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Synthesis of Heterosubstituted Hexaarylbenzenes via Asymmetric Carbonylative Couplings of Benzyl Halides

Robert G. Potter and Thomas S. Hughes*

*Department of Chemistry, Cook Physical Sciences Building, 82 University Place,
University of Vermont, Burlington, Vermont 05401*

thomas.s.hughes@uvm.edu

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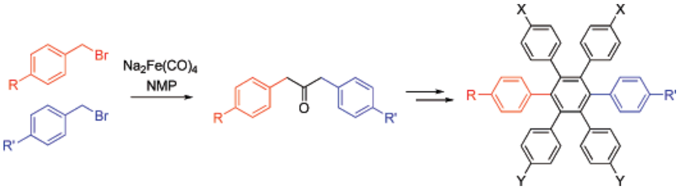
ABSTRACT



Asymmetric carbonylative couplings of benzyl halides have been shown to give heterosubstituted 1,3-diarylacetones in moderate to high yields. These asymmetric ketones were converted via Knoevenagel condensations to tetraarylcyclopentadienones, and further conversion via dehydro-Diels–Alder cycloadditions gave highly heterofunctionalized hexaarylbenzenes with uniquely functionalized aryl groups at the para positions of the central benzene. This method allows control of the substituents on each of four unique pendent aryl group positions, giving rise to substitution patterns not available using symmetrical 1,3-diarylacetones.

The synthesis of phenylene oligomers and dendrimers has received much attention in recent years. These compounds have been synthesized as conductive polymers[1] and as precursors for conductive discotic liquid crystals[2] and graphitic materials.[3] Polymers containing cyclopentadienone moieties in the main chain have also been synthesized as low-band gap materials.[4] Further development of these materials depends on the ability to synthesize specific arrangements of phenylene units, as well as to substitute certain phenyl groups in a controllable fashion. Early syntheses of tetraarylcyclopentadienones (tetracyclones) and hexaarylbenzenes (HABs) have employed the route shown in Scheme 1, which involves the initial Knoevenagel condensation of a 1,3-diarylacetone **1** with a derivative of benzil, followed by the Diels−Alder cycloaddition of the resulting tetraarylcyclopentadienone **2** with a diarylethyne **3** to give **4**.[5]

While the substituents on the various synthons can easily be altered to give the substitution pattern shown in Scheme 1,[6] the lack of regiocontrol in both the Knoevenagel condensation and the Diels−Alder cycloaddition prevent the formation of a HAB with certain sets of distinctly and differently substituted aryl rings. However, a single regio-

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[1] Wu, J.; Gherghel, L.; Watson, M.; Li, J.; Wang, Z.; Simpson, C. D.; Kolb, U.; Müllen, K. *Macromolecules* **2003**, *36*, 7082.

[2] Schmidtke, J. P.; Friend, R. H.; Kastler, M.; Müllen, K. *J. Chem. Phys.* **2006**, *124*, 174704. Warman, J. M.; Piris, J.; Pisula, W.; Kastler, M.; Wasserfallen, D.; Müllen, K. *J. Am. Chem. Soc.* **2005**, *127*, 14257. Fechtenkotter, A.; Saalwachter, K.; Harbison, M. A.; Müllen, K.; Speiss, H. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 3039.

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[4] Tamao, K.; Yamaguchi, S.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 229.

[5] Dilthey, W.; Hurtig, G. *Ber.* **1934**, *67*, 2007. Ried, W.; Boennighausen, K. H.; *Chem. Ber.* **1960**, *93*, 1769. Bergmann, P.; Paul, H. *Chem. Ber.* **1967**, *100*, 828. Broser, W.; Siegle, P.; Kurreck, H. *Chem. Ber.* **1968**, *101*, 69. Broser, W.; Reusch, J.; Kurreck, H.; Siegle, P. *Chem. Ber.* **1969**, *102*, 1715.

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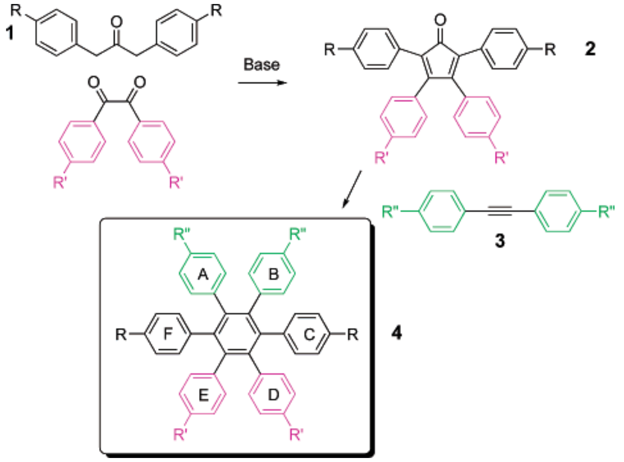
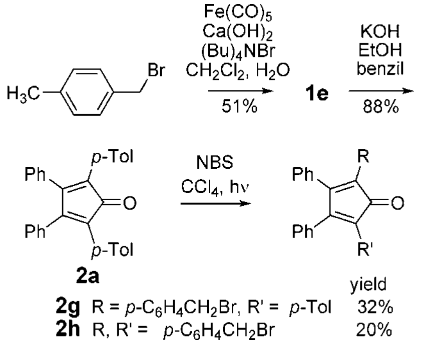
Scheme 1. Established Synthesis of Hexaarylbenzenes



Scheme 2. Desymmetrization of a Tetraarylcyclopentadienone



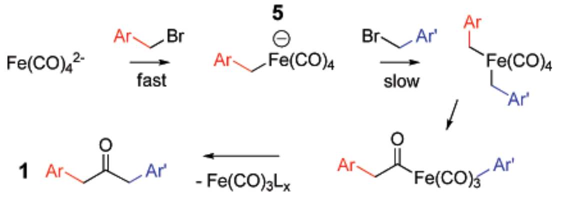
isomer would result if exactly one of the synthons was asymmetric. Asymmetrically substituted benzils and diarylethynes would give HABs with distinguishable ortho-related A and B or D and E rings, while rings C and F, which are para to each other on the central aromatic ring, could be distinguished by using an asymmetric 1,3-diarylacetone. Such regiospecificity is especially desirable if the resulting tetracyclones or HABs are to be linked further into oligomers or polymers, and the chemistry employed should allow the installation of substituents that can be readily converted into functional groups that can be used to attach additional tetracyclone and/or HAB moieties.

One approach to the synthesis of such asymmetric tetraarylcyclopentadienones is the desymmetrization of symmetrical **2a** by radical bromination (Scheme 2). Controlling the stoichiometry of this reaction favors the monobrominated product, but a statistical mixture is still obtained that is quite difficult to resolve by column chromatography or any other method. This non-regiospecific chemistry resulted in a 32% yield of purified asymmetric tetraarylcyclopentadienone, which is much less than desired if this methodology is to be applied to the construction of larger oligomers of cyclopentadienones. Since the 1,3-diarylacetones are convenient synthetic precursors of the cyclopentadienones, a route to asymmetric 1,3-diarylacetones was sought.

Symmetrical 1,3-diarylacetones can be conveniently synthesized in a phase-transfer carbonylative coupling of 2 equiv of benzyl halide.[7] However, if an asymmetric ketone is desired, a reaction that allows more control over the addition of the halides is required. Collman et al. demonstrated the synthetic utility of iron tetracarbonyl disodium as a carbonylative coupling agent to transform 2 equiv of alkyl halide to a dialkyl ketone (Scheme 3).[8]

The two oxidative additions that must occur during this reaction occur at different rates, with the first being much faster than the second. The presumed mechanism of this reaction is depicted in Scheme 3.[8,9] It predicts the addition of 1 equiv of halide to give the intermediate **5**, which then undergoes oxidative addition to the potentially different second alkyl halide, followed by rearrangement to an acyl intermediate that reductively eliminates the asymmetric ketone **1**. This reaction was shown to be functional group tolerant but has previously only been applied in an intermolecular sense to aliphatic primary halides,[9,10] and to intramolecular cyclizations.[7,11] This paper describes the application of this carbonylative coupling to the synthesis of asymmetric 1,3-diarylacetones from benzyl halides.

Scheme 3. Presumed Mechanism of Carbonylative Coupling of Benzyl Bromides



The synthesis of an asymmetric ketone via the Collman reagent requires that the first oxidative addition is complete before the second halide is added to the reaction mixture. However, since kinetic data for the oxidative additions in homogeneous solution has previously only been measured for aliphatic alkyl halides,[12] it was necessary to determine the rate of the first oxidative addition of iron tetracarbonyl to a benzyl bromide. The reaction of 4-methylbenzyl bromide with iron tetracarbonyl disodium in *N*-methyl-2-pyrrolidone (NMP) was monitored by in situ IR. Principal component analysis showed two dominant species in solution, as can be seen in Figure 1. The disappearance of the absorption at 1876 cm^{-1}, and its shoulder at 1907 cm^{-1}, characteristic of

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(7) Tanguy, G.; Weinberger, B.; des Abbayes, H. *Tetrahedron Lett.* **1984**, *25*, 5529. des Abbayes, H.; Clément, J.-C.; Laurent, P.; Tanguy, G.; Thilmont, N. *Organometallics* **1988**, *7*, 2293.

(8) Collman, J. P.; Winter, S. R.; Clark, D. R. *J. Am. Chem. Soc.* **1972**, *94*, 1788.

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(10) Winter, S. R. Ph.D. Thesis, Stanford University, Stanford, CA, 1973

(11) Johnson, B. F. G.; Lewis, J.; Thompson, D. J. *Tetrahedron Lett.* **1974**, 3789

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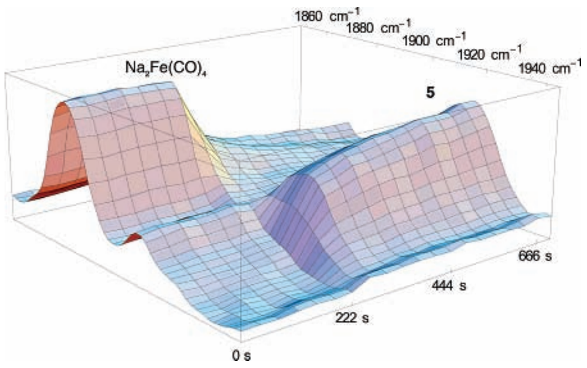


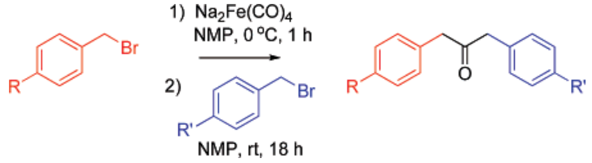
Figure 1. In situ solution IR of the reaction of 4-methyl benzyl bromide and iron tetracarbonyl disodium in NMP. See the text for details. Absorbance units (*z*-axis) are arbitrary. Addition of the benzyl bromide occurred at 222 s.

iron tetracarbonyl and the appearance of an absorption at 1916 cm^{-1}, characteristic of the intermediate **5**,[13] indicated the first oxidative addition was complete within minutes. In a solution of 0.095 M bromide and 0.033 M iron tetracarbonyl disodium in NMP, the second-order rate constants were determined to be 0.1 M^{-1} s^{-1} for the disappearance of Na$_2$Fe(CO)$_4$ and 0.07 M^{-1}s^{-1} for the formation of **5**. A rate constant of 0.12 M^{-1}s^{-1} was measured for the oxidative addition of Na$_2$Fe(CO)$_4$ to 1-bromo-2,2-dimethylpropane,[12] so there does not appear to be a large rate increase arising from the benzylic nature of the sites of nucleophilic attack in the present study. For the synthesis of each of the asymmetric ketones described below, the second benzyl bromide was added to the reaction mixture within 1 h after the first.

The diarylacetones synthesized by this method are shown in Table 1. Moderate to high yields were obtained for most of the functional groups employed. The protected benzyl alcohols were of particular interest because they can be conveniently converted into benzyl halides, which can then in turn be subjected to the same reaction conditions to build oligoHABs. While Collman's reagent has been shown to be fairly functional-group tolerant, this study represents the first application of this reaction to a variety of benzyl halides.

While most functional groups allowed good coupling yields, if a strong enough electron withdrawing group is attached to the aromatic ring of the benzyl bromide the yield of the corresponding ketone decreases to zero (Table 1**)**. This dramatic decrease in yield is proposed to result from competing redox reactions between iron tetracarbonyl disodium and the benzyl bromide since electron-poor aryls have sufficiently low reduction potentials.[14] The benzyl protons of a dihydrostilbene product consistent with a dissociative electron-transfer reaction[15] are present in the ^{1}H NMR of the 4-nitrobenzyl bromide homocoupling product mixture.

Table 1. Asymmetric 1,3-Diarylacetones Synthesized via Carbonylative Coupling with Collman's Reagent[a]



	R	R′	yield (%)
1a	CH_2OCH_3	CH_2OCH_3	64
1b	CH_2OTIPS	CH_2OTIPS	90
1c	CH_2OBn	CH_2OBn	60
1d	CH_2OTBS	CH_2OTBS	64
1e	CH_3	CH_3	94
1f	OCH_3	OCH_3	83
1g	Br	Br	77
1h	NO_2	NO_2	0
1i	CO_2CH_3	CO_2CH_3	37
1j	CH_2OCH_3	CH_2OTIPS	74
1k	CH_2OTBS	CH_2OBn	66
1l	OCH_3	NO_2	>10[b]
1m	OCH_3	Br	63

[a] The first halide was stirred with the Na$_2$Fe(CO)$_4$ for 1 h at 0 °C under an inert N$_2$ atmosphere. The second halide was then added, and the reaction mixture was warmed to room temperature. Yields of homocouplings are reported based on recovered starting material. Yields of heterocouplings are based on the recovered first halide reagent, and in most cases recovery of the second halide added was nearly quantitative. [b] Yield based on ES-LCMS.

Both dilute homogeneous and phase-transfer carbonylative couplings were attempted on **2g** and **2h** to prepare ketone macrocycles and elongated diarylacetones, but the negligible yields were obtained of the desired macrocycles and oligomers, respectively. These results were consistent with the bimolecular rate-determining step of the coupling being disfavored under the dilute conditions of the attempted macrocyclization, as well as the competitive redox chemistry of the easily reduced cyclopentadienones.[16]

Protected benzyl alcohols were employed in this study because they can serve as masked benzyl bromides that can be coupled in similar reactions to synthesize larger phenylene dendrimers with widely varied substituents. The regiocontrol made possible by the use of asymmetric 1,3-diarylacetones now allows the syntheses of specific oligophenylenes and oligotetracyclones that were not previously possible. Such syntheses, including those of cyclic oligotetracyclones and oligo-*p*-phenylenes, are currently being pursued in our laboratories.

Various tetraarylcyclopentadienones were synthesized by Knoevenagel condensation with benzil or 4,4′-dibromobenzil. In the reactions reported in Table 2, the lower yields are most likely the result of the reaction of the strong hydroxide base with the moderately labile silyl ether protected benzyl alcohols.

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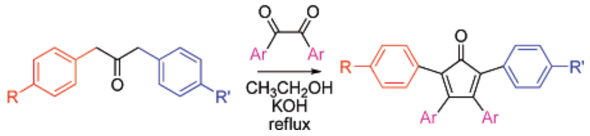
[13] The IR of $(CO)_4FeCH_2PPh_3$ has peaks at 1905(vs) and 1880(s): des Abbayes, H.; Clement, J. C.; Laurent, P.; Yaouanc, J. J.; Tanguy, G.; Weinberger, B. *J. Organomet. Chem.* **1989**, *359*, 205.

[14] Redox potential *E* is -0.49 V for $PhNO_2$ (Meisel, D.; Neta, P. *J. Am. Chem. Soc.* **1975**, *97*, 5198) and −1.95 V for Na$_2$Fe(CO)$_4$ (Amatore, C.; Verpeaux, J.-N.; Krusic, P. J. *Organometallics* **1988**, *7*, 2426).

[15] Savéant, J.-M. *Advances in Electron Transfer Chemistry*; JAI Press: Greenwich, CT, 1994; Vol. 4, p 53.

[16] Redox potential $E_{1/2}$ of **2**(R = R′ = H, Ar = Ph) was measured to be −0.87 V (van Willigen, H.; Gieger, W. E.; Rausch, M. D. *Inorg. Chem.* **1977**, *16*, 581) and *E*, −0.83 V (Kawase, T.; Ohsawa, T.; Enomoto, T.; Oda, M. *Chem. Lett.* **1994**, *7*, 1333).

Table 2. Cyclopentadienones Synthesized from Asymmetric 1,3-Diarylacetones

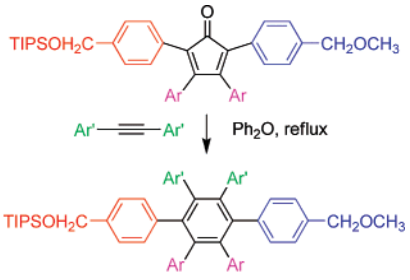


	R	R′	Ar	yield (%)
2a	CH_3	CH_3	C_6H_5	88
2b	CH_2OTIPS	CH_2OTIPS	C_6H_5	83
2c	CH_2OBn	CH_2OBn	C_6H_5	85
2d	CH_2OTBS	CH_2OBn	C_6H_5	64
2e	CH_2OTIPS	CH_2OCH_3	C_6H_5	78
2f	CH_2OTIPS	CH_2OCH_3	p-BrC_6H_4	75

Several hexaarylbenzenes were prepared via a Diels–Alder cyclization with 1,2-diarylethynes as shown in Table 3. The yields obtained were moderate to high, and most likely reflect the relative difficulty in the purification of substituted hexaarylbenzenes. Unsubstituted hexaphenylbenzene usually crystallizes from the reaction mixture in the protocol used,[17] but column chromatography was required to purify the compounds shown which contained side chains that frustrated spontaneous crystallization. Melting point determinations for all compounds **4** showed decomposition before melting near the boiling point of phenyl ether; lower temperatures and longer reaction times may increase cycloaddition yields.

In conclusion, a variety of uniquely and asymmetrically substituted tetracyclones and HABs suitable for further elongation into oligomers and polymers have been synthesized in good yields. The key to their synthesis is an asymmetric carbonylative coupling reaction with Collman's reagent that converts two different benzyl halides into a 1,3-diarylacetone by the addition of each halide at appropriate reaction times. The tetracyclones and HABs obtained herein are currently being coupled to form longer oligophenylenes, as well as being oxidized to form fused polycyclic aromatic hydrocarbons with novel substitution patterns.

Table 3. Hexaarylbenzenes with Specific, Unique Groups at the 1,4 Positions



	Ar	Ar′	yield (%)
4a	C_6H_5	C_6H_5	86
4b	C_6H_5	p-$C_6H_4OCH_3$	80
4c	p-C_6H_4Br	p-$C_6H_4OCH_3$	72
4d	p-C_6H_4Br	p-C_6H_4Br	62

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and details of the determination of rate constant for the carbonylative coupling reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1968; Vol. 1, p 241.