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Synthetically Useful Aryl–Aryl Bond Formation via Grignard Generation and Trapping of Arynes. A One-Step Synthesis of *p*-Terphenyl and Unsymmetric Biaryls

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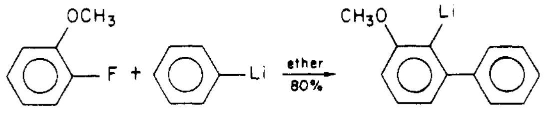
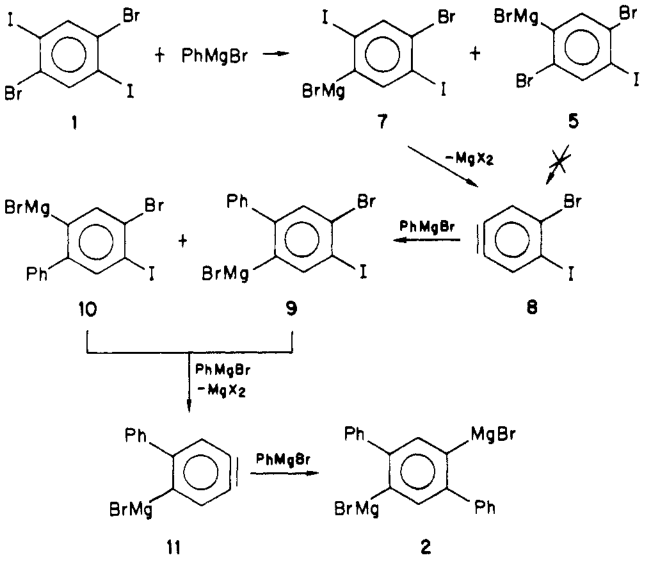
A one-pot route to *p*-terphenyls is described. Addition of 1,4-dibromo-2,5-diiodobenzene, 1, to excess aryl Grignard reagent gives the terphenyl di-Grignard 2 and the trihalo mono-Grignard 5. After aqueous quench, *p*-terphenyls are isolated in 30% to 50^+% yield (Table I). This yield can be improved to 70–80% by adding potassium *tert*-butoxide or lithium tetramethylpiperidide to the reaction mixture prior to workup. Mechanisms involving organometallic aryne intermediates are proposed. With *o*-bromoiodoarenes in place of tetrahaloarenes the method can be adapted to prepare unsymmetric biaryls in good yield (Table II).

The formation of aryl–aryl bonds continues to be an important problem in organic synthesis, and a substantial number of methods for effecting this construction are known.[2,3] Venerable methods still used, often with improved modifications, include the Ullmann, the Pschorr and Gomberg–Bachmann–Hey reactions, and the benzidine rearrangement. Newer methods involve mainly oxidative coupling of arenes, aryl halides, phenols, and other aromatic derivatives, using as reagents transition metals, chemical oxidants, or electrochemical methods.[4] Photochemical aryl–aryl bond formation is also widely used.[5]

Another method for aryl–aryl bond formation which, however, has seen only limited synthetic use, is the nucleophilic addition of aryllithiums or other aryl organometallics to arynes. This reaction was pioneered by Wittig, Huisgen, and co-workers.[6,7] It was a key reaction in the early recognition of benzyne as a reactive intermediate[8] 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.[9]



Scheme I



Here the intermediate aryne is formed by proton removal, but similar results may be obtained when the aryne is generated from 1,2-dihaloarenes by halogen–metal exchange.[10]

In connection with our interest in synthetic applications of diaryne equivalents,[11] we studied the reaction of Grignard reagents with polyhalogenated aromatics. We find that the reaction can be extremely useful in aryl–aryl bond formation and describe here the initial discovery and its application to *p*-terphenyl synthesis.[12,13] This new terphenyl synthesis has the following unique features: (1) two

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[1] On leave from Ube Industries, Ube, Japan.

[2] For general reviews, see: Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. Cheeseman, G. W. H.; Praill, P. F. G. In "Rodd's Chemistry of Carbon Compounds", 2nd Ed.; Elsevier: Amsterdam, 1974, Vol. IIIF, pp 1–9; MacBride, J. A. H. 1982 supplement; pp 301–314.

[3] For more specialized reviews, see: Grimshaw, J.; deSilva, A. P. *Chem. Soc. Rev.* **1981**, *10*, 181. Kozhevnikov, I. V.; Matveer, K. I. *Russ. Chem. Rev.* (*Engl. Transl.*) **1978**, *47*, 649. Dhingra, O. P. in "Oxidation in Organic Chemistry, Part D."; Trahanovsky, W. S., Ed.; Academic Press: New York, 1982, p 207. Ried, W.; Freitag, D. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 835. Laarhoven, W. H. *Recl. J. R. Neth. Chem. Soc.* **1983**, *102*, 185, 241.

[4] A recent extensive series of papers on the synthesis of a large variety of polyphenyls relies almost exclusively on only two reactions, the Ullmann and the nickel-catalyzed oxidative coupling of aryl Grignards with aryl iodides, see: Ozasa, S.; Fujioka, Y.; Hashino, H.; Kimura, N.; Ibuki, E. *Chem. Pharm. Bull. Jpn.* **1983**, *31*, 2313 and earlier references cited therein.

[5] Mallory, F. B.; Mallory, C. W. *Org. React.* (*N.Y.*) **1984**, *30*, 1.

[6] For a review, see: Hoffmann, R. W. "Dehydrobenzene and Cycloalkynes"; Academic Press: New York, 1967; Chapter 2. See also: Heaney, H. *Fortschr. Chem. Forsch.* **1970**, *16*, 35.

[7] The reaction has an old history, the formation of biphenyls from aryl halides and sodium dating back to 1864: Fittig, R. *Liebigs Ann. Chem.* **1864**, *132*, 202.

[8] Wittig, G.; Pieper, G.; Fuhrmann, G. *Chem. Ber.* **1940**, *73*, 1193. Wittig, G. *Naturwissenschaften* **1942**, *30*, 696.

[9] Huisgen, R.; Rist, H. *Justus Liebigs Ann. Chem.* **1955**, *594*, 137.

[10] Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334. Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217. Heaney, H.; Mann, F. G.; Millar, I. T. *J. Chem. Soc.* **1957**, 3930.

[11] (a) Sy, A.; Hart, H. *J. Org. Chem.* **1979**, *44*, 71. (b) Hart, H.; Lai, C.-Y.; Nwokogu, G.; Shamouilian, S.; Teuerstein, A.; Zlotogorski, C. *J. Am. Chem. Soc.* **1980**, *102*, 6649. (c) Hart, H.; Nwokogu, G. *J. Org. Chem.* **1981**, *46*, 1251. (d) Hart, H.; Shamouilian, S. *J. Org. Chem.* **1981**, *46*, 4874. (e) Hart, H.; Shamouilian, S.; Takehira, Y. *J. Org. Chem.* **1981**, *46*, 4427. (f) Hart, H.; Raju, N.; Meador, M. A.; Ward, D. L. *J. Org. Chem.* **1983**, *48*, 4357. (g) Hart, H.; Nwokogu, G. C. *Tetrahedron Lett.* **1983**, *24*, 5721. (h) Nwokogu, G. C.; Hart, H. *Tetrahedron Lett.* **1983**, *24*, 5725.

[12] For a brief preliminary account, see: Hart, H.; Harada, K. *Tetrahedron Lett.* **1985**, *26*, 29.

[13] The synthesis and chemistry of terphenyls is briefly reviewed by Cheeseman and Praill: Cheeseman, G. W. H.; Praill, P. F. G. In "Rodd's Chemistry of Carbon Compounds", 2nd ed.; Elsevier: Amsterdam, 1974; Vol. IIIF, pp 51–57; MacBride, J. A. H. 1982 supplement; pp 322–323. Clar, E. "Polycyclic Hydrocarbons"; Academic Press: New York, 1964; Vol. 2, pp 221–223. *p*-Terphenyls see extensive use as liquid crystals, see: Saeva, F. D., Ed. "Liquid Crystals"; Marcel Dekker, Inc.: New York, 1979.

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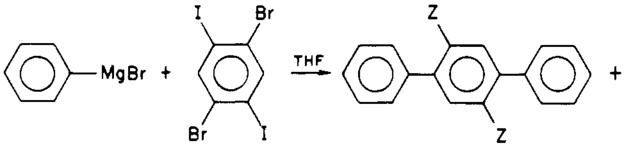
aryl–aryl bonds are formed in a one-pot reaction, (2) although the potential for forming both *m*- and *p*-terphenyls exists, only the latter are formed, (3) the reaction proceeds via a novel two-aryne sequence, (4) aryl Grignard reagents are used to generate and trap arynes, and (5) the product terphenyl has functionality which allows elaboration of the central ring. The method also has considerable utility for the synthesis of unsymmetric biaryls.

Results and Discussion

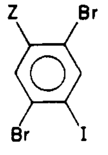
The essence of our method is to use a Grignard reagent to generate an aryne through metal–halogen exchange and then to trap it by nucleophilic addition. The Grignard reagent is therefore used in excess.

Addition of 1,4-dibromo-2,5-diiodobenzene (1)[14] in tetrahydrofuran (THF) to 4 equiv (or more) of phenylmagnesium bromide in THF at room temperature gave, after an aqueous quench, *p*-terphenyl 3 (54%) and 1,4-dibromo-2-iodobenzene, 6 (43%).[15] Quenching with iodine gave instead the diiodo terphenyl 4 (55%) and the starting dibromodiiodobenzene 1 (30%).[16] Hence it is clear that the principal reaction products from 1 and excess phenylmagnesium bromide are the terphenyl di-Grignard 2 and the trihalo mono-Grignard 5.



1

2, Z=MgX
3, Z=H
4, Z=I

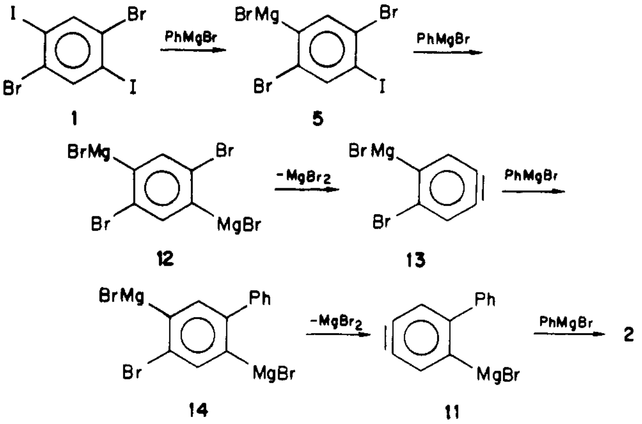


5, Z=MgX
6, Z=H
1, Z=I

Reaction Mechanism. In our preliminary account,[12] we proposed the mechanism outlined in Scheme I. If initial Grignard exchange can occur either at iodine or bromine, one would obtain 5 or 7, respectively. Aryne formation from 5 apparently does not occur at room temperature,[17] so that 5 remains as one of the two observed reaction products, trapped with water or iodine to give 6 or 1. However, if the halogen adjacent to the metal is iodine, as in 7, elimination may occur 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 terphenyl di-Grignard product 2.

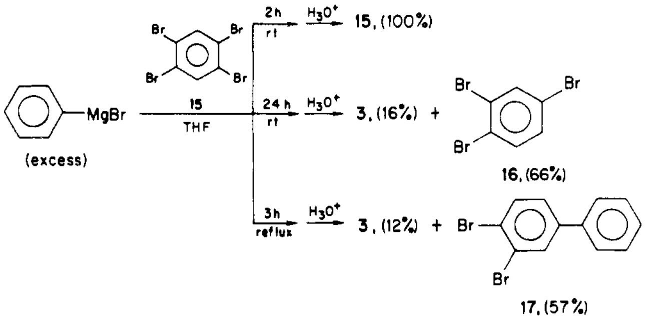
An alternate mechanism which also can account for our results and which we favor is shown in Scheme II. If we assume that Grignard exchange is more facile at iodine than at bromine, then we obtain first mono-Grignard 5 and then di-Grignard 12. If this step (5 → 12) is slow, then some 5 may remain even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

Scheme II



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 II) is regiospecific. This specificity probably arises from the need to have like charges in 2 (or 14) and in the transition state leading to it, as far apart as possible.

It is not a trivial matter to distinguish between the two mechanisms, although several observations favor Scheme II. For example, 1,2,4,5-tetrabromobenzene (15) is not an effective replacement for 1 *under the same reaction conditions*, though under more severe reaction conditions it does give some *p*-terphenyl. For example, phenylmagnesium bromide and 15 at room temperature gave, after 2 h, recovered starting material. However, after 24 h, 16% of *p*-terphenyl and 66% of 1,2,4-tribromobenzene were obtained after aqueous quench. And after 3 h at reflux (THF), 12% of *p*-terphenyl and 57% of 3,4-dibromobiphenyl were obtained. Apparently Grignard exchange can occur at bromine *slowly* at room temperature to give (2,4,5-tribromophenyl)magnesium bromide, which at room temperature mainly remains (to give 66% of 16; if Scheme II is correct, a small amount gives di-Grignard and ultimately 3). At reflux, however, the tribromo-Grignard eliminates to give 4,5-dibromobenzyne, the precursor of 17.



These results show that Grignard exchange with 1 is more likely to occur at iodine than at bromine. This conclusion is reinforced by some low temperature results.

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(14) Fields, E. K. U.S. Patent 4012454, May 15, 1975. See also: Beilsteins "Handbuch der Organischen Chemie", Hauptwerke Vol. 5, p 228, under 1,4-dibromo-*x*,*x*-diiodobenzene; the original reference mentioned there is unavailable to us. Aside from these, we can find no other references to 1.

(15) Varma, P. S.; Shankarnarayanan, S. *J. Ind. Chem. Soc.* **1936**, *13*, 31.

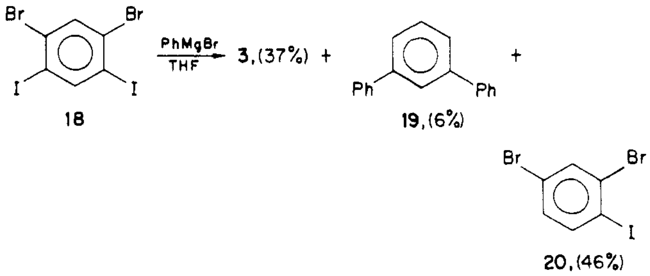
(16) With a bromine quench, the corresponding dibromo-*p*-terphenyl and 1,2,4-tribromo-5-iodobenzene are formed, but these products are contaminated with the iodobromoterphenyl and 1, as a consequence of oxidation of iodide ion (present as result of the Grignard exchange reaction) to iodine by the bromine.

(17) It seems likely, though we have no evidence for it, that exchange in 9 and 10 would occur at the halogen para to the existing Grignard site, so as to minimize repulsion between like charges.

Phenylmagnesium bromide (1.8 equiv) was added to 1 equiv of 1 at −78 °C, stirred for 1 h, and quenched to give 52% of recovered 1 and 43% of 6. No terphenyl and no bromodiiodobenzene was observed. Thus, exchange appears 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*.[18] The presence of *p*-dibromobenzene shows that 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 analogue). Thus our mechanistic evidence indicates that Scheme II is permissible; it also argues against Scheme I in that we can find no direct evidence for 7. However, Scheme I cannot be entirely discounted, since some Grignard exchange does occur at bromine in 15. Still, it would seem that the major Grignard exchange occurs at iodine, favoring Scheme II.

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. If the reaction follows a path analogous to Scheme I, aryne 8 should be an intermediate; if it follows Scheme II, 13 should be an intermediate. In either case we 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,[19] was also formed. We think the results with 19 support the proposal of aryne intermediates in these reactions, but the precise origin of the minor amount of 19 from 18 requires further study.



Clearly, further mechanistic experiments are required. However, regardless of mechanistic details these reactions are synthetically useful as we now show.

Synthetic Applications

A variety of aryl Grignard reagents react with 1 to give *p*-terphenyls. Table I summarizes the results. The reactions were carried out by adding a THF solution of 1 to 4 equiv of the Grignard reagent at room temperature over modest addition times. Aqueous quench gave the terphenyl shown, as well as byproduct 6. The products were separated and purified by column chromatography and the yields shown (not optimized) are of pure, isolated products. Except for 22, which is new, the terphenyls had melting points which agree with those reported in the literature and showed spectra consistent with the assigned structures.

As the table shows, the reaction is quite general. We will not take the considerable space that would be required to compare our method with the various literature syntheses of each of the known compounds in Table I. However, our method is simpler, shorter, and in general gives as good or better overall yields than all of the literature methods (this claim is even more valid with the improvements to be described below). One especially noteworthy example is the much simplified synthesis of *p*-quinquephenyl 21 as compared to the procedure in ref 21.

Consistent with the proposed aryne mechanism, the reaction is not particularly susceptible to steric factors, as the preparation of 24 and 25 shows. All of the products in Table I result from an aqueous quench, but, of course, the reaction product is really a di-Grignard reagent; consequently quenching with other electrophiles greatly expands the reaction scope over that indicated in the table.[28]

Although *p*-terphenyls could easily be prepared in one step by this method, the reaction as so far described has an annoying feature, namely, the formation of byproduct 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, with its ensuing separation problems. We therefore sought a method to convert more of 5 to terphenyl product.

This objective was achieved in several ways. The best to date (we are continuing to search for improvements) is to carry out the reaction between 1 and the aryl Grignard reagent in the usual way (1:4 molar ratio) and then add 1 equiv of either lithium tetramethylpiperidide (LiTMP) or potassium *tert*-butoxide[29] 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.

Replacement of the aryl Grignard reagent by an aryllithium does not improve the synthesis. Indeed, using the same reaction conditions as for the experiments in Table I, the yield of *p*-terphenyl from 1 and phenyllithium was only 12–23%.[30]

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[18] Analogous results were obtained at −78 °C using 6 equiv of phenylmagnesium bromide and a reaction time of 6 h. The products were 85% of 6, 2% of 1,2,4-tribromobenzene, and 5% of *p*-dibromobenzene.

[19] Loh, S. M.; Turner, E. E. *J. Chem. Soc.* **1955**, 1274.

[20] France, H.; Heilbron, I. M.; Hey, D. H. *J. Chem. Soc.* **1938**, 1364.

[21] Campbell, T. W.; McDonald, R. N. *J. Org. Chem.* **1959**, *24*, 730. Campbell, T. W.; McDonald, R. N. *Org. Synth.* **1960**, *40*, 85.

[22] Kotlyarevskii, I. L.; Bardamova, M. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1963**, *33*, 3573.

[23] Wirth, H. L.; Gönner, K. H.; Stück, R.; Kern, W. *Makromol. Chem.* **1963**, *63*, 30.

[24] Böckmann, K.; Vögtle, F. *Liebigs Ann. Chem.* 1981, 467.

[25] This material was identical with an authentic sample prepared by the reaction of 1,4-diiodobenzene with 1-naphthylmagnesium bromide in the presence of Ni(acac)$_2$: Lin, Lon-tang Wilson, Ph.D. Thesis, Michigan State University, 1982.

[26] Bahurel, Y.; Billion, J.; Descotes, G. *Bull. Soc. Chim. Fr.* **1968**, 4255.

[27] Price, C. C.; Mueller, G. P. *J. Am. Chem. Soc.* **1944**, *66*, 632.

[28] Applications to other electrophiles, to other types of Grignard reagents, and to the synthesis of polynuclear aromatic compounds are under study and will be reported separately.

[29] We thank Professor M. R. Rathke for this suggestion.

[30] With 1,2,4,5-tetrabromobenzene and excess phenyllithium under the same conditions no terphenyl was formed: however, more severe conditions may bring about the reaction.

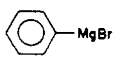
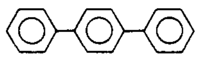
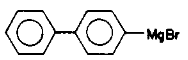
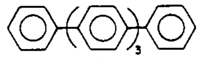
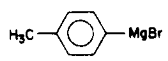
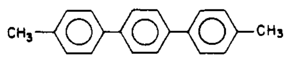
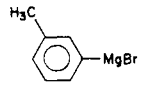
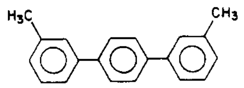
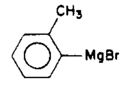
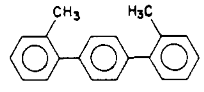
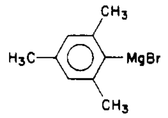
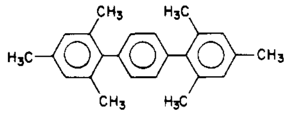
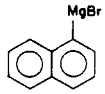
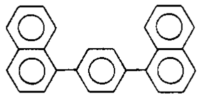
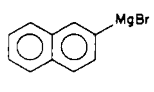
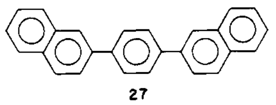
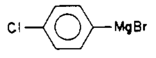
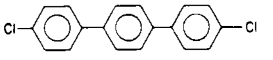
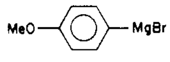
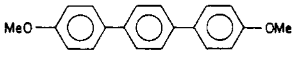
[31] Haworth, J. W.; Hey, D. H.; Elks, J. *J. Chem. Soc.* **1940**, 1284.

[32] Koelsch, C. F.; Masley, P. T. *J. Am. Chem. Soc.* **1953**, *75*, 3596. Mann, F. G.; Watson, J. *J. Chem. Soc.* **1947**, 505.

[33] Johnson, E. A. *J. Chem. Soc.* **1957**, 4155.

[34] Blatchly, J. M.; McOmie, J. F. W.; Watts, M. L. *J. Chem. Soc.* **1962**, 5085.

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

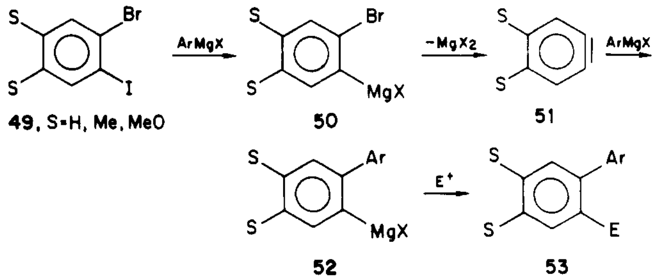
Grignard reagent	reactn time, h	product	yield %	m.p., °C^b	ref	yield of 6, %
	2.5	 **3**	54	212–213	20	42
	1.0	 **21**	53	387.5–388.5	21	39
	3.0^a	 **22**	53	248–249	22	41
	3.0^a	 **23**	50	141	23	42
	3.0^a	 **24**	45	145.5–146	24	40
	6.0	 **25**	49	181–183		35
	2.5	 **26**	30	206–207	25	21
	4.0	 **27**	35	259–260	22	18
	4.0	 **28**	43	293.5	26	43
	3.0	 **29**	30	273–274.5	27	

^{a}Ratio of 1 to Grignard reagent was 1:6. ^{b}Melting points agree with those in the cited literature reference.

This reaction can also be applied to biaryl synthesis and is particularly useful for unsymmetric biaryls. Table II summarizes our results; characterization of new compounds is found in the Experimental Section. Several features are worthy of mention. Comparison of entry 3 with entries 1 and 2 shows that at least one iodine is needed on the arene under these mild reaction conditions. This suggests that Grignard exchange occurs mainly at iodine (cf. Scheme II). 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 (extensions, for example, to the synthesis of specifically labeled, i.e. deuterated, diaryls are obvious). Comparison of entries 8 and 9 illustrates how the yield may be improved, in some instances, by adding 1 equiv of LiTMP to the reaction mixture prior to workup.

The bromoiodoarenes in Table II 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. We intend in the future to apply the reaction to unsymmetric aryne precursors, to determine the orientation of Grignard addition and the possible synthetic utility in such cases.

Scheme III



All of the reactions listed in Table II are presumed to proceed via Scheme III. Following initial Grignard exchange at iodine to give **50**, loss of MgXBr to furnish aryne **51** is apparently rapid at room temperature, since little or no byproduct corresponding to the reaction of **50** with the quenching electrophile is observed. This is true when the substituent S is H, Me, or MeO, as in all the entries in Table II. It is somewhat disturbing, then, to recall that when one S is bromine and the other iodine (as in **5** or in the Grignard precursor of **20**), aryne is apparently not

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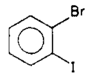
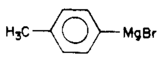
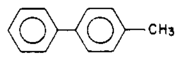
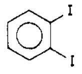
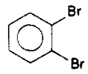
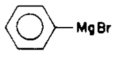
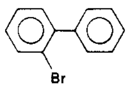
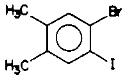
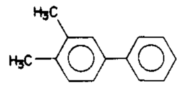
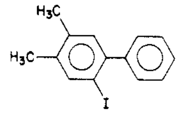
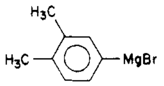
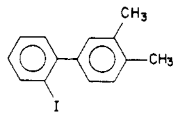
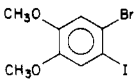
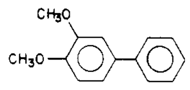
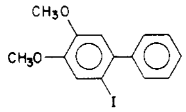
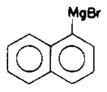
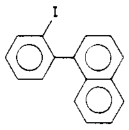
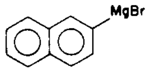
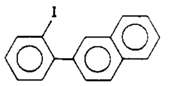
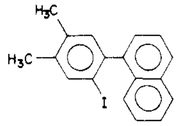
(35) Henderson, W. A.; Lopresti, R., Jr.; Zweig, A. *J. Am. Chem. Soc.* **1969**, *91*, 6049.

Table II. Unsymmetric Biaryls from Aryl Grignard Reagents and *o*-Bromoiodoarenes

entry	dihaloarene	Grignard reagent	procedure[a]	quench	product	yield, %	mp, °C[c]	ref
1	 **30**	 **31**	A	H_2O	 **32**	71	48–49	31
2	 **33**	**31**	A	H_2O	**32**	69		
3		**31**	A	H_2O		*b*		
4	**30**	 **34**	A	Br_2	 **35**	63		32
5	 **36**	**34**	A	H_2O	 **37**	66		33
6	**36**	**34**	A	I_2	 **38**	65		
7	**30**	 **39**	A	I_2	 **40**	64		
8	 **41**	**34**	A[d]	H_2O	 **42**	37	68–69	34
9	**41**	**34**	B	H_2O	**42**	69		
10	**41**	**34**	B	I_2	 **43**	58	107–108.5	34
11	**30**	 **44**	B	I_2	 **45**	64	108–110	35
12	**30**	 **46**	B	I_2	 **47**	60	80–82	
13	**36**	**44**	B	I_2	 **48**	63	145–146.5	

[a] The molar ratio of bromoiodoarene to Grignard reagent was in all cases 1:2; in procedure B, LiTMP was added prior to quenching. For details, see the Experimental Section. [b] No biphenyl was isolated and >75% of **34** was recovered. [c] Melting points agree with those in the cited literature reference. [d] When the corresponding dibromo analogue was used in place of **41**, under the same conditions, it was recovered unreacted (>75%).

formed from the mono-Grignard under very similar conditions (that is, **6** and **20**, and not bromoiodobiphenyls, are the main byproducts of the terphenyl synthesis).[36] Perhaps the electron-withdrawing halogen substituents stabilize **50** whereas donors (Me, MeO) favor aryne formation. This is one somewhat murky feature of the reactions which will have to be clarified in further mechanistic studies. Other such features are the role of the metal (Mg vis-a-vis Li, for example) and of the counterion X in ArMgX, and

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[36] In some instances, when the reaction time was lengthened, small (<10%) yields of 3,4- or 4,3-bromoiodobiphenyls were detected.

the yield-enhancing effect of LiTMP and KO-*t*-Bu.

In conclusion, we have found **1** to be a useful diaryne equivalent which reacts with excess Grignard reagent to give *p*-terphenyl di-Grignards **2**. With the subsequent addition of LiTMP or KO-*t*-Bu to convert the simultaneously formed mono-Grignard **5** to **2**, yields of *p*-terphenyls in the 70–80% range are easily obtained from simple precursors in one step. This method is in general an improvement over most other *p*-terphenyl syntheses and it is uniquely useful if a *p*-terphenyl with substituents in the central ring is desired. With *o*-bromoiodoarenes, the method is adaptable to the synthesis of unsymmetric biaryls in good yield. Although some mechanistic details remain to be elucidated, it is likely that the biaryl synthesis proceeds via ordinary arynes and that the terphenyl synthesis proceeds via organometallic arynes (i.e., **11**).

Extension of these reactions to heterocyclic, vinyl, and other Grignard reagents is under study.

Experimental Section

General Procedures. ^{1}H NMR spectra were determined on a Varian T-60 or Bruker WM-250 spectrometer in $CDCl_3$ solution containing tetramethylsilane as an 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, Divison of Research Resources, NIH. 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.

1,4-Dibromo-2,5-diiodobenzene (1).[14,37] 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 125–135 °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.[14] mp 161–163 °C); ^{1}H NMR δ 7.97 (s); mass spectrum, *m/e* (relative intensity) 490 (28), 488 (54), 486 (28), 363 (11), 361 (18), 359 (9), 236 (15), 234 (30), 232 (17), 153 (26), 155 (25), 74 (100).

1,5-Dibromo-2,4-diiodobenzene (15). The procedure and workup is essentially the same as for **1**. From 5.9 g (25 mmol) of 1,3-dibromobenzene and 12.7 g (50 mmol) of iodine in 80 mL of concentrated sulfuric acid was obtained 7.9 g (65%) of **15** 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 (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.

Typical Procedure for Table I. Preparation of *p*-Terphenyl 3. A solution of **1** (2.44 g, 5 mmol) in 20 mL of THF was added slowly over 30 min to a solution of phenylmagnesium bromide (prepared from 3.92 g (25 mmol) of bromobenzene, 0.57 g (25 mmol) of magnesium in 80 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 0.42 g of nearly pure *p*-terphenyl. Chromatography of the filtrate using hexane as the eluent gave 0.77 g (42%) of 1,4-dibromo-2-iodobenzene (**6**); mp 45–46 °C[19] and 0.2 g of additional **3** (total yield 54%), whose mixed melting point with an authentic sample showed no depression.

When the reaction was carried out by reverse addition (i.e., adding the Grignard reagent to **1**) the yield of *p*-terphenyl was unaffected. When phenyllithium replaced phenylmagnesium bromide the yield of *p*-terphenyl was very low (9–12%); however, by adding phenyllithium to **1** at −20 °C and then gradually warming to room temperature, this yield was improved to about 20%.

Iodine Quench. 2′,5′-Diiodo-*p*-terphenyl (4). The standard procedure for *p*-terphenyl described above was followed, but before quenching with ice, the reaction mixture was cooled to 10 °C, 5.1 g (20 mmol) of iodine were added, and the mixture was stirred at 10 °C for 1 h. It was then quenched with ice-water and 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 **4** contaminated with a little **1**. Recrystallization from benzene gave 1.25 g of pure **4** as white needles. Chromatography of the filtrate using hexane as eluent gave 0.8 g (39%) of iodobenzene, 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 (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.

2,4,6,2″,4″,6″-Hexamethyl-*p*-terphenyl (25). The general procedure was followed. For **25**: ^{1}H NMR δ 7.16 (s, 4 H), 6.96 (s, 4 H), 2.06 (s, 12 H), 2.34 (s, 6H); mass spectrum, *m/e* (relative intensity) 315 (23), 314 (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.

1,4-[1′,1″-Dinaphthyl]benzene (26). The general procedure was followed. For **26**: ^{1}H NMR δ 7.18–8.0 (m); mass spectrum, *m/e* (relative intensity) 330 (100), 202 (30), 163 (27); high resolution mass spectrum, calcd for $C_{26}H_{18}$ 330.14103, found 330.14084.

Reaction of 1 with Phenylmagnesium Bromide at Low Temperatures. A solution of phenylmagnesium bromide (2.7 mmol) in 20 mL of dry THF was added slowly (90–120 min) to 1.5 mmol (0.732 g) of **1** in 30 mL of THF at −78 °C (acetone–dry ice bath). The mixture was stirred for an additional hour and then quenched with dilute hydrochloric acid. After the mixture warmed to room temperature, the THF was removed under reduced pressure. The aqueous layer was extracted with chloroform, and the organic extract was washed with sodium bicarbonate, water, and dried ($MgSO_4$). After removal of the chloroform under reduced pressure, the oily residue was diluted to 10 mL with benzene and analyzed by gas chromatography and GC–MS. There was obtained 51.6% of recovered **1** and 43% of **6**. Using the same procedure, but with 9 mmol of phenylmagnesium bromide and stirring for 6 h at −78 °C before quenching, the products were **6** (85%), 1,2,4-tribromobenzene (~2%), and *p*-dibromobenzene (5%).

In a similar experiment at −42 °C (acetonitrile–dry ice bath), the products were 72% of **6** and traces of 1,4-dibromobenzene and 1,2,4-tribromobenzene. At −22 °C (CCl_4–dry ice bath) the products were 73% of **6**, 1.1% of 1,4-dibromobenzene, and 6.4% of 1,2,4-tribromobenzene. When phenylmagnesium bromide was replaced by ethylmagnesium bromide at −22 °C, the products were 86% of **6**, 5.5% of 1,4-dibromobenzene, and 5.5% of 1,2,4-tribromobenzene.

Reactions of 1,2,4,5-Tetrabromobenzene (15) with Phenylmagnesium Bromide. These reactions were carried out as described under the typical procedure for Table I, but using **15** in place of **1**. The results are summarized in the text. The products **16** and **17** were identified by comparison with authentic samples.[38]

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 and 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

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[37] The alternate way of making **1**, by bromination of 1,4-diiodobenzene, gives a mixture of **1**, 1,2,4-tribromo-5-iodobenzene, and 1,2,4,5-tetrabromobenzene from which it is difficult to obtain pure **1**.

[38] For 1,2,4-tribromobenzene: Derbyshire, D. H.; Waters, W. A. *J. Chem. Soc.* **1950**, 573. For 3,4-dibromobiphenyl: Case, F. H. *J. Am. Chem. Soc.* **1936**, *58*, 1249.

to give 0.72 g (46%) of 1,3-dibromo-4-iodobenzene (**20**), mp 45–46 °C (lit.[19] mp 45–46 °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, $^1/_4$ in. × 6 ft, 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.

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 at room temperature, 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 I to 74% and 71%, respectively.

Effect of Potassium *tert*-Butoxide on the Reaction of 1 with Phenylmagnesium Bromide. The reaction was carried out according to the general procedure, but prior to the aqueous quench a solution of 5 mmol of potassium *tert*-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**.

Typical Procedures for Table II. Preparation of 4-Methylbiphenyl (29) (Procedure A). A solution of *o*-bromoiodobenzene (**30**)[39] (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, 0.48 g of Mg in 60 mL of THF). The mixture was stirred for an additional 2 h at room temperature and 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 eluent to give 1.20 g (71%) of 4-methylbiphenyl, mp 48–49 °C (lit.[31] mp 49–50 °C).

Preparation of 3,4-Dimethoxybiphenyl (42) (Procedure B). The reaction was carried out according to procedure A, by using 10 mmol of 4-bromo-5-iodoveratrole[40] 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 as usual afforded 1.47 g (69%) of 3,4-dimethoxybiphenyl, mp 68–69 °C (from methanol; lit.[34] mp 67–68 °C).

Preparation of 2-Bromobiphenyl (35) (Bromine Quench). The reaction between *o*-bromoiodobenzene (10 mmol) and phenylmagnesium bromide (20 mmol) was carried out by using procedure A, 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.[41] The mixture was then warmed to room temperature, treated with 10% sodium bisulfite 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.

Preparation of 2-Iodo-4,5-dimethyoxybiphenyl (43) (Iodine Quench). Procedure B was followed as described above for the preparation of **42**, 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 bisulfite and the usual workup gave 1.97 g (58%) of **40**, mp (methanol) 107–108.5 °C (lit.[34] mp 109 °C).

Properties of New Compounds in Table II. 2-Iodo-4,5-dimethylbiphenyl (38): bp 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); MS, *m/e* 308 (M^+). Anal. Calcd for $C_{14}H_{13}I$: C, 54.54; H, 4.22. Found: C, 54.72; H, 4.11.

2-Iodo-3′,4′-dimethylbiphenyl (40): bp 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); MS, *m/e* 308 (M^+). Anal. Calcd for $C_{14}H_{13}I$: C, 54.54; H, 4.22. Found: C, 54.33; H, 4.39.

2-(2′-Iodophenyl)naphthalene (47): 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); MS, *m/e* 330 (M^+). Anal. Calcd for $C_{16}H_{11}I$: C, 58.18; H, 3.33. Found: C, 58.23; H, 3.34.

1-(2′-Iodo-4′,5′-dimethylphenyl)naphthalene (45): mp 145–146.5 °C from benzene; ^{1}H NMR δ 2.25 (s, 3 H), 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); MS, *m/e* (M^+). Anal. Calcd for $C_{18}H_{15}I$: C, 60.33; H, 4.19. Found: C, 60.30; H, 4.16.

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Registry No. **1**, 63262-06-6; **3**, 92-94-4; **4**, 96843-21-9; **6**, 89284-52-6; **15**, 96843-23-1; **16**, 615-54-3; **17**, 60108-72-7; **19**, 92-06-8; **20**, 19393-94-3; **21**, 3073-05-0; **22**, 97295-31-3; **23**, 4499-84-7; **24**, 53092-64-1; **25**, 97295-32-4; **26**, 64065-97-0; **27**, 17096-38-7; **28**, 21711-52-4; **29**, 13021-19-7; **30**, 583-55-1; **31**, 4294-57-9; **32**, 644-08-6; **33**, 615-42-9; **34**, 100-58-3; **35**, 2052-07-5; **36**, 96843-22-0; **37**, 4433-11-8; **38**, 97295-33-5; **39**, 89980-68-7; **40**, 97295-34-6; **41**, 89978-46-1; **42**, 17423-55-1; **43**, 92199-01-4; **44**, 703-55-9; **45**, 18937-93-4; **46**, 21473-01-8; **47**, 97295-35-7; **48**, 97295-36-8; *m*-$C_6H_4Br_2$, 108-36-1; PhLi, 591-51-5; *p*-C_6H_4Br2, 106-37-6; C_2H_5-MgBr, 925-90-6; *p*-PhC_6H_4MgBr, 3315-91-1; *m*-$CH_3C_6H_4MgBr$, 28987-79-3; *o*-$CH_3C_6H_4MgBr$, 932-31-0; 2,4,6-$(CH_3)_3C_6H_2MgBr$, 2633-66-1; *p*-ClC_6H_4MgBr, 873-77-8; *p*-$MeOC_6H_4MgBr$, 13139-86-1; *o*-$C_6H_4Br_2$, 583-53-9.

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(41) It is essential to add the mixture to bromine and was not vice versa; when bromine was added to the reaction mixture, considerable 2-iodobiphenyl was formed, presumably as a consequence of oxidation of iodide to iodine by the added bromine. This was true regardless of how fast the bromine was added. Hence in this and all bromine quenches, the reaction mixture was added to excess bromine.