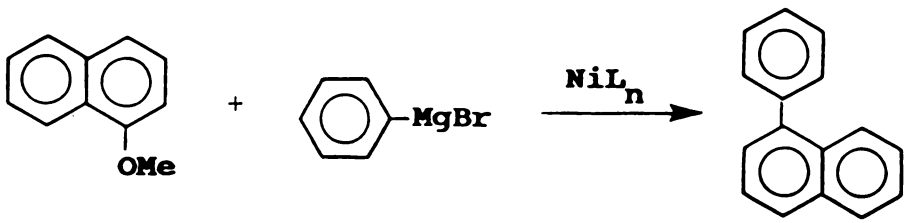
(eq. 29)



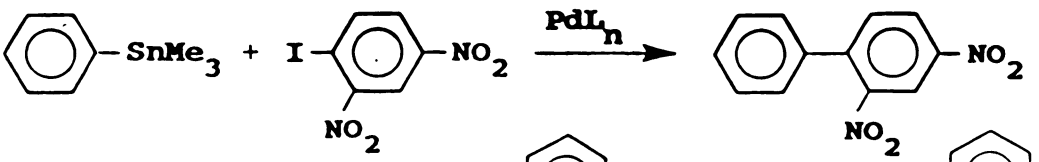
(eq. 30)



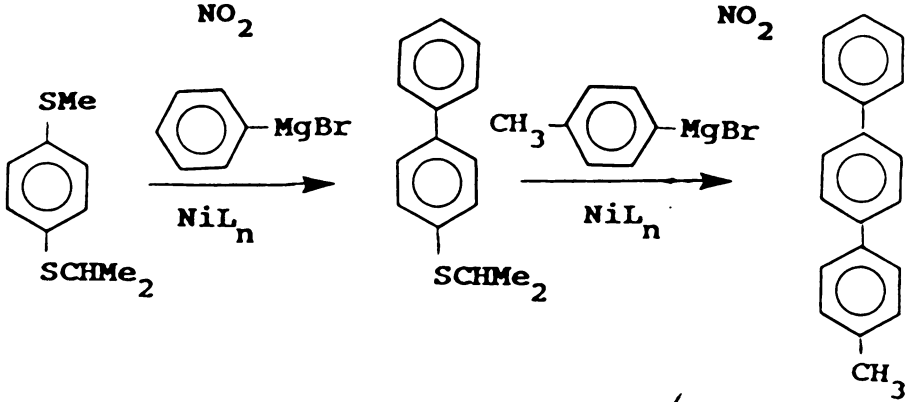
(eq. 31)



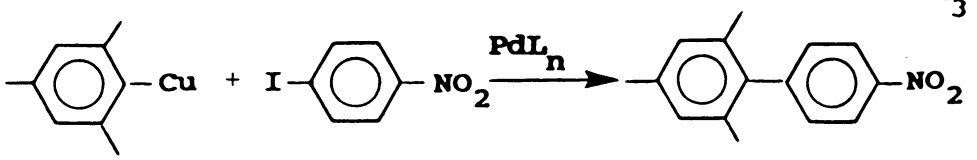
(eq. 32)



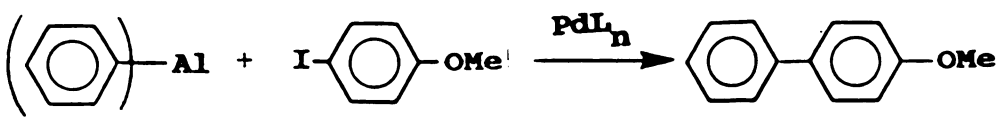
(eq. 33)



(eq. 34)



(eq. 35)



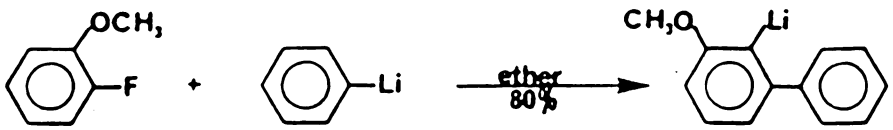
(eq. 36)

Plausible mechanisms for these coupling reactions involving transition metals as catalysts include oxidative addition, transmetallation and reductive elimination.[43]

F. Benzyne-mediated Arylations

Another method for aryl-aryl bond formation which has seen only limited synthetic use is the nucleophilic addition of an aryl lithium or other aryl organometallic to an aryne. The reaction was pioneered by Wittig, Huisgen and

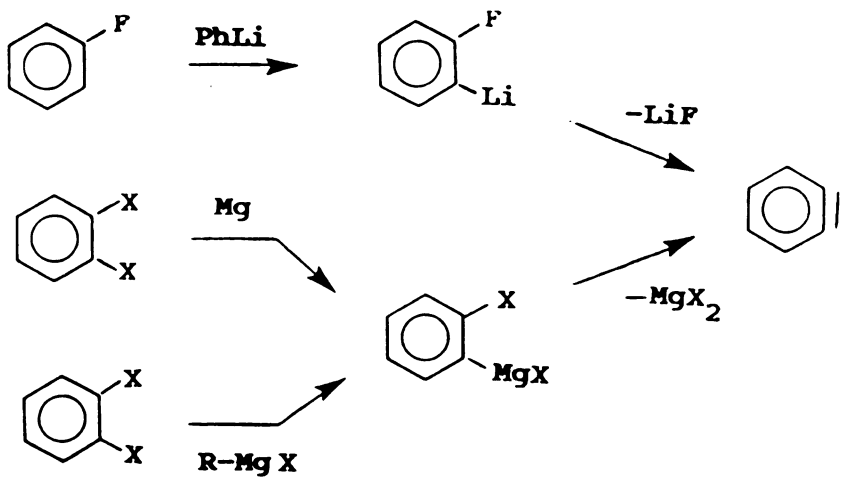
coworkers.[44,45] It was a key reaction in the early recognition of benzyne as a reactive intermediate,[46] but is usually looked upon as an unavoidable side reaction in the preparation, via aryl halides and phenyllithium, of arynes to be used for other purposes. However, the yield of biaryls by this route can sometimes be quite high, as in the following example (eq. 37).[47]



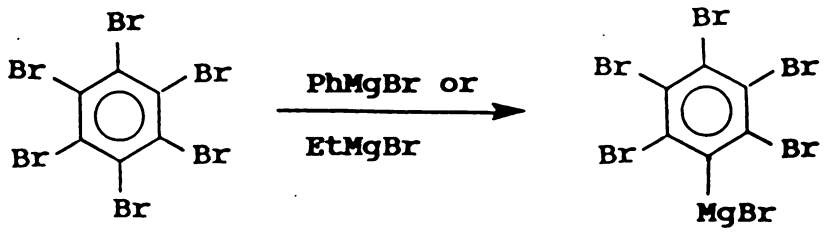
(eq. 37)

In this example, the intermediate aryne is formed by proton removal, but a similar result may be obtained when the aryne is generated from a 1,2-dihaloarene and magnesium metal by halogen-metal exchange (Scheme 3).[48] Though metal

Scheme 3



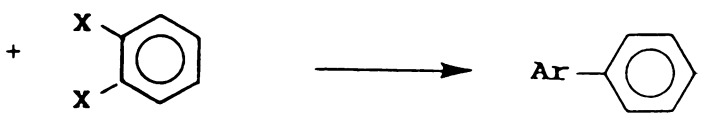
transfer between a polyhaloarene and an aryl or alkyl Grignard reagent has been observed (eq. 38),[49] o-bromophenylmagnesium bromide, the precursor of benzyne, has not been prepared by exchange between a dihaloarene and a Grignard reagent.



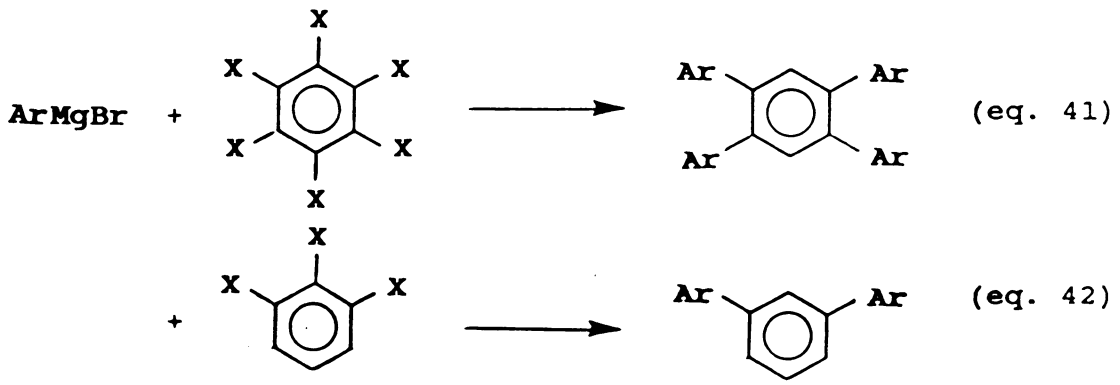
(eq. 38)

In connection with our interest in synthetic application of aryne chemistry, we studied the reaction of aryl Grignard reagents and polyhalogenated aromatics. We find that aryl Grignard reagents can be used to generate and trap arynes resulting in the formation of one or more aryl-aryl bonds in an one pot reaction. The reaction yields are satisfactory and comparable with the known literature methods outlined above. The main reactions that we have studied and that are to be discussed in detail in this thesis are presented below (eq. 39-42).

(eq. 39)



(eq. 40)



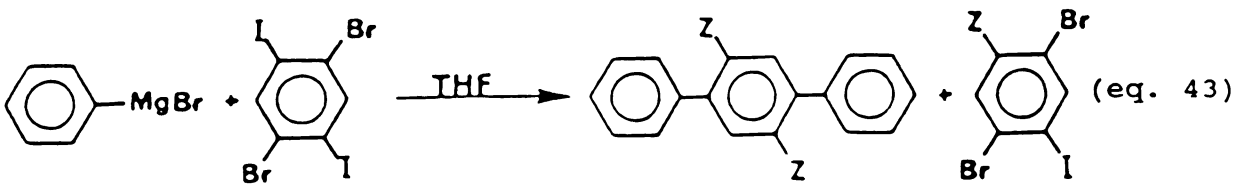
X= I, Br, Cl.

RESULTS AND DISCUSSION

A. A New Synthesis of p-Terphenyls

Because of their interesting structural, electronic and optical properties, p-terphenyls have many practical uses. For example, p-terphenyls, which have a rigid rod-like structure in the solid state, have been widely investigated for their liquid crystal properties.[50] The exposure of p-terphenyl to AsF_5 forms an electrically conducting complex which is a potential organic conductor.[51] The highly fluorescent p-terphenyls have also been used as liquid scintillators for radiation detection[52] and as laser dyes to generate short wavelength UV light.[53]

The whole spectrum of our discoveries originated from a study of the reaction between phenylmagnesium bromide and 1,4-dibromo-2,5-diiodobenzene **1**.[54] The addition at room temperature of a solution of **1** in THF to four equivalents or more of phenylmagnesium bromide, also in THF, gave, after an aqueous quench, p-terphenyl **3** (54%) and 1,4-dibromo-2-iodobenzene[55] **6** (43%) (eq. 43). Quenching with iodine gave instead the diiodoterphenyl **4** and the starting dibromo-diiodobenzene **1**. Hence, the actual reaction products are the terphenyl di-Grignard **2** and trihalomono-Grignard **5**. This



1

2 (Z = MgX) 5 (Z = MgX)

3 (Z = H) 6 (Z = H)

4 (Z = I) 1 (Z = I)

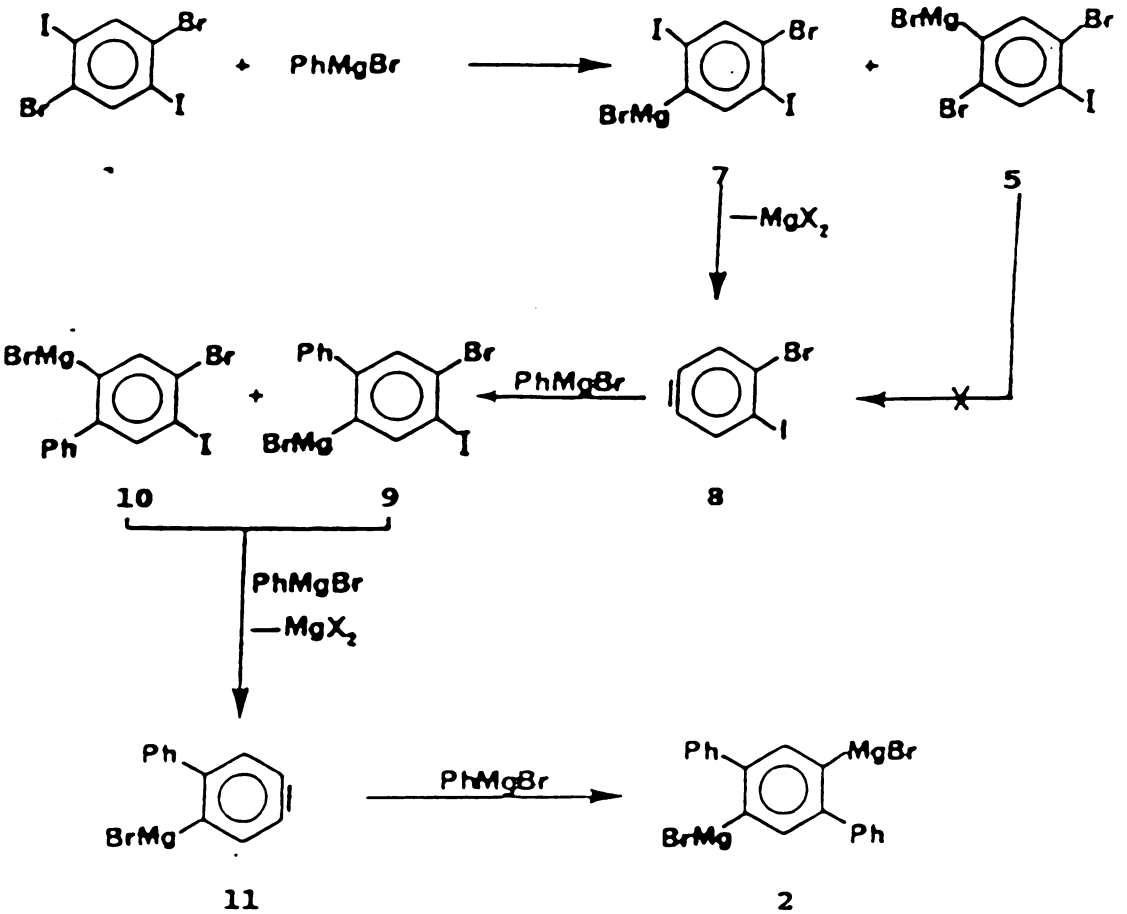
finding provides a new general method for the synthesis of p-terphenyls whose two outer rings are identical.

This new synthetic method has the following unique features (1) two aryl-aryl bonds are formed in a one-pot reaction, (2) although, regiochemically, the potential for forming m- and p-terphenyls exists, the latter predominate, (3) the reaction proceeds via a novel two aryne sequence, (4) aryl Grignard reagents are used to generate and to trap arynes and (5) the product terphenyl has functionality which allows elaboration of the central ring.

A.1. Reaction mechanism. Two plausible mechanisms were considered to account for our reaction. In the first mechanism we assume that Grignard exchange can occur either at iodine or bromine to obtain 5 or 7 respectively (Scheme 4). In this case we are forced to conclude that aryne formation from 5 does not occur at room temperature, so that 5 remains as one of the two observed reaction products, trapped with water or iodine to give 6 or 1. However, elimination must occur from 7 to give aryne 8 which is trapped by the Grignard reagent presumably to give 9 and/or

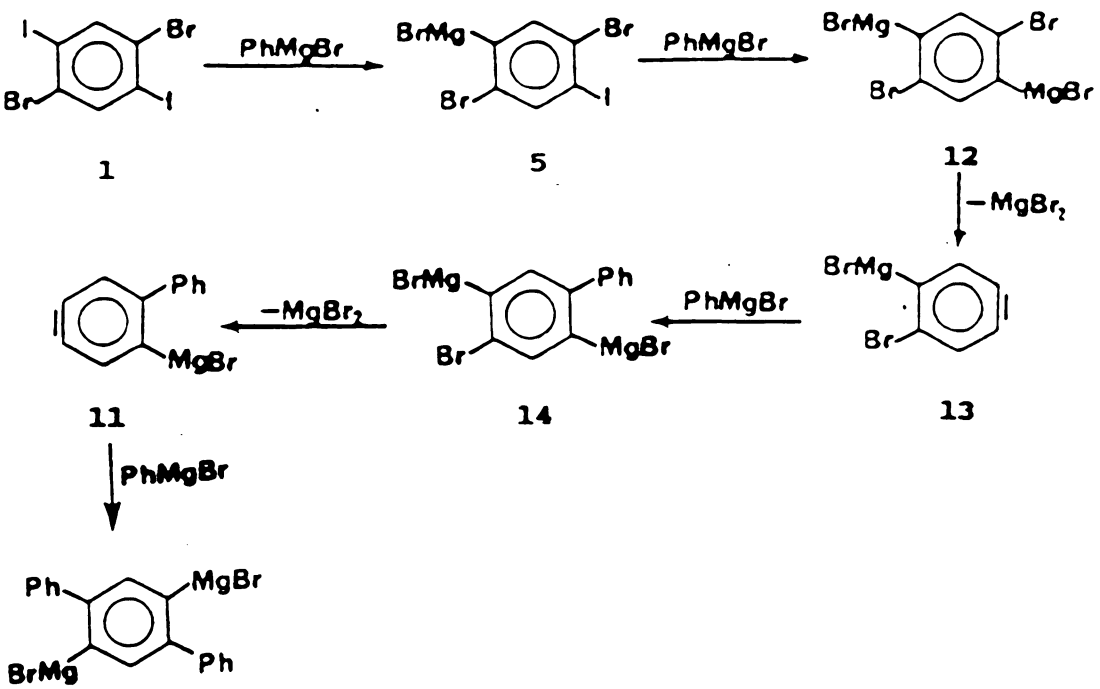
10. Grignard exchange and elimination is then repeated to give aryne 11 which is trapped to give the observed terphenyl di-Grignard product 2.

Scheme 4



An alternate mechanism is shown in Scheme 5. If we assume that Grignard exchange is more facile at iodine than at bromine, we then obtain first mono-Grignard 5, then di-Grignard 12. If this step (5→12) is slow, then some 5 may remain even in the presence of excess phenylmagnesium bromide. Intermediate 5 then leads to the observed products 6 or 1, whereas di-Grignard 12 leads to terphenyls 2 or 4 by reactions analogous to those in Scheme 4.

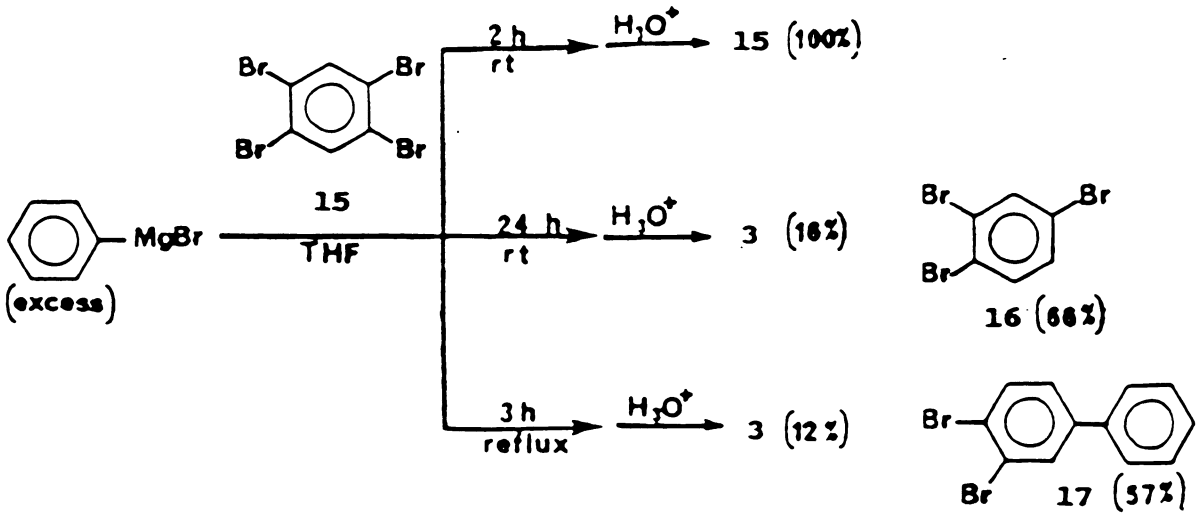
Scheme 5



Both mechanisms have certain common features. The exclusive formation of p-terphenyls (<1% of m-terphenyl is detectable by gas chromatography when the reaction mixture is quenched with water) implies that addition of phenylmagnesium bromide to the organometallic aryne intermediate (**11**→**2** in both Schemes, and presumably also **13**→**14** in Scheme 5) is regiospecific. This specificity probably arises from the importance of having like charges in **2** or **14**, and the transition states leading to them, as far apart as possible.

Several observations favor Scheme 5 over Scheme 4. For example, 1,2,4,5-tetrabromobenzene[56] **15** is not an effective replacement for **1** under the same reaction conditions, although under more severe reaction conditions it does give some p-terphenyl (Scheme 6). For example, phenylmagnesium

Scheme 6



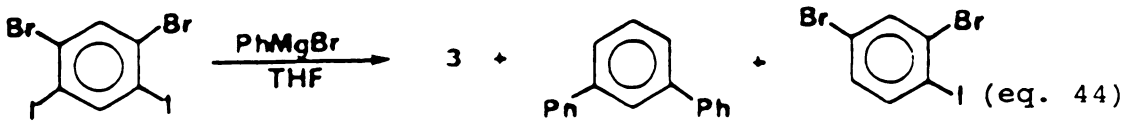
bromide and **15** at room temperature gave, after 2 hour, mainly recovered starting material. However after 24 hour, 16% of p-terphenyl and 66% of 1,2,4-tribromobenzene[57] were obtained after aqueous quench. After 3 hour at reflux (THF), 12% of p-terphenyl and 57% of 3,4-dibromobiphenyl[58] were obtained. Apparently Grignard exchange can occur at bromine, but it is very slow at room temperature. The resulting 2,4,5-tribromophenylmagnesium bromide remains at room temperature (to give 66% of **16**: if Scheme 4 is correct, a small amount is converted to di-Grignard and ultimately gives **3**). At reflux, however the tribromo-Grignard eliminates to give 4,5-dibromobenzyne, the precursor of biphenyl **17**.

These results suggest that Grignard exchange with **1** is more likely to occur at iodine than at bromine. This conclusion is reinforced by some low temperature results. Phenylmagnesium bromide (1.8 eq.) was added to one equiva-

lent of **1** at -78°C, stirred for 1 hour and quenched, to give 52% of recovered **1** and 43% of **6**. No terphenyl and no bromoiodobenzene was observed. Thus exchange appeared to be rapid at iodine even at -78°C, furnishing good evidence for **5** but not for **7**.

There is also some evidence for the formation of di-Grignard **12**. A similar experiment to that just described, but at -22°C gave after aqueous quench 73% of **6**, 1.1% of p-dibromobenzene and 6.4% of 1,2,4-tribromobenzene. The presence of p-dibromobenzene suggests that di-Grignard **12** is formed, though not to a great extent at -22°C. The formation of tribromobenzene suggests that the conversion of **5** to **12** is reversible (i.e., **12** can react with PhX to reform **5** when X=I or, if X=Br, its tribromo analog). Thus our mechanistic evidence indicates that Scheme 5 is a permissible mechanism; it also tends to argue against Scheme 4 in that we can find no direct evidence for **7**. However Scheme 4 cannot be entirely discounted, since some Grignard exchange does occur at bromine in the case of **15**. Still, it would seem that the major Grignard exchange occurs at iodine, favoring Scheme 5.

Both schemes postulate aryne intermediates. To check this out we carried out the reaction of phenylmagnesium bromide with 1,5-dibromo-2,4-diiodobenzene **18** in place of **1** (eq. 44). If the reaction follows a path analogous to Scheme 4, aryne **8** should be an intermediate; if it follows Scheme 5, **13** should be an intermediate. In either case we



(eq. 44)

18 **19** **20**

expect p-terphenyl to be formed even though like halogens in **18** are meta to each other instead of para, as in **1**. The situation is somewhat complicated by opposing factors in di-Grignard formation from **18**; preferred exchange at iodine would give a meta di-Grignard, whereas to keep like charges as far apart as possible, exchange at one iodine and one bromine might be favored. In fact, the predominant product after aqueous quench was p-terphenyl **3**; however some m-terphenyl **19** was also formed. As in the reaction with **1**, a dibromoiodobenzene, this time **20**,[60] was also formed. We think the results with **19** support the proposal of aryne intermediates in these reaction, but the precise origin of the minor amount of **19** from **18** requires further study.

A.2. Synthetic scope. A variety of aryl Grignard reagents react with **1** to give p-terphenyls. Table 1 summarizes the results. The reactions were carried out by adding a THF solution of **1** to four equivalents of the Grignard reagent at room temperature over modest addition times. Aqueous quench gave the terphenyl shown, as well as by-product **6**. The products were separated and purified by column chromatography and the yields shown (not optimized) are of pure, isolated products. Except for **25** which is new, the terphenyls had melting points which agree with those

Table 1. p-Terphenyls from Aryl Grignard Reagents and 1

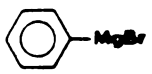
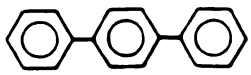
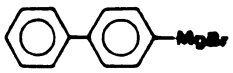
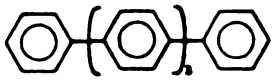
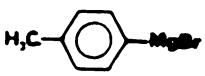
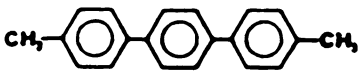
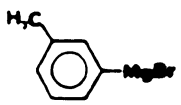
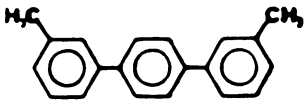
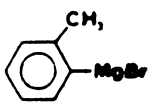
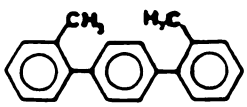
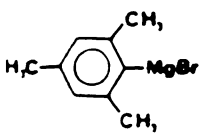
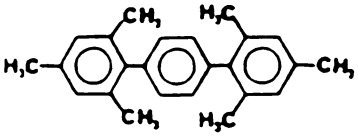
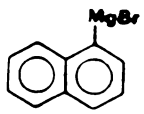
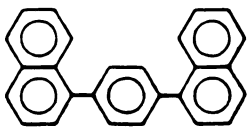
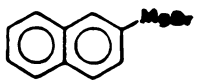
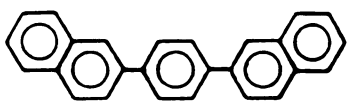
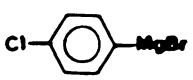
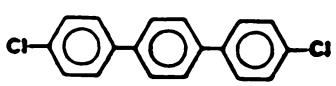
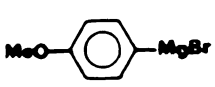
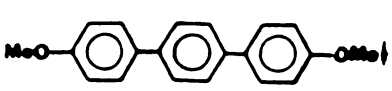
entry	Grignard reagent	reactn time, h	product	yield %	m.p.	ref.
1		2.5		54	212-213	61
			3			
2		1.0		53	387-388	62
			21			
3		3.0		53	248-249	63
			22			
4		3.0		50	141	64
			23			
5		3.0		45	145.5-146	65
			24			
6		6.0		49	181-183	
			25			

Table 1. (Cont'd)

7		2.5		30	206-207	66
			26			
8		4.0		35	259-260	63
			27			
9		4.0		43	283.5	67
			28			
10		3.0		30	273-274	68
			29			

reported in the literature, and spectra consistent with the assigned structures.

There are several types of p-terphenyl syntheses in the literature. Our method in general provides a simpler and shorter route and gives as good or better overall yields than all of the literature methods for the known p-terphenyls in Table 1. One especially noteworthy example is the much simplified synthesis of p-quinquephenyl **21** over the Organic Syntheses procedure.[62] The preparation of **24** and **25** in fairly good yield also shows that the reaction is not particularly susceptible to steric factors.

It is clear at this stage that although p-terphenyls can easily be prepared in one step by this method, the reaction as so far described has an annoying feature, namely the formation of by-product **6**. The products are in fact the di-Grignard **2** and the mono-Grignard **5**, so that efforts to elaborate **2** with electrophiles other than the proton would be hampered by the simultaneous elaboration of **5**, leading to separation problems. We therefore sought a method to eliminate the undesired by-product.

This objective was achieved in several ways. The best to date is to carry out the reaction between **1** and the aryl Grignard reagent in the usual way (1:4 mol ratio), and then to add one equivalent of either lithium tetramethylpiperidide (LiTMP) or potassium t-butoxide to complete the reaction. In this way, the yields of **3**, **22** and **24** were increased to 75-80% and very little or no **6** was present in

the final product. Exactly how these reagents function remains to be clarified.

It should be mentioned that replacement of the aryl Grignard by an aryllithium does not improve the synthesis. Indeed, using the same reaction conditions as for the experiments in Table 1, the yield of p-terphenyl from **1** and phenyllithium was only 12-23%. The reason why Grignard reagents are superior to aryllithiums is a subject that requires study.

B. The Synthesis of Unsymmetric Biaryls

Since the extensive studies on the rotational energy barriers and substituent effects on the racemization of chiral biphenyls in the 1930s[69] until, very recently, with the total synthesis of the potent antileukemic lignan like stegane,[70] compounds with a biphenyl skeleton have attracted chemists' attention. All of the methods described in the introduction section can be adapted to the construction of unsymmetric biphenyls, but each method has limitations. The best synthetic route to a particular biphenyl depends on its structure. As mentioned, nucleophilic addition of aryl organometallics to arynes is one method to effect the aryl-aryl bond formation. Its most attractive feature is that the aromatic ring derived from the polyhalobenzene subtrate possesses an organometallic functionality adjacent to the newly formed aryl-aryl bond in the final product. Elaboration of this funtionality with various electrophiles is the unique synthetic characteristic which broadens the scope of our method.

The reaction of aryl Grignard reagents with o-dihalobenzenes can be readily extended to the unsymmetric biaryl synthesis. A diluted solution of o-dihalobenzene in THF was added to 2 equivalents (or more) of an arylmagnesium bromide at room temperature. The reaction mixture was

stirred for several hours, followed by electrophilic workup. The results are summarized in Table 2.

Several features of the results are worthy of mention. Comparison of entry 3 with entries 1 and 2 shows that at least one iodine is needed on the dihaloarene under these mild reaction conditions. This suggests that Grignard exchange occurs mainly at iodine (see Scheme 5). Comparison of entries 5 and 6 or 9 and 10 illustrates how capture of the o-biaryl Grignard product with different electrophiles can be useful. Entries 6 and 7 illustrate how a complementary choice of iodobromoarene and Grignard reagent, followed by quench with an electrophile, can place the latter at the ortho position of either aryl ring (extentions, for example, to the synthesis of specifically labeled, i.e. deuterated, biaryls are obvious). Comparison of entries 8 and 9 illustrates how the yield may be improved, in some instances, by adding one equivalent of LiTMP to the reaction mixture prior to workup.

The bromoiodoarenes in Table 2 were selected such that the derived aryne would be symmetric and give a single product on nucleophilic addition of the Grignard reagent. They were also selected, in this initial study, for their ease of synthesis.

All of the reactions listed in Table 2 are presumed to proceed via Scheme 7. Following initial Grignard exchange at iodine to give **51**, loss of MgXBr to furnish arynes **52** is apparently rapid at room temperature, since little or no by-

Table 2. Biaryls from Aryl Grignard reagents and o-Dihaloarenes

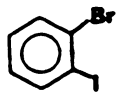
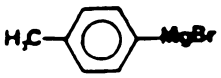
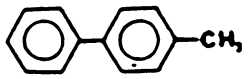
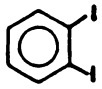
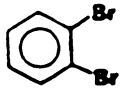
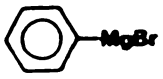
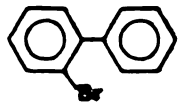
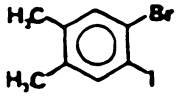
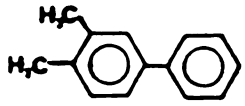
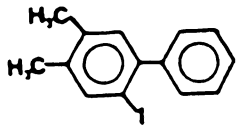
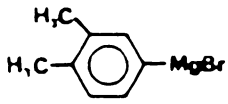
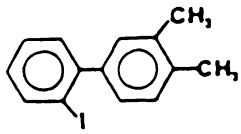
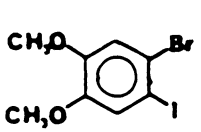
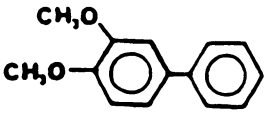
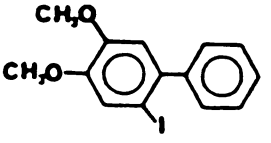
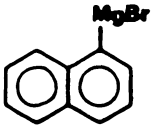
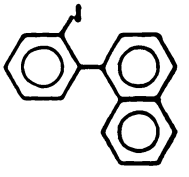
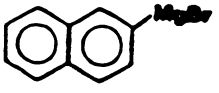
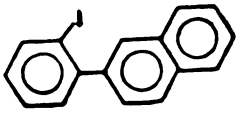
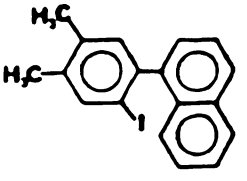
entry	dihalo-arene	Grignard reagent	procedure /quench	product	yield %	ref.
1	 **30**	 **35**	B/H_2O	 **40**	71	71
2	 **31**	**35**	B/H_2O	**40**	69	
3	 **32**	**35**	B/H_2O	---[b]		
4	**30**	 **36**	B/Br_2	 **41**	63	72
5	 **33**	**36**	B/H_2O	 **42**	66	73
6	**33**	**36**	B/I_2	 **43**	65	
7	**30**	 **37**	B/I_2	 **44**	64	

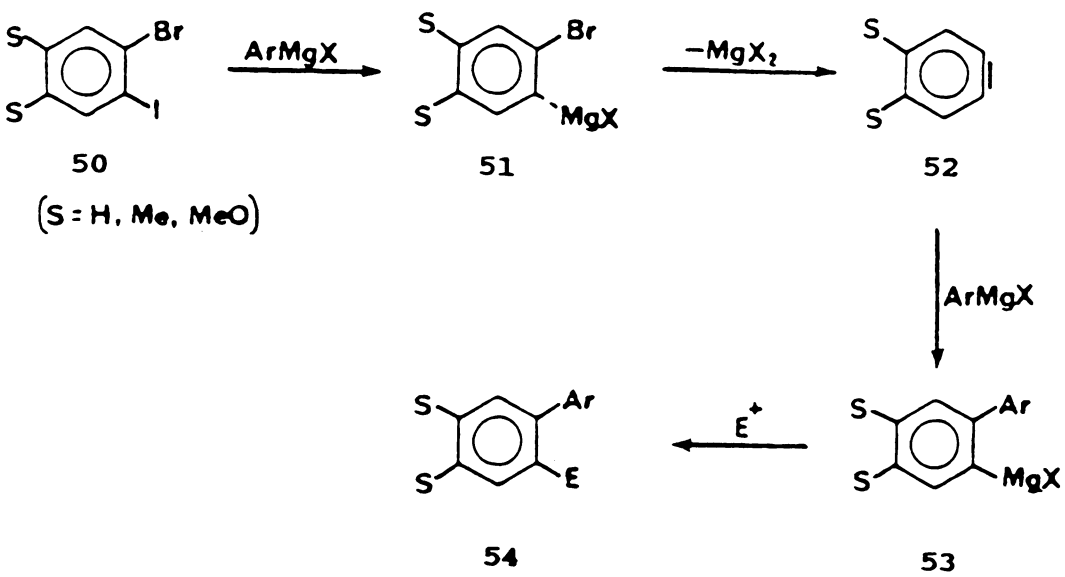
Table 2. (Cont'd)

8	 **34**	36	B/H_2O	 **45**	37	74
9	**34**	36	C/H_2O	**45**	69	
10	**34**	36	C/I_2	 **46**	58	74
11	**30**	 **38**	C/I_2	 **47**	64	75
12	**30**	 **39**	C/I_2	 **48**	60	
13	**33**	**38**	C/I_2	 **49**	63	

[a] In procedure C, LiTMP was added prior to quenching. [b] No biphenyl was isolated and >75% of 32 was recovered.

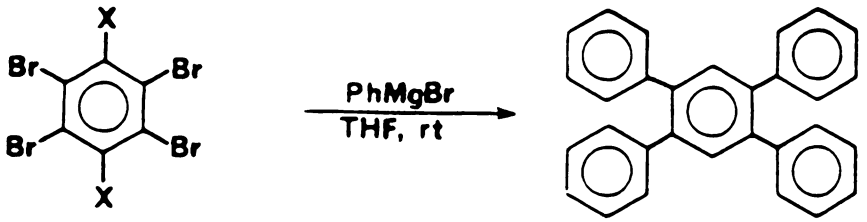
product correponding to the reaction of **51** with the quenching electrophile was observed. This was true when the substituent S was H, Me or MeO, as in all of the entries in Table 2. It is somewhat disturbing, then, to recall that when one S is bromine and the other is iodine (as in **5** or in the Grignard precursor of **20**), aryne is apparently not formed from the mono-Grignard under very similar conditions (that is, **6** and **20**, and not bromoiodobiphenyls, are the main by-products of the p-terphenyl synthesis. Perhaps the electron-withdrawing halogen substituents in these particular substrates stabilize **51** whereas electron-donors such as Me and MeO favor aryne formation. Other features that require further study are the role of the metal (Mg or Li, for example), of the counterion X in ArMgX, and the yield-enhancing effect of LiTMP and KO-t-Bu.

Scheme 7



C. A New Synthesis of 1,2,4,5-tetraarylbenzenes.

In continuing our study of the reaction of aryl Grignard reagents with polyhaloarenes, we observed that the reaction of excess aryl Grignard reagents with hexabromobenzene (or with dichlorotetrabromobenzenes) in THF solution at room temperature gave a good yield of 1,2,4,5-tetraarylarenes compounds not readily available by any other method (eq. 45). In a literature survey, it was found that



55 (X = Br)

56 (X = Cl)

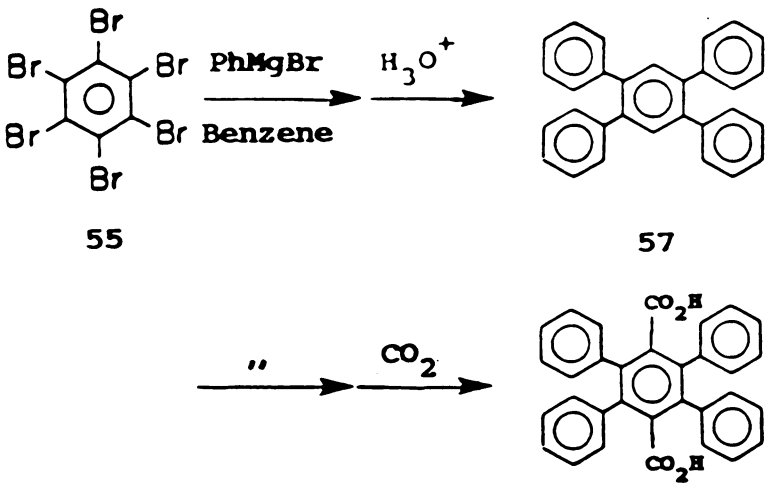
57 (57-65%)

(eq. 45)

the origins of this chemistry are quite old. Durand reported that hexabromobenzene 55 reacts with phenylmagmesium bromide to give hexaphenylbenzene,[76] but shortly afterwards, Dilthey showed through independent synthesis that the product was in fact 1,2,4,5-tetraphenylbenzene 57.[77] Geissman confirmed these results,[78] and showed through obtaining 1,2,4,5-tetraphenylbenzene-3,6-dicarboxylic acid on carbonation that the actual reaction product was the tetraphenyl-1,4-diGrignard (Scheme 8). In these early studies, the solvents

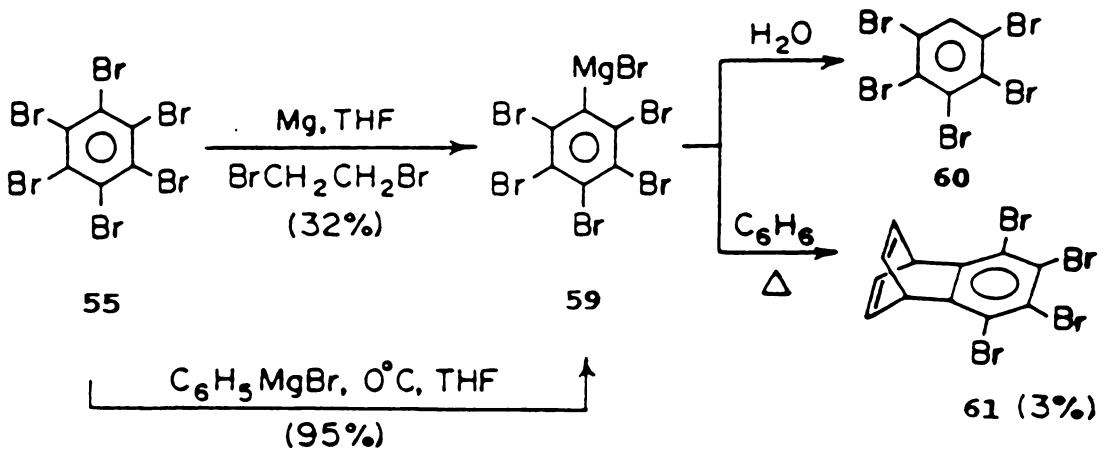
were ether, in which 55 is nearly insoluble, or benzene, a poor Grignard solvent. It is not surprising, then, that the product yields were well below 10% and that considerable tars were formed.

Scheme 8



Thirty years later, Berry and Wakefield treated 55 with magnesium in tetrahydrofuran (THF) using 1,2-dibromoethane as the entrainer and obtained pentabromophenylmagnesium bromide 59 in 32% yield (based on aqueous quench to give

Scheme 9



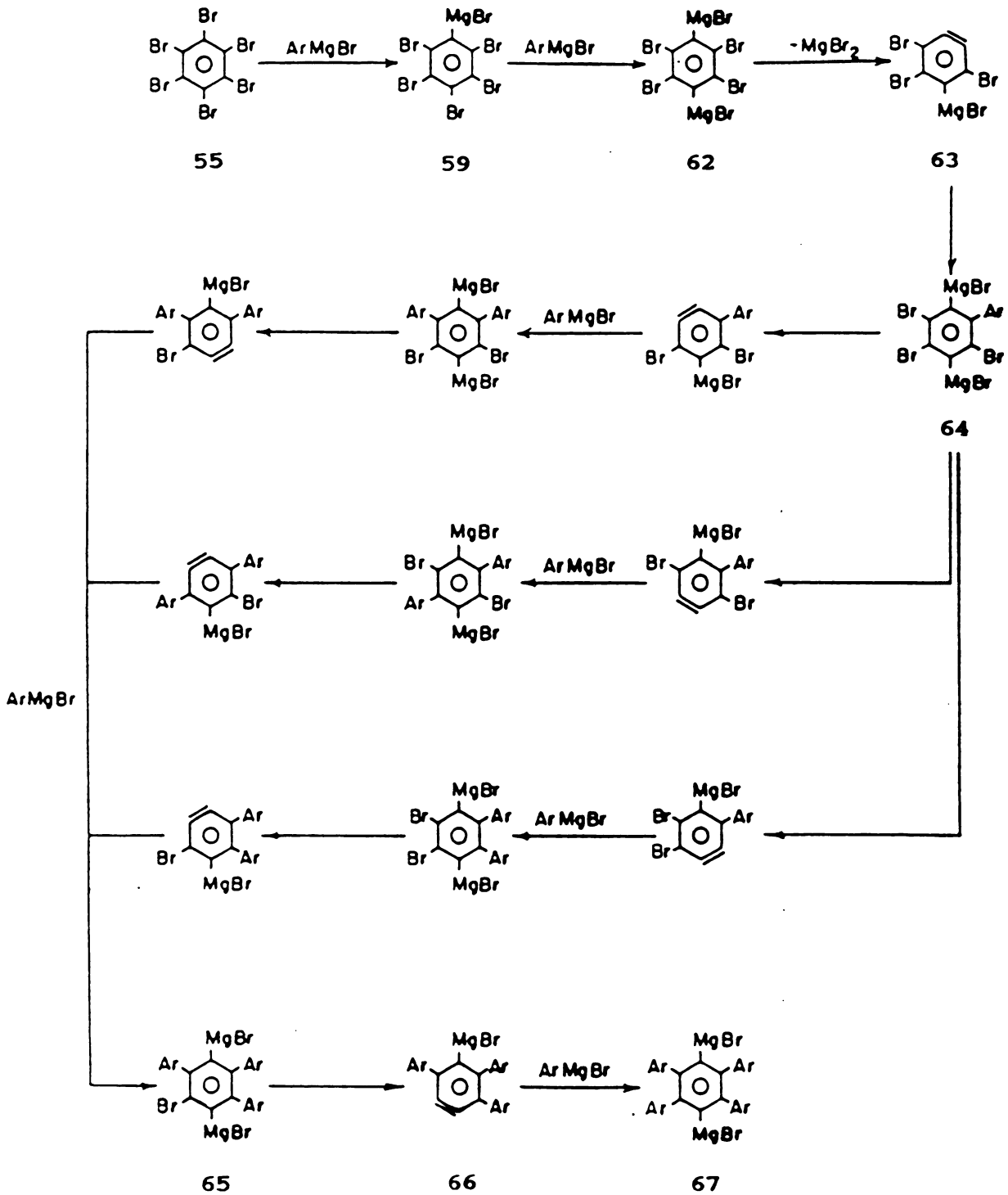
pentabromobenzene); with ether as the solvent, the yield was under 5%.[79] Significant for our work (Scheme 9), they found that if the solution of **59** was heated at reflux with benzene prior to the aqueous quench, a 3% yield of tetrabromobenzobarrelene **61** was obtained. Thus, at reflux **59** eliminated magnesium bromide to give some tetrabromobenzyne.

A little later, Tamborski and coworkers reported that the conversion of **55** to **59** could be greatly improved using exchange with phenyl- or ethylmagnesium bromide in place of magnesium.[49] The yield was better when the reaction was run in THF than in diethyl ether. In addition, a substantial amount (51%) of 1,2,4,5-tetrabromophenyl-bis-magnesium bromide **62** was formed when 2 equivalents of ethylmagnesium bromide were employed in the exchange process.

The synthesis of tetraarylarenes from aryl Grignard reagents and hexahalobenzenes (Durand and Geissman's reaction) had no synthetic importance owing to the low reaction yield. This situation changed when we found that the yield improved dramatically with THF as the solvent. Also, since the actual reaction product is a di-Grignard reagent, elaboration of the final product by treatment with various electrophiles broadens the reaction's synthetic scope.

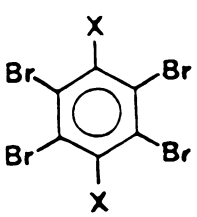
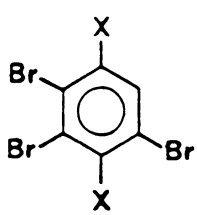
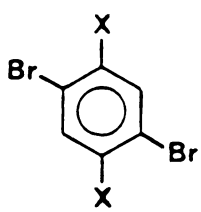
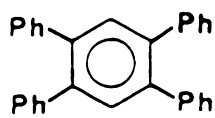
C.1. Mechanism. The mechanism we propose involves as key intermediates the 1,4-di-Grignard reagent **62** and various organometallic arynes as outlined for hexabromobenzene in

Scheme 10



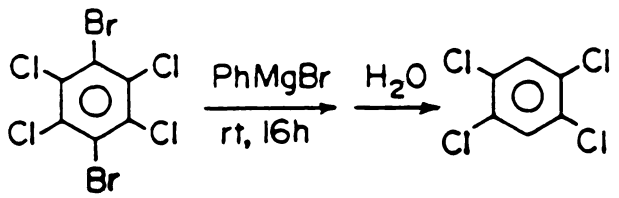
Scheme 10. As already mentioned the rapid formation of **59** from **55** and phenylmagnesium bromide is well established. We found that with excess phenylmagnesium bromide and low reaction temperatures, the presence of substantial amounts of the 1,4-di-Grignard also can be demonstrated, as shown by the quenching results in Table 3. When X=Cl, only the bromines exchanged, and the 1,4-di-Grignard was the principal product. The mechanism of such Grignard exchange is not well established, but we believe that other factors being equal, the isomer with the charges as far apart as possible is preferred. The results in Table 3 show that under the same conditions, more di-Grignard is formed when X=Br than when X=Cl. The results in Table 3 establish the plausibility of the first two steps in Scheme 10.

Table 3 Reaction of Hexahaloarenes with PhMgBr at 7°C[a]

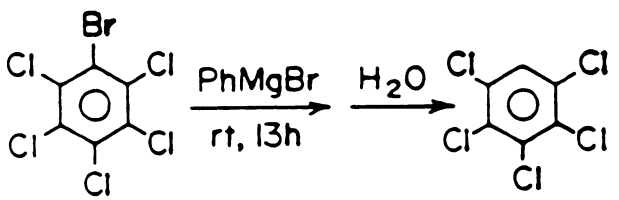
substrate	products after aqueous quench, %		
			
X=Br	26	32	22
X=Cl	58	27	8

[a] Substrate (2.5 mmol) and phenylmagnesium bromide (15 mmol) in 80 mL of THF were stirred at 7°C for 4 h, then quenched with water and the product mixture analyzed by gas chramatography.

The observation that Grignard exchange occurs at bromine but not at chlorine in **56** was used to test the proposal in Scheme 10 that di-Grignard formation is essential to the tetraarylation reaction. At least two bromines must be present on the bromochloroarene. Thus, dibromotetrachlorobenzene **68** reacts with phenylmagnesium bromide to give **57**[81] (eq. 46); on the other hand, bromopentachlorobenzene **70** gives, under the same conditions, only pentachlorobenzene **71** (eq.47). These observations tend to confirm the proposal in Scheme 10 that the product derives from the di-Grignard **62** and not from the monoGrignard **59**.



68 **69 (61%)** + **57 (36%)** (eq. 46)



70 **71** (eq. 47)

The remaining reactions in Scheme 10, once **62** is formed, involve one main assumption, i.e., that the addition of an arylmagnesium bromide to the intermediate organometallic arynes (i.e., **63**, **66** and so on) occurs regiospecfically always to give a 1,4-(and not a 1,3-) di-Grignard. Thus,

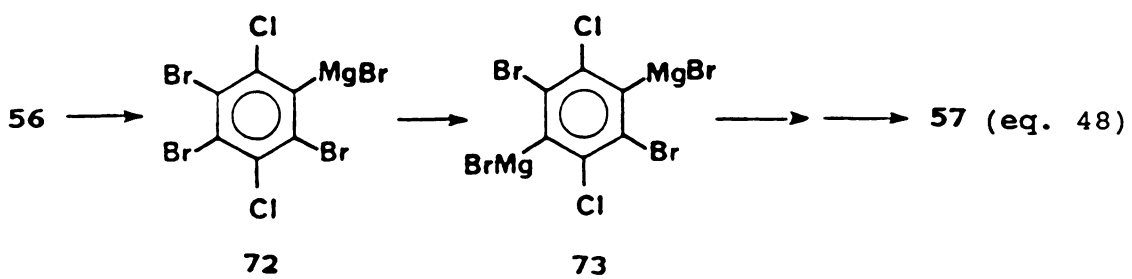
after aryne formation from **62** and Grignard addition, we obtain only di-Grignard **64** which may give three possible arynes. Each of these in turn can give but a single diaryl di-Grignard. Each of these di-Grignards can give only one aryne, and addition of aryl Grignard to any of these three arynes will give only **65** which leads to the observed 1,2,4,5-tetraaryl di-Grignard **67**.

Regiospecificity in the nucleophilic addition of aryl Grignards to the various organometallic arynes in Scheme 10 may be a consequence of two factors. One of these is the maintenance of like charges in the di-Grignards as far apart as possible. The second is the electronic effect of substituents (especially the organometallic substituent) on the charge distribution in the aryne intermediates. If, of the two aryne carbons, the one most remote from the organometallic substituent is the most negative, then a nucleophile will always attack meta to the organometallic substituent, giving the para-di-Grignard. Whatever the reason, the observed specificity is remarkable; only 1,2,4,5-tetraarylbenzenes are formed.

Although it is possible to arrive at product **67** from the mono-Grignard **59** by loss of magnesium bromide to give tetrabromobenzyne, this alternative mechanism requires, in its early stages, some arbitrary choices regarding the regiochemistry of nucleophilic addition to neutral arynes. In its later stages, this mechnism requires arbitrary regiochemistry in the Grignard exchange reaction. Finally at

the di-Grignard stage, which is eventually necessary, it requires the same regiospecificity assumption as outlined in Scheme 10. Without these multiple assumptions, it would be difficult to rationalize why the two regioisomers of **67** (*i.e.*, 1,2,3,5- and 1,2,3,4-tetraarylbenzene) as well as pentaarylphenylmagnesium bromide are not also observed as products.

We therefore believe that Scheme 10 is essentially correct and that di-Grignard **62** is a necessary intermediate in the reaction mechanism. We cannot tell, however, whether all of the multiple paths between **64** and **65** are essential or whether there is a preference among them. Finally, it should be noted that when 1,2,4,5-tetrabromo-3,6-dichlorobenzene **56** is used in place of hexabromobenzene, Scheme 10 must be modified. The first Grignard exchange presumely occurs at bromine to give **72** and the second exchange would then give **73**. One can proceed to **67** by steps analogous to those in Scheme 10, except that aryne can be formed from **73** by elimination of either bromide or chloride, making the mechanism similar to, but formally somewhat more complex than, Scheme 10 (eq. 48).



Since many of the intermediates proposed in Scheme 10 are nucleophiles, as is the final product **67**, they could replace the original arylmagnesium bromide reagent in adding to the intermediate arynes, leading to a complex mixture of products. The original reagent is present in large excess, however, so its addition predominates. In this way, the good yields reported in Table 4 are obtained. Some higher molecular weight by-products are formed, however, perhaps in the manner just indicated. They are easily removed from the desired product through chromatography.

C.2. Synthetic Scope. Addition of a THF solution of hexabromobenzene to eight equivalents of phenylmagnesium bromide in the same solvent at room temperature, followed by stirring for 12 h, gave, after hydrolysis. A 57% yield of 1,2,4,5-tetraphenylbenzene **57**. The less expensive precursor 1,2,4,5-tetrabromo-3,6-dichlorobenzene **56**, under the same conditions, gave a 65% of **57**. In general, reactions with **56** tended to be cleaner in workup that those with **55**. Other aryl Grignard reagents gave analogous products, as summarized in Table 4.

Except for the first entry, all of the products in Table 4 are new compounds. Their structures rest on elemental analysis and mass spectra, on analogy with the first entry, and for those products with methyl substituents, on the symmetry required of their proton NMR spectra. For example, **74**, **75** and **76** each showed sharp 12-proton singlets for the methyl protons (at δ 2.33, 2.27 and

Table 4. Tetraarylarenes from Aryl Grignard Reagents and Hexahalobenzenes

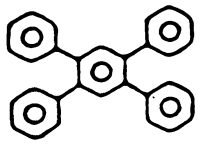
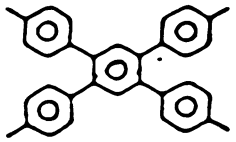
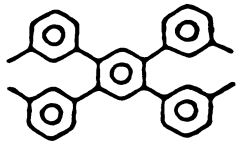
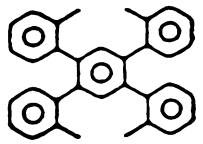
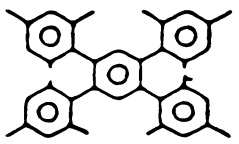
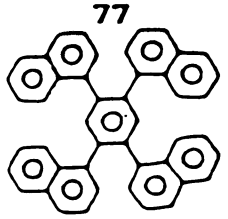
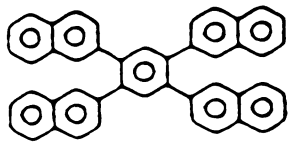
entry	hexahalo-arene	Grignard reagent	product	yield %	m.p. °C
1	55	C_6H_5-MgBr	 **57**	57(65)	267-268
2	56	p-CH_3-C_6H_4-MgBr	 **74**	73	247-249
3	56	m-CH_3-C_6H_4-MgBr	 **75**	71	157-158
4	56	o-CH_3-C_6H_4-MgBr	 **76**	70	205-206
5	55	2,4,6-$(CH_3)_3$-C_6H_2-MgBr	 **77**	30	258-259
6	56	1-$C_{10}H_7$-MgBr	 **78**	50	352-355
7	56	2-$C_{10}H_7$-MgBr	 **79**	57	324-325

Table 4. (Cont'd)

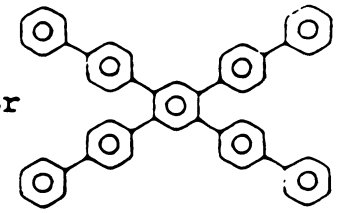
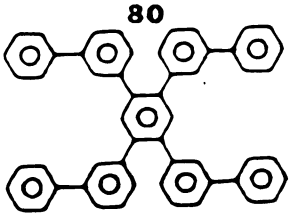
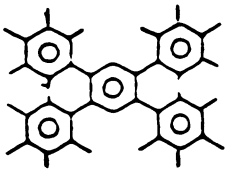
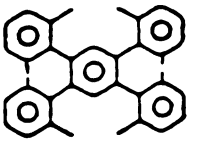
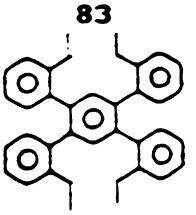
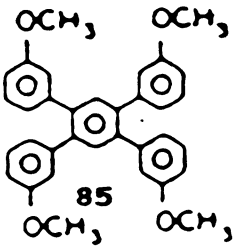
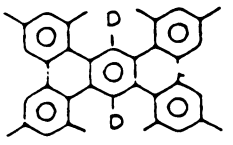
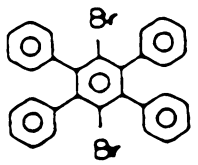
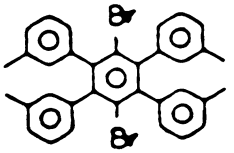
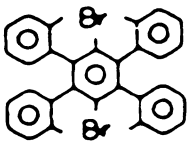
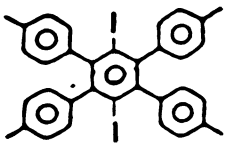
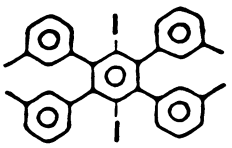
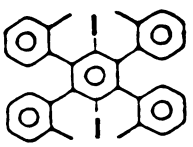
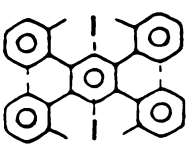
8	56	4-C_6H_5-C_6H_4-MgBr	 **80**	52	380-381
9	56	3-C_6H_5-C_6H_4-MgBr	 **81**	62	257-259
10	55	$(CH_3)_5$-C_6-MgBr	 **82**	57	376-378
11	55	2,6-$(CH_3)_2$-C_6H_3-MgBr	 **83**	52	288-290
12	55	o-(CH_3CH_2)-C_6H_4-MgBr	 **84**	50	223-225
13	56	m-CH_3O-C_6H_4-MgBr	 **85**	57	199-200
14	55	2,4,6-$(CH_3)_3$-C_6H_2-MgBr	 **86**	30	258-259

Table 4. (cont'd)

15	56	C_6H_5-MgBr		50	423-424
			87		
16	56	m-CH_3-C_6H_4-MgBr		55	327-330
			88		
17	56	o-CH_3-C_6H_4-MgBr		64	329-330
			89		
18	56	p-CH_3-C_6H_4-MgBr		48	387-389
			90		
19	56	m-CH_3-C_6H_4-MgBr		40	327-329
			91		
20	56	o-CH_3-C_6H_4-MgBr		42	320-322
			92		
21	56	2,6-$(CH_3)_2$-C_6H_3-MgBr		38	352-354

93

2.18, respectively) and **77** showed two such singlets, at δ 2.21 and 1.99 in the ratio of 12:24, respectively. These results clearly established the 1,2,4,5-orientation of the aryl groups around the central aromatic ring.

The reaction is not particularly susceptible to steric effects. Thus, the compounds **77**, **82** and **83** were prepared in comparable yields to less-hindered analogs. The peripheral rings in these compounds are twisted with respect to the central ring and almost certainly do not rotate freely. This conclusion is based on our observation that although the methyl signal in 1,2,4,5-tetra-o-tolylbenzene **76** is a singlet (broad), that signal in the hindered **89** (obtained by quenching the reaction with bromine) shows a complex pattern with five broad peaks at room temperature in $CDCl_3$. In the case of the more hindered **92**, seven peaks in methyl region were observed under the same conditions. Thus rotation in **89** and **92**, each of which has five possible conformers with a total of eight possible methyl peaks, is clearly restricted at room temperature. In **77**, rotation is expected to be much more hindered. Indeed, CPK space-filling models of **77** are exceedingly difficult or impossible to construct, even with the mesityl rings at 90^{o} to the central ring.

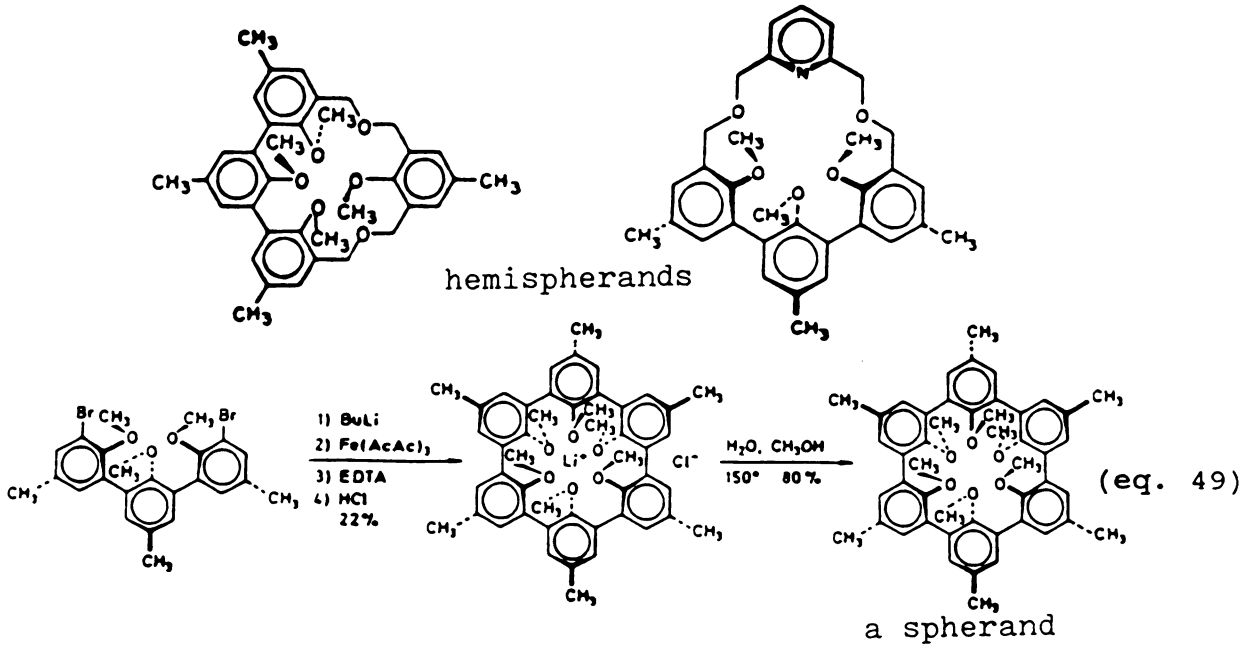
The central ring can be elaborated by treating the reaction mixture with various electrophiles prior to workup. For instances, compounds **87-89** were obtained with a bromine quench, **90-93** with an iodine quench, and **86** with a D_3O^+

quench.

The reaction of aryl Grignard reagents with certain hexahalobenzenes provide a unique one-step synthesis of 1,2,4,5-tetraarylbenzenes. Four new carbon-carbon bonds are generated in a one-pot reaction. The products are interesting for their restricted rotation properties. It is possible that they may also be useful intermediates in the synthesis of polynuclear aromatic compounds and for other purposes.

D. A New Synthesis of m-Terphenyls

A recent development of host-guest chemistry[82] recognizes spherands and hemispherands as two new classes of host molecules that form the complexes with a number of metal ions. Because the synthesis of spherands usually relies on the coupling of m-terphenyl dibromide derivatives (eq. 49), the construction of m-terphenyl moieties is essential for the preparation of both types of hosts. Therefore, efficient methods for the preparation of m-terphenyls is still an area of active exploration. For example, Reinbount recently reported a synthetic route to

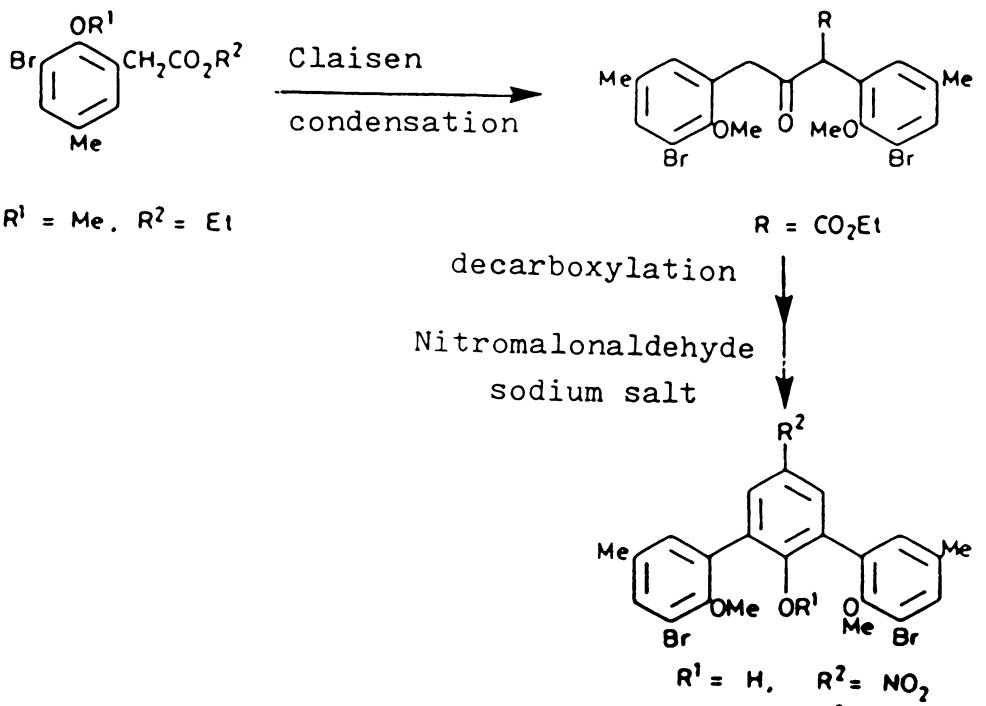


(eq. 49)

modified m-terphenyls which can be used as precursors for spherand synthesis.[83] The key steps of the preparation are outlined (Scheme 11). The nitro-m-terphenyl is prepared from

a highly sophisticated arene precursor in 57% overall yield, and subsequent convertion to the m-terphenyls needed for the coupling reaction takes a few more steps.

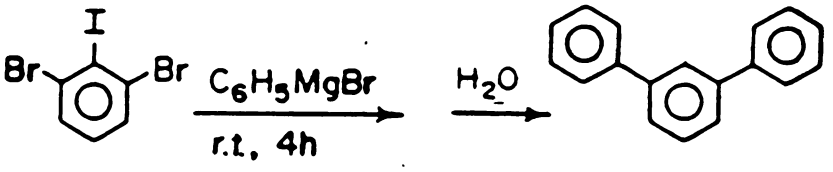
Scheme 11



In previous chapters of this thesis, several interesting aspects of the reaction of aryl Grignard reagents with polyhaloarenes were described. They include (1) halogen-metal exchange occurs preferentially at iodine rather than at bromine at ambient temperatures in several polyhaloarenes, (2) the subsequent elimination of magnesium bromide to form an aryne and the nucleophilic addition to the aryne takes place repeatedly when possible, resulting in multiple aryl-aryl bond formation, (3) owing to steric and electronic effects, the reaction usually leads to one predominant product. These considerations prompted us to

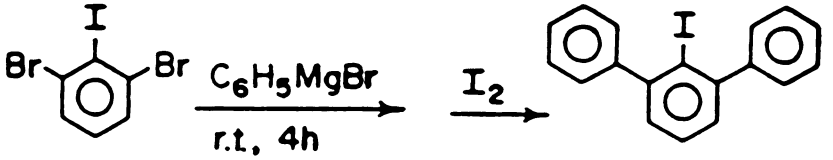
investigate the reactions of aryl Grignard reagents with 1,2,3-trihalobenzenes.

2,6-Dibromoiodobenzene[84] in dry THF was added to three (or more) equivalents of phenylmagnesium bromide at room temperature. After aqueous workup, the reaction gave m-terphenyl in excellent yields (80-90%) (eq. 50). Using an iodine quench under otherwise similar conditions, 2'-iodo-m-terphenyl[85] was isolated in 88% yield (eq. 51). Hence, it is clear that the reaction product prior to electrophilic quench possesses one reactive organometallic functionality between the two newly-created aryl-aryl bonds in the central ring.



(eq. 50)

94 **95**



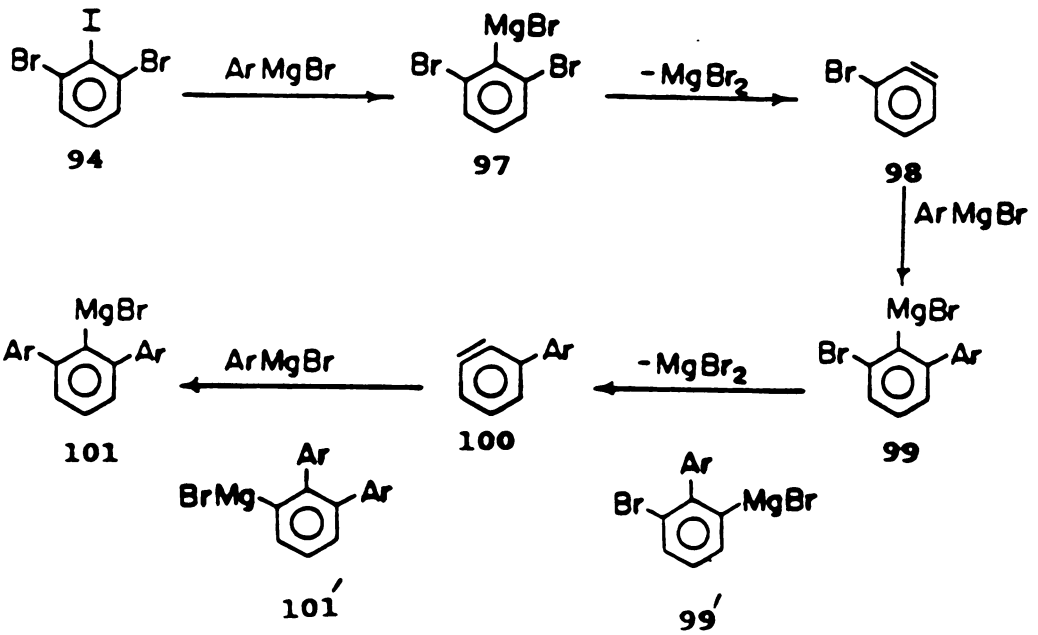
(eq. 51)

94 **96**

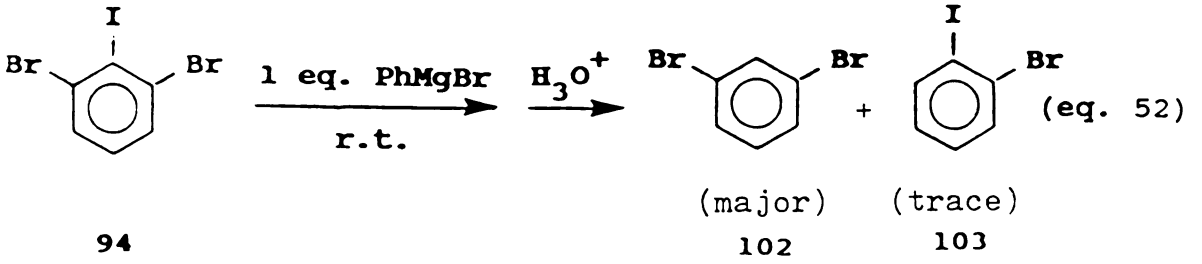
D.1. Mechanism. We postulate the reaction mechanism shown in Scheme 12. 2,6-dibromoiodobenzene **94** should undergo halogen-metal exchange preferentially at iodine to give Grignard **97**. If this mono-Grignard were to eliminate magnesium bromide to form aryne **98**, trapping should give **99** rather than its regioisomer **99'**. Nucleophilic addition to 3-bromobenzyne is known to occur predominantly in this manner

as a consequence of electron-withdrawal by the bromine substituent.[121] This addition mode sets the stage for a second aryne raction, and the resulting 3-arylaryne **100** should again add the nucleophile meta to give **101** instead of its regioisomer **101'**, probably for both electronic and steric reasons. This reaction mechanism, which was anticipated, leads only to m-terphenyl products.

Scheme 12

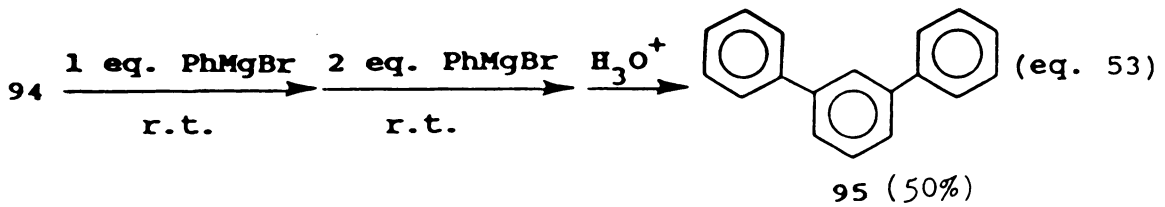


While studying the mechanism of this reaction, we observed an interesting phenomenon. when only one equivalent of phenylmagnesium bromide was added to a solution of 2,6-dibromoiodobenzene with a reaction time of two hours, aqueous workup gave mainly 1,3-dibromobenzene **102**, together with a trace of o-bromoiodobenzene **103**. The usual product, m-terphenyl **95**, was not observed (eq. 52). However, if two

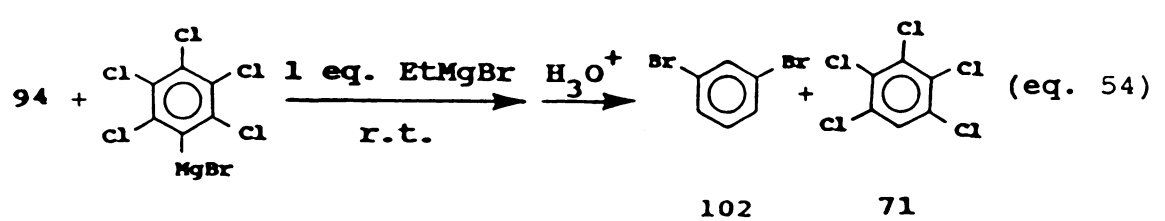


(eq. 52)

more equivalents of phenyl Grignard were added before workup, the major product was m-terphenyl **95** (eq. 53). Thus



it appears that the elimination of magnesium halide from the intermediate 2,6-dibromophenylmagnesium bromide, to generate 3-bromobenzyne, was facilitated by the presence of excess Grignard reagent. In a relevent example, 2,6-dibromophenylmagnesium bromide (prepared by the exchange reaction between 2,6-dibromoiodobenzene and ethylmagnesium bromide) was mixed with excess pentachlorophenylmagnesium bromide at room temperature. After aqueous workup, we obtained only 1,3-dibromobenzene **102** and pentachlorobenzene **71** as a result of quenching each Grignard reagent (eq. 54).



This implies that 2,6-dibromophenylmagnesium bromide is quite stable under these reaction conditions. These observations lead to the conclusion that the presence of excess Grignard is necessary for elimination of magnesium halide to form an aryne intermediate. In the first two

chapters, we have described a catalytic effect of strong bases, such as LiTMP and t-BuOK, on the p-terphenyl and biaryl syntheses. So far we are not quite sure about the relation between the new observations and the previous data. Further studies on the mechanistic aspects of these reactions should help us to understand the reactions in more detail.

D.2. Synthetic scope. 2,6-Dibromoiodobenzene **94** was readily prepared in quantity from 2,6-dibromoaniline[88] via diazotization and treatment with potassium iodide. A solution of **94** in THF was added dropwise to somewhat over the theoretically required three equivalents of aryl Grignard in the same solvent, usually at room temperature but in some instances at reflux. After additional stirring for a few hours, the mixture was quenched with dilute aqueous acid. Results are summarized in Table 5.

In general, the yields of m-terphenyls are quite good, the only poor example being entry 11. The product structures were clear from spectral data and from comparison of melting points with literature values, except for **104**, **109**, **110** and **113** which are new compounds. 1,2,3-Tribromobenzene and 2,6-dichloroiodobenzene can be used in place of **94**. They gave somewhat lower, but still good, yields of **95** with phenylmagnesium bromide.

The value of our method can be seen by comparison with literature syntheses of the known compounds in Table 5. Woods developed what appears to be the best general route to

Table 5. m-Terphenyls from Aryl Grignard Reagents and Trihaloarenes

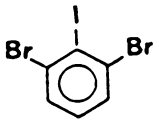
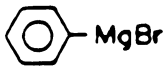
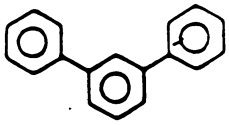
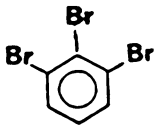
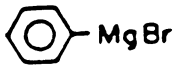
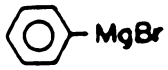
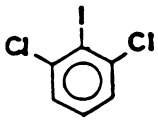
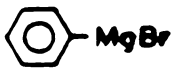
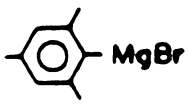
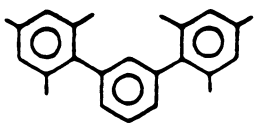
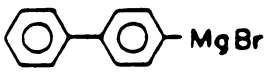
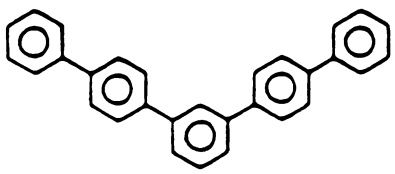
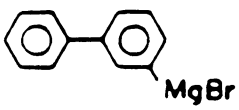
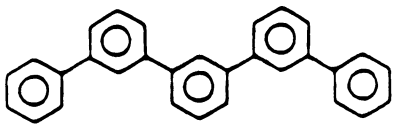
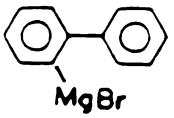
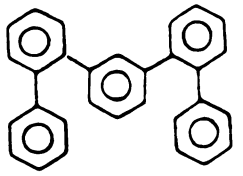
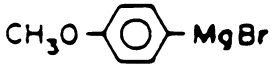
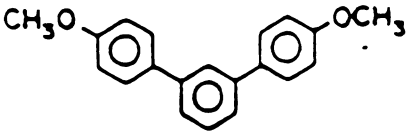
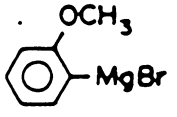
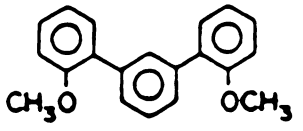
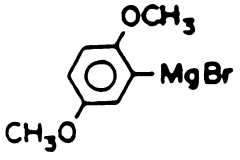
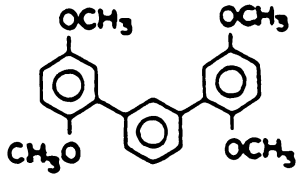
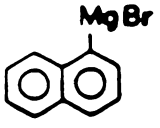
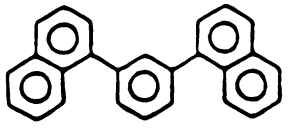
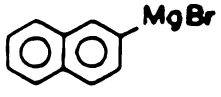
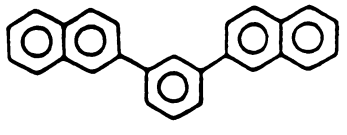
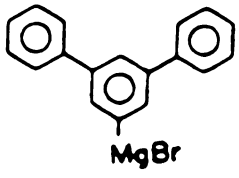
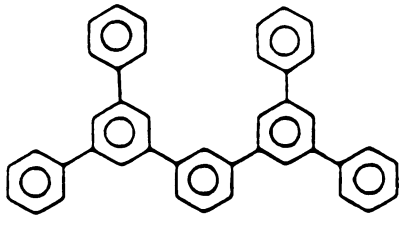
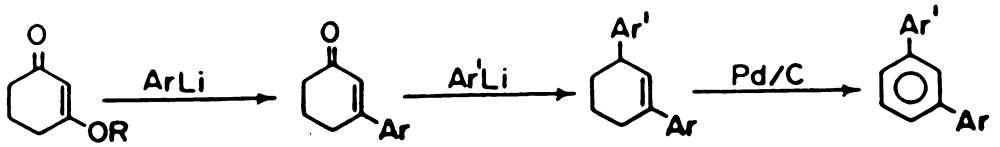
entry	trihalo-arene	Grignard reagent	conditions	product	yield %	ref.
1	 **94**		rt,3h	 **95**	77	81
2	 **184**		rt,15h	**95**	61	
3	**184**		reflux,3h	**95**	64	
4	 **185**		rt,24h	**95**	53	
5	**94**		rt,3h	 **104**	70	
6	**94**		rt,5h	 **105**	73	89
7	**94**		rt,5h	 **106**	62	90

Table 5. (Cont'd)

8	94		reflux,3h	 **107**	57	93
9	94		rt,5h	 **108**	80	91
10	94		reflux,10h	 **109**	85	
11	94		reflux,10h	 **110**	25	
12	94		rt,5h	 **111**	57	92
13	94		rt,5h	 **112**	64	92
14	94		reflux,5h	 **113**	57	

m-diarylbenzenes, via the enol ether of dihydroresorcinol (eq. 55). Using this three-step sequence, with Ar =Ar' =p-biphenylyl, he obtained a 72% yield of **105**;[89] our yield is comparable and requires only one step. In other cases, his method gave significantly lower yields than ours (for **106**,[90] 17%; for **108**,[91] 18%; for **111** and **112**,[92] 23%). The advantage



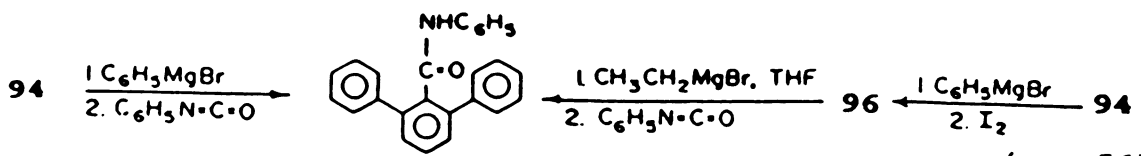
(eq. 55)

of the Woods synthesis is that the added external aryl rings may be different from one another since they are incorporated in a stepwise sequence. In this sense, the method is more versatile than ours. On the other hand, if the two external rings are identical, our synthesis is shorter and qenerally gives superior yields.

Another advantage of our method is that substituents are easily incorporated on the central ring. The actual reaction product is the m-terphenyl Grignard **101** which, in principle, can be treated with various electrophiles other than the proton. In practice, this may lead to difficultly separable mixtures because some excess or unreacted aryl Grignard reagent is present and will also react with the added electrophile. Quenching with a halogen (bromine or iodine), however, works well. For example, 2'-iodo-m-terphenyl **96** was obtained in 88% yield as described in the previous section. This route to **96** is superior to a three-step literature route involving an Ullman cross-coupling.[85]

Of course, **96** can then be reconverted to Grignard reagent **101** and treated with other electrophiles.

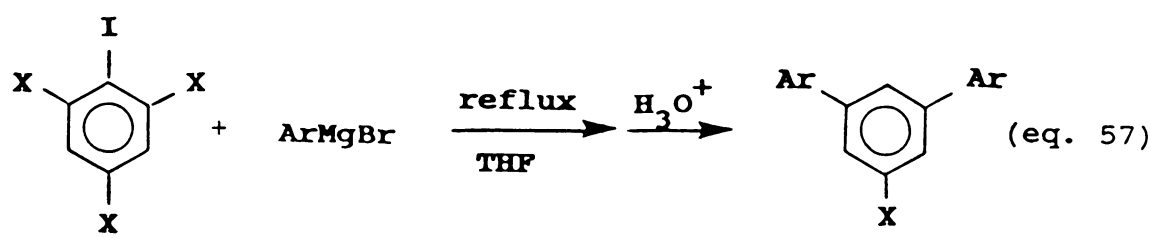
This two-step sequence is sometimes cleaner and preferable to direct quenching with complex electrophiles. For example, quenching of the reaction of **94** and phenylmagnesium bromide with phenyl isocyanate gave anilide **114** in one step and 63% yield. The same product was obtained in two steps from **94** via iodoarene **96** in higher overall yield (88% x 85% =75% overall) and with an easier workup (eq. 56).



114

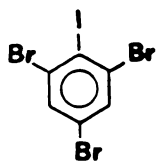
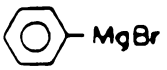
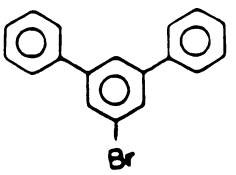
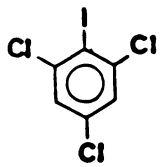
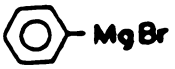
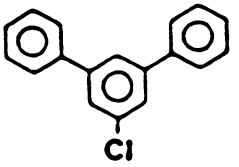
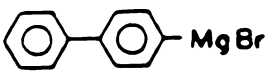
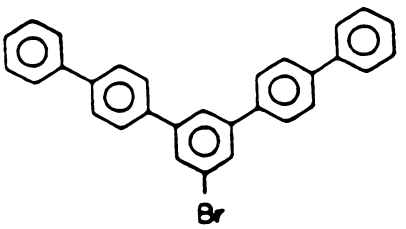
(eq. 56)

Substituents can also be incorporated elsewhere in the central ring by starting with an appropriately substituted derivative of **94** (eq. 57). For example, some m-terphenyls with a halogen (bromine or chlorine) at carbon 5 in the central aromatic ring were prepared in good yields by the reaction of aryl Grignard reagents with 1,3,5-trihaloiodobenzenes (Table 6).



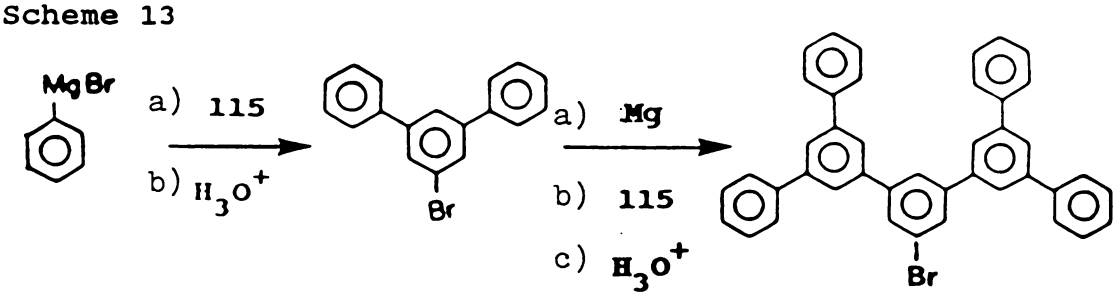
(eq. 57)

Table 6. 5-Halo-1,3-diarylbenzenes from Aryl Grignard Reagents and 1,2,3,5-Tetrahalobenzenes

tetrahalo-arene	Grignard reagent	product	yield %
 **115**		 **117**	80
 **116**		 **118**	60
115		 **119**	42

Further exploitation of these halogen substituents by converting the halo-m-terphenyls to the corresponding Grignard reagents and repeating the sequence with trihaloiodobenzene provides an efficient route the oligoarenes. For example, the 5'-bromo-m-terphenyl **117**, prepared from the phenylmagnesium bromide and tribromoiodobenzene **115**, was converted to the corresponding Grignard reagent and treated with **115** again to give a 42% yield of the 5"-bromo-5',5"'-diphenyl-quinquephenyl **120** which has seven aromatic rings. Thus, it only requires two steps to synthesize **120** starting from materials with a single aromatic ring. This simple synthetic route may be generally useful for preparing polyphenyls, which are widely studied for their electrical conductivities[94] and thermal stabilities.[95]

Scheme 13

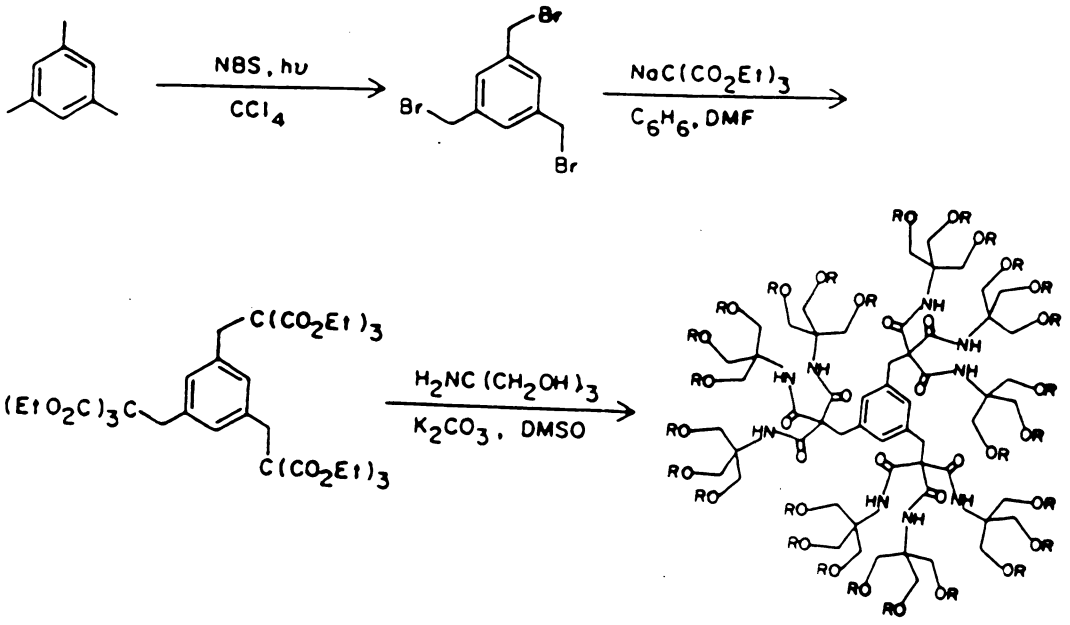


117 **120**

For the construction of large molecules, synthetic pathways that allow the frequent repetition of similar steps are advantageous. For example, a recent synthesis of arborals[96] and starburst dendritic polymers[97] clearly demonstrated the synthetic advantages of a cascade-like sequence (Scheme 14). Our synthetic route, shown in Scheme

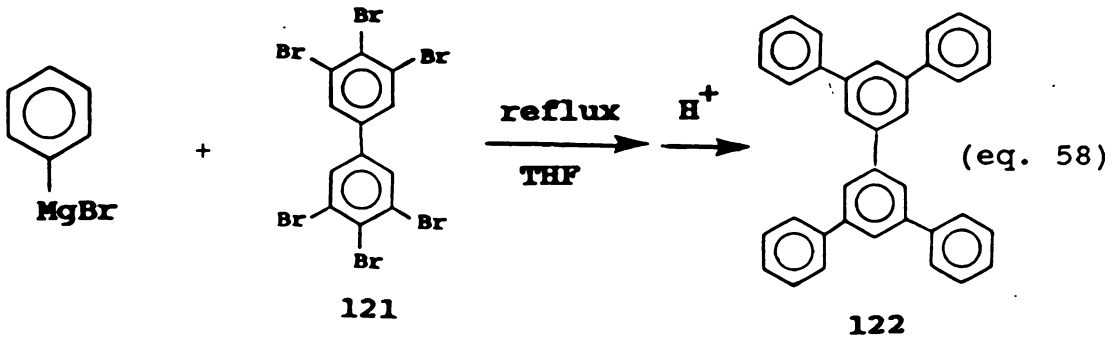
13, follows a similar repeating-step principle and can be readily adapted to the synthesis of new polyphenyls with a particular structure. The main difference in the two approaches is the site where the manipulation take place. It is at the side arms of a "seed" molecule in the cascade-like

Scheme 14



route whereas it is at the tetrahalobenzene, which is eventually transformed into the central ring of the final molecule in our reaction. Both methodologies are useful from a synthetic viewpoint and deserve extensive study.

The reaction was extended to molecules with two vicinal trihalo moieties. For example, slow addition of 3,4,5,3',4',5'-hexabromobiphenyl[98] **121** in THF to a solution of phenylmagnesium bromide in THF at reflux gave, after aqueous quench, the anticipated 5',5"-diphenyl-quaterphenyl **122** in 79% yield (eq. 58).



121 122 (eq. 58)

The reaction of aryl Grignard reagents with vicinal trihalobenzenes, as described here, provides a simple one-step route to m-terphenyls. The method has wide general applicability, the surface of which has just been scratched by the work described in this thesis.

E. Reactions of Polyhalobenzenes with Vinyl, Alkyl, Acetylenic and Heterocyclic Grignard Reagents.

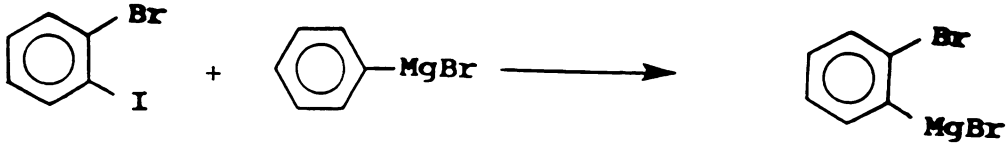
The reactions of several types of polyhaloarenes with aryl Grignard reagents described in the preceding chapters constitute useful methods for aryl-aryl bond formation. Extension of these reactions to the construction of multiple aryl-carbon bonds between aromatic substrates and other carbon moieties, by using other types of Grignard reagents, was studied in an exploratory way. In this chapter, some preliminary results of the reactions of selected vinyl, alkyl, acetylenic, and heterocyclic Grignard reagents with polyhaloarenes are presented.

The mechanism of the reaction of an aryl Grignard reagent with a polyhaloarene follows these important sequential steps: (1) halogen-metal exchange to form a polyhalogenated aryl Grignard reagent, (2) elimination of magnesium halide to form the aryne, and (3) nucleophilic addition of the Grignard reagent to the aryne. In cases of multiple bond formation, the last two steps are repeated. It is evident that halogen-metal exchange plays a crucial role in triggering the reaction.

From a thermodynamic viewpoint, the ability of two reactants to undergo halogen-metal exchange might be determined by two factors. One of these is the inductive

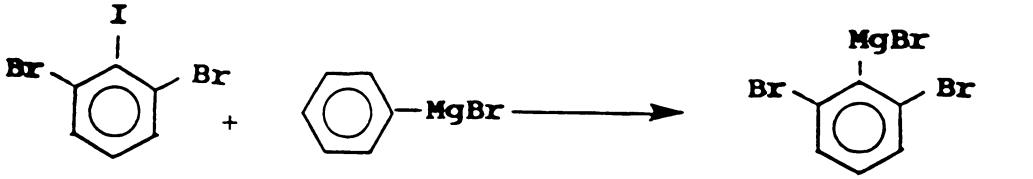
effect of substituents on the reactants; that is, electron-withdrawing groups can stabilize the resulting negative charge. The other important factor is the difference in carbon hybridization of the two reactants. In general, the greater the s-character at the carbanionic center, the more stable it will be.

The importance of substituent inductive effects is seen in the reactions of unsubstituted aryl Grignard reagents with polyhaloarenes. Metal transfer from the aryl Grignard to the polyhaloarene is thermodynamically favorable, because the adjacent halogen substituents are capable of stabilizing the resulting negative charge. For example, the reactions in equations 59 and 60 proceed in the forward direction because the product Grignard is favored over the reactant Grignard due to the inductive effect of the halogen substituents in the product Grignard. In these examples, the carbon-hybridization is identical in the reactant and product Grignards (<u>i.e.</u>, sp^2).



(eq. 59)

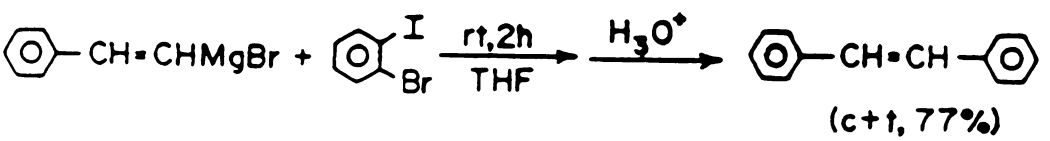
30 123



(eq. 60)

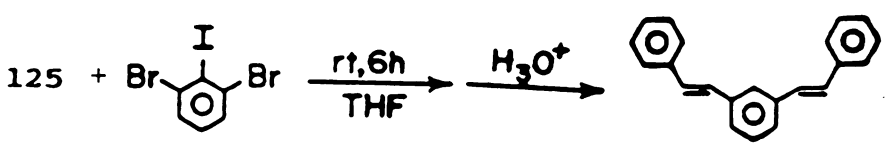
94 124

Extension of these reactions to other types of Grignard reagents was initiated with vinyl Grignard reagents because of their carbon hybridization is identical with that of aryl Grignard reagents. We studied the reaction of styrylmagnesium bromide **125** with polyhalobenzenes such as o-bromoiodobenzene **30**, 2,6-dibromoiodobenzene **94**, 1,4-dibromo-2,5-diiodobenzene **1** and 3,6-dichloro-1,2,4,5-tetrabromobenzene **56**. Each reaction was conducted in dry THF at room temperature, and the results are shown in eq. 61-64. Distyrylbenzenes **127**[99] and **128**,[100] prepared by this method, were isolated as the E,E isomers in 48% and 44% yields respectively. The synthesis of 1,2,4,5-tetrastyrylbenzene **129**[101] has been reported previously via a multiple step sequence, with an overall yield of only 28%. Our method required only one step and gave the desired product in a 49% yield.



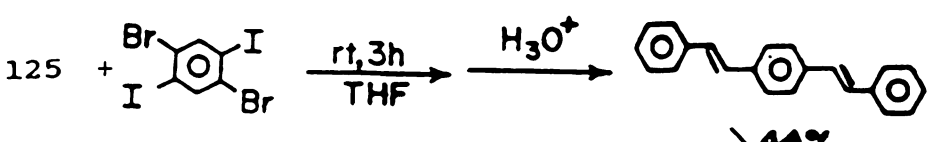
(eq. 61)

125 **30** **126**



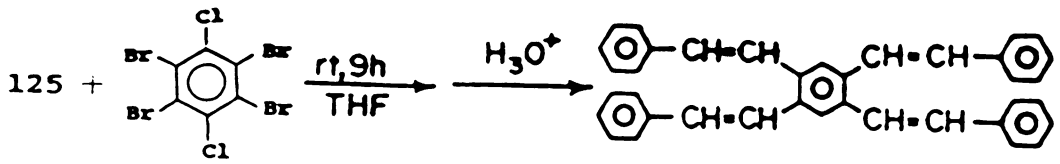
(eq. 62)

94 **127**



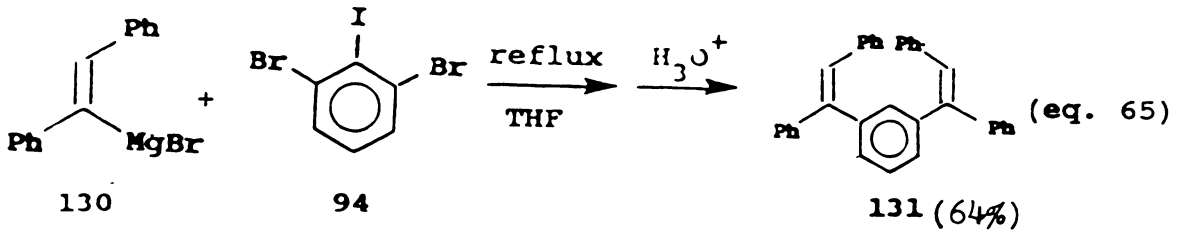
(eq. 63)

1 **128**

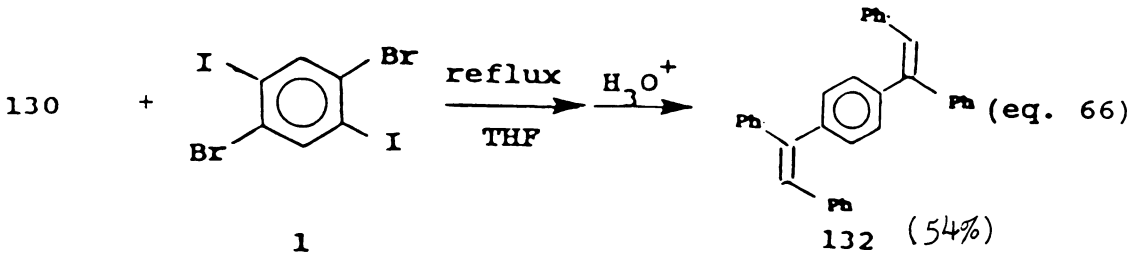


56 49% 129 (eq. 64)

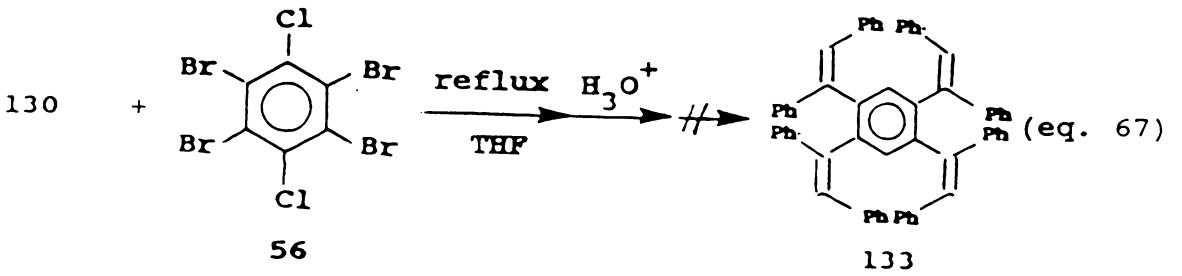
In a similar manner, 1,2-diphenylvinylmagnesium bromide **130** reacted with **94** or **1** in dry THF at reflux to give, after aqueous workup, **131** and **132**[102] in 64% and 60% yields respectively (eq. 65 and 66). However, the reaction of **130** with **56** failed to produce the highly sterically hindered compound **133** (eq. 67).



130 94 131 (64%) (eq. 65)



1 132 (54%) (eq. 66)

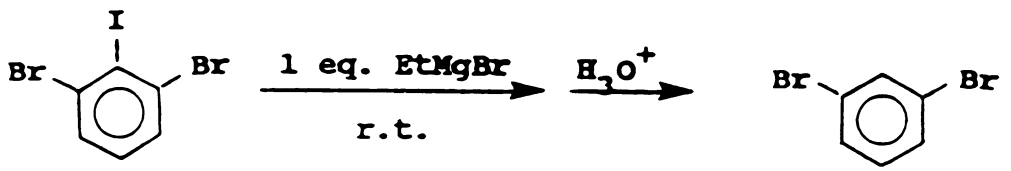


56 133 (eq. 67)

It is clear from these preliminary results that the reaction of vinyl Grignard reagents with various polyhalobenzenes can be a useful synthetic method for

preparing polyvinylarenes. Extension of this methodology to other vinyl Grignards, including those with substituents that provide latent functionality, should be fruitful.

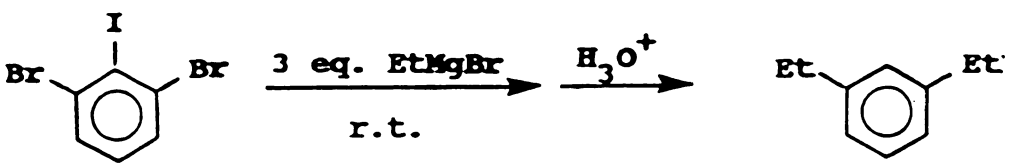
The transposition of negative charge from a less electronegative sp^3 carbon to a more electronegative sp^2 carbon should be thermodynamically favorable. We may take advantage of this thermodynamic preference. For example, the reaction of one equivalent of 2,6-dibromoiodobenzene **94** with one equivalent of ethylmagnesium bromide **134** gave mainly, after aqueous workup, 1,3-dibromobenzene **102** (eq. 68). This



(eq. 68)

94 **102**

result indicates that the desired exchange occurs quite readily. With 3 equivalents of ethylmagnesium bromide under the same conditions, a 20% yield of the anticipated 1,3-diethylbenzene **135** was observed (eq. 69). The product was identified by gas chromatographic analysis. Although the reaction yield was not good, this result suggests that further investigations, including a study of reaction conditions, should be fruitful.

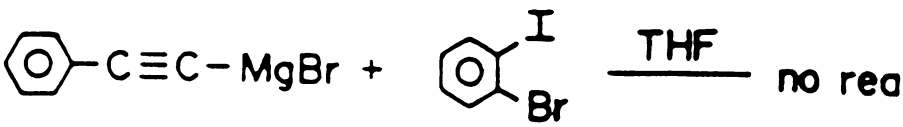


(eq. 69)

(20%)

94 **135**

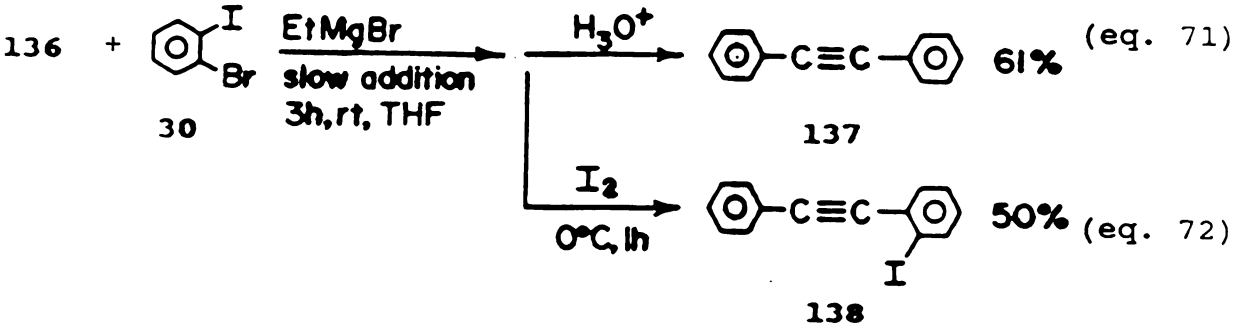
For thermodynamic reasons, the transfer of negative charge from a more electronegative sp carbon to a less electronegative sp^2 carbon is not favorable. For example, in the reaction of phenylacetylenic Grignard **136** with o-bromoiodobenzene **30**, the o-dihalobenzene was recovered unchanged (eq. 70). The inductive effect of the halogen substituent is insufficient to overcome the hybridization change, and the reaction fails.



(eq. 70)

136 **30**

But to construct an aryl-carbon bond between the acetylenic moiety and the aromatic substrate, the problem of the inability of the acetylenic Grignard to initiate metal-halogen exchange needed to be solved. A simple solution for this problem was to use another Grignard reagent to undergo halogen-metal exchange. The best candidate to satisfy this need is an alkyl Grignard reagent (eg. 69). Thus, when ethylmagnesium bromide was added to 2,6-dibromoiodobenzene in the presence of excess phenylacetylenic Grignard at room temperature, aqueous workup gave the expected diphenylacetylene **137** in 61% yield (eq. 71). This procedure also proved to be effective with an iodine quench (eq. 72).

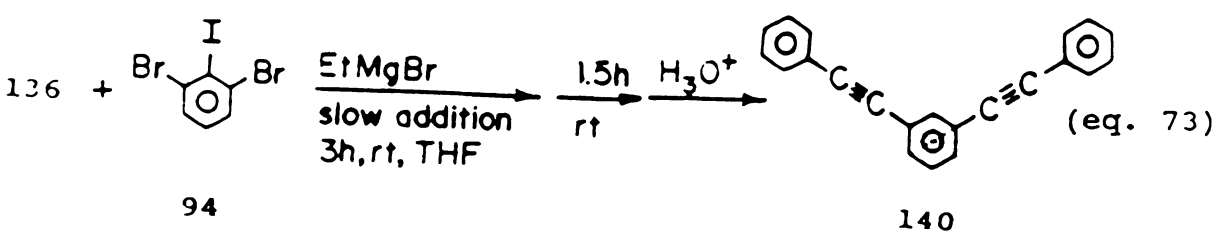


(eq. 71)

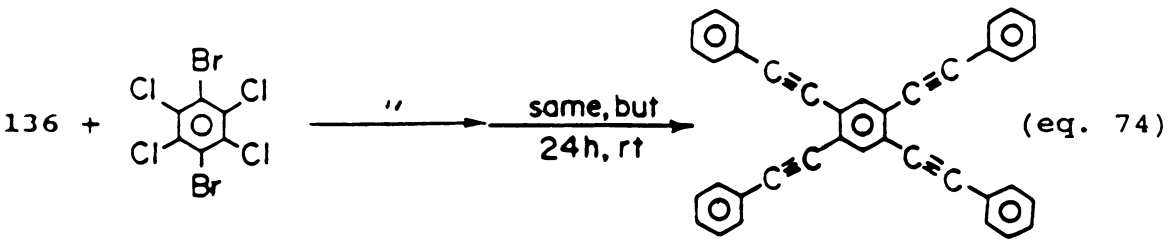
(eq. 72)

This reaction modification demonstrates the use of two different Grignard reagents for different purposes, one to bring about halogen-metal exchange and the other to trap the aryne. Its synthetic merits are two fold. First, it allows Grignard reagents that cannot undergo halogen-metal exchange to be used to form the desired aryl-carbon bond. Second, the quantity of Grignard reagent used to trap the aryne can be reduced to the stoichiometric amount without the loss of one equivalent of reagent for halogen-metal exchange.

Following a similar procedure, the reaction of phenylethynylmagnesium bromide with 2,6-dibromoiodobenzene **94** and with dibromotetrachlorobenzene **56** gave 1,3-bis-phenylethynyl-benzene **140**[103] and 1,2,4,5-tetrakis-phenylethynyl-benzene **141**[101] in 38% and 25% yields respectively (eq. 73 and 74).

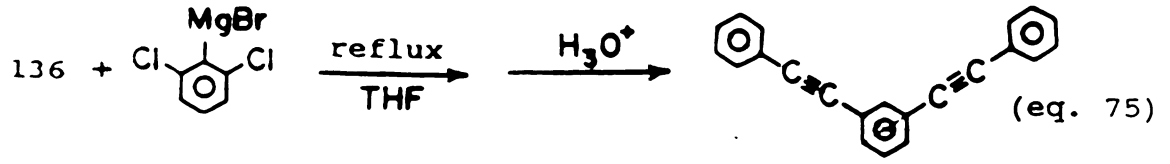


(eq. 73)



156 141 (eq. 74)

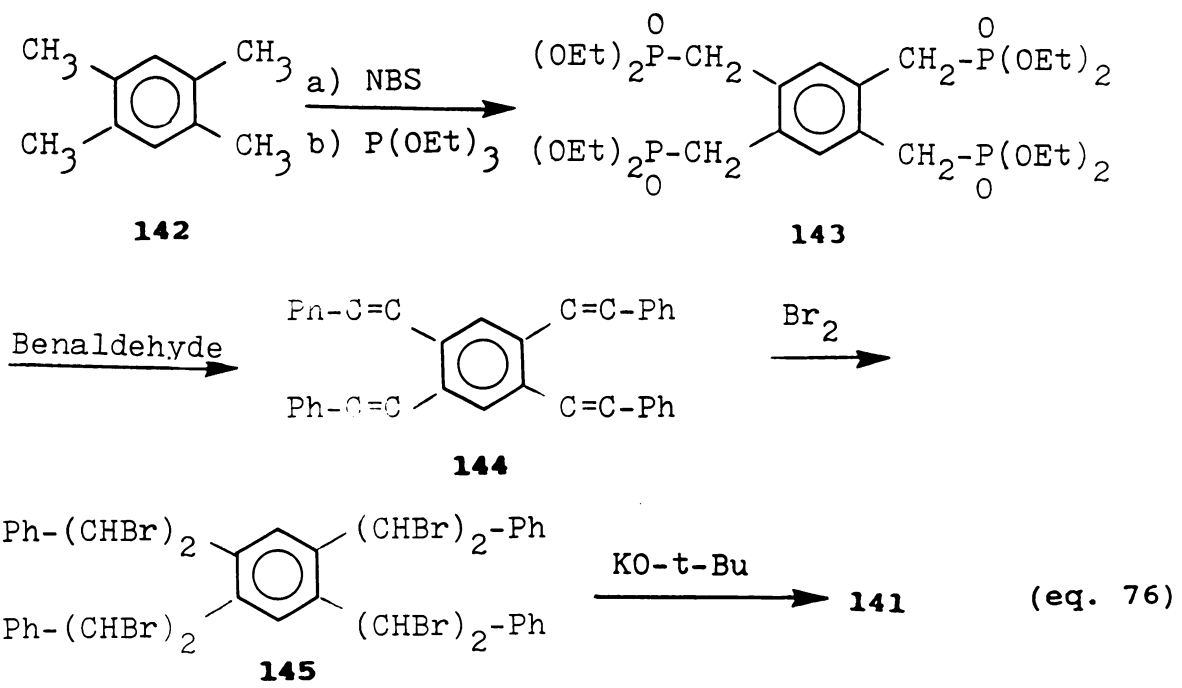
Attempts to optimize the reaction yields resulted in another modification. It was found, in the preparation of **140**, that the slow addition of 2,6-dichlorophenylmagnesium bromide **139**, (prepared from 2,6-dichloroiodobenzene and ethylmagnesium bromide at 0°C), to a THF solution of **136** gave, after aqueous workup, a higher yield of **140** (52%) (eq. 75).



(eq. 75)

139 **140**

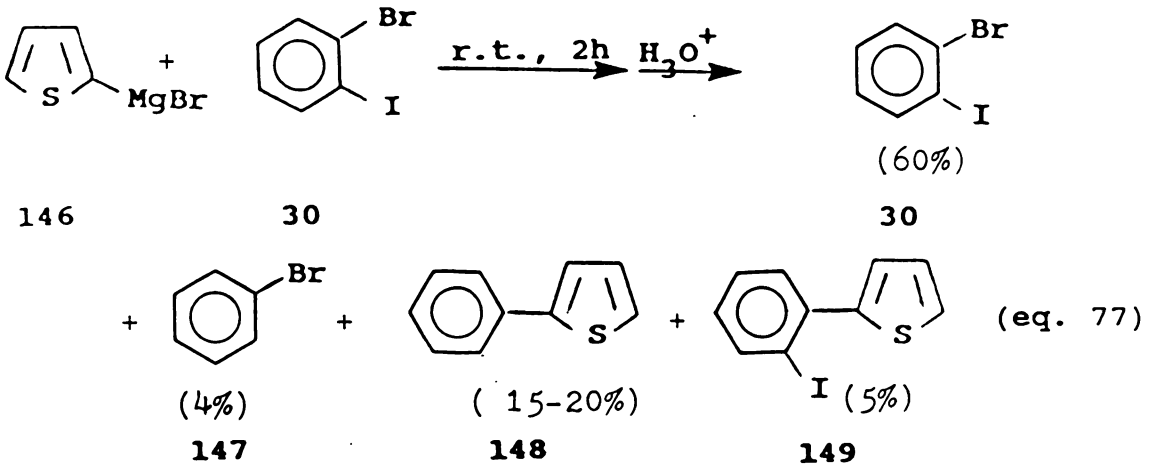
The advantage of this methodology can be seen by comparing the present one-step synthesis of **141** from readily available starting materials with the multiple-step literature method,[104] outlined in the following equation. Tetramethylbenzene **142** was initially brominated, then converted to the corresponding phosphate ester **143**. The subsequent reaction of **143** with benzaldehyde gave tetrastyrylbenzene **144**. The bromination of **144** and dehydrohalogenation of **145** led to **141** in an overall yield of 13% (eq. 76).



Extension of this methodology to heterocyclic Grignard reagents was expected to work, although some complications might be anticipated. For example, extensions to thienyl (or furyl) Grignard might be complicated by the change in ring size, which alters (slightly) the carbon hybridization of the Grignard reagent from that in carbocyclic aryl Grignard. Also, the electronegativity of the heteroatom might affect the metal-halogen exchange step.

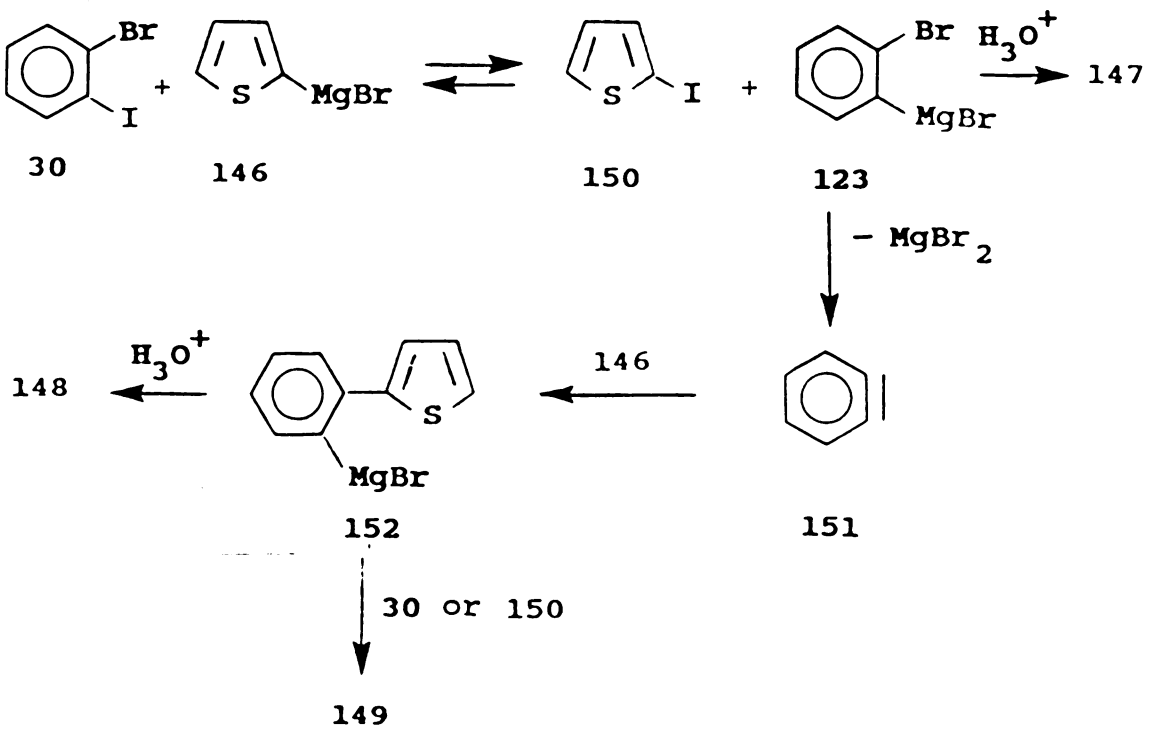
In fact, a preliminary study of the reaction of o-bromoiodobenzene 30 with 2-thienylmagnesium bromide 146 gave quite a complex product mixture. The products, after aqueous workup, included only a modest yield of the desired 2-phenylthiophene 148. There was a considerable amount of

recovered o-bromoiodobenzene **30**, as well as low yields of **147** and **149** (eq. 77). The presence of **149** was very

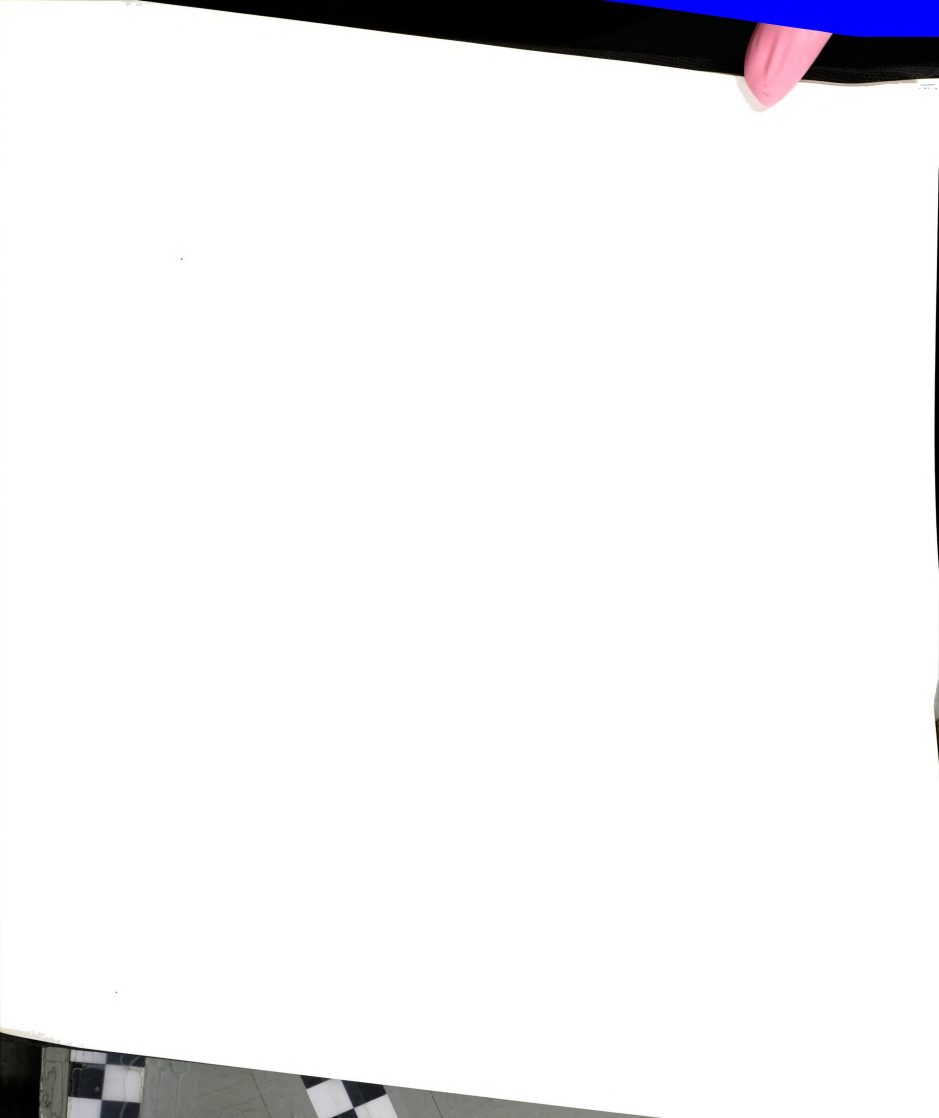


interesting. One rationalization for its formation is shown in Scheme 15. Initial halogen-metal exchange between **30** and

Scheme 15

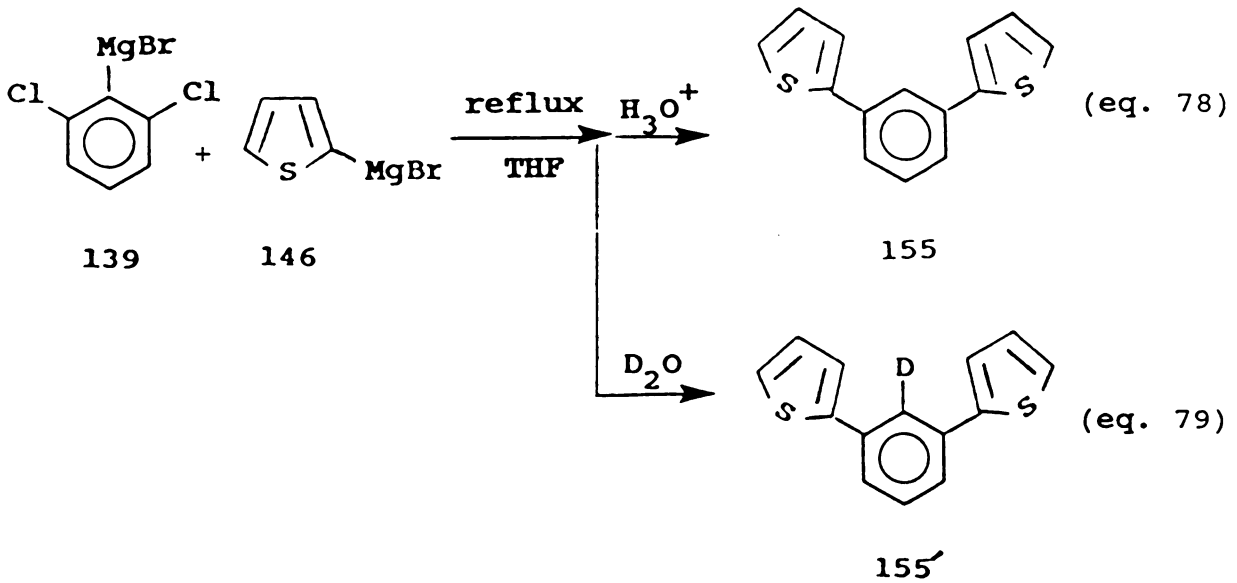


146 would give **150** and **123**. Elimination of magnesium halide from **123** gives benzyne **151**, which is trapped by the thienyl



Grignard to generate the adduct **152**. The possible halogen-metal exchange between **152** and **150** or **30** could lead to **149**. At this point, it is somewhat premature to draw any conclusions about the reaction mechanism; further study is certainly required.

Another example of the reaction between a heterocyclic Grignard reagent and a polyhalobenzene was carried out in a somewhat different manner. The heterocyclic Grignard reagent was used solely to trap the aryne. The aryne precursor was generated in a separate step by metal-halogen exchange with an alkyl Grignard reagent. Thus 2,6-dichlorophenylmagnesium bromide **139** (prepared from 2,6-dichloroiodobenzene and ethylmagnesium bromide at $0^{\circ}C$) was added dropwise to a solution of 2-thienylmagnesium bromide in dry THF at $60^{\circ}C$, with stirring for an additional 1.5 hours at the same temperature. Aqueous workup and column chromatography gave the desired 1,3-dithienylbenzene **155** in 41% yield (eq. 78). The product structure was mainly confirmed by it NMR spectrum, in which the isolated proton at the 2-position of the central ring in **155** coupled with two meta protons in the same ring and showed a triplet signal at δ 7.88. To establish that the immediate precursor of **155** contained an organometallic functionality at the 2 position of the central ring, the reaction was quenched with D_2O (eq. 79). The NMR spectrum of the product **155'** now lacked the triplet signal at δ 7.88.



139 146 155 (eq. 78)

155' (eq. 79)

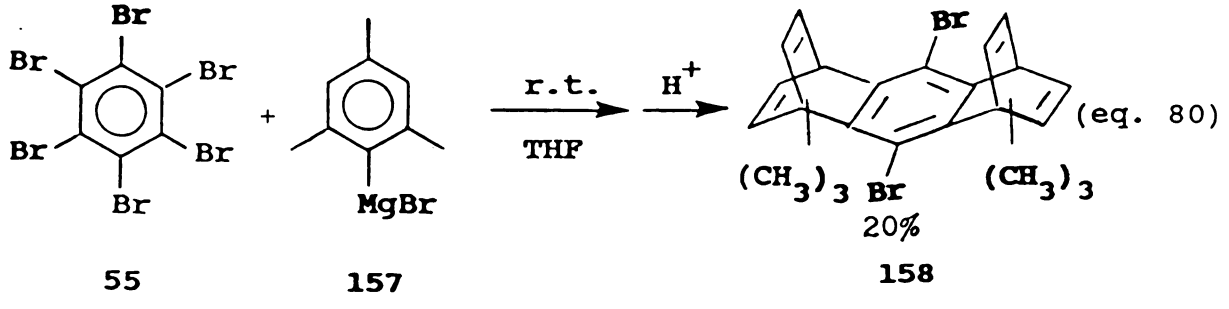
Our preliminary studies of the reaction of polyhalobenzenes with vinyl, alkyl, acetylenic and heterocyclic Grignard reagents demonstrate some features that deserve comment. (1) The initial and crucial step for the reaction is halogen-metal exchange, which depends on thermodynamic factors, and in particular on the carbon hybridization at the negative carbon of the Grignard reagent. (2) The exchange can be initiated using an alkyl Grignard reagent. (3) The quantity of Grignard used to trap the aryne can be limited to the stoichiometric amount without loss of one equivalent for exchange. (4) Although several different types of Grignard reagents were employed, the mechanisms and the incorporation of organometallic functionality in the product follow the same pattern as discussed in the first four chapters of this thesis.

F. An Unusual Diels-Alder Reaction Between An Anionic Diene and Benzyne

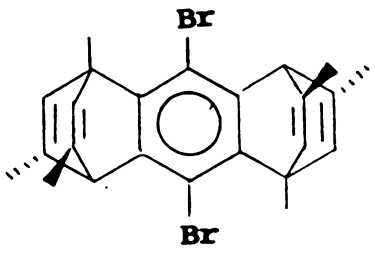
During our study of the reactions of polyhaloarenes with Grignard reagents, two instances of unusual by-products were observed. The structures of these by-products suggested that they were formed via [4+2] cycloaddition reactions (Diels-Alder reactions). Furthermore, the diene component in these reactions appeared to be aryl or heteroaryl Grignard reagents. These novel findings are described in this final section of the thesis.

F.1. The Reaction Between Mesitylmagnesium bromide and Hexabromobenzene.

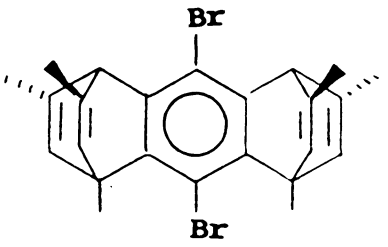
Using the typical procedure, the reaction was carried out by adding hexabromobenzene to an excess of mesitylmagnesium bromide **157** at room temperature. An aqueous workup gave, besides the expected 1,2,4,5-tetramesitylbenzene (30%), a 20% yield of a biscycloadduct assigned the overall structure **158** (eq. 80).



55 **157** **158**



158a

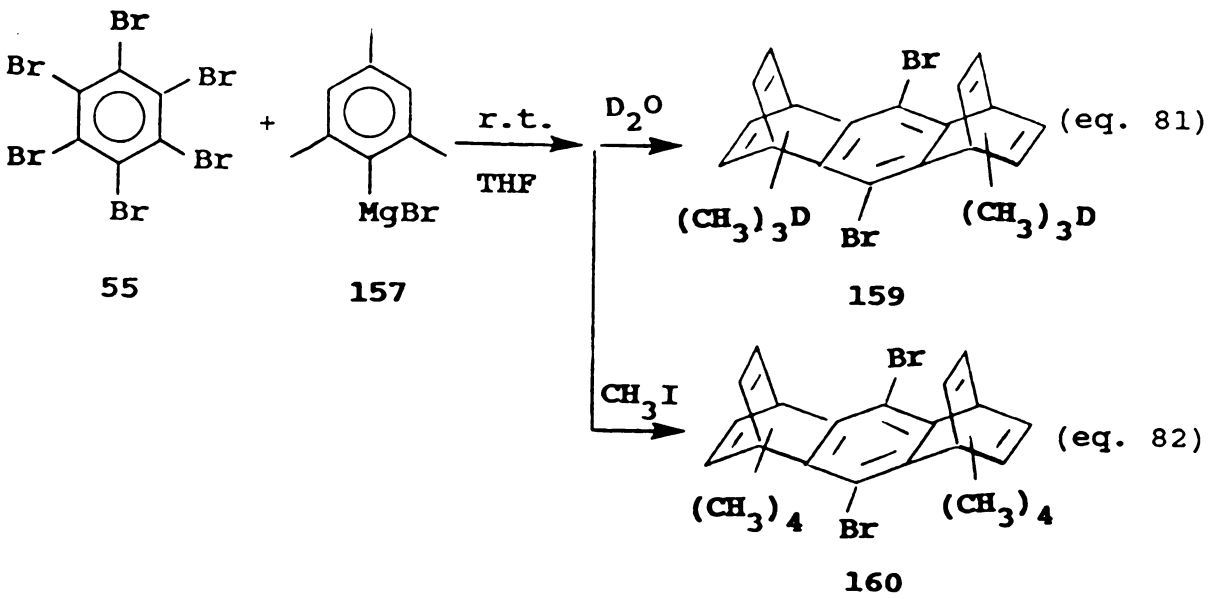


158 b

The product was in fact an inseparable mixture of two regioisomers, **158a** (which has a C_2 symmetry axis), and **158b** (which has a mirror plane). The structures were assigned on the basis of mass and NMR spectral data. The mass spectrum of the mixture showed the presence of two bromine atoms (m/e 470, 472, 474). The proton NMR spectrum showed peaks corresponding to four vinyl protons (δ 6.00), two bridgehead protons (δ 4.98), two bridgehead methyl groups (δ 2.12) and four vinyl methyl groups (δ 1.89).

The products seem to arise from the [4+2] cycloaddition of 3,6-dibromo-1,4-benzadiyne (or its synthetic equivalent) to two eqivalents of either mesitylene of mesitylmagnesium bromide. To determine whether the hydrocarbon or the Grignard reagent provided the diene component, the reaction was quenched with deuterium oxide or with methyl iodide (eq. 81 and 82). The products were **159** and **160** respectively; their NMR and mass spectral data are summarized in Table 7.

The molecular ion of **159** is two mass units higher than that of **158**, which clearly shows that two organometallic functionalities are present in the product prior to electrophilic quenching. By comparing the proton NMR spectrum of **159** with that of **158**, we can see that two vinyl



55 157 159 160

(eq. 81) (eq. 82)

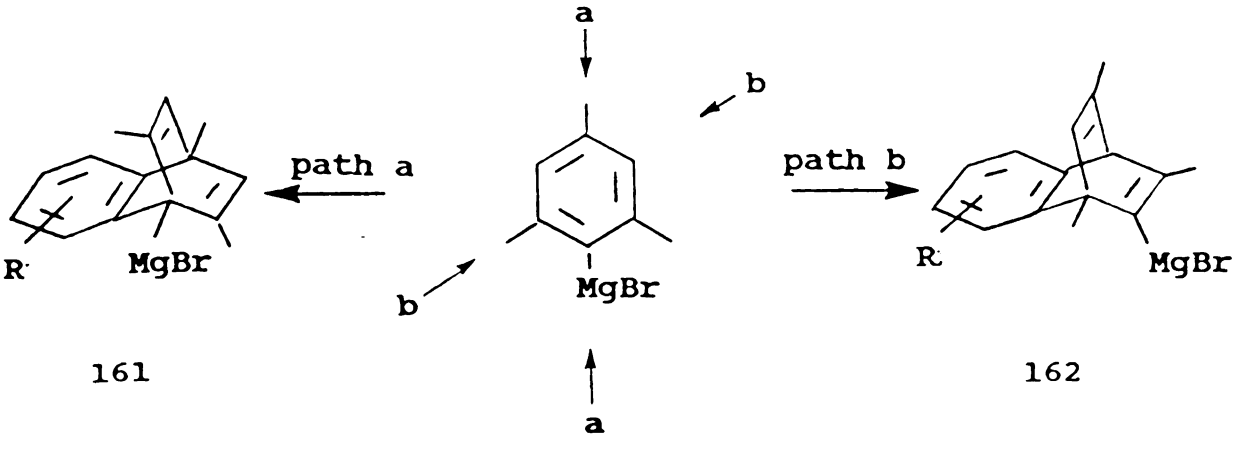
Table 7 Mass and NMR spectral data of biscycloadducts

biscycloadduct	158	159	160
molecular ion mass	472	474	500
NMR (in δ)			
(vinyl) H	6.00 (4H)	6.00 (2H)	5.90 (2H)
(bridgehead) H	4.98 (2H)	4.98 (2H)	4.96 (2H)
(bridgehead) CH_3	2.12 (6H)	2.12 (6H)	2.12 (6H)
(vinyl) CH_3	1.89 (12H)	1.89 (12H)	1.89 (6H) 1.81 (6H) 1.67 (6H)

protons are replaced by deuterium. Thus the organometallic functionality is located at the vinyl positions. The results of methyl iodide quenching confirm this conclusion. Therefore the mesityl Grignard reagent is indeed involved in the Diels-Alder cycloaddition and cycloaddition occur across C_2 and C_5 of that reagent.

An interesting question arises. We can see (Scheme 16) that there are two paths by which an aryne can approach the mesityl Grignard reagent. Path a will generate a product with a organometallic functionality at the bridgehead, whereas path b will place the that functionality at the double bond. The results show that path b is favored. We may now try to rationalize this preference.

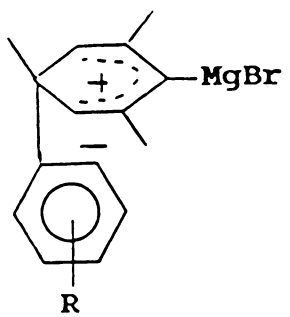
Scheme 16



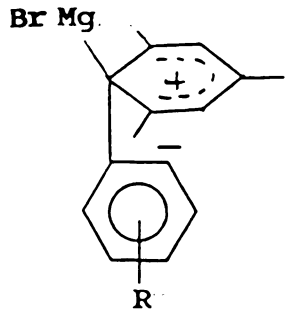
161 162

The mechanism of the Diels-Alder reaction is still controversial.[105] The reaction can proceed in a concerted or a non-concerted fashion, and even if concerted (the usual path), the new bonds can be formed in a synchronous or a nonsynchronous manner. Even though the reactions being

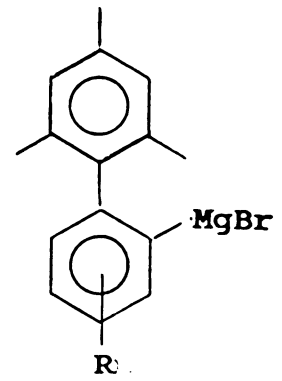
discussed may occur in a concerted manner, it will be useful here to consider the possible zwitterionic forms of the transition states. These are shown below, excluding those structures which place a negative charge on the diene, because the diene already carries a substantial negative charge. The transition states for path a are **163** and **164**,whereas those for path b are **166** and **167**. Transition



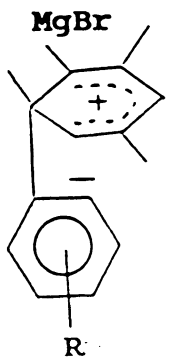
163



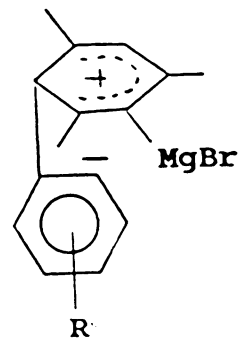
164



165



166

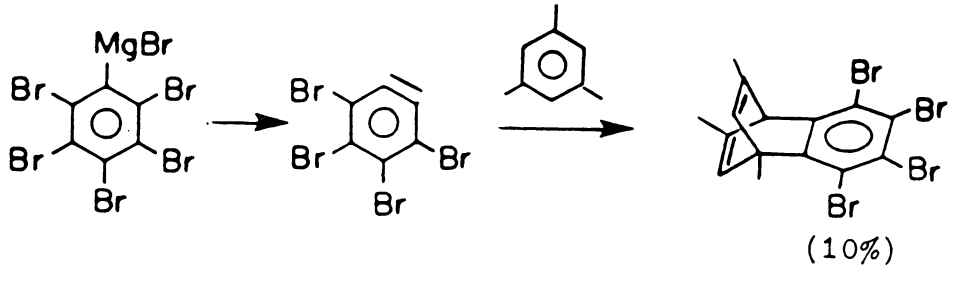


167

states **163** and **166** suffer from a steric interaction between the aryl methyl group and the incoming benzyne, and should be disfavored. If transition state **164** were involved, it should collapse to the more stable **165**, which is not related to the cycloaddition process. Therefore, **167** would seems to be the most favorable transition state, and would lead to

the observed regiochemistry in the product. Also, the methyl groups in **167** are located ortho and para to the new bond and should stabilize the partial positive charge that is present. Finally, this transition state leads to a product with the negative charge at an sp^2 carbon, as contrasted with path a transition states, that would give a product with a negative charge at an sp^3 (bridgehead) carbon. To the extent that the product energies are reflected in the transition states that lead to them, path b should be favored, as observed.

Barry and coworkers[49] reported that tetrabromobenzyne reacted with mesitylene to give a cycloadduct **169** in a 10% yield. In the present reaction, the biscycloadducts are obtained in a somewhat better yield (20%). To the extent that any direct comparison is possible, it would seems that the presence of an anion in the diene component may facilitate cycloaddition to some extent. It has been reported theoretically and experimentally that the Diels-Alder reaction can be greatly improved by the introduction of an electron-donating substituent on a diene. Since carbon-magnesium bond is substantially ionic, this moiety acts as an electron-donating group, even though the orbital bearing the negative charge is, to a first approximation, orthogonal to the diene π orbitals.

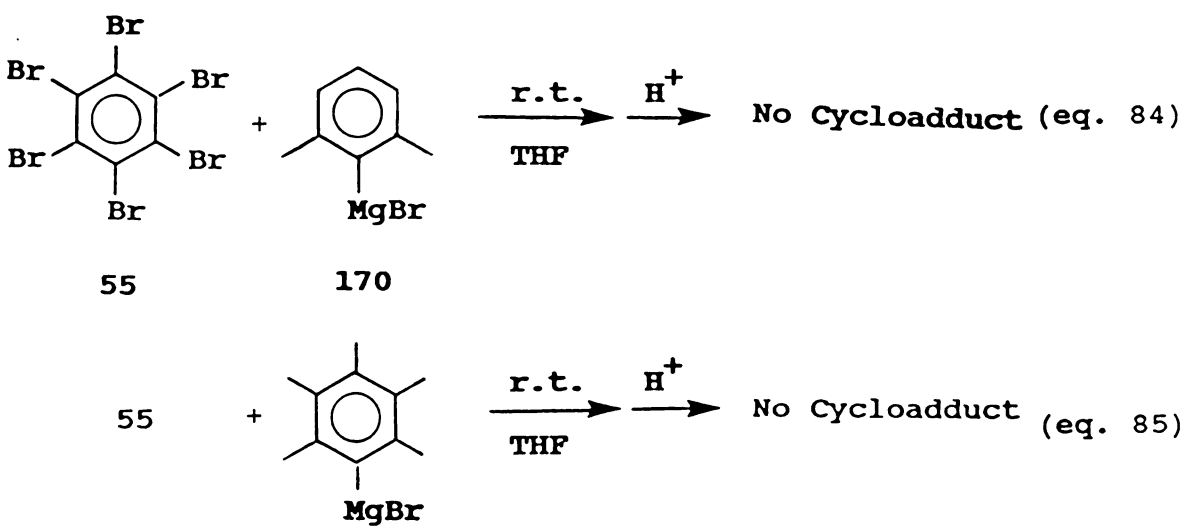


(eq. 83)

One other factor may be the steric crowdedness of having three adjacent substituents in the mesityl Grignard reagent. Relief of strain on cycloaddition may make a mesityl Grignard reagent more reactive than mesitylene itself as a diene.

Clearly there are many unanswered mechanistic questions regarding this unusual cycloaddition reaction.

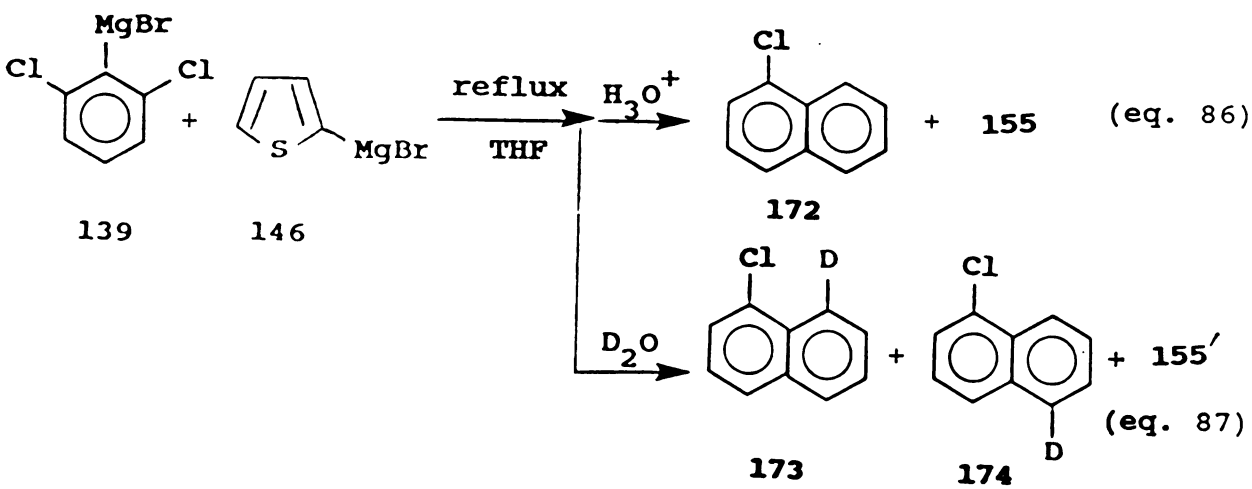
Two reactions were carried out with the hope of extending the reaction scope. The reaction of 2,6-dimethylphenylmagnesium bromide **170** or pentamethylphenyl-magnesium bromide **171** with hexabromobenzene was carried out under the same conditions. Disappointingly, no Diels-Alder biscycloadduct was found in either case.



F.1. The Reaction of 2,6-Dichlorophenylmagnesium bromide with 2-Thienylmagnesium bromide.

The reaction of 2-thienylmagnesium bromide with 2,6-

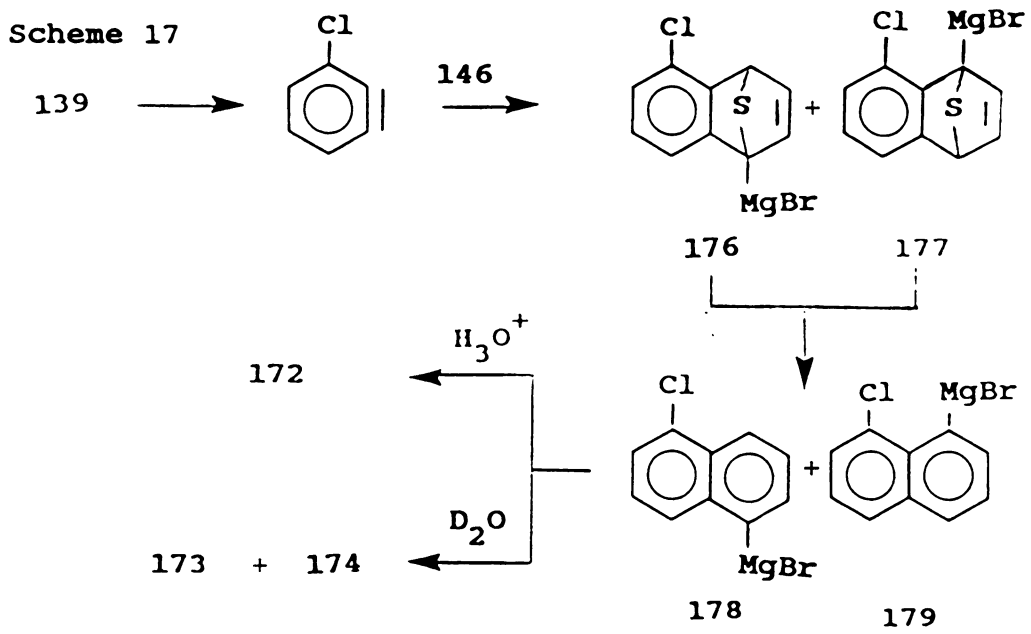
dichlorophenylmagnesium bromide described in chapter five gave, after aqueous workup, a 6-10% yield of 1-chloronaphthalene in addition to the anticipated bisadduct **155** (eq. 86). The presence of 1-chloronaphthalene **172** is



attributed to the occurrence of a [4+2] cycloaddition followed by sulfur extrusion. A plausible mechanism is proposed in Scheme 17. 3-Chlorobenzyne **175** could add to the 2-thienyl Grignard reagent to give cycloadducts **176** and/or **177**. Spontaneous cycloreversion with loss of sulfur would then give naphthalenic Grignard **178** and/or **179**. The hydrolysis of **178** and/or **179** would then give the observed 1-chloronaphthalene.

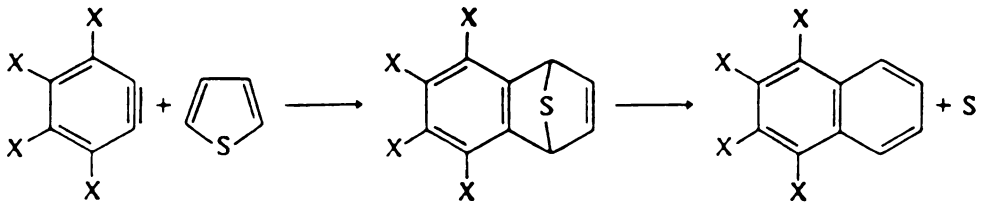
The involvement of 2-thienylmagnesium bromide in the cycloaddition was confirmed by quenching the reaction with deuterium oxide. The GC-MS analysis of reaction mixtures illustrated the presence of monodeuterated chloronaphthalene, which may be either **173** or **174** or a

Scheme 17



mixture of those. Attempts to isolate and identify the particular deuterated chloronaphthalene were not successful (eq. 87).

The failure to obtain cycloaddition intermediates **176** and **177**, which would have provided direct evidence for cycloaddition, is attributed to the rapid retro-cycloaddition in which a sulfur atom is extruded. This is a general phenomenon for cycloadditions involving thiophene derivatives as the diene.[106] For example, the reaction of tetrafluorobenzyne and thiophene gave tetrafluoronaphthalene **183** instead of cycloadduct **182**.[107] But transient NMR absorptions attributable to the bridgehead and vinyl protons of the intermediate **182** were observed. Therefore, we believed that the formation of 1-chloronaphthalene is correctly rationalized by Scheme 17 (eq. 88).



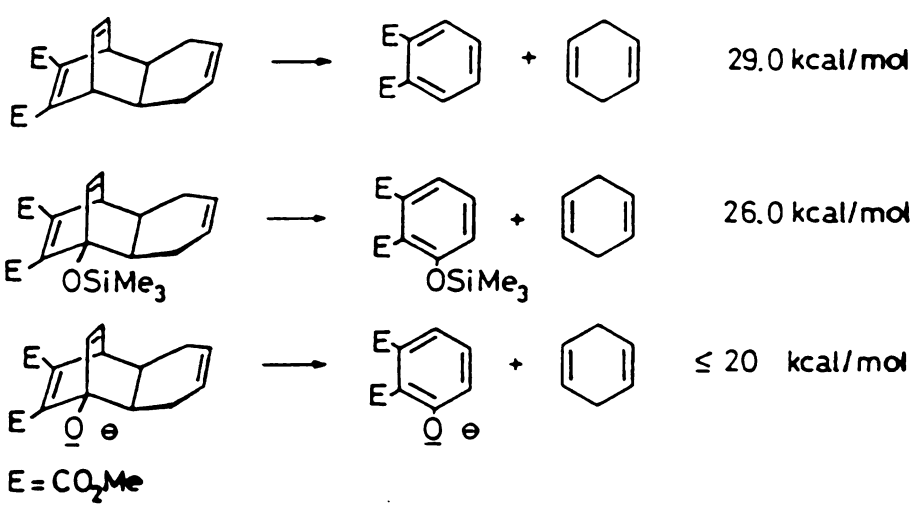
(eq. 88)

180 **181** **182** X = F **183** X = F

Relevant to our finding, anion-assisted pericyclic reactions have attracted a great deal of attention recently. Examples include Ireland's ester enolate-Claisen rearrangement,[108] Evans' anionic oxy-Cope rearrangement[109] and the carbanionic Claisen rearrangement.[110] For the Diels-Alder reaction, no such report has yet been published. On the other hand, an anionic-accelerated retro-Diels-Alder reaction was reported as early as 1967 by our group.[111] A recent quantitative measure of the rate enhancement of retro-Diels-Alder reactions shows that the presence of an alkoxide group can increase the rate by a factor of 10^6 (Scheme 18).[112]

Scheme 18

Free Enthalpy of Activation ($\Delta G^{\ddagger}$) for (4+2)-Cycloreversion



In summary, two unusual cycloaddition reactions involving Grignard reagents as the diene component have been encountered. The possible role that anionic substituents placed directly on the diene component might play in Diels-Alder cycloadditions is clearly a subject worthy of further study.

Experimental

1. **General procedures.** ^1H NMR spectra were determined on a Varian T-60 or Bruker WM-250 spectrometer in $CDCl_3$ solution containing tetramethylsilane as the internal standard. Chemical shifts are reported in δ units. Infrared spectra were obtained on a Perkin-Elmer 167 spectrometer, using KBr pellets. Mass spectra were recorded at 70 eV on a Finnigan 4000 spectrometer or, for high resolution, a Varian CHS spectrometer at the Michigan State University Mass Spectrometry Facility supported by a grant (RR-00480) from the Biotechnology Resources Branch, Division of Research Resources, NIH. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Anhydrous magnesium sulfate was the drying reagent throughout, and the silica gel for chromatography was 230-400 mesh. Analyses are by Guelph Chemical Laboratories, Ltd. and by Spang Microanalytic Laboratory.

2. **1,4-Dibromo-2,5-diiodobenzene 1.** A solution of 1,4-dibromobenzene (5.8 g, 24.6 mmol) and iodine (24 g, 94.5 mmol) in 80 mL of concentrated sulfuric acid was vigorously agitated with a magnetic stirrer while the reaction mixture was held at 125-130°C for 6 h. The mixture was poured into

ice-water and the precipitated crystalline solid was filtered and washed successively with aqueous sodium bisulfite, sodium bicarbonate and water. Recrystallization from benzene gave 8.4 g (70%) of 1 as white needles, mp 163-165°C (lit. 161-163°C) ^{1}H-NMR δ 7.97 (s); mass spectrum, m/e (relative intensity) 490 (28), 488 (54), 486 (M^+, 28), 363 (11), 361 (18), 359 (9), 236 (15), 234 (30), 232 (17), 155 (25), 153 (26), 74 (100).

3. **1,5-Dibromo-2,4-diiodobenzene 18.** The procedure and workup is essentially the same as for **1**. From 5.9 g (25 mmol) of 1,3-dibromobenzene, 12.7 g (50 mmol) of iodine in 80 mL of concentrated sulfuric acid there was obtained 7.9 g of **18** as white needles from benzene, mp 166-167°C ^{1}H-NMR δ 7.78 (s, 1 H), 8.17 (s, 1 H); mass spectrum, m/e (relative intensity) 490 (40), 488 (81), 486 (M^+, 41), 363 (14), 361 (24), 359 (11), 236 (18), 234 (34), 232 (18), 74 (100). Anal. Calcd for $C_6H_2Br_2I_2$: C, 14.78; H, 0.41; Br, 32.77; I, 52.04. Found: C, 14.64; H, 0.34; Br, 32.73; I, 51.96.

4. **General Procedure A for p-Terphenyl Synthesis.** A solution of 1,4-dibromo-2,5-diiodobenzene (2.44 g, 5 mmol) in 40 mL of THF was added slowly over 30 min to a solution of arylmagnesium bromide (prepared from 25 mmol of aryl bromide, 27.5 mmol of magnesium in 60 mL of THF), and the mixture was stirred for an additional 2 h at room temperature. The reaction was quenched with ice and dilute

hydrochloric acid and the mixture was extracted with chloroform. The organic layer was dried and the solvent was evaporated under reduced pressure to give a mixture of a solid and an oil, which was washed with hexane and filtered to give the first crop of terphenyl product. Chromatography of the filtrate using hexane as the eluent gave the second crop of terphenyl. The yields reported in Table 1 are based on the sum of two crops of the products collected.

5. **Iodine Quench; 2',5'-diiodo-p-terphenyl** 4. The general procedure A for p-terphenyl described above was followed, but before quenching with ice, the reaction mixture was cooled to 10°C, 7.6 g (30 mmol) of iodine was added and the mixture was stirred at 10°C for 1 h, then warmed to room temperature. It was successively treated with ice-water, extracted with chloroform and the organic layer was dried and evaporated under reduced pressure. The residue, a solid and oil, was washed with a little benzene and filtered to give mainly diiodo-p-terphenyl. Recrystallization from benzene gave 1.25 g of pure 4 as white needles. Chromatography of the filtrate using hexane as eluent gave 0.7 g (29%) of 1 and an additional 0.1 g of 4 (overall yield 57%); mp 262-263°C, ^{1}H-NMR δ 7.34-7.50 (m, 10 H), 7.88 (s, 2 H); mass spectrum, m/e (relative intensity) 483 (10), 482 (M^+, 59), 241 (13), 228 (100), 227 (24), 226 (72). Anal. Calcd for $C_{18}H_{12}I_2$: C, 44.84; H, 2.51. Found: C, 44.92; H, 2.60.

6. **2,4,6,2",4",6"-Hexamethyl-p-terphenyl 25.** The general procedure A was followed. For **25**: ^{1}H-NMRδ2.06 (s, 12 H), 2.34 (s, 6 H), 6.96 (s, 4 H), 7.16 (s, 4 H); mass spectrum, m/e (relative intensity) 315 (23), 314 (M^+, 100), 157 (22), 142 (20), 133 (30). Anal. Calcd for $C_{24}H_{26}$: C, 91.72; H, 8.28. Found: C, 91.96; H, 8.30.

7. **1,4-[1',1"-Dinaphthyl]benzene 26.** The general procedure A was followed. For **26**: ^{1}H-NMR δ 7.18-8.0 (m); mass spectrum, m/e (relative intensity) 330 (M^+, 100), 202 (30), 163 (27); high resolution mass spectrum; Calcd for $C_{26}H_{18}$: 330.14103. Found: 330.14084.

8. **Reaction of 18 with phenylmagnesium bromide.** A solution of **18** (2.44 g, 5 mmol) in 20 mL of THF was added over 15 min to a stirred solution of phenylmagnesium bromide (20 mmol) in 80 mL of THF. The mixture was stirred at room temperature for 2.5 h, then quenched with ice and dilute hydrochloric acid. Extraction with chloroform, drying and evaporation of the solvent gave a solid mixed with an oil. This mixture was washed with a little hexane and filtered to give 0.16 g of nearly pure p-terphenyl. The filtrate was chromatographed using hexane as eluent to give 0.72 g (46%) of 1,3-dibromo-4-iodobenzene **20**, mp 45-46^{o}C (lit.[60] mp 45-46^{o}C) and 0.32 g of terphenyls. The separation of p- and m-terphenyls by column chromatography was difficult, so the

mixture was analyzed by gas chromatography (SE-30 column, 1/4"x6", 180-300°C at 8°C/min) The procedure was standardized with authentic commercially available (Aldrich) P- and m-terphenyls and showed that a total of 0.41 g (37%) of p-terphenyl and 0.07 g (6%) of m-terphenyl was present.

9. **The effect of lithium 2,2,6,6-tetramethylpiperidide on the reaction of 1 with phenylmagnesium bromide.** The reaction was carried out according to the general procedure A but prior to the aqueous quench a solution of LiTMP (5 mmol) in 10 mL of hexane was added over 30 min to the reaction mixture. After 1 h of additional stirring at room temperature, the reaction was worked up as usual. There was obtained 0.85 g (74%) of p-terphenyl.

A similar procedure increased the yields of **22** and **24** from those shown in Table 1 to 74% and 71% respectively.

10. **The effect of potassium t-butoxide on the reaction of 1 with phenylmagnesium bromide.** The reaction was carried out according to the general procedure A but prior to the aqueous quench a solution of 5 mmol of potassium t-butoxide in 10 mL of THF was added over 30 min to the reaction mixture. After 1 h of additional stirring at room temperature the reaction was worked up as usual, to give 0.86 g (75%) of p-terphenyl and 0.14 g (8%) of **6**.

11. General Procedure B for Biaryl Synthesis. Preparation of 4-Methylbiphenyl 40. A solution of o-bromoiodobenzene **30** (2.83 g, 10 mmol) in 20 mL of dry THF was added slowly over 90 min to a freshly prepared solution of p-tolylmagnesium bromide (from 3.42 g 20 mmol of p-bromotoluene and 0.48 g of Mg in 60 mL of THF). The mixture was stirred for an additional 2 h at room temperature, then quenched with ice and dilute HCl. The THF was removed under reduced pressure and the aqueous solution was extracted with chloroform. The organic extract was washed with sodium bicarbonate, water, and dried ($MgSO_4$). Evaporation of the solvent left a brown oil (4.2 g) which was chromatographed on silica gel using hexane as the eluent to give 1.20 g (71%) of 4-methylbiphenyl, mp 48-49^{o}C (lit.[71] value 49-50^{o}C).

12. General Procedure C for Biaryl Synthesis. Preparation of 3,4-Dimethoxybiphenyl 45. The reaction was carried out according to procedure B, using 10 mmol of 4-bromo-5-iodo-veratrole and 20 mmol of phenylmagnesium bromide. Prior to aqueous quench, a solution of lithium tetramethylpiperidide (10 mmol) in 10 mL of hexane was added over 30 min and the reaction mixture was stirred at room temperature for an additional 3 h. Then aqueous workup was followed as uaual. The gradient elution of the reaction mixture on silica gel using a hexane and benzene mixture afforded 1.47 g (69%) of 3,4-dimethoxybiphenyl, mp 68-69^{o}C

(from methanol; lit.[74] value 67-68°C).

13. **Preparation of 2-bromobiphenyl 41 (Bromine quench).** The reaction between o-bromoiodobenzene (10 mmol) and phenylmagnesium bromide (30 mmol) was carried out using procedure B, but instead of an aqueous quench the reaction mixture was added to 16 g of bromine in 15 mL of carbon tetrachloride cooled in an ice bath. The mixture was then warmed to room temperature, treated with 10% sodium bicarbonate to destroy the excess bromine, extracted with chloroform and worked up as usual to give 1.46 g (63%) of 2-bromobiphenyl and about 3% of 2-iodobiphenyl.

14. **Preparation of 2-iodo-4,5-dimethoxybiphenyl 46 (Iodine quench).** Procedure C was followed as described above for the preparation of **45**, but instead of an aqueous quench, 7.6 g (30 mmol) of iodine was added to the reaction mixture which was then stirred for an additional hour. Excess iodine was destroyed with sodium sulfite and the usual workup gave 1.97 g (58%) of **46** mp (methanol) 107-108.5°C (lit.[74] value 109°C).

15. **2-Iodo-4,5-dimethylbiphenyl 42.** Procedure B was followed to afford a 65% yield of **42**. B.p. 155-157°C at 1 Torr, ^{1}H-NMR: δ 2.20 (s, 3 H), 2.22 (s, 3 H), 7.05 (s, 1 H), 7.28-7.40 (m, 5 H), 7.69 (s, 1 H); mass spectrum, m/e (relative intensity) 308 (M^+, 100), 166 (53), 165 (72);

Anal. Calcd for $C_{14}H_{13}I$: C, 54.54; H, 4.22. Found: C, 54.72; H, 4.11.

16. **2-Iodo-3',4'-dimethylbiphenyl 44.** Procedure B was followed to afford a 64% yield of **44**. B.p. 157-158°C at 1 Torr, ^{1}H-NMR: δ 2.30 (s, 6 H), 6.94-6.99 (m, 1 H), 7.03-7.18 (m, 3 H), 7.20-7.37 (m, 2 H), 7.90-7.94 (m, 1 H); mass spectrum, m/e (relative intensity) 308 (M^+, 100), 166 (59), 165 (68), 154 (21); Anal. Calcd for $C_{14}H_{13}I$: C, 54.54; H, 4.22. Found: C, 54.33; H, 4.39.

17. **2-(2'-Iodophenyl)naphthalene 48.** Procedure C was followed using hexane as the eluent in column chromatography to afford a 60% yield of **48**. mp 80-82°C from benzene; ^{1}H-NMR δ 7.02-7.09 (m, 1 H), 7.38-7.44 (m, 2 H), 7.45-7.78 (m, 3 H), 7.82 (s, 1 H), 7.85-7.93 (m, 3 H), 7.97-8.05 (m, 1 H); mass spectrum, m/e (relative intensity) 330 (M^+,39), 204 (100), 203 (46), 202 (72), 101 (26); Anal. Calcd for $C_{16}H_{11}I$: C, 58.18; H, 3.33. Found: C, 58.23; H, 3.34.

18. **1-(2'-Iodo-4',5'-dimethylphenyl)naphthalene 49.** Procedure C was followed using hexane as the eluent in column chromatography to afford a 63% yield of **49**. mp 145-146.5°C from benzene; ^{1}H-NMR: δ 2.25 (s, 3H), 2.31 (s, 3 H), 7.11 (s, 1 H), 7.20-7.28 (d, 1 H), 7.30-7.56 (m, 4 H), 7.77 (s, 1 H), 7.84-7.90 (m, 2 H); mass spectrum, m/e (relative intensity) 358 (M^+, 59), 231 (72), 215 (100); Anal. Calcd

for $C_{18}H_{15}I$: C, 60.33; H, 4.19. Found: C, 60.30; H, 4.16.

19. **Hexabromobenzene 55.** A solution of 1,4-dibromobenzene (29.5 g, 125 mmol), bromine (80 g, 500 mmol) and a catalytic amount of iron (1.0 g) and iodine (1.0 g) in 200 mL of oleum (29% SO_3) was vigorously stirred (magnetic) at 60-70°C for 6 h. The mixture was poured into ice water and the precipitated solid was filtered and washed successively with aqueous sodium bisulfite, sodium bicarbonate and water. Recrystallization from benzene gave 60 g (89%) of hexabromobenzene **55** as white needles, mp 320°C (lit.[113] value 319-321°C).

20. **1,2,4,5-Tetrabromo-3,6-dichlorobenzene 56.** The procedure and workup were essentially the same as for **55**. From 8.2 g (56 mmol) of 1,4-dichlorobenzene, 36 g (225 mmol) of bromine, 0.25 g of iron and 0.25 g of iodine in 82 mL of oleum (29% SO_3), there was obtained 23.7 g (92%) of **56** as white needles from toluene, mp 279-280°C (lit.[114] value 281°C).

21. **General Procedure D for Tetraarylbenzene Synthesis. Preparation of 1,2,4,5-Tetraphenylbenzene 57.** A suspension of 1,2,4,5-tetrabromo-3,6-dichlorobenzene **56** (2.2 g, 5 mmol) in 20 mL of THF was added slowly over 30 min. to a solution of phenylmagnesium bromide (prepared from 6.28 g, 40 mmol, of bromobenzene, 0.92 g, 40 mmol, of magnesium in 80 mL of

THF) and the mixture was stirred for an additional 12 h at room temperature. The reaction was quenched with ice and dilute hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was dried and the solvent was evaporated under reduced pressure to give a mixture of a solid and an oil. This mixture was washed with hexane and filtered to give 0.85 g of nearly pure 1,2,4,5-tetraphenylbenzene **57**. Chromatography of the filtrate using hexane as the eluent gave 0.35 g (18%) of 1,2,4-tribromo-3,6-dichlorobenzene and 0.40 g of additional **57** (total yield 65%), mp 267-268°C from benzene (lit.[77] value 263-264°C).

22. **Preparation of 1,4-dibromo-2,3,5,6-tetraphenylbenzene 87 (Bromine quench)**. The general procedure D was followed, but prior to quenching with ice, the reaction mixture was cooled to 10°C and a solution of bromine (9.6 g, 60 mmol) in 40 mL of CCl_4 was added and the mixture was stirred at 10° C for 1 h. It was then quenched with ice water and worked up as usual to give a solid and oil. This mixture was washed with a little benzene and filtered to give 0.8 g of **87** contaminated with a little **56**. Chromatography of the filtrate using hexane-benzene (V:V=1:1) as the eluent gave 0.5 g of additional **87**. Recrystallization from methylene chloride gave 1.30 g (50%) of pure **87** as white needles mp 423-424°C; ^{1}H-NMR δ 7.07-7.22 (m); mass spectrum, m/e (relative intensity) 542 (21), 540 (47), 538 (20), 380 (38), 302 (45), 273 (21), 271 (47), 269

(21), 182 (100), 181 (97). Anal. Calcd for $C_{30}H_{20}Br_2$: C, 66.69; H, 3.72. Found: C, 66.40; H, 3.81.

23. **Preparation of 1,4-diiodo-2,3,5,6-tetra-p-tolylbenzene 90 (Iodine quench).** The general procedure D was followed, but prior to aqeuous quench, the reaction mixture was cooled in the ice-water bath and 50 mmol of iodine was added in several portions. The quenched mixture was warmed to room temperature and worked up as usual to give a solid and oil. The mixture was washed with 10-15 mL of benzene and filtered to give 1.25 g of **90**. Chromatography of the filtrate using hexane-CH_2Cl_2 as eluent gave 0.3 g of additional **90**. Recrystallization from benzene gave 1.55 g of pure **90** as white crystals mp 387-389°C; ^{1}H-NMR δ 2.25 (s, 12 H), 6.89-6.92 (d, 8 H), 6.96-6.99 (d, 8 H); mass spectrum, m/e (relative intensity) 690 (M^+, 100), 436 (58); Anal. Calcd for $C_{34}H_{28}I_2$: C, 59.15; H, 4.09. Found: C, 59.22; H, 4.02.

24. **Preparation of 1,4-dideutero-2,3,5,6-tetramesitylbenzene 86 (Deuterium oxide quench).** The general procedure D was followed. The reaction mixture, which contained a heavy precipitate, was poured to a mixture of deuterium oxide and d^1-acetic acid cooled in ice-water bath and worked up as usual to generate a solid mixture. The mixture was treated with 30-50 mL of benzene and gave a solid product which was later identified as the [4+2] biscycloadduct **159**.

Chromatography of the residue using hexane-CH_2Cl_2 (V:V=9:1) gave a 30% yield of **86**, mp 258-259°C (from benzene); ^{1}H-NMR δ 1.99 (s, 24 H), 2.20 (s, 12 H), 6.73 (s, 8 H); mass spectrum, m/e (relative intensity) 553 (44), 552 (M^+, 100), 551 (24), 537 (16), 376 (25), 231 (21), 216 (21); Anal. Calcd for $C_{42}H_{44}D_2$: C, 91.25. Found: C,91.37.

25. **Reaction of 1,4-dibromo-2,3,5,6-tetrachlorobenzene with Phenylmagnesium Bromide.** The general procedure D was followed, using 5 mmol of **68**, 40 mmol of phenylmagnesium bromide and a reaction time of 16 h at room temperature. The usual workup afforded 2.1 g of crude solid product which was chromatographed on silica gel to give first, with petroleum ether as the eluent, 0.66 g (61%) of 1,2,4,5-tetrachlorobenzene which was recrystallized from benzene, mp 138-140°C (lit.[115] value 139-140°C). Further elution with benzene-petroleum ether (V:V=40:60) gave 0.69 g (36%) of 1,2,4,5-tetraphenylbenzene with properties identical to those described above.

26. **Reaction of Bromopentachlorobenzene 70 with Phenylmagnesium Bromide.** The general procedure D was followed, using 1 mmol of **70** suspended in 10 mL of THF added over 10 min to 8 mmol of phenylmagnesium bromide in 40 mL of THF, with a reaction time of 13 h at room temperature. The usual workup gave, after chromatography on silica gel with hexane as eluent, 225 mg (90%) of pentachlorobenzene.

The product was recrystallized from benzene-ethanol to give white needles, mp 84-85°C (lit.[116] value 85-86°C). No tetraphenylbenzene was isolated on further elution of the silica gel column.

27. **1,2,4,5-Tetra-p-tolylbenzene 74.** The general procedure D was followed. mp 247-249°C; ^{1}H-NMR δ 2.33 (s, 12 H), 7.02-7.12 (m, 16 H), 7.48 (s, 2 H); mass spectrum, m/e (relative intensity) 440 (5), 439 (36), 438 (M^+, 100), 219 (5), 204 (13), 196 (16), 189 (16), 130 (18), 85 (20). Anal. Calcd for $C_{34}H_{30}$: C, 93.11; H, 6.89. Found: C, 93.15; H, 6.91.

28. **1,2,4,5-Tetra-m-tolylbenzene 75.** The general procedure D was followed. mp 157-158°C; ^{1}H-NMR δ 2.27 (s, 12 H), 6.95-7.15 (m, 16 H) 7.50 (s,2 H); mass spectrum, m/e (relative intensity) 440 (5), 439 (27), 438 (M^+, 100), 423 (4), 407 (4), 219 (9), 189 (50). Anal. Calcd for $C_{34}H_{30}$: C, 93.11; H, 6.89. Found: C, 92.91; H, 6.91.

29. **1,2,4,5-Tetra-o-tolylbenzene 76.** The general procedure D was followed. mp 205-206°C; ^{1}H-NMR δ 2.0-2.3 (very broad s, 12 H), 6.88-7.16 (m, 16 H), 7.26 (s,2 H); mass specturm, m/e (relative intensity) 440 (5), 439 (32), 438 (M^+, 100), 423 (4), 397 (2), 347 (4), 333 (4), 219 (40), 189 (16). Anal. Calcd for $C_{34}H_{30}$: C, 93.11; H, 6.89. Found: C, 92.94; H, 6.81.

30. **1,2,4,5-Tetramesitylbenzene 77.** The general procedure D was followed. mp 258-259°C; ^{1}H-NMR δ 1.99 (s, 24 H), 2.21 (s, 12 H), 6.73 (s, 8 H), 7.05 (s, 2 H); mass spectrum, m/e (relative intensity) 552 (6), 551 (25), 550 (M^+, 88), 535 (12), 520 (3), 430 (3), 275 (4), 85 (100). Anal. Calcd for $C_{42}H_{46}$: C, 91.58; H, 8.42. Found: C, 91.56; H, 8.38.

31. **1,2,4,5-Tetra-1'-naphthylbenzene 78.** The general procedure D was followed. mp 352-355°C; ^{1}H-NMR δ 8.03-8.16 (m); mass spectrum, m/e (relative intensity) 584 (2), 583 (11), 582 (M^+, 23), 455 (1), 291 (5), 87 (32), 85 (100). Anal. Calcd for $C_{46}H_{30}$: C, 94.81; H, 5.19. Found: C, 94.66; H, 5.24.

32. **1,2,4,5-Tetra-2'-naphthylbenzene 79.** The general procedure D was followed. mp 324-325°C; ^{1}H-NMR δ 7.29 (dd, 4 H), 7.42-7.46 (m, 8 H), 7.59 (d, 4 H), 7.75-7.77 (m, 8 H), 7.85 (s, 2 H), 7.96 (s, 4 H); mass spectrum, m/e (relative intensity) 584 (7), 583 (27), 582 (M^+, 76), 491 (3), 455 (9), 415 (12), 291 (18), 126 (84), 40 (100). Anal. Calcd for $C_{46}H_{30}$: C, 94.81; H, 5.19. Found: C, 94.48; H, 5.23.

33. **1,2,4,5-Tetra-p-biphenylylbenzene 80.** The general procedure D was follwed. mp 380-381°C; ^{1}H-NMR δ 7.32-7.72 (m); mass spectrum, m/e (relative intensity) 686 (M^+, 14),

44 (100). Anal. Calcd for $C_{54}H_{38}$: C, 94.42; H, 5.58. Found: C, 94.26; H, 5.69.

34. **1,2,4,5-Tetra-m-biphenylylbenzene 81.** The general procedure D was followed. mp 257-259°C; ^{1}H-NMR δ 7.37-7.63 (m, 36 H), 7.73 (s, 2 H); mass spectrum, m/e (relative intensity) 688 (5), 687 (20), 686 (M^+, 58), 595 (4), 143 (8), 77 (11), 57 (12), 55 (12), 44 (100). Anal. Calcd for $C_{54}H_{38}$: C, 94.42; H, 5.58. Found: C, 94.25; H, 5.73.

35. **1,2,4,5-Tetra(o-ethylphenyl)benzene 84.** The general procedure D was followed. mp 223-225°C; ^{1}H-NMR δ 0.88-1.38 (broad m, 12 H), 2.22-2.82 (broad m, 8 H), 6.82-7.23 (m, 16 H), 7.24 (s, 2 H); mass spectrum, m/e (relative intensity) 495 (36) 494 (M^+, 100), 315 (11), 215 (17), 129 (29), 119 (46), 117 (26), 105 (39); Anal. Calcd for $C_{38}H_{38}$: C, 92.26; H, 7.74. Found C, 92.06; H, 7.74.

36. **1,2,4,5-Tetra(2,6-dimethylphenyl)benzene 83.** The general procedure D was followed. mp 288-290°C; ^{1}H-NMR δ 2.05 (s, 24 H), 6.88-6.94 (d, 4 H), 6.98-7.05 (dd, 4 H), 7.14 (s, 2 H); mass spectrum, m/e (relative intensity) 495 (37), 494 (M^+, 100), 479 (13), 439 (10); Anal. Calcd for $C_{38}H_{38}$: C, 92.26; H, 7.74. Found C, 92.56; H, 7.67.

37. **1,2,4,5-Tetra(pentamethylphenyl)benzene 82.** The general procedure D was followed. mp 376-378°C; ^{1}H-NMR δ

1.94 (s, 24 H), 2.09 (s, 24 H), 2.15 (s, 12 H), 7.04 (s, 2 H); mass spectrum, m/e (relative intensity) 661 (M^+-1, 2), 337 (7), 149 (13); Anal. Calcd for $C_{50}H_{62}$: C, 90.57; H, 9.43. Found C, 90.35; H, 9.27.

38. **1,4-Dibromo-2,3,5,6-tetra-m-tolylbenzene 88.** The general procedure D was followed. Prior to quenching with ice, the reaction mixture was treated with bromine and worked up as usual. mp 327-330°C; ^{1}H-NMR δ 2.22 (s, 6 H), 2.23 (s, 6 H), 6.82-7.00 (m, 12 H), 7.02-7.12 (m, 4 H); mass spectrum, m/e (relative intensity) 598 (16), 596 (50), 594 (22), 436 (17), 420 (11), 218 (11), 210 (29), 203 (33), 202 (23), 201 (15), 200 (12), 195 (100), 188 (47), 187 (21), 182 (30), 163 (22). Anal. Calcd for $C_{34}H_{28}Br_2$: C, 68.47; H, 4.73. Found: C, 68.62; H, 4.74.

39. **1,4-Dibromo-2,3,5,6-tetra-o-tolylbenzene 89.** The general procedure D was followed. Prior to quenching with ice, the reaction mixture was treated with bromine and worked up as usual. mp 329-330°C; ^{1}H-NMR (300°K) δ 2.11, 2.16, 2.19, 2.25, 2.28 (singlets of nonintegral intensity, 12 H), 6.85-7.15 (m, 16 H); mass spectrum, m/e (relative intensity) 598 (19), 596 (37), 594 (19), 437 (15), 436 (38), 252 (30), 163 (62), 91 (100). Anal. Calcd for $C_{34}H_{28}Br_2$: C, 68.47; H, 4.73. Found: C, 68.55; H, 4.76.

40. **1,4-Diiodo-2,3,5,6-tetra-o-tolylbenzene 92.** The

general procedure D was followed. Prior to quenching with ice, the reaction mixture was treated with iodine and worked up as usual. mp 320-322°C (from benzene); ^{1}H-NMR δ 2.12, 2.16, 2.17, 2.18, 2.21, 2.24, 2.25 (singlets of nonintegral intensity, 12 H), 6.87-7.10 (m, 16 H); mass spectrum, m/e (relative intensity) 690 (M^+, 100), 436 (46); Anal. Calcd for $C_{34}H_{28}I_2$: C, 59.15; H, 4.09. Found: C, 59.24; H, 4.14.

41. **1,4-Diiodo-2,3,5,6-tetra-m-tolylbenzene 91.** The general procedure D was followed. Prior to quenching with ice, the reaction mixture was treated with iodine and worked up as usual. mp 327-329°C (from benzene); ^{1}H-NMR δ 2.20 (s, 6 H), 2.22 (s, 6 H), 6.78-6.92 (m, 12 H), 7.01-7.10 (m, 4 H); mass spectrum, m/e (relative intensity) 690 (M^+, 6), 689 (20), 436 (29), 43 (100); Anal. Calcd for $C_{34}H_{28}I_2$: C, 59.15; H, 4.09. Found: C, 59.06; H, 4.18.

42. **1,4-Diiodo-2,3,5,6-tetra-(2,6-dimethylphenyl)-benzene 93.** The general procedure D was followed. Prior to quenching with ice, the reaction mixture was treated with iodine and worked up as usual. mp 352-354°C (from benzene); ^{1}H-NMR δ 2.03 (s, 24 H), 6.87-6.93 (d, 8 H), 7.01-7.09 (m, 4 H); mass spectrum, m/e (relative intensity) 746 (M^+, 7), 745 (30), 492 (17), 41 (100); Anal. Calcd for $C_{38}H_{36}I_2$: C, 61.18; H, 4.36. Found: C, 61.17; H, 4.48.

43. **1,2,4,5-Tetra-m-anisylbenzene 85.** The general

procedure D was followed. mp 199-200°C; ^{1}H-NMR δ 3.63 (s, 12 H), 6.80-7.30 (m, 16 H), 7.56 (s, 2 H); mass spectrum, m/e (relative intensity) 504 (8), 503 (37), 502 (M^+, 100), 396 (2), 78 (8), 43 (9). Anal. Calcd for $C_{34}H_{30}O_4$: C, 81.25; H, 6.02. Found: C, 81.19; H, 6.06.

44. **2,6-Dibromoiodobenzene 94.** To a solution of 2,6-dibromoaniline (15 g 0.06 mol) in 30 mL of concentrated HCl was added dropwise at 0-5°C a solution of sodium nitrite (4.32 g, 0.062 mol) in 20 mL of water. After being stirred for 30 min, the diazonium solution was poured through a glass wool filter into a solution of potassium iodide (99.3 g) in 150 mL of water. The solution was stirred vigorously for 1 h, then 200 mL of CH_2Cl_2 and 20 ml of 1 N Na_2SO_3 were added successively. The aqueous layer was separated, washed with CH_2Cl_2 and the combined organic layers were washed with 10% aqueous NaOH, water and dried. The light-red solid residue obtained after solvent removal was washed with a little petroleum ether (35-60°C) and recrystallized from benzene-ethanol to give 17 g (73%) of **94**, mp 98-99°C (lit.[84] value 99.0-99.5°C).

45. **General procedure E for m-Terphenyl Synthesis.** To a stirred arylmagnesium bromide solution (prepared from 17.5 mmol of aryl bromide and 19.3 mmol of magnesium in 40 mL of THF) under argon was added dropwise over 1 h at the temperature shown in Table 5 5 mmol of 2,6-dibromoiodoben-

zene in 20 mL of THF. Stirring was continued for 3-10 h, after which the reaction was quenched with 40 mL of cold, dilute HCl. The THF was removed under reduced pressure and the aqueous solution was extracted several times with CH_2Cl_2. Combined organic layers were washed with Na_2SO_3, water and dried. The residue obtained after solvent removal was chromatographed and/or recrystallized to give the products in the isolated yields shown in Table 5.

46. **Effect of Reactant Ratio on Yield.** The reaction in entry 1 Table 5 was studied briefly to determine the effect of phenylmagnesium bromide/2,6-dibromoiodobenzene ratio on the yield of m-terphenyl. With the theoretical ratio of 3:1, the yield of m-terphenyl was 70%. The yield increased to 77% with a ratio 3.5:1 as given in Table 5 and to 80-90% with a ratio 5:1.

47. **2,4,6,2",4",6"-Hexamethyl-1,1':3',1"-terphenyl 104.** The general procedure E was followed. mp 133-134°C, ^{1}H-NMR δ 2.03 (s, 12 H), 2.31 (s, 6 H), 6.93-7.43 (m, 8 H); mass spectrum, m/e (relative intensity) 315 (25), 314 (M^+, 100), 299 (26), 157 (33), 133 (28), Anal. Calcd for $C_{24}H_{26}$: C, 91.66; H, 8.33. Found: C, 91.87; H, 8.11.

48. **2,2"-Dimethoxy-1,1':3',1"-terphenyl 109.** The general procedure E was followed. mp 97-98.5°C, ^{1}H-NMR δ 3.80 (s, 6 H), 6.96-7.69 (m, 12 H); mass spectrum, m/e

(relative intensity) 290 (M^+, 100), 260 (16), 231 (16), 215 (26), 131 (16), 119 (27), 115 (19), 101 (18), 94 (16). Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.71; H, 6.33.

49. **2,5,2",5"-Tetramethoxy-1,1':3',1"-terphenyl 110.** The general procedure E was followed. mp 122-124°C, ^{1}H-NMR δ 3.76 (s, 6 H), 3.79 (s, 6 H), 6.82-7.69 (m, 10 H); mass spectrum, m/e (relative intensity) 351 (23), 350 (100), 175 (21), 160 (34), 152 (35). Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.40; H, 6.40.

50. **2'-Iodo-1,1':3',1"-terphenyl 96 (Iodine quench).** The general procedure E was followed using 2,6-dibromoiodobenzene (10 mmol) and phenylmagnesium bromide (50 mmol), but instead of quenching with dilute HCl, the reaction mixture was cooled in an ice bath and iodine (60 mmol) was added. The mixture was stirred vigorously as it warmed to room temperature. It was then washed with aqueous Na_2SO_3, extracted several times with ether, and the combined ether extracts were washed with water and saturated NaCl solution, and dried. The residue after removal of the solvent was chromatographed (silica gel, hexane) and recrystallized from ethanol to give **96** (88%), mp 113.5-115°C (lit.[85] 114.4°C).

51. **1,1':3',1"-Terphenyl-2'-carboxanilide 114. From**

96. The iodoterphenyl **96** was prepared as described above. To 356 mg (1 mmol) of iodoterphenyl in 10 mL THF at room temperature under argon was added ethylmagnesium bromide (1.15 mmol in 10 mL of THF). The mixture was stirred for 6 h and then heated at reflux for 30 min. After it was cooled to room temperature, phenyl isocyanate (1.6 mmol in 5 mL of THF) was added dropwise and stirring was continued overnight. Dilute HCl was added, and the mixture was extracted with ether. The combined extracts were dried and evaporated. The residue was chromatographed on silica gel with petroleum ether-ethyl acetate (V:V=70:30) as the eluent. The product was recrystallized from acetic acid to give 296 mg (85%) of **114**. mp 270-271^{o}C, ^{1}H-NMR: δ 6.85-7.59 (m). IR (KBr) 3230, 3190, 3130, 3060, 1645, 1605 cm^{-1}. mass spectrum, m/e (relative intensity) 349 (M^{+}, 19), 257 (100), 228 (30). Anal. Calcd for $C_{25}H_{19}NO$: C, 85.93; H,5.48. Found: C, 85.87; H, 5.54.

52. **1,1':3',1"-Terphenyl-2'-carboxanilide 114. From 94.** The general procedure E was followed with **94** (5 mmol) and phenylmagnesium bromide, but prior to aqueous quench, a solution of phenyl isocyanate (35 mmol) in 20 mL of THF was added at room temperature, and stirring was continued for 1 h. The mixture was poured into dilute HCl and extracted with CH_2Cl_2. The combined extracts were washed with water, dried and the solvent removed to leave a residue that was chromatographed as above to give 1.1 g (63%) of **114**.

53. **5'-bromo-1,1':3',1"-terphenyl 117.** The general procedure E was followed, but with 2,4,6-tribromoiodobenzene **115** in place of **94**, and the mixture was heated at reflux for 1.5 h before quenching with aqueous HCl. The usual workup gave, after chromatography (silica gel, hexane as eluent), 80% of **117** which was recrystallized from benzene-ethanol, mp 105-106°C (107.5-109°C after sublimation). ^{1}H-NMR δ 7.35-7.50 (m, 7 H), 7.57-7.63 (m, 4 H), 7.70 (s, 2 H). mass spectrum, m/e (relative intensity) 310 (69), 308 (M^+, 100), 228 (56), 152 (51), 113 (30), 77 (32); Anal. Calcd for $C_{18}H_{13}Br$: C, 69.90; H, 4.20. Found: C, 69.71; H, 4,40.

54. **5'-Chloro-1,1':3',1"-terphenyl 118.** The general procedure E was followed, but with 2,4,6-trichloroiodobenzene **116** in place of **94**. The mixture was heated at reflux for 1 h before quenching with aqueous HCl. The usual workup gave, after chromatography, 60% of **118** which was recrystallized from benzene-ethanol, mp 91-91°C; ^{1}H-NMR δ 7.34-7.48 (m, 6 H), 7.52-7.54 (m, 2 H), 7.55-7.63 (m, 4 H), 7.65 (t, 1 H); mass spectrum, m/e (relative intensity) 266 (46), 265 (28), 264 (M^+, 100), 228 (34), 226 (19), 114 (15), 113 (20), 101 (18); Anal. Calcd for $C_{18}H_{13}Cl$: C, 81.66; H, 4.96. Found: C, 81.68; H, 4.87.

55. **5"-Bromo-1,1':4',1":3",1"':4"',1""-quinquiphenyl 119.** The general procedure E was followed, but with **115** in

place of **94**. The mixture was heated at reflux for 2.5 h before quenching with aqueous HCl. Extraction with chloroform, drying and evaporation of the solvent gave a solid mixture which was recrystallized from benzene to afford 0.96 g of nearly pure **119**. The filtrate obtained from recrystallization was concentrated and chromatographed with CH_2Cl_2-hexane (V:V=2:8) to give 0.08 g of **119** (total yield 45%). mp 211-213°C (from benzene) ^{1}H- NMR δ 7.35-7.50 (m, 7 H), 7.62-7.80 (m, 14 H); mass spectrum, m/e (relative intensity) 462 (90), 460 (M^+, 100), 230 (72); Anal. Calcd for $C_{30}H_{21}Br$: C, 78.11; H, 4.59. Found: C, 78.28; H, 4.52.

56. **5',5"'-Diphenyl-1,1':3',1":3",1"':3"',1""-quinquiphenyl 113**. To a stirred 5'-m-terphenylmagnesium bromide solution (prepared from 1.5 g of **117**, 0.5 mL of 1,2-dibromoethane and 1 g of magnesium turnings in 25 mL of dry THF solution at reflux for 24 h) under argon was added dropwise over 1 h at reflux 452 mg (1.25 mmol) of **94** in 10 mL of THF. After stirring for 4 h, the reaction was worked up in the same way described in general procedure E. Elution of the reaction mixture with hexane-CH_2Cl_2 (V:V=9:1) on silica gel gave 385 mg (58%) of **113** mp 210.5-212°C (from benzene-ethanol), ^{1}H-NMR δ 7.34-7.65 (m, 13 H), 7.67-7.77 (m, 10 H), 7.80-7.86 (m, 6 H), 7.98 (s, 1 H); mass spectrum, m/e (relative intensity) 534 (M^+, 10), 306 (39), 243 (31), 165 (14), 78 (100); Anal. Calcd for $C_{42}H_{30}$: C, 93.34; H, 5.66. Found: C, 94.16, H, 5.75.

57. 5"-bromo-5',5"'-diphenyl-1,1':3',1":3",1"':3"',1""-quinquephenyl 120. To a stirred 5'-m-terphenylmagnesium bromide solution (prepared from 1.5 g of **117**, 0.5 mL of 1,2-dibromoethane and 1 g of magnesium turnings in 25 mL of dry THF at reflux for 6-8 h) under argon was added slowly over 1 h at reflux 441 mg (1 mmol) of 2,4,6-tribromoiodobenzene in 10 mL of THF. Stirring was continued for 2 h, and the reaction was worked up as usual. The mixture, after chromatography on silica gel with hexane-CH_2Cl_2 (V:V=9:1), gave 257 mg (42%) of **120**. mp 214-215°C (from benzene) ^{1}H-NMR δ 7.35-7.53 (m, 10 H), 7.65-7.75 (m, 8 H), 7.77-7.85 (m, 8 H), 7.88 (t, 1 H); mass spectrum, m/e (relative intensity) 614 (78), 612 (M^+, 100), 307 (38), 137 (75), 83 (69); Anal. Calcd for $C_{42}H_{29}Br$: C, 82.21; H, 4.76. Found: C, 82.21; H, 4.76.

58. 5',5"-Diphenyl- 1,1':3',1":3",1"'-quaterphenyl 122. The general procedure E was followed, using 164 mg (0.26 mmol) of 3,4,5,3',4',5'-hexabromobiphenyl **121** and 2.08 mmol of phenylmagnesium bromide. After being maintained for 2 h at room temperature and then for 4 h at reflux, the reaction was worked up and chromatographed on silica gel with hexane-CH_2Cl_2 (V:V=9:1) to give 95 mg (79%) of **122**. The product was recrystallized from benzene-ethanol to give white needles, mp 229-230°C (lit.[117] value 231-232°C).

59. **Reaction of o-bromoiodobenzene and styrylmagnesium bromide.** A solution of o-bromoiodobenzene **30** (1.41 g, 5 mmol) in 20 mL of dry THF was added slowly over 1 h at room temperature to a freshly prepared solution of styrylmagnesium bromide (from 2.7 g, 14.7 mmol, of β-bromostyrene and 0.4 g, 16.7 mmol, of Mg turnings in 30 mL of THF). The mixture was stirred for an additional 2 h and then quenched with ice and saturated NH_4Cl. The THF was removed and the aqueous solution was extracted with chloroform. The organic extract was washed with sodium bicarbonate and water and dried over $MgSO_4$. The reaction mixture, after evaporation of the solvent, was chromatographed on silica gel with hexane. The cis-stilbene and trans-stilbene were collected in two different portions. The total 77% yield included 0.64 g of trans-stilbene (recrystallized from benzene, mp 125-126°C, lit.[118] value 126-127°C) and 0.05 g of cis-stilbene (mp 3-4°C, lit.[120] value 5.6°C).

60. **Reaction of 1,4-dichloro-2,3,5,6-tetrabromobenzene and styrylmagnesium bromide.** To a solution of styrylmagnesium bromide solution (prepared from 7.3 g of β-bromostyrene and 1.06 g of Mg turnings in 50 mL of dry THF) was added a suspension of **56** in 30 mL of THF over 45 min at room temperature. Stirring was continued for an additional 9 h, and the reaction was then treated with dilute HCl. The suspension mixture was filtered to obtain

0.35 g of 1,2,4,5-tetrastyrylbenzene **129**. The filtrate was extracted with chloroform, and the extract was washed with Na_2SO_3 and water and dried over $MgSO_4$. The residue after solvent removal was chromatographed on silica gel with hexane-CH_2Cl_2 (V:V=8:2) to afford 0.85 g of **129** (total yield 49%). mp 268-274°C, ^1H NMR δ 7.07 (s), 7.13 (s), 7.28-7.44 (m), 7.45 (s), 7.52-7.59 (m), 7.80 (s). mp (lit.[101]) 273-275°C.

61. **Reaction of 2,6-Dibromoiodobenzene and styrylmagnesium bromide.** A soluton of dibromoiodobenzene **94** (1.8 g, 5 mmol) in 20 mL of dry THF was added dropwise over 1 h at room temperature to a freshly prepared solution of styrylmagnesium bromide (from 4.57 g of β-bromostyrene and 0.66 g of Mg turnings in 40 mL of THF). The mixture was stirred for an additional 6 h, then quenched with ice and saturated NH_4Cl. The THF was removed and the aqueous solution was extracted with chloroform. The organic layer was washed with sodium bicarbonate and water and dried over $MgSO_4$. The reaction mixture, after solvent removal, was chromatographed on silica gel with hexane-CH_2Cl_2 (V:V=9:1) to obtain 0.67 g (48%) of (E,E)-1,3-distyrylbenzene **127**. mp 162-165°C (from benzene), ^1H NMR δ 7.14 (s), 7.26 (s), 7.35 (s), 7.38 (s), 7.42 (s), 7.52 (s), 7.55 (d), 7.64 (s). mp (lit.[99]) 166-170°C; ^1H NMR (lit.[99]) δ 7.13-7.16 (J=16.5), 7.26 (t), 7.35 (t), 7.37 (t), 7.42 (d), 7.54 (d), 7.64 (s).

62. **Reaction of 1,4-Dibromo-2,5-Diiodobenzene and styrylmagnesium bromide.** To a solution of styrylmagnesium bromide solution (prepared from 5.49 g of β-bromostyrene and 0.79 g of Mg turnings in 50 mL of dry THF) was added a solution of **1** in 30 mL of THF over 1 h at room temperature. After stirring for an additional 3 h, the reaction was quenched with ice and dilute HCl. The suspension was filtered to afford 0.16 g of 1,4-(E,E)-Distyrylbenzene **128**. The filtrate was extracted with CH_2Cl_2 and the organic extract was washed with water and dried over $MgSO_4$. The reaction mixture was chromatographed, after solvent removal, with hexane-CH_2Cl_2 (V:V=9:1) to give 0.45 g (total yield, 44%) of **128**. mp 263-264°C (from benzene), lit.[100] value 266-267°C.

63. **Preparation of 1,2-diphenylvinylmagnesium bromide 130.** A solution of 1-bromo-1,2-diphenylethene[104] (3.87 g, 15 mmol) in 30 mL of dry THF was added to 0.43 g of Mg turnings over 30 min at ambient temperature. The solution was then refluxed for 1 h. The reaction was successively quenched with ice and dilute HCl and the aqueous layer was extracted with ether. The ether layer was washed with sodium sulfite and water and dried over $MgSO_4$. The crude reaction mixture, after solvent removal, gave 2.43 g (90%) of 1,2-trans-diphenylethene. mp 122-124°C, lit.[118] value 126-127°C.

64. **Reaction of 2,6-dibromoiodobenzene and 1,2-**

diphenylvinylmagnesium bromide 130. To a solution of **130** (prepared from 6.47 g of 1-bromo-1,2-diphenylethene[104] and 0.72 g of Mg turnings in 40 mL of dry THF) was added a solution of **94** (1.81 g, 5 mmol in 30 mL of THF) over 2 h at reflux. Stirring was continued for an additional 2 h. The reaction was quenched with ice and dilute HCl and extracted with chloroform. The organic extract was washed with water and dried. The reaction mixture, after evaporation of solvent, was eluted on silica gel with hexane-CH_2Cl_2 (V:V=9:1) to give 1.4 g (64%) of 1,3-bis(1,2-diphenylvinyl)benzene **131**. mp 149-150°C (from benzene-ethanol); ^{1}H-NMR δ 6.92 (s, 2 H), 7.07-7.88 (m, 24 H); mass spectrum, m/e (relative intensity) 435 (36), 434 (M^+, 100), 196 (39), 178 (44), 167 (33), 105 (63), 90 (32), 89 (33), 84 (50), 77 (65); Anal. Calcd for $C_{34}H_{26}$: C, 93.97; H, 6.03. Found: C, 94.02; H, 6.10.

65. **Reaction of 1,4-dibromo-2,5-diiodobenzene and 1,2-diphenylvinylmagnesium bromide 130.** To a solution of **130** (prepared from 6.2 g of 1-bromo-1,2-diphenylethene and 0.69 g of Mg turning in 40 mL of THF) was added a solution of dibromo-diiodobenzene (1.95 g in 30 mL of THF) over 2.5 h at reflux. After stirring was continued for an additional 3 h, the reaction was treated with ice and dilute HCl and worked up as usual. The chromatography of reaction residue on silica gel using hexane as the eluent gave 1.04 g (54%) of trans,trans-1,4-bis(1,2-diphenylvinyl)benzene **132**. mp 145-

146.5°C, lit.[102] value 145-146°C.

66. **Reaction of o-bromoiodobenzene and phenylethynylmagnesium bromide 136.** To a solution of **136** (prepared by the addition of 31 mmol of ethylmagnesium bromide to 30 mmol of phenylacetylene in 20 mL of THF at room temperature) was added a solution of 2.83 g (10 mmol) of o-bromoiodobenzene in 10 mL of THF at room temperature over 1 h. The solution was stirred for an additional 2 h. To the reaction mixture was added a solution of ethylmagnesium bromide (10 mmol in 25 mL of dry THF) over 3 h at room temperature. The reaction mixture was stirred for an additional 1.5 h, then quenched with ice and dilute HCl. The reaction mixture was extracted with chloroform, washed with water and dried. Chromatography of the reaction residue with hexane gave 1.10 g (61%) of diphenylacetylene. mp 58-60°C, lit.[119] value 61-62°C.

67. **Reaction of o-bromoiodobenzene and phenylethynylmagnesium bromide (iodine quench).** The reaction was carried out as described above. Prior to aquous workup, the reaction mixture was treated with 40 mmol of iodine and was worked up as usual. Column chromatography with hexane as the eluent gave 1.5 g (50%) of crude 1-iodo-2-(phenylethynyl)benzene **138**, which was purified by fractional vacuum distillation. B.p. 160-162°C at 1 torr ^{1}H-NMR δ 6.90-7.00 (m, 1 H), 7.24-7.38 (m, 4 H), 7.45-7.62 (m, 3 H), 7.85

(dd, 1 H): mass spectrum, m/e (relative intensity) 305 (12), 304 (84), 177 (29), 176 (100), 152 (29), 151 (51), 150 (38), 127 (20); Anal. Calcd for $C_{14}H_9I$: C, 55.15; H, 2.98. Found: C, 55.24; H, 2.85.

68. **Reaction of 2,6-dibromoiodobenzene and phenylethynylmagnesium bromide 136.** To a solution of **136** (prepared from 21 mmol of ethylmagnesium bromide and 20 mmol of phenylacetylene) was added a solution of 1.8 g (5 mmol) of **94** in 20 mL of THF at room temperature, Stirring was continued for an additional 2 h. Ethylmagnesium bromide (5 mmol) in 10 mmol of THF was added dropwise over 2 h at room temperature, and the reaction mixture was stirred for additional 1.5 h. Workup as usual and chromatography with hexane-CH_2Cl_2 (V:V=95:5) as the eluent afforded 0.52 g of 1,3-di-(phenylethynyl)benzene **140** mp 105-108°C, lit.[103] value 111-113.5°C.

69. **Reaction of 1,4-dibromo-2,3,5,6-tetrachlorobenzene 68 and phenylethynylmagnesium bromide 136.** To a solution of **136** (prepared from 52 mmol of ethylmagnesium bromide and 50 mmol of phenylacetylene) was added a suspension of **68** (1.87 g, 5 mmol in 20 mL of THF) at room temperature, and the stirring was continued for 1 h. Then, 5 mmol of ethylmagnesium bromide in 20 mL of THF was added over 2 h at room temperature, and the reaction mixture was continuously stirred for 30 min. The mixture was then

heated at reflux for 1.5 h and worked up as described above. Chromatography on silica gel with hexane-CH_2Cl_2 (V:V=80:20) gave 0.75 g (25%) of 1,2,4,5-tetra-(phenylethynyl)benzene **141**. mp 198-204°C, lit.[101] value 204-205°C.

70. **Preparation of 2,6-dichlorophenylmagnesium bromide 139.** 2,6-dichloroiodobenzene (5 mmol) in 10 mL of THF was cooled in a dry-ice/CCl_4 bath and ethylmagnesium bromide (5.5 mmol in 10 mL of THF) was added dropwise over 30 min. The mixture was stirred for an additional 1 h at the same temperature, then, treated with dilute HCl and worked up as usual. The product was nearly pure m-dichlorobenzene, which indicates that 2,6-dichlorophenylmagnesium bromide is generated and stable under these conditions. The yield, determined by gas chromatography, is 95%.

71. **Reaction of 2-thienylmagnesium bromide and 2,6-dichlorophenylmagnesium bromide.** 5 mmol of 2,6-dichlorophenylmagnesium bromide in 20 mL of THF, prepared as described above, was added dropwise to 2-thienylmagnesium bromide solution (15 mmol in 25 mL of THF) over one and half hours and stirred for an additional 2 h. Aqueous workup and column chromatography of reaction mixture gave 0.48 g (41%) of 1,3-di(2'-thienyl)-benzene, which recrystallized from ethanol as flakes. mp 86-87°C; ^{1}H-NMR δ 7.07-7.11 (dd, 2 H), 7.28-7.31 (dd, 2 H), 7.34-7.40 (m, 3 H), 7.50-7.53 (m, 2 H), 7.88 (t, 1 H); ^{13}C-NMR δ 123.49, 123.58, 125.14, 128.05,

129.43, 135.10, 143.99; mass spectrum, m/e (relative intensity) 243 (16), 242 ($^{+}$M, 100); Anal. Calcd for: $C_{14}H_{10}S_2$: C, 69.38; H,4.16. Found: C, 69.58; H, 4.17.

72. **Reaction of ethylmagnesium bromide and 2,6-dichloroiodobenzene 94.** To a solution of 20 mmol of ethylmagnesium bromide in 20 mL of THF was added 5 mmol of **94** in 20 mL of THF over 1 h at room temperature, and stirring was continued for an additional 2 h. The reaction mixture was quenched with dilute HCl and worked up as usual. The analysis of the reaction mixture by gas chromatography (SE-52 column, 1/4"x15", 60-200^{o}C at 10^{o}C/min) and comparison with authentic 1,3-diethylbenzene (purchased from Aldrich) showed a yield of 20 %.

73. **Biscycloadduct 158 (aqueous quench).** mp 306-308^{o}C (dec.); ^{1}H-NMR δ 1.89 (d, 12 H), 2.12 (s, 6 H), 4.98 (t, 2 H), 6.00 (t, 4 H); mass spectrum, m/e (relative intensity) 474 (20), 472 (47), 470 ($^{+}$M, 23), 312 (36), 311 (31), 297 (65), 296 (29), 282 (23), 281 (18); Anal. Calcd for $C_{24}H_{24}Br_2$: C, 61.04; H, 5.12. Found C, 60.99; H, 5.16.

74. **Biscycloadduct 159 (deuterium oxide quench)** . mp 306-308^{o}C (dec.); ^{1}H-NMR δ 1.89 (d, 12 H), 2.13 (s, 6 H), 4.98 (d, 2 H), 6.00 (t,2 H); mass spectrum, m/e (relative intensity) 476 (64), 474 (98), 472 ($^{+}$M, 53), 314 (57), 313 (52), 299 (100), 298 (44).

75. **Biscycloadduct 160 (methyl iodide quench)** . mp 240-245°C (dec.); ^{1}H-NMR δ1.67 (s, 6 H), 1.81 (s, 6 H), 1.89 (s, 6 H), 2.12 (s, 6 H), 4.96 (d, 2 H), 5.90 (t, 2 H); mass spectrum, m/e (relative intensity) 502 (14), 500 (33), 498 ($^{+}$M, 22), 421 (14), 419 (17), 339 (54), 325 (100), 324 (53), 310 (33), 309 (29), 295 (27), 119 (66); Anal. Calcd for $C_{26}H_{28}Br_2$: C, 62.42; H, 5.64. Found C, 62.53; H, 5.55.

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