52–53.2 °C). The IR and NMR spectra were identical with those reported for **6a**.[11b]

Preparation of *exo*-2-Ethynylbicyclo[2.2.1]heptan-7-one (7). Chromium trioxide (1 g, 10 mmol) was added to a stirred solution of pyridine (1.6 g, 20 mmol) in 25 mL of methylene chloride.[14] After 15 min at room temperature, 0.15 g (1.5 mmol) of **2** in 2 mL of methylene chloride was added, and the suspension was stirred at room temperature for 18 h, after which it was poured into water (20 mL) and filtered through a bed of celite. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were then washed with cold dilute hydrochloric acid and water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give a yellow oil. This was distilled to give **7** (0.08 g, 50%), bp 50 °C (0.08 mm). It was homogeneous by VPC (5% carbowax 20 M, 160 °C): IR (neat) 3300 (s), 1830 (m), 1775 (s), and 1742 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.86–2.43 (m, 1 H), 2.2 (d, $J = 2$ Hz, 1 H), 1.36–2.18 (m, 8 H). The 2,4-dinitrophenylhydrazone of **7** melted at 110–111 °C.

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.27; H, 4.47; N, 17.73.

Reduction of 7 with Diisobutylaluminum Hydride to 2a. To a stirred solution of **7** (0.095 g, 0.8 mmol) in 1 mL of toluene at −18 °C was added a toluene solution of diisobutylaluminum hydride (1 mL, 2 M). Stirring was continued for 1 h at −18 °C. The reaction mixture was then hydrolyzed with a minimum amount of water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give **2a** (0.09 g, 82%), which showed IR and NMR spectra identical with that of **2a** prepared earlier.

Acknowledgments. We thank Professor B. Snider for helpful discussions, Hoffmann-La Roche, Inc., for microanalytical services, and Matthey-Bishop, Inc., for a generous loan of $PdCl_2$. This investigation was supported by Grant CA 18546 and by training grants (to T.M. and V.V.) awarded by the National Cancer Institute, DHEW.

Registry No.—**2a**, 64130-75-2; **3**, 3146-39-2; **4**, 64130-76-3; **6a**, 16709-78-7; **7**, 64130-77-4; **7** DNP, 64130-78-5.

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Synthesis and Circular Dichroism Spectral Studies of Arylamides of *trans*-2-Phenylcyclohexanecarboxylic Acid and *trans*-1-Amino-2-phenylcyclohexane[1,2]

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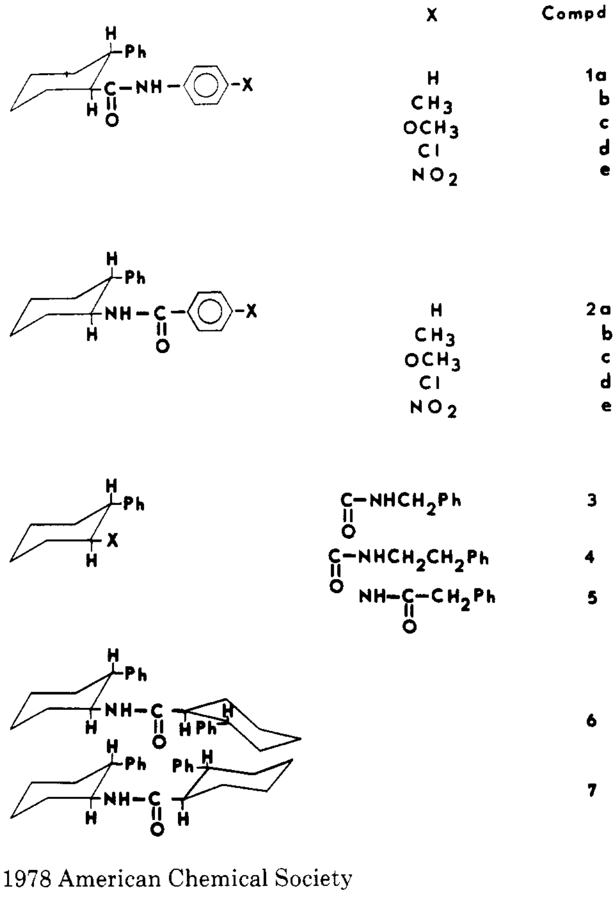
Although the chiroptical phenomena exhibited by aromatic compounds have been studied extensively,[3] papers on benzamides are few,[4–6] and a systematic study of anilides has not been reported. We report the CD and isotropic UV spectra of a series of aromatic amides (Scheme I) derived from *trans*-2-phenylcyclohexanecarboxylic acid (A) and *trans*-1-amino-2-phenylcyclohexane (B).

These amides are of interest because they have structural features in common with amides of the amino acid phenylalanine. The C-1 and C-2 substituents in these amides form a fixed dihedral angle of approximately 60°, resulting in a chromophoric system which resembles a staggered conformer of the analogous phenylalanine amides. Absolute configurational assignments and conformational analysis are available from previously reported studies on the precursors, A and B.[7,8] Finally, the CD spectra of these amides show *separately* the effects of changing the para substituent on an anilide or benzamide, inverting the amide chromophore, or changing the proximity (number of intervening carbons) of the amide and benzene chromophores.

Experimental Section

CD and ORD measurements were made at 25 °C in methanol on a Jasco Model ORD/UV/CD-5 instrument under conditions described by Verbit et al.[7,9] Isotropic UV measurements were made on a Cary Model 11 instrument. For CD, ORD, and isotropic UV measurements, solution concentrations were 2.5–3.0 × 10^{-4} M, except that the $[\alpha]_D$'s of all compounds and the ^1L_b bands (CD and UV) of compounds 3–7

Scheme I



0022-3263/78/1943-0355$01.00/0

Table I. Experimental Data for Amides of +A and +B [a]

Compd	Mp	$[\alpha]_D$	IR, ν(C=O)	Registry no.
1a	135–138	+105	1651	64163-48-0
b	182–186	+136	1650	64163-49-1
c	217–221	+183	1648	64163-50-4
d	182–185	+124	1655	64163-51-5
e	175–179	+84	1670	64163-52-6
2a	210–212	+105	1634	64200-03-0
b	219–221	+88	1633	64163-53-7
c	232–233	+75	1630	64163-54-8
d	230–231	+79	1637	64163-55-9
e	202–203	+65	1639	64163-56-0
3	121–125	+36	1636	64163-57-1
4	109–112	+11	1632	64163-58-2
5	145–146	−43	1634	64163-59-3
6	258–259	+71	1633	64163-60-6
7	255–256	−65	1633	64200-04-0

[a] The melting points are corrected. Specific rotations were obtained in methanol at 25 °C. The carbonyl stretching IR band (in cm^{-1}) was obtained as a Nujol mull. Additional details are in the experimental Section of the text.

were obtained at 6.0–7.0 × 10^{-3} M. IR spectra were obtained as Nujol mulls between NaCl plates on a Perkin-Elmer Model 467 instrument. Compound melting points were obtained on a Fisher-Johns melting point apparatus and are corrected. Organic solvents were anhydrous unless otherwise stated. Elemental analyses were conducted by Galbraith Laboratories, Knoxville, Tenn.

Synthesis of Acid Chlorides. Acid chlorides were obtained from their corresponding carboxylic acids. The synthesis and resolution of *trans*-2-phenylcyclohexanecarboxylic acid was described in ref 7. The conversion of acids to acid chlorides was as follows. A 1-g amount of the acid was refluxed for 1 h with 5 mL of $SOCl_2$. Most of the excess $SOCl_2$ was evaporated under a stream of nitrogen at 40–45 °C. The remaining $SOCl_2$ was removed by the addition and evaporation of two portions of benzene, yielding the acid chloride.

Synthesis of Amines. The synthesis and resolution of *trans*-1-amino-2-phenylcyclohexane was as described in ref 7. Other amines were reagent grade and were recrystallized or vacuum distilled prior to use.

Synthesis of Amides. The acid chloride (0.0015 mol) dissolved in 5 mL of benzene was added to a solution of the amine (0.0015 mol) in 5 mL of benzene and 2 mL of pyridine. The reaction mixtures were allowed to stand in the dark at 25–30 °C for 3 days. The reaction mixture was taken up in 50 mL of diethyl ether. The ether solution was washed with 50-mL portions of the following aqueous solutions: 5% Na_2CO_3 (twice), saturated NaCl, 1 M HCl (twice), and saturated NaCl. The ether solution was then washed with two 30-mL portions of water and dried over anhydrous Na_2SO_4. The ether was driven off under a stream of N_2, and the amides were recrystallized from benzene or benzene–hexane solutions, except compounds **3** and **5** were recrystallized from CCl_4 and compound **4** from ethanol. Yields of recrystallized amides (based on chiral acid or amine) were 60–78%, except **1a**, **1e**, and **2d** were 40–50%. Silica gel G TLC of the amides gave single spots in the two developing solvents, 2:1 benzene/$CHCl_3$ and 10:2:1 cyclohexane/acetone/CH_3OH. The IR spectra of the amides were characterized by secondary amide NH bands between 3270 and 3340 cm^{-1} and carbonyl bands between 1630 and 1670 cm^{-1}. The melting points, $[\alpha]_D$'s, and carbonyl IR bands for the amides are summarized in Table I.

Results and Discussion

This discussion, as well as spectral and other experimental data, is presented for amides having absolute configurations as shown in Scheme I (although the amide actually synthesized may be the enantiomer). Thus, compounds **1a–e, 2a–e, 3, 4,** and **5** all have the same absolute configuration and are derived from (+)-(1*S*,2*S*)-*trans*-2-phenylcyclohexanecarboxylic acid (+A) or (+)-(1*S*,2*R*)-*trans*-1-amino-2-phenylcyclohexane (+B). Compound **6** is derived from +A and +B and compound **7** from −A and +B.

For the aromatic amides, **1a–d** and **2a–d**, two bands predominate in the CD spectra: the charge transfer (CT)[10] amide band appearing between 225 and 250 nm and the aromatic ^1L_a band (Platt's notation)[11] between 210 and 220 nm. (See Figures 1 and 2 and Table II.)

The aromatic ^1L_b band is largely obscured by the CT band in these compounds but is partially observable in **1a, 2a, 2b,** and **2d.** The nitro CT transition gives rise to a broad CD band around 300 nm for **1e** and **2e.** Thus, the *p*-nitroanilide **1e** shows three positive CD bands: ^1L_a (210 nm), amide CT (229 nm), and nitro CT (317 nm). For the *p*-nitrobenzamide **2e,** however, only two bands (both positive) are observed: the nitro CT band at 289 nm and a weak band at 218 nm. We assign the positive 218-nm band primarily to the amide CT transition, probably superimposed on a weaker negative ^1L_a Cotton effect. This assignment is consistent with trends in the CD spectra of the benzamide series (**2a–d**) where amide CT bands are all positive, an electron-withdrawing parasubstituent producing a hypsochromic shift, and a lessened ellipticity

Table II. CD and Isotropic UV Extrema for Anilides, Benzamides, and Homologues [a]

Compd	205–220 nm bands, [λ(ε), λ([±θ])]	CT and ^1L_b bands, [λ(ε), λ([±θ])]
1a	206 (24 800), 210 (+26 300)	242 (13 300), 240 (+24 400)
b	206 (26 600), 210 (+27 500)	245 (14 100), 243 (+27 800)
c	206 (28 200), 210 (+34 300)	249 (18 600), 245 (+34 500)
d	206 (27 500), 210 (+34 800)	249 (17 800), 247 (+31 300)
e	206 (19 700), 210 (+16 000)	, 229 (+8200); 316 (13 800), 317 (+9700)
2a	206 (16 600), 216 (−7900)	, 227 (+11 300)
b	206 (23 600), 216 (−12 900)	234 (13 200), 234 (+19 500)
c	206 (29 800), 213 (−35 900)	250 (16 600), 251 (+24 600)
d	206 (22 600), 215 (−9 300)	234 (13 400), 237 (+15 300)
e	206 (19 400), [218 (+7800)]	, 218 (+7800); 261 (11 750), 289 (+6300)
3	208 (17 400), 212 (−9000)	252 (320), 254 (+150); 258 (380), 261 (+265) 264 (290), 268 (+250
4	208 (19 300), 212 (+15 500)	252 (448), 254 (+25); 258 (504), 259 (+75) 264 (398), 266 (+73)
5	206 (19 400), 211 (−35 500)	252 (520), 253 (+154); 258 (570), 260 (+255) 264 (452), 267 (+256)
6	208 (18 900), 220 s (−12 300) 210 n (−21 000)	252 (330), 257 (−216); 258 (406), 263 (−265) 264 (308), 269 (−141)
7	208 (19 600), 217 s (−24 800) 209 (−49 000)	252 (363), 255 (−226); 258 (435), 262 (−253) 264 (338), 268 (−155)

[a] s = shoulder and n = extrema not reached. For several amides shoulders were evident in the high-wavelength side of the 206–208 nm isotropic UV band. Isotropic UV amide CT bands of **1e, 2a,** and **2e** are obscured by the ^1L_a band. The 218-nm CD band of **2e** is assigned primarily to the amide CT transition. (See the Results and Discussion Section.)

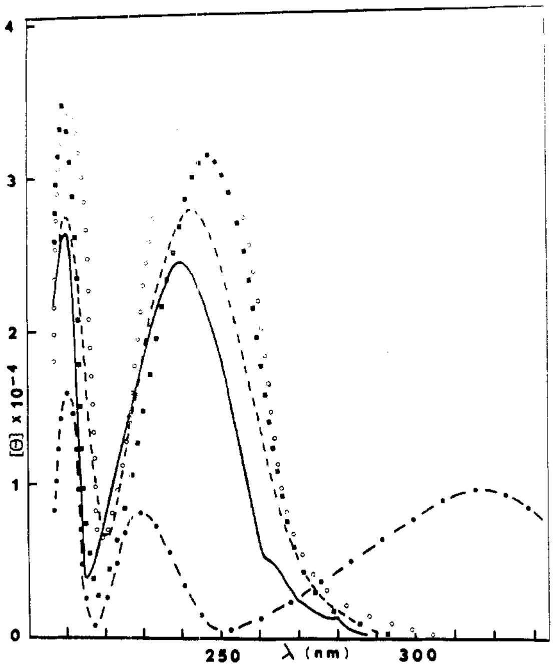


Figure 1. Circular dichroism spectra of anilides of (+)-(1*S*,2*S*)-*trans*-2-phenylcyclohexanecarboxylic acid in methanol; **1a** (–), **1b** (- - -), **1c** (○), **1d** (■), **1e** (●-●).

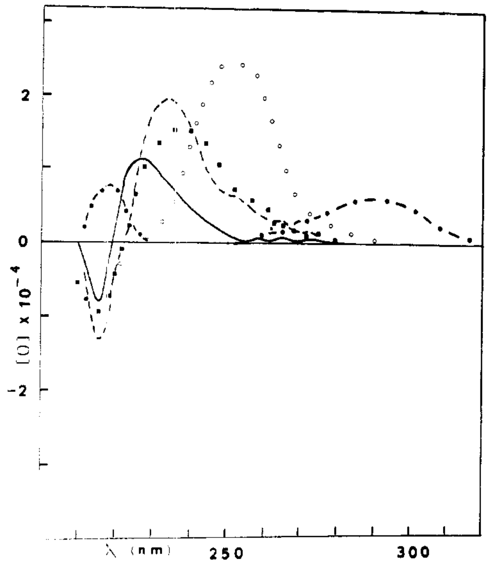


Figure 2. Circular dichroism spectra of benzamides of (+)-(1*S*,2*R*)-*trans*-1-amino-2-phenylcyclohexane in methanol; **2a** (—), **2b** (- - -), **2c** (○), **2d** (■), **2e** (●-●).

in the amide CT band; the ^1L_a bands are negative and, with the exception of **2c**, of lower intensity than the amide CT bands.

In general, an increased electron-donating capability in the parasubstituent increases the intensity of the ^1L_a Cotton effect and isotropic absorption in both aromatic amide series, **1a–e** *and* **2a–e**. The shifts in λ_{max} are small and measurable only for the benzamide series (**2a–e**). The amide CT bands (both UV and CD) of both series are markedly influenced by the para substituent: bands generally increasing in intensity and undergoing a bathochromic shift as the electron-donating capacity of the substituent increases. The more-pronounced changes in the amide CT band are observed for the benzamide series (**2a–e**). In contrast, a *p*-nitro substituent shifts the carbonyl IR stretching frequency more in the anilide series (1a–e). (See Table I.)

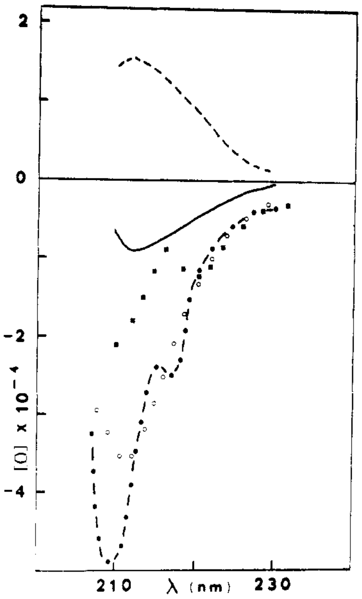


Figure 3. Circular dichroism spectra of compounds 3 (—), 4 (- - -), 5 (○), 6 (■), and 7 (●-●) in methanol.

The sign of the ^1L_a Cotton effect changes when the amide chromophore is inverted in the aromatic amide series (*cf. any anilide with its corresponding benzamide*) *or when the amide nitrogen is increasingly separated from the benzene ring as in the series* **1a, 3,** *and* **4,** where the ^1L_a Cotton effects are (+), (−), and (+), respectively. (See Figure 3 and Table II.)

The ellipticity of the ^1L_a Cotton effect in the *p*-methoxybenzamide **2c** is triple that of *p*-chlorobenzamide **2d,** whereas in the corresponding anilides, the bands of **1c** and **1d** are of nearly equal intensity. The unique electronic effects of a *p*-methoxy group on a benzamide CD spectra have been noted by Krueger et al,[4] but as yet no adequate explanation is available.

All amides derived from +B (*including* **6** *and* **7**) *exhibit negative ^1L_a Cotton effects.* (The amine, +B itself, exhibits a positive ^1L_a band.)[7] The CD spectra of diastereomers **6** and **7** show ^1L_a bands that are interpreted as two overlapping bands. (See Figure 3.) The ORD spectra of these compounds (not shown) are consistent with this interpretation. One can approximate the ellipticity of the ^1L_a bands of **6** and **7** by considering them to be the sum of (1) a strong negative Cotton effect (such as that observed for **5**) contributed by the +B component and (2) a contribution from the A component. The contribution from the A component for **6** (derived from +A and +B) would be a positive Cotton effect similar to that of **4**; for **7** (derived from −A and +B) it would be a negative Cotton effect, the inverse of that observed for **4**.

For compounds **3, 4,** and **5,** no amide CT bands are present, and the ^1L_b bands, with their characteristic vibronic fine structure, are clearly observed in the CD and isotropic UV spectra. (See Table II.) Enough of the ^1L_b Cotton effect can be discerned in the spectra of **1a, 2a, 2b,** and **2d** so that the sign can be reliably determined. *All seven of these compounds exhibit positive ^1L_b Cotton effects. Thus, unlike the ^1L_a Cotton effect, the ^1L_b effect does not change sign in the series* **1a, 3,** *and* **4**; *nor does it change upon inversion of the amide chromophore* (*cf.* **1a** *and* **2a**). As has been pointed out for a series of 2-substituted phenylcyclohexanes,[7,8] conformational mobility apparently obviates sign/chirality correlations for the ^1L_b Cotton effects for these series of amides as well. Consequently, there is no obvious rationale for the interesting feature that the ^1L_b Cotton effects exhibited by diastereomers **6** and **7** are virtually identical. (See Table II.)

We anticipate the further study of related anilides and benzamides with the intent of testing further the generality of the correlations of chirality with amide CT and aromatic ^1L_a bands. Of particular interest are amides derived from the cis isomers of A and B and isomers of the phenylalanine analogue 1-amino-2-phenylcyclohexanecarboxylic acid.

Registry No.—$\mathrm{H_2NCH_2Ph}$, 100-46-9; $\mathrm{H_2N(CH_2)_2Ph}$, 64-04-6; $\mathrm{ClCOCH_2Ph}$, 103-80-0; $\mathrm{H_2NPh}$, 62-53-3; $\mathrm{H_2NC_6H_4}$-p-$\mathrm{CH_3}$, 106-49-0; $\mathrm{H_2NC_6H_4}$-p-$\mathrm{OCH_3}$, 104-94-9; $\mathrm{H_2NC_6H_4}$-p-Cl, 106-47-8; $\mathrm{H_2NC_6H_4}$-p-$\mathrm{NO_2}$, 100-01-6; ClCOPh, 98-88-4; $\mathrm{ClCOC_6H_4}$-p-$\mathrm{CH_3}$, 874-60-2; $\mathrm{ClCOC_6H_4}$-p-$\mathrm{OCH_3}$, 100-07-2; $\mathrm{ClCOC_6H_4}$-p-Cl, 122-01-0; $\mathrm{ClCOC_6H_4}$-p-$\mathrm{NO_2}$, 122-04-3; 2-phenylcyclohexane-1-carbonyl chloride, 34713-97-8; 1-amino-2-phenylcyclohexene, 37982-23-3.

References and Notes

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(2) This work is taken in part from the M.S. Thesis of M.F.

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A General Synthesis of Terminal and Internal Arylalkynes by the Palladium-Catalyzed Reaction of Alkynylzinc Reagents with Aryl Halides

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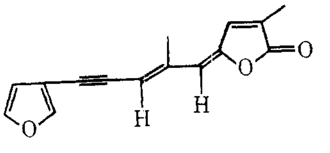
Arylalkynes represent a number of natural products such as freelingyne[1] (1) and junipal[2] (2). They have been most commonly prepared by Cu-promoted aryl–alkynyl coupling,[3] which involves either the reaction of alkynylcoppers with aryl halides[3a] or that of arylcoppers with alkynyl halides.[3b] More recently, an alternate approach consisting of the Pd-catalyzed reaction of alkynes with aryl halides in the presence of suitable bases has been developed.[4] While these known procedures are satisfactory in many cases, none of them appears to provide a satisfactory direct procedure for the synthesis of terminal arylalkynes which does not require any protection–deprotection sequence.[5] The difficulty largely stems from the fact that, under the reaction conditions, the required ethynyl reagents, such as ethynylcopper[6] and ethynylalkali metals,[7] are unstable with respect to disproportionation.



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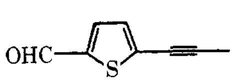

2

We have recently found that organozinc compounds react rapidly with various aryl and alkenyl halides to produce cross-coupled products even at room temperature in the presence of a catalytic amount of a Pd or Ni catalyst, whereas the corresponding reactions of organoalkali metals and Grignard reagents are not only slower but generally less satisfactory.[8] We have also noted that ethynylzinc chloride can be conveniently prepared by the reaction of either ethynyllithium[7] or its ethylenediamine complex[9] with anhydrous zinc chloride as a reagent stable at room temperature.[10]

We now report that these findings can be exploited in developing a procedure for aryl–alkynyl coupling applicable even to the direct and selective synthesis of terminal arylalkynes (eq 1).

$$\mathrm{RC{\equiv}CZnCl} + \mathrm{ArX} \xrightarrow{\text{cat Pd complex}} \mathrm{RC{\equiv}CAr} \qquad (1)$$

$$\mathrm{R} = \mathrm{H}, \text{ alkyl, or aryl}; \ \mathrm{X} = \mathrm{I} \text{ or } \mathrm{Br}$$

The aryl–alkynyl coupling reaction reported here is essentially complete within several hours at room temperature when either aryl iodides or activated aryl bromides such as p-cyanobromobenzene are used. In such cases, the formation of arylalkynes proceeds cleanly without producing any other byproducts in significant amounts (<5%). On the other hand, unactivated aryl bromides such as bromobenzene are quite inert at room temperature. Thus, while the formation of tolan from 2-phenylethynylzinc chloride and iodobenzene is complete within 0.5 h at room temperature, the corresponding reaction of bromobenzene does not give any more than a trace of tolan even after 4 days under comparable conditions. Similar difficulties have also been observed with p-methoxybromobenzene and p-chlorobromobenzene. No aryl fluorides have been tested.

The present study corroborates our earlier finding that organozinc reagents are superior to the corresponding Grignard and organoalkali metal reagents in Pd or Ni-catalyzed cross-coupling.[8] Thus, for example, the reaction of 1-heptynylmagnesium bromide with o-iodotoluene gives only a 49% yield of 1-(o-tolyl)-1-heptyne after 24 h, and the corresponding reaction of 1-heptynyllithium does not produce the desired product in any more than a trace amount under comparable conditions. For the preparation of terminal alkynes, both ethynyllithium generated at −78 °C and its ethylenediamine complex serve as satisfactory sources of ethynylzinc chloride, although the latter appears to give somewhat cleaner results. In some experiments, 5 mol % of a Pd catalyst has been used. However, the subsequent studies have indicated that even 1 mol % of the catalyst gives entirely satisfactory results. Both $\mathrm{Pd(PPh_3)_4}$ and a Pd catalyst generated in situ from $\mathrm{Cl_2Pd(PPh_3)_2}$ and diisobutylaluminum hydride seem almost equally satisfactory. The use of $\mathrm{Pd(PPh_3)_4}$, which does not require any additional treatment, is operationally simpler than that of the latter catalyst. On the other hand, the shelf-life of the former appears considerably shorter than that of the latter, although we have not yet determined how long $\mathrm{Pd(PPh_3)_4}$ can be kept without a significant loss of its catalytic activity. Nickel–phosphine complexes, such as $\mathrm{Ni(PPh_3)_4}$, do induce the desired cross-coupling reaction. However, the product yields have been low (<50%), and no complete consumption of aryl halides has been observed when the amount of the Ni catalyst is 5 mol %.[11] Unlike certain alkynylcoppers and related organotransition metals, which tend to be explosive, the Pd-catalyzed reaction of alkynylzinc derivatives does

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