Table II. NMR Data ($CDCl_3$) for Conformational Calculations

X	compd	δ_H,[a] ppm	δ_X,[b] ppm	J_{av},[c] Hz	J_{23},[d] Hz
F	**13a**	4.68		8.80	4.80
				(50.80[e])	
	2	4.90		20.39	17.40
				(49.00[e])	
	13e	4.96		22.74	19.00
				(48.60[e])	
Cl	**14a**	4.25		8.74	8.04
	3	4.39		16.49	14.00
	14e	4.54		20.89	18.70
Br	**15a**	4.37		9.18	8.00
	4	4.45		13.12	10.90
	15e	4.69		21.64	19.20
I	**16a**	4.69		9.38	8.40
	5	4.69		10.95	9.60
	16e	4.92		21.60	19.60
MeO	**17a**	3.50	3.29	9.14	6.80
	6	3.73	3.43	17.80	15.60
	17e	3.81	3.48	21.18	18.50
MeS	**18a**	3.18	2.05	9.72	8.80
	7	3.24	2.05	12.34	9.80
	18e	3.43	2.12	20.33	18.40
MeSe	**19a**	3.45	2.03	9.94	8.80
	8	3.49	2.01	10.70	6.80
	19e			20.50[f]	
Me_2N	**20a**	2.38[g]	2.18	9.50[f]	
	9	2.91	2.32	16.16	13.60
	20e	3.23	2.43	20.84	18.20
Me	**21a**	2.53[g]	1.16	6.40[h]	
	10	2.40[g]	1.03	6.80[h]	
	21e	2.40[g]	1.02	7.80[h]	
tert-Bu	**22a**	2.23[g]	1.01		
	11	2.14[g]	1.01		
	22e	2.13[g]	0.99		

[a] Chemical shift for the 2-proton. [b] Proton chemical shift for the 2-substituent. [c] Line width at half-height of the 2-proton resonance. [d] Sum of the two measured 2–3 coupling constants. [e] Geminal H–F coupling. [f] Determined by analogue (see text). [g] Determined from the HETCOR spectrum. [h] The CH_3–H coupling.

dimensional $^1H/^{13}C$ spectra). Carbon-13 assignments were assisted by the attached proton test and are described elsewhere.[16]

Conformational preferences were determined in chloroform by the Eliel method, eq 5, in which the observable R was (1) the chemical shift of the 2-proton (δ_H), (2) the chemical shift of protons on the 2-substituent (δ_X), (3) the line width at half-height of the 2-proton resonance, used traditionally in this context because previous observations were on low-field machines, corresponding to the sum of the vicinal couplings ($J_{2,3}$) plus any long-range couplings (J_{av}), (4) the actual measured couplings ($J_{2,3}$), or (5) the carbon chemical shifts expressed as substituent parameters (δ_C). In the last case, we found that best results were obtained for carbons 1 and 2, closest to the X group. Table II contains the proton data used for the conformational calculations. Except as noted, these figures were obtained by inspection from the ^1H spectra. The ^{13}C data have been given elsewhere.[16] In each case the 2-proton resonance is the X part of an ABX spectrum. For the hydrocarbons, the 2 resonance was overlain by other aliphatic resonances. The actual resonance position was measured from the proton–carbon-13 2D spectrum (HETCOR). The COSY spectrum was used to correlate the 2-proton and the 2-methyl protons. Normally, a 2-axial proton is more deshielded than the 2-equatorial proton[17] (the opposite to cyclohexanes). The 2-axial proton resonance in the *cis-tert*-butyl isomers was identified as a doublet of doublets (plus long-range splittings) with a wide total width because of the axial–axial splitting. The 2-equatorial resonance in the *trans-tert*-butyl isomers was identified as a much narrower doublet of triplets or as a poorly resolved multiplet. One anomaly that arose from the analysis was the observation that the 2-axial and -equatorial resonances were reversed in the hydrocarbons (**21** and **22**), the axial proton now being more shielded.

Estimations were required in two cases. The cis isomer of the methylseleno compound **19e** was not able to be prepared, either directly or by equilibration. The J_{av} value of 20.50 Hz in Table II was estimated from the values for other substituents with similar electronegativity, e.g., the value of 20.33 Hz for methylthio. For the trans isomer of the dimethylamino compound **20a**, the 2-proton resonance and the methyl resonances of the dimethylamino group overlapped. The chemical shift of the 2-proton resonance was obtained from the HETCOR spectrum, but the coupling constants were not available by this procedure. Again, the value of 9.50 Hz for this coupling was estimated from cases with substituents of similar electronegativities, e.g., 9.72 Hz for methylthio. We made these estimates only for the line widths at half-height (J_{av} in Table II) and made no effort to estimate the actual couplings.

Application of eq 5 to the data in Table II readily gave conformer populations, which we express in Table III as axial percentages. We include in this table the results of the calculations for each datum in Table II, as well as analogous calculations from two-carbon resonances (more precisely, from chemical shift substituent parameters[16]).

We attempted low-temperature measurements on all systems but succeeded in obtaining slow-exchange spectra only for the dimethylamino case (**9**). Figure 1 shows the ^{13}C spectra as a function of temperature in CF_2Cl_2 containing 3% CD_2Cl_2. From such spectra we were able to determine that the percentage of axial dimethylamino is about 60% in pure CF_2Cl_2, 50% in CF_2Cl_2 containing 3% CD_2Cl_2, and 5% in $CHClF_2$.

Discussion

Past work concentrated on the 2-halocyclohexanones (Table I). The large differences between the results obtained from chemical shifts and coupling constants indicated the inherent difficulties of the method. Errors in conformational proportions could arise either statistically because the Eliel method relies on small differences between numbers or systematically because the *tert*-butyl system has structural differences from the monosubstituted cyclohexanone. These errors should affect the chemical shift and coupling constant measurements differently, so that comparison of results from the two data can give some indication of accuracy. Precision of measurement probably generates an error of only ±3% (calculated from repeated measurements of the same quantity).

In the present study we endeavored to improve accuracy by developing a whole family of observables that could independently provide data R for eqs 4 and 5. As Table III shows, we succeeded in obtaining at least five observables for all the substituents except MeSe and Me. In the case of MeSe our failure to prepare one of the *tert*-butyl isomers prevented direct application of the method. The single value of 92% axial conformer was obtained by estimating J_{av} for the missing conformer from values for

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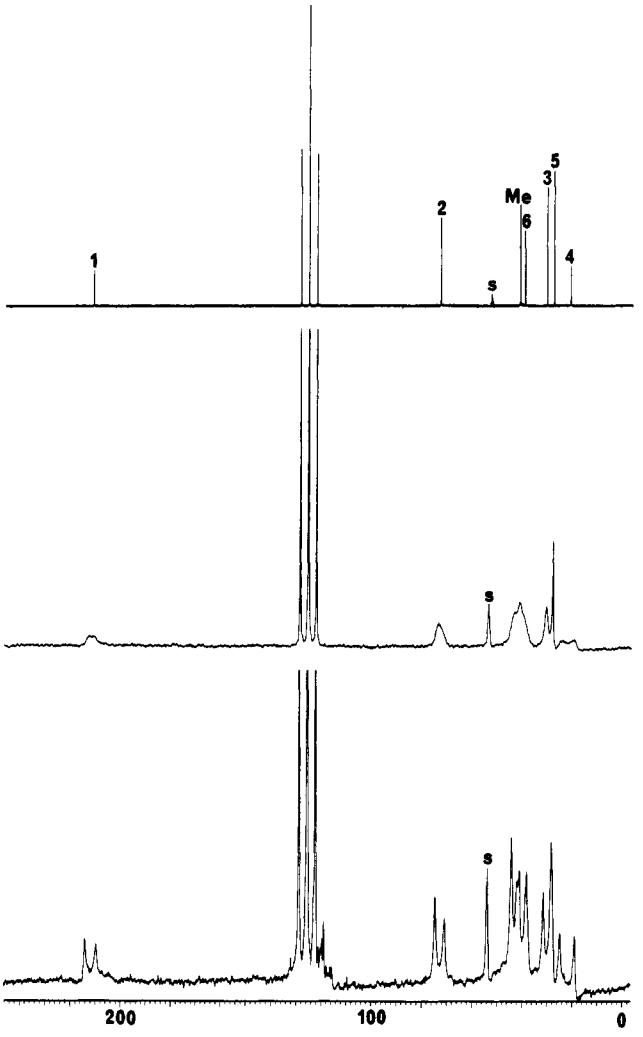

Figure 1. The carbon-13 spectrum of 2-(*N*,*N*-dimethylamino)-cyclohexanone in CF_2Cl_2 containing 3% CD_2Cl_2 as a function of temperature: (top) −70 °C, (middle) −110 °C, (bottom) −118 °C. The resonance from CD_2Cl_2 is indicated by s. The large triplet at δ 120–130 is from CF_2Cl_2.

Table III. Axial Conformer Populations of 2-Substituted Cyclohexanones in $CDCl_3$

X	δ_H[a]	δ_X[a]	J_{av}[a]	J_{23}[d]	δ_{C1}[d]	δ_{C2}[b]	Av[c]
F	21		17 (18[d])	11	20		17 ± 3
Cl	49		36	44	44	50	45 ± 4
Br	76		68	74	63	73	71 ± 4
I	99		87	89	75	88	88 ± 5
MeO	27	28	28	25	20	37	28 ± 4
MeS	75	93	75	89	94	85	85 ± 7
MeSe			92				(92)
Me_2N	38	45	41		38	47	44 ± 3
Me	0	6		50	49		(26)

[a] See footnotes *a*–*d* in Table II. [b] From the ^{13}C chemical shifts of C1 and C2. [c] Mean of all values for the substituent. [d] From the geminal H–F coupling.

other substituents with similar electronegativity to MeSe. We recognize that the value obtained is only an estimate and should be regarded as such in any future, more direct studies. In Table III we indicate the lack of confidence in the result by the parentheses in the final, averaged column.

The alkyl substituents, methyl and *tert*-butyl, suffered from very small chemical shift differences between the axial and equatorial 4-*tert*-butyl isomers. As a result, small differences between very similar numbers provided a large spread in results, from 0 to 50% for Me. Again, we have little confidence in the average result in the final column of Table III and place it in parentheses. For the *tert*-butyl substituent, the axial and equatorial numbers are very similar and would provide inaccurate results. Moreover, there is no assurance that the trans isomer is in the chair conformation. Large deformations or changes in the structure of the trans isomer of course would render the Eliel method entirely inapplicable. For this reason we do not even include the results in Table III.

For the remaining substituents, we believe that our results are the best available for the conformational preferences of 2-substituted cyclohexanones. The average value in each case is the result of at least five independent measurements. The errors shown on the averages are the mean deviations of the separate values from the mean. The errors average under 10% of the mean values.

We calculated the deviations of the data in each column from the means in the last column. The following are the average deviation for each method from the means: δ_H, 5.9; δ_X, 3.0; J_{av}, 3.7; J_{23}, 3.0; δ_{C1}, 6.9; δ_{C2}, 3.2. We cannot say whether in general the ^1H and C1 chemical shifts provide the least reliable results, but in this study their results deviated much more from the means than did the other measurables.

The proportion of axial conformer increases from 17% for fluorine to 88% for iodine. These numbers parallel those observed by Pan and Stothers in Table I. They reflect the increased steric, polar, and electronic repulsion of the larger halogens with the carbonyl group in the equatorial form. Straight steric (nonbonded) effects clearly are paramount, as the larger but less-polar iodine atom has the largest proportion of axial conformer (it should be borne in mind that the 2-axial position should be viewed as less sterically demanding than the 2-equatorial position). Similarly, methoxyl is 28% axial, dimethylamino is 42%, and methylthio is 85%. Size again is of prime importance, as the larger but less-polar sulfur group exhibits the largest axial proportion.

We succeeded in obtaining slow exchange spectra only from the ^{13}C spectra of the dimethylamino system. The melting point of chloroform does not permit such experiments, so that comparisons may not be made with the conformational proportions of Table III. The solvent of lowest polarity, pure CF_2Cl_2, provides the closest approach to a gas-phase conformational preference, 60%. Increased solvent polarity stabilizes the more-polar equatorial form, lowering the axial percentage to 50% in CF_2Cl_2 containing 3% CD_2Cl_2 and to 5% in $CHClF_2$. These observations confirm those of Pan and Stothers with halogen substituents (Table I), but with a new substituent (Me_2N) and for the first time by direct measurement at slow exchange.

Experimental Section

Proton NMR spectra were recorded on Bruker Model AW-80 and Varian Models XLA-400 and Gemini 300 spectrometers. Carbon-13 NMR spectra were recorded on Varian models XL-100, XLA-400, and Gemini 300 spectrometers. Low-temperature ^{13}C spectra were recorded on the XLA-400. Infrared spectra were recorded on a Perkin-Elmer Model 300B spectrophotometer. Cyclohexanone (1), 2-chlorocyclohexanone (3), 2-methoxycyclo-

hexanone (6), 2-methylcyclohexanone (10), and 4-*tert*-butylcyclohexanone (12) were commercially available from Aldrich.[18]

2-Fluorocyclohexanone (2). Cyclohexene oxide was ring-opened to 2-fluorocyclohexanol by treatment with KHF_2, and the alcohol was oxidized to the ketone with CrO_3.[19,20]

2-Bromocyclohexanone (4) was prepared by the addition of Br_2 to cyclohexanone.[21]

2-Iodocyclohexanone (5) was prepared by the addition of I_2 to the cyclohexanone enolate (from cyclohexanone and lithium diisopropylamide).[22]

2-(Methylthio)cyclohexanone (7) was prepared by the addition of methyl methanethiosulfonate to the cyclohexanone enolate.[23]

2-(Methylseleno)cyclohexanone (8) was prepared in two steps from the cyclohexanone enolate, first by the addition of elemental selenium to form the selenide and then by the addition of methyl iodide.[24]

2-(*N*,*N*-Dimethylamino)cyclohexanone (9) was prepared by treatment of 2-bromocyclohexanone (4) with dimethylamine.[25]

2-*tert*-Butylcyclohexanone (11).[26-28] Cyclohexanone was converted to 1-(trimethylsiloxy)cyclohexene by treatment with lithium diisopropylamide and chlorotrimethylsilane. The enol ether was treated with $TiCl_4$ and *tert*-butyl chloride to produce the ketone.

4-*tert*-Butyl-2-chlorocyclohexanone (14)[29] was obtained as a mixture of cis and trans isomers by treatment of 4-*tert*-butylcyclohexanone (12) with Cl_2.

4-*tert*-Butyl-2-bromocyclohexanone (15)[13,30] was obtained as a mixture of cis and trans isomers by treatment of 4-*tert*-butylcyclohexanone (12) with Br_2.

4-*tert*-Butyl-2-fluorocyclohexanone (13)[31] was prepared in three steps from 4-*tert*-butyl-2-bromocyclohexanone (15). Treatment of the bromo ketone with NaCN in DMSO produced *trans*-1-cyano-4-*tert*-butylcyclohexene oxide. Hydrogen fluoride was generated from KHF_2 and BF_3 etherate and was allowed to react with the epoxide to produce 1-cyano-2-fluoro-4-*tert*-butylcyclohexanol, which, on treatment with $AgNO_3$ in NH_4OH solution, produced the desired fluoro ketone as the cis isomer. A mixture of cis and trans isomers was obtained by epimerization with 1 M HCl in diethyl ether.[32]

4-*tert*-Butyl-2-iodocyclohexanone (16)[22] was obtained as a mixture of cis and trans isomers by the addition of I_2 to the enolate of 4-*tert*-butylcyclohexanone (from 4-*tert*-butylcyclohexanone (12) and lithium diisopropylamide).

4-*tert*-Butyl-2-methoxycyclohexanone (17)[33,34] was obtained in four steps from 4-*tert*-butylcyclohexanone (12). The carbonyl group was protected as the enamine with pyrrolidine, and the α-position was brominated. The bromine was replaced with methoxyl by treatment with NaOMe, and the ketone was liberated as a mixture of cis and trans isomers by acid hydrolysis.

4-*tert*-Butyl-2-(methylthio)cyclohexanone (18)[23] was obtained as a mixture of cis and trans isomers by the addition of methyl methanethiosulfate to the enolate of 4-*tert*-butylcyclohexanone (12).

4-*tert*-Butyl-2-(methylseleno)cyclohexanone (19) was prepared as the trans isomer in two steps from the enolate of 4-*tert*-butylcyclohexanone (12), first by the addition of elemental selenium to form the selenide and then by quenching with methyl iodide.[24] Epimerization efforts failed, so the cis isomer was never obtained.

4-*tert*-Butyl-2-(dimethylamino)cyclohexanone (20) was obtained by treatment of 4-*tert*-butyl-2-cyclohexanone (15) with dimethylamine.[25]

4-*tert*-Butyl-2-methylcyclohexanone (21) was obtained in three steps from 4-*tert*-butylcyclohexanone (12).[29,35,36] The ketone was converted to the hydrazone with 1,1-dimethylhydrazine. Deprotonation with lithium diisopropylamide, treatment with iodomethane, and deprotection with BF_3 etherate gave the desired ketone as a mixture of cis and trans isomers.

2,4-Di-*tert*-butylcyclohexanone (22).[26-28] 4-*tert*-Butylcyclohexanone (12) was converted to 1-(trimethylsiloxy)-4-*tert*-butylcyclohexene with lithium diisopropylamide and chlorotrimethylsilane. The enol ether was treated with $TiCl_4$ and *tert*-butyl chloride to produce the ketone as a mixture of cis and trans isomers.

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Synthetic Routes to Bridged Dicyclooctatetraenes and Alkynylcyclooctatetraenes

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Dicyclooctatetraenylethyne, (*E*)-1,2-dicyclooctatetraenylethylene and 1,4-dicyclooctatetraenylbenzene (**3a–c**) have been prepared through a convergent synthesis by the palladium-catalyzed coupling of 1,2-bis(tributylstannyl)ethyne, (*E*)-1,2-bis(tributylstannyl)ethylene, and 1,4-bis(tributylstannyl)-benzene (**2a–c**), respectively, with bromocyclooctatetraene (**1**). Modified Stille coupling conditions with tri(2-furyl)phosphine and triphenylarsine as ligands were employed. Alkynylcyclooctatetraenes, including **3a**, have been prepared by the palladium/copper-catalyzed coupling of terminal alkynes with **1**. Bridged dicyclooctatetraenes **3a** and **3c** were also prepared through a linear synthesis starting from 2,6-cyclooctadien-1-one.

Introduction

The transfer of charge density between identical electrophores connected by organic and inorganic bridges represents an attractive strategy for relating the rate of charge transfer to molecular structure. Our research has been focused on the cyclooctatetraene electrophore[1,2] and has led to the need to develop methods for the preparation of dicyclooctatetraenes with various bridging groups. These compounds can then be reduced to the corresponding dianions and the rate of degenerate charge transfer can be determined by dynamic NMR spectrometry. Such studies are expected to give new information regarding how charge associated with carbanions and their counterions is transferred across organic bridges.

A few examples of bridged dicyclooctatetraenes or their dianions have been reported in the literature. The "parent" molecule, bicyclooctatetraenyl, can be prepared through the coupling of bromocyclooctatetraene with cyclooctatetraenyllithium catalyzed by $CoCl_2$[3] or $Ni(acac)_2$.[4] Staley and co-workers prepared 9,9′-bi-*cis*-bicyclo[6.1.0]nona-2,4,6-triene, which affords 1,2-dicyclooctatetraenylethylenedipotassium upon treatment with 2 equiv of potassium amide.[1] Ethynyl-bridged dicyclooctatetraenes were prepared by Auchter–Krummel and Müllen by the Wittig or McMurry coupling reaction starting from cyclooctatetraenecarboxaldehyde.[5] A series of alkyl- and silyl-bridged dicyclooctatetraenes were prepared by Echegoyen et al. by coupling cyclooctatetraenylmagnesium bromide with dibromoalkanes and dichlorosilanes in the presence of Li_2CuCl_4.[6] Finally, Eaton has cited unpublished results from his laboratory regarding the preparation of 1,4-dicyclooctatetraenylbenzene by the Rh(I)-catalyzed ring opening of 1,4-dicubylbenzene.[7]

We are interested in developing general synthetic routes to bridged dicyclooctatetraenes through which a wide variety of bridging groups can be incorporated and are particularly interested in the preparation of alkynyl-bridged dicyclooctatetraenes. The only previous examples of alkynylcyclooctatetraenes were recently prepared by Eaton and Stössel through the palladium-catalyzed reaction of terminal acetylenes with iodocubanes.[8] In this paper we discuss the preparation of alkynyl-, aryl-, and alkenyl-bridged dicyclooctatetraenes by the Stille coupling reaction, by the palladium/copper-catalyzed coupling of terminal alkynes with organohalides, and by a route that begins with nucleophilic addition to 2,6-cyclooctadien-1-one.[9]

Results and Discussion

(1) Stille Coupling Route. The Stille coupling of organostannanes with organic halides catalyzed by palladium complexes has been shown to proceed with a wide variety of substrates and has the advantage that the intermediate stannanes can be isolated and purified.[10] Because of the reasonable availability of bromocyclooctatetraene (**1**)[11] and of distannanes **2a,b**[12] and **2c**,[13] we chose to investigate the coupling of **1** with **2a–c**. Furthermore, the expense of cyclooctatetraene (COT) argued for a convergent synthesis with the COT ring being involved in as few steps as possible.

We anticipated that a Stille coupling route would work with **2a–c** because of the recent work of Farina and co-

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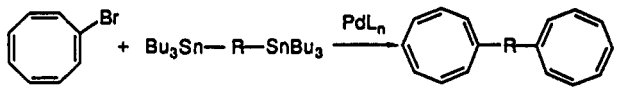


1 2a: R= C≡C 3a: R= C≡C
2b: R= (E)-HC=CH 3b: R= (E)-HC=CH
2c: R= 1,4-C6H4 3c: R= 1,4-C6H4

workers, who found that the use of the tri(2-furyl)-phosphine and triphenylarsine ligands permits the coupling of stannanes with organohalides and triflates under very mild conditions.[14] This was important for us because temperatures above ca. 50 °C must be avoided owing to the known thermal isomerization of 1 to β-bromostyrene.[15] Farina has concluded that the use of tri(2-furyl)phosphine and triphenylarsine in the Stille reaction increases the rate of transmetalation of the stannane to palladium, which is thought to be the rate-determining step of the catalytic cycle.[14,16]

Our results for the couplings of **2a–c** with 1 are summarized in Table I and in an earlier publication.[9] In accord with Farina's results, we were able to employ shorter reaction times and obtain higher yields with tri(2-furyl)-phosphine and triphenylarsine than with the more commonly used triphenylphosphine ligand.

Another effect of ligand and solvent occurs in the coupling of **2c** with 1, where a significant amount (ca. 20%) of bicyclooctatetraenyl is produced under the conditions employed in Table I. The formation of this side product can be almost completely eliminated by employing toluene as the solvent or by using twice as much triphenylarsine. The reaction in toluene gives only a 17% yield of product after 48 h, but the appearance of a black precipitate in the reaction flask indicated that some of the catalyst may have decomposed. When an extra 2 mol % of catalyst in toluene was added at this point, the yield of **3c** increased to 30–35% after an additional 24 h. Similarly, doubling the quantity of triphenylarsine gave a 28% yield of **3c** after 48 h.

A plausible explanation for the above results is that oxidative addition of 1 to the palladium(II) species occurs prior to reductive elimination to give a palladium(IV) species. Reductive elimination from this intermediate could lead either to **3c** or to bicyclooctatetraenyl.[17] Oxidative addition of methyl iodide to a palladium(II) complex has been shown to be slower by 2 orders of magnitude in toluene than in polar aprotic solvents such as dimethyl sulfoxide or acetonitrile.[18] Furthermore, an increased concentration of triphenylarsine could also suppress oxidative addition of 1 to palladium(II) by coordination of the ligand to vacant coordination sites on the metal.

(2) Synthesis of Alkynylcyclooctatetraenes. The coupling of organohalides with terminal alkynes catalyzed by palladium and copper salts is another method of introducing an ethynyl group. We compared the couplings of 1 with ethynyltrimethylsilane and ethynylbenzene with those of the corresponding stannanes. The procedure of Hagihara and co-workers,[19] slightly modified,[20] was employed in this study.

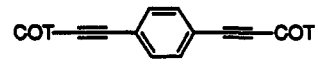
Table I. Effect of Ligand on the Coupling of Bromocyclooctatetetraene with Bis(tributyl)stannanes

entry	stannane	ligand	time (h)	yield (%)
1	**2a**	PPh_3	24	45
2		$Pfur_3$	3	55
3		$AsPh_3$	1	45
4	**2b**	PPh_3	24	45
5		$Pfur_3$	5	60
6		$AsPh_3$	2	40
7	**2c**	PPh_3	48	0
8		$Pfur_3$	48	23
9		$AsPh_3$	24	30

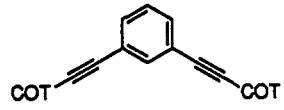
As seen in Table II, the coupling with a terminal alkyne gives a higher yield than with the corresponding stannane in all three cases. Also note that we were able to increase the yield of **3a** from 55 to 80% upon coupling 1 with acetylene versus distannane **2a**.[9]

The role of the cuprous ion in the couplings of 1 with ethynyltrimethylsilane was briefly examined. No coupling took place in the absence of cuprous iodide. Cupric acetate monohydrate has been shown to be as effective as cuprous iodide in the ethynylation of aryl halides.[21] However, the use of the former compound led to a decrease in the yield of the coupling of 1 with ethynyltrimethylsilane to 60% from 95% with cuprous iodide.

We employed the conditions established for the alkynes in Table II to couple 1,4-[22] and 1,3-diethynylbenzene[21] with 1. The former reaction afforded **4** in a disappointing 25% yield. There is potential for improving this reaction because we were able to obtain **4** in 65% yield in one experiment; however, we could only reproduce the 25% yield. The coupling of 1,3-diethynylbenzene with 1 afforded **5** reproducibly in 60% yield. The use of triphenylphosphine as ligand afforded **5** contaminated with residual triphenylphosphine. This problem was eliminated by changing the ligand to tri(2-furyl)phosphine, which, unlike triphenylphosphine, does not cochromatograph with **5**.



4



5

It is possible that the low yield of **4** is due to the lability of 1,4-diethynylbenzene. Therefore, we explored the coupling of 1-ethynylcyclooctatetraene with 1,4-diiodobenzene. Treatment of 1-[(trimethylsilyl)ethynyl]cyclooctatetraene (entry 1, Table II) with a catalytic amount of aqueous KOH in MeOH effected the removal of the TMS group to afford 1-ethynylcyclooctatetraene in 90% yield. This compound was then coupled with 1,4-diiodobenzene to produce **4** in 60% yield (Scheme I). The latter synthesis afforded **4** in 50% overall yield from 1 compared to a 25% yield obtained from the coupling of 1,4-diethynylbenzene with 1.

(3) Preparation of Bridged Dicyclooctatetraenes from 2,6-Cyclooctadien-1-one. Bridged Dicyclooctatrienes. A third synthetic route to bridged dicyclooc-

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