highly reactive 10-I-4 species have been isolated and characterized. The key precursor for the other 10-I-4 species reported here, iodinane oxide **5b** with a nucleophilic equatorial oxygen atom and an electrophilic iodine center, is also stabilized by the tridentate ligand. Its reaction at oxygen with a variety of electrophiles leads to cationic 10-I-4 species, periodonium ions. The 12-I-5 periodinanes, formed by attack of nucleophiles at the cationic iodine center of 10-I-4 species, have Ψ-Oc geometry about iodine. Because the five ligand sites in this Ψ-Oc geometry include four identical sites incorporated in three-center bonds, plus a two-center bond opposite to the iodine lone pair, the 12-I-5 species also benefit from the difference in electronegativity between the fluoroalkoxy oxygens and the electropositive carbon of the tridentate ligand. The C–I two-center bond therefore provides stabilization by donating electrons to the iodine, which has positive charge because of its central location in two perpendicular three-center bonds. This would not be as likely for species with 12-I-6 Oc geometry in which all six sites are identical. Ionization of 12-I-5 species to give 10-I-4 species was found to be sufficiently facile to provide a wide range of isolable 10-I-4 species of types which have hitherto received little attention. Both the Ψ-Oc 12-I-5 species and the Ψ-TBP 10-I-4 species receive stabilization from the geometric consequences of the two five-membered rings formed by the tridentate ligands of this study. Both types of bicyclic hypervalent iodine species are therefore less reactive, and more easily isolable, than their acyclic or monocyclic analogues which have been studied earlier.

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Registry No. **4a**, 80360-39-0; **4b**, 136213-44-0; **4c**, 136213-45-1; **5a**, 136213-46-2; **5b**, 136213-47-3; **6b**, 101697-28-3; **7b**, 101697-29-4; **8**, 101697-29-4; **9**, 136213-51-9; **10**, 136213-52-0; **11**, 136213-53-1; **12**, 136213-55-3; **13**, 136213-56-4; **14**, 32133-82-7; **15**, 136213-58-6; **16**, 136213-59-7; **17**, 101697-32-9; $PhC(CF_3)_2OK$, 37818-31-8; $(p\text{-}ClC_6H_4)_2S$, 5181-10-2; $(p\text{-}ClC_6H_4)_2SO$, 3085-42-5; $(p\text{-}ClC_6H_4)_2SO_2$, 80-07-9; CH_3COCH_3, 67-64-1; pinacol, 76-09-5.

Preparation of N-Substituted Phthalimides by the Palladium-Catalyzed Carbonylation and Coupling of *o*-Dihalo Aromatics and Primary Amines

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A novel method for the formation of N-substituted phthalimides is described which is based on the palladium-catalyzed carbonylation and coupling of *o*-dihalo aromatics and primary amines. Optimal conditions established for the reaction using *o*-diiodobenzene and aniline were DMAc (0.2 M), 115 °C, 90 psi of CO, 3% $PdCl_2L_2$, and 2.4 equiv of DBU. This process is tolerant of a wide variety of functional groups and gives good yields of the desired products. Variables such as temperature, catalyst type and loading, CO pressure, solvent, and base were examined to optimize this reaction. The reaction of aniline with 1,2-dibromocyclopentene under similar conditions gave a variety of products.

Introduction

In 1974 Heck reported that high yields of amides and esters could be obtained from the treatment of aromatic halides (bromides or iodides) with a catalytic amount of a palladium(0) or palladium(II) species and a primary or secondary amine or alcohol in the presence of carbon monoxide (CO) and a base. These "Heck" reactions have been well documented for not only the formation of amides[1] and esters[2] but also α-keto amides,[3] α-keto esters,[3e,4] α-keto acids,[5] α-hydroxy acids,[6] anhydrides,[7] acid fluorides,[8] acids,[9] lactams,[10] lactones,[11] aldehydes,[12] and ke-

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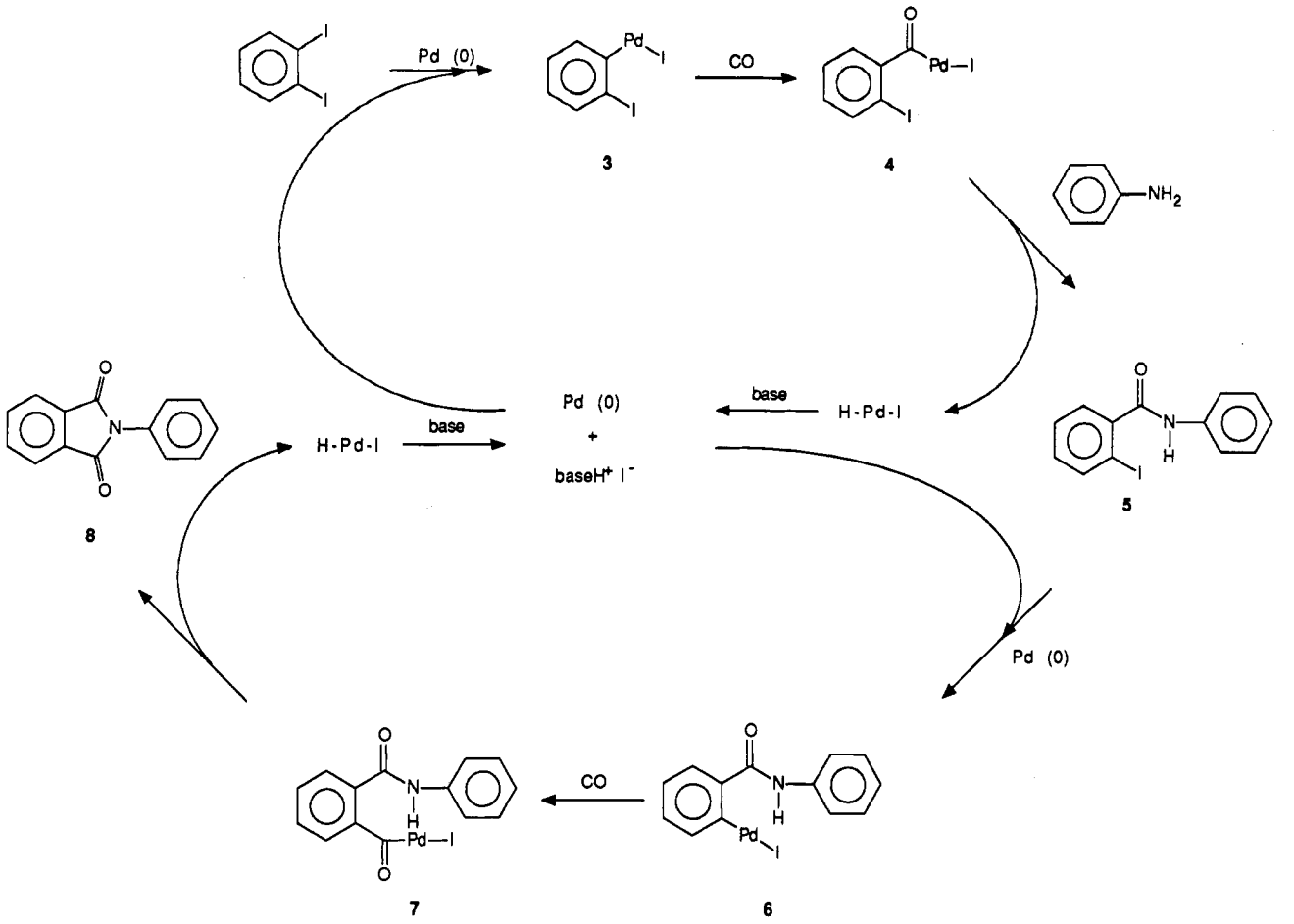
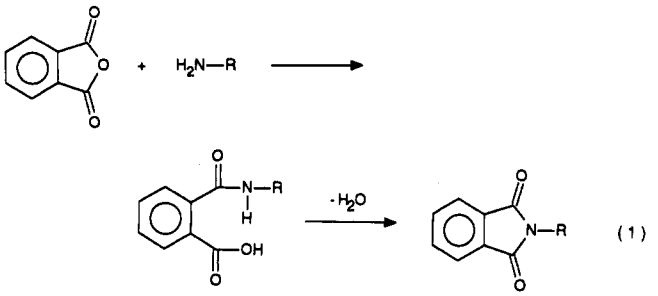
Scheme I



tones[13] through the judicious choice of reaction conditions and nucleophiles. In an effort designed to expand this chemistry it was discovered that cyclic imides could be formed using Heck chemistry with diiodo or dibromo aromatics.

Cyclic imides, most commonly phthalimides, are formed by the condensation of a phthalic acid anhydride and a primary amine as illustrated in eq 1. Initial ring opening by nucleophilic attack of the amine produces an amic acid intermediate which is thermally or chemically dehydrated to form the phthalimide and a molecule of water.



(1)

A decade ago, Ban et al. reported a palladium-catalyzed formation of phthalimides from *o*-bromobenzamides and CO.[14] However, this route used a preformed amide group and involved only a single CO insertion step to form product. This current work demonstrates that *o*-dihalo (iodo or bromo) aromatic compounds readily form aromatic imides in good yield in the presence of CO, a primary amine, a catalytic amount of palladium, and a base in dipolar aprotic solvents. To optimize reaction conditions the effects of temperature, catalyst type, catalyst loading, CO pressure, and concentration of reagents were examined. The model system used in this study was the formation of *N*-phenylphthalimide (8) from aniline and *o*-diiodobenzene. Herein are reported the results of this investigation which offers an alternative route to phthalimides and compliments the current conventional methods.

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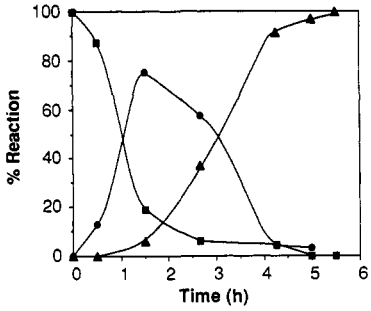

Figure 1. Production and consumption of intermediate **5**. Reaction in DMAc (0.2 M), 90 °C, 90 psi of CO, 3% $PdCl_2L_2$, 6% PPh_3, 2.4 equiv of DBU. (■) aniline; (●) **5**; (▲) *N*-phenylphthalimide.

Results and Discussion

Scheme I shows a plausible mechanistic pathway for the formation of *N*-phenylphthalimide (**8**). Ligands on palladium (CO or triphenylphosphine) have been omitted for clarity. A palladium(0) species oxidatively adds to one of the aryl iodide bonds giving **3** that rapidly inserts CO, producing the palladium acyl complex **4**. This complex is attacked by aniline, and *o*-iodo amide **5** is formed. (An alternate possibility involves the nucleophilic attack of aniline on a coordinated CO bound to the arylpalladium complex **3** to give an arylcarbamoylpalladium intermediate. This route has been established as a pathway when secondary aliphatic amines are used.[3]) The palladium(II) hydroiodide generated from this last step reductively eliminates HI, which is neutralized by the base, and a palladium(0) species is reformed. The regenerated catalyst can then again oxidatively add to an aryl iodine bond to give **6**. CO insertion produces another acyl complex **7**, but now the nitrogen of the amide bond can attack in an intramolecular fashion resulting in ring closure and formation of the cyclic imide **8**.

This mechanistic pathway is supported by analogy to the generally accepted route for Heck amidation. Further support comes from GC observation of **5** which is seen to appear and then diminish with time during the reaction (Figure 1). This intermediate has been isolated and compared to an authentic sample prepared from *o*-iodobenzoyl acid chloride and aniline.

It is well documented that aryl iodides undergo oxidative addition with zero-valent palladium compounds faster than do the corresponding bromides.[15] In ester formation with aryl bromides oxidative addition is slower than CO insertion.[2a,f,3a] This may be the reason why only 1 atm of CO is employed in reactions with bromides. At higher CO pressures, the Pd(0) species will be coordinated by a greater number of CO molecules,[16] rendering the palladium less nucleophilic and therefore less susceptible to oxidative addition. With aryl iodides, CO insertion is much slower than oxidative addition.[3a] This suggests that the rate of imide formation could be increased under higher CO pressures. The pressure would have to be such that the palladium could still achieve coordinative unsaturation. Inhibition by high CO concentrations is well documented in the hydroformylation of olefins,[17] the nickel-catalyzed carboxylation of aryl halides,[18] and has been reported in palladium-catalyzed carbomethoxylation of iodobenzene.[2c,f]

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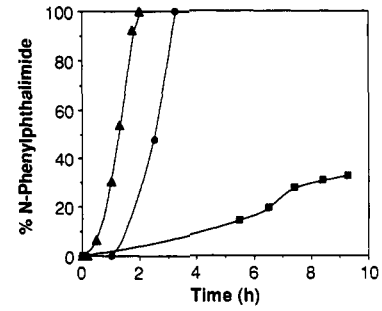


Figure 2. Effect of CO pressure on *N*-phenylphthalimide formation. Reaction in DMAc (0.2 M), 115 °C, 6% $PdCl_2L_2$, 12% PPh_3, 2.4 equiv of DBU. (■) 1 atm; (●) 40 psi; (▲) 90 psi.

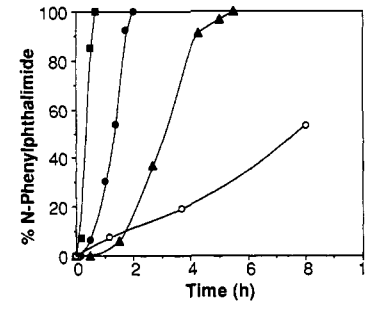


Figure 3. Effect of temperature on *N*-phenylphthalimide formation. Reaction in DMAc (0.2 M), 90 psi of CO, 6% $PdCl_2L_2$, 12% PPh_3, 2.4 equiv of DBU. (■) 150 °C; (●) 115 °C; (▲) 90 °C; (○) 65 °C. The data at 65 °C indicate formation of intermediate **5**. No *N*-phenylphthalimide was detected.

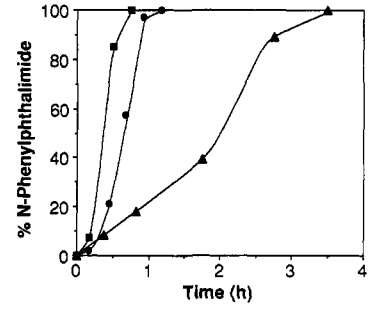


Figure 4. Effect of catalyst loading on *N*-phenylphthalimide formation. Reaction in DMAc (0.2 M), 150 °C, 90 psi of CO, 2 equiv of PPh_3/Pd, 2.4 equiv of DBU. (■) 6%; (●) 3%; (▲) 1%.

Figure 2 illustrates that under 1 atm of CO at a 6% catalyst loading and at 115 °C, only 30% phthalimide had been formed after 10 h. When the CO pressure was increased to 40 psi, complete reaction occurred in 3 h. At 90 psi of CO (the practical limitations to the reaction vessel), only 2 h were needed for conversion to the cyclic imide. This rate enhancement has been seen in a kinetic study of the carbomethoxylation of aryl iodides.[2c] In that report, maximum rates were seen to occur between 6 and 60 atm of CO, depending on the nature of other aryl substituents.

As expected, imide formation was faster at higher reaction temperatures. Figure 3 shows that at 65 °C only about a 50% yield of the *intermediate* **5** and no phthalimide had been formed after 8 h. Raising the temperature to 90 °C resulted in complete imide formation in less than 6 h. Further increases in temperature, to 150 °C, allowed the cyclization reaction to occur in less than 45 min. A more moderate temperature of 115–120 °C gave the desired product in about 2 h. Further optimization reactions were performed at this temperature.

Also, not unexpectedly, higher catalyst loading resulted in faster reaction times as shown in Figure 4. With 6%

Table I. Effect of Catalyst and Ligand on Imidization Reaction Rate

entry	catalyst	reaction time (h)[a,b]	comments
a	$PdCl_2L_2$	1.3	clean reaction
b	$Pd(OAc)_2$	2.0	benzanilide + byproducts
c	$PdCl_2$·2MeCN	1.5	benzanilide + byproducts
d	$PdCl_2$·2BzCN	2.5	benzanilide + byproducts
e	$PdCl_2$	2.5	benzanilide + byproducts
f	$PdCl_2$ + $2PPh_3$	1.2	clean reaction
g	PdL_4	1.7	clean reaction
h	$Pd_2(dba)_3$	2.7	benzanilide + byproducts
i	$PdCl_2$DPPE	1.2	clean reaction
j	$Pd(DPPE)_2$	1.6	clean reaction

[a] Time for disappearance of starting material and intermediate. [b] Reaction run in DMAc (0.2 M), 115 °C, 90 psi of CO, 3% catalyst, 2.4 equiv of DBU.

catalyst present (as $PdCl_2L_2$, where L = PPh_3, and two additional PPh_3 ligands per palladium) the reaction was complete in 45 min at 150 °C. Decreasing the catalyst concentration 2-fold to 3% still resulted in a fast reaction, ending after 1.5 h. When the catalyst was dropped to a 1% loading level, the reaction took significantly longer, nearly 3.5 h.

The type of catalyst employed had little effect on the imidization reaction, but the presence of triphenylphosphine had a pronounced influence as shown in Table I. All reactions were complete within about $2^1/_2$ h when Pd(II) salts (entries a–f, i) or Pd(0) complexes (entries g, h, j) were employed. The notable difference was whether a phosphine was present, either bound or as free added ligand. Bis(triphenylphosphine)palladium(II) chloride (a) promoted an imidization reaction that was both fast and clean as evidenced by the observation of only starting materials, intermedite **5**, product imide, and a small quantity of benzanilide by GC. This latter compound may have formed from the deiodination of **5**.

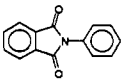
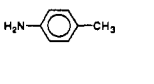
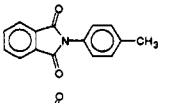
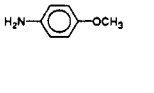
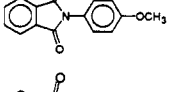
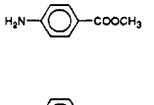
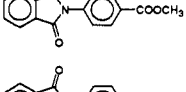
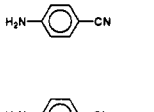
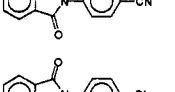
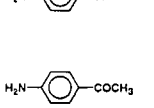
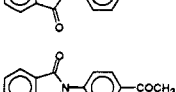
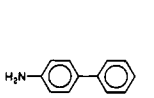
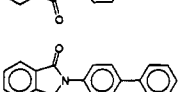
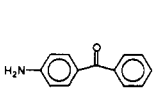
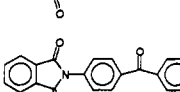
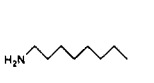
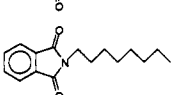
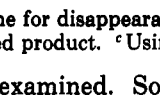
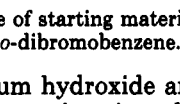
Palladium chloride with other ligands such as nitriles (entries c and d) or free Pd(II) salts such as the free acetate (b) or the chloride (e) all resulted in the formation of sustantial amounts of benzanilide and other byproducts.

Free $PdCl_2$ with added phosphine (f) behaved much as did $PdCl_2L_2$ with the bound phosphine. Zero-valent palladium without PPh_3 also did not give a clean reaction (h) while PdL_4 did (g). The palladium complexes with the bis chelated phosphine 1,2-bis(diphenylphosphino)ethane (DPPE) (i and j) also resulted in clean production of *N*-phenylphthalimide.

Examination of the model reaction in various dipolar aprotic solvents (DMAc, DMF, NMP, DMSO, and DMI) revealed few differences at 115 °C, 90 psi of CO, 2.4 equiv of DBU, 3% $PdCl_2L_2$, 6% PPh_3, and 0.2 M solvent. The exception to this was DMSO. The use of this solvent gave reaction times 2–3 times longer than the others and also resulted in the formation of about 5% benzanilide. DMAc was chosen as the optimum solvent because of its slightly faster reaction time (1.3 h versus 1.6 h for NMP, 1.9 h for DMF, and 2.1 h for DMI).

The nature of the neutralizing base also played a role in this reaction. Use of the hindered amine DBU under the following conditions, 0.2 M DMAc, 115 °C, 90 psi of CO, 3% $PdCl_2L_2$, 6% PPh_3, and 2.4 equiv of base, gave a clean high-yielding reaction that was over in 1.3 h as determined by GC. Other tertiary amines bases such as DMAP, DABCO, and proton sponge took 2–5 h for the reaction to be complete. The most ineffective base used was tributylamine, which resulted in the formation of a variety of products as seen by GC. Two inorganic bases were examined. Sodium hydroxide and potassium carbonate permitted fast reaction times but 5–10% aniline remained after the iodobenzene had been consumed. Residual aniline could be explained if some of the hydroxide ion or water formed during neutralization reacted with a palladium acyl species thereby generating a benzoic acid derivative. The reaction of hydroxide ion with palladium acyl complexes under phase-transfer conditions has already been reported.[9b]

Table II. Reactions of Arylamines with *o*-Diiodobenzene

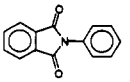
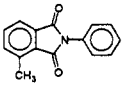
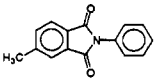
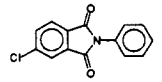
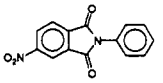
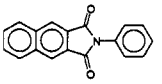
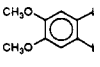
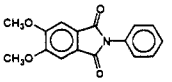
entry	amine	imide (8)	time (h)[a]	yield (%)[b]
a			1.5 (12)[c]	63 (68)[c]
b			1.0	70
c			1.2	70
d			5.5	70
e			5.1	57
f			4.3	60
g			4.6	55
h			3.6	71
i			6.1	62
j			2.5	55

[a] Time for disappearance of starting material. [b] Yield of isolated, purified product. [c] Using *o*-dibromobenzene.

Optimal conditions were thus established for the imidization reaction using *o*-diiodobenzene and aniline and these parameters [DMAc (0.2 M), 115 °C, 90 psi of CO, 3% $PdCl_2L_2$, 2.4 equiv of DBU] were employed in determining the scope and limitations of imides that could be formed by this reaction. Table II shows the wide variety of arylamines that readily reacted with *o*-diiodobenzene to give substituted *N*-arylphthalimides. In general, shorter reaction times were obtained with electron-rich amines compared to the electron-deficient ones.

In all cases good yields (55–71%) of products were isolated from the reaction mixtures. Commonly the solvent was removed in vacuo, and the oily residue remaining crystallized within several hours. Isolation by filtration and washing with a suitable solvent, usually methanol, gave pure imide. A greater recovery of product could be realized by subjecting the concentrated filtrate to chromatography on silica gel. Reaction completion could be determined by monitoring the color change in the reactor. During imidization the reaction mixture was a yellow-orange color. When imidization was complete (as determined by GC)

Table III. Reactions of Aniline with *o*-Diiodobenzenes

entry	diiodo-benzene	imide (8)	time (h)[a]	yield (%)[b]
a			1.5	63
k			1.0	53
l			1.0	72
m			4.0	65
n			12	c
o			2.5	76
p			1.2	75

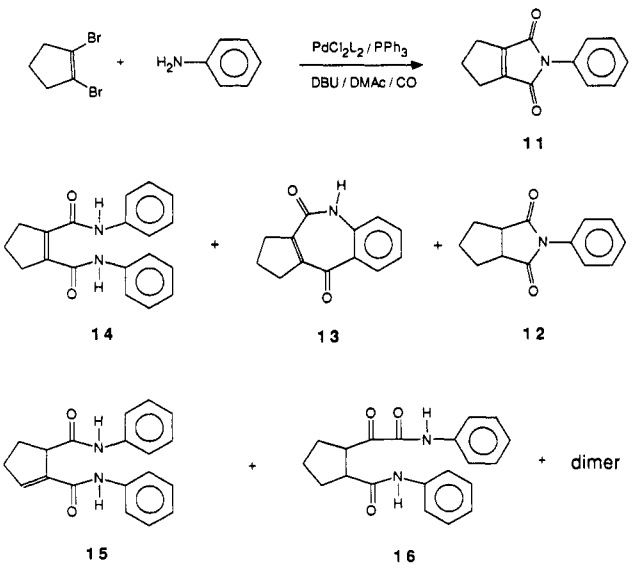
[a] Time for disappearance of starting materials and intermediates. [b] Yields of isolated, purified products. [c] No desired product was observed.

the mixture turned a deep red-black color. This may be due to the precipitation of finely divided palladium. In some instances a black solid was removed by filtration prior to concentration in vacuo.

Imide formation is not limited to the use of *o*-diiodo aromatics. *o*-Dibromo aromatics work also. Under standard conditions used in Table II, *o*-dibromobenzene and aniline formed *N*-phenylphthalimide in 68% isolated yield. The yield was slightly higher, but the reaction time was approximately 12 h, 8 times longer than with *o*-diiodobenzene. In addition, free triphenylphosphine had to be added to the reaction mixture so as to make the Pd(0) species nucleophilic enough to oxidatively add to the aryl bromide. Obviously the diiodo compounds are more desirable than the corresponding bromo ones from a reactivity standpoint, but where the dibromo aromatic compounds are more readily available, they can be used.

Substituents on the halo aromatic ring may also have an influence on the outcome of the imidization reaction. To this end a number of functional groups in varying positions were placed on the *o*-diiodobenzene moiety. The results are summarized in Table III. Changing the location of the methyl group from the 3-position (k) to the 4-position (l) had no effect on the length of time for complete reaction to occur, but the yield increased from 53% to 72%. This may be due to the marked solubility decrease in the 4-isomer which made isolation easier. It was also unexpected that the reaction time for the more electron-rich methyl derivatives was shorter than the parent, unsubstituted *o*-diiodobenzene. In ester formation, it has been shown that electron-withdrawing substituents on iodobenzene enhance the rate and electron-donating substituents retard the rate.[19]

Scheme II



Dimethoxydiiodobenzene (p) and aniline gave a good yield of the desired imide in the same length of time as the parent, unsubstituted system. The fused ring, naphthalene derivative (o) also gave high yields, but the time for reaction was over 2.5 h. A good yield of imide from the electron-poor chlorodiiodobenzene (m) was achieved but the time for complete reaction was 4 times that required for the methyl-substituted cases. 4-Nitrodiiodobenzene failed to give any detectable product under these reaction conditions. Whether this was because of the decreased reactivity of the substrate or side reactions which are known to occur with nitro groups in the presence of palladium[20] is not known at this time.

Vinyl iodides and bromides have been reported to undergo oxidative addition with palladium(0) complexes, followed by CO insertion and subsequent reaction with nucleophiles to give vinyl esters,[2] vinyl amides,[1] α-methylene γ-lactones,[11] allenyl esters and amides,[20] and vinyl keto amides.[21] It was anticipated that *cis*-1,2-dihalo olefins would react in an analogous manner to give cyclic imides. Thus, 1,2-dibromocyclopentene was allowed to react with aniline in the presence of DBU, PPh_3, and $PdCl_2L_2$ in DMAc at 90 °C and 95 psi of CO (Scheme II).

The reaction produced a number of products in addition to about 20% of the desired *N*-phenylimide **11**. GC–MS indicated the presence of the fully saturated cyclopentane ring structure **12** as well as an isomer of **11**, which may be the ring-expanded compound **13**. Diamides **14** and **15** were also formed as was the α-keto amide **16**. Another compound that was tentatively identified by GC–MS was a dimer of **11**, the structure of which is still unknown. Further work needs to be done in this area to make this reaction synthetically useful.

Summary

This paper has detailed a new synthetic method for the formation of N-substituted phthalimides in high yield from the reactions of *o*-dihalo aromatic compounds with primary amines in the presence of CO, a palladium catalyst and a base in a dipolar aprotic solvent. The starting materials

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for this novel process are readily available, and the reaction is compatible with a large variety of functional groups including nitriles, esters, ketones, and ethers. Optimization of this reaction was achieved by examining the effect of solvent, catalyst type and loading, CO pressure, temperature, concentration, and base. Work is continuing in this area to extend this reaction to other systems including polymeric materials.

Experimental Section

General Procedures. Reactions were performed in a 3-oz pressure reaction vessel (containing a stir bar) from Aerosol Laboratory Equipment Corp. fitted with a pressure gauge, a pressure release valve, a gas inlet, and a straight ball valve for degassing and sample withdrawal.

All reactions were monitored on an HP 5890 gas chromatograph using a 15-m, 0.1-μm DB-5 column (0.32-mm i.d.) and a flame ionization detector. Helium flow rate through the column was 4.0 mL/min. The GC parameters employed for analysis were as follows: injection port, 300 °C; detector, 350 °C; temperature ramp from 50 °C (hold 1 min) to 300 °C (hold 10 min) at 20 °C/min. ^{1}H NMR and ^{13}C NMR spectra were acquired on a General Electric QE-300 (300 MHz) spectrometer using either $CDCl_3$ or DMSO-d_6 as both solvent and reference. Fourier transform infrared spectra were recorded on a Nicolet 60SX spectrometer as KBr pellets. Chromatography was performed on a Harrison Research radial layer chromatographic device, "Chromatotron", using 4-mm PF-254 silica gel plates. Elemental analyses were performed by the Analytical Technology Division of Eastman Kodak Company.

Chemicals. *N,N*-Dimethylacetamide (DMAc) was freshly distilled from BaO or purchased from Aldrich (anhydrous). *N,N*-Dimethylformamide (DMF, Aldrich, anhydrous), 1,3-dimethyl-2-imidazolidinone (DMI, Aldrich), Dimethyl sulfoxide (DMSO, Aldrich, anhydrous), *N*-methylpyrrolidinone (NMP, Aldrich, anhydrous), and CO (Air Products, UPC grade) were all used as received.

All palladium catalysts were obtained from Aldrich and used as received. Triphenylphosphine (Kodak) was recrystallized from hexanes, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, Aldrich) and tributylamine (Bu_3N, Kodak) were fractionally distilled under reduced pressure. 1,4-Diazabicyclo[2.2.2]octane (DABCO, Aldrich), (*N,N*-dimethylamino)pyridine (DMAP, Aldrich), proton sponge (1,8-bis(dimethylamino)naphthalene, Aldrich), K_2CO_3 (Kodak), and NaOH (Kodak) were used as received.

Aniline (Kodak) was fractionally distilled, but *p*-toluidine (Kodak), *p*-anisidine (Kodak), methyl *p*-aminobenzoate (Kodak), 4-aminobenzonitrile (Kodak), *n*-octylamine (Kodak), 4-chloroaniline (Kodak), 4'-aminoacetophenone (Kodak), 4-aminobiphenyl (Aldrich), and 4-aminobenzophenone (Aldrich) were used as received.

1,2-Diiodobenzene (Kodak) and 1,2-dibromobenzene (Kodak) were distilled before use, and 1,2-dibromocyclopentene (Aldrich) was used as received. Other *o*-diiodo aromatic compounds were synthesized from the following anthranilic acids: 4-nitroanthranilic acid (Aldrich), 2-amino-4-chlorobenzoic acid (Aldrich), 2-amino-4,5-dimethoxybenzoic acid (Aldrich), 2-amino-5-methylbenzoic acid (Aldrich), 2-amino-5-methylbenzoic acid (Aldrich), 2-aminonicotinic acid (Aldrich), and 3-amino-2-naphthoic acid (Aldrich).

Optimization Reactions. A typical reaction was as follows: A pressure vessel was charged with *o*-diiodobenzene (200 μL, 1.53 mmol), aniline (140 μL, 1.53 mmol), a palladium catalyst ($PdCl_2L_2$, 32 mg, 0.046 mmol, 3%), and solvent (DMAc, 7.7 mL, 0.2 M). The reagents were degassed, heated in an oil bath (115 °C), and placed under a CO atmosphere. When all the reagents had dissolved, a base (DBU, 550 μL, 3.69 mmol, 2.4 equiv) was added by syringe and the vessel was charged to the appropriate pressure with CO (90 psi). Aliquots were removed over time and analyzed by GC to determine extent of reaction. Solid bases were added at the same time as the other reagents.

2-Iodo-*N*-phenylbenzamide (5). Thionyl chloride (2.0 mL, 27.4 mmol) was added to a slurry of *o*-iodobenzoic acid (5.20 g, 20.2 mmol) in toluene (35 mL) and DMF (0.5 mL) and heated for 1 h at 70 °C. Excess thionyl chloride was removed by distillation, the heat was removed, and aniline (5.50 mL, 60.4 mmol) was added. There was an immediate exotherm and formation of a precipitate. The mixture was stirred for 45 min and then diluted with ether (100 mL), and the solids were removed by filtration. The ether washings were collected, concentrated, and slurried with ether (5 mL). The crystalline solid was collected by filtration and washed with cold ether to give 2.16 g (33%) product as an off-white solid. The filtrate was concentrated and triturated with pentane to give 2.76 g (42%) of product: mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (br s, 1), 7.85 (t, J = 8.0 Hz, 1), 7.61 (d, J = 8.0 Hz, 2), 7.35 (m, 4), 7.15 (t, J = 7.5 Hz, 1), 7.09 (t, J = 7.5 Hz, 1); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 167.3, 141.9, 139.8, 137.5, 131.3, 129.0, 128.4, 128.2, 124.7, 120.1, 92.4; IR (KBr) 3230, 1650, 1600, 1540, 1440, 1330, 755, 695 cm^{-1}. Anal. Calcd for $C_{13}H_{10}INO$: C, 48.32; H, 3.12; N, 4.33. Found: C, 48.05; H, 3.30; N, 4.56.

Preparation of *o*-Diiodo Aromatic Compounds.[22] **4-Chloro-1,2-diiodobenzene.** In a 2-L, three-neck, round-bottom flask under an argon atmosphere and equipped with a mechanial stirrer, a dropping funnel, a reflux condenser, and a gas inlet, a solution of 5-chloroanthranilic acid (24.5 g, 143 mmol) in dioxane (300 mL) was added to a solution of isoamyl nitrite (29.4 mL, 219 mmol) and iodine (40.7 g, 160 mmol) in chloroform (525 mL). When addition was complete (several hours to control gas evolution), the mixture was heated to reflux and allowed to react for 18 h. The mixture was cooled, and then 10% NaOH (400 mL) was added. The organic layer was separated, washed with water (1 × 300 mL), $Na_2S_2O_3$ solution (2 × 200 mL), water (2 × 200 mL), and brine (1 × 200 mL), dried over $MgSO_4$, and then concentrated in vacuo to give a yellow oil which turned red. The oil was chromatographed on silica gel (elute with hexanes) to give a red liquid which slowly crystallized on standing after concentration. The crystals were isolated by filtration and washed with cold pentane to give the product as slightly yellow crystals: mp 34–35 °C (lit.[23] mp 34.5–35 °C), ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 2.3 Hz, 1), 7.68 (d, J = 8.3 Hz, 1), 6.96 (dd, J = 8.4, 2.3 Hz, 1); IR (KBr) 1560, 1435, 1350, 1100, 1000, 870, 810, 760 cm^{-1}. Anal. Calcd for $C_6H_3ClI_2$: C, 19.78; H, 0.83. Found: C, 19.66; H, 0.88.

3-Methyl-1,2-diiodobenzene. 2-Amino-3-methylbenzoic acid (7.6 g, 50 mmol) in dioxane (100 mL) was added over 1 h to a refluxing solution of iodine (14 g, 55 mmol) and isoamyl nitrite (8.8 g, 75 mmol) in chloroform (180 mL). At the end of the addition, the reaction mixture was heated until all evidence of gas evolution ceased. After being cooled to room temperature, the mixture was treated as above (dilute with 10% NaOH, wash with water, thiosulfate then water again, then dried, and concentrated). The concentrate was distilled at 60 °C/10–15 Torr. The residue was diluted with ligroin, passed through a pad of silica gel, concentrated to ca. 30 mL, and refrigerated. The crystals which formed were collected by filtration to give 4.7 g (27%) of product: mp 34–35 °C (lit.[24] bp 80–82 °C/0.4 Torr); ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 7.7 Hz, 1), 7.17 (d, J = 7.4 Hz, 1), 6.96 (t, J = 7.7 Hz, 1), 2.60 (s, 3); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 144.5, 136.9, 129.3, 128.3, 114.4, 109.8, 32.7; IR (KBr) 1545, 1435, 1380, 1175, 1015, 820, 765, 680 cm^{-1}. Anal. Calcd for $C_7H_6I_2$: C, 24.45; H, 1.76. Found: C, 24.74; H, 1.75.

4-Nitro-1,2-diiodobenzene. 4-Nitro-2-aminobenzoic acid (12.7 g, 70 mmol) in dioxane (200 mL) was added over 1 h to a refluxing solution of iodine (38 g, 150 mmol), isoamyl nitrite (21 g, 180 mmol), and chloroform (1000 mL) and treated as above. After concentration the residue was diluted with ligroin, passed through a pad of slica gel, and concentrated to ca. 250 mL. A solid began forming. The mixture was heated until homogeneous and then allowed to cool to room temperature. The pale yellow crystals were collected by filtration to give 8.5 g (32%) of product: mp 111–113 °C; ^{1}H NMR (DMSO-d_6) δ 8.46 (d, J = 2.4 Hz, 1), 8.10 (d, J = 8.6 Hz, 1), 7.82 (dd, J = 8.6, 2.4 Hz, 1); ^{13}C NMR (DMSO-d_6) {^{1}H} δ 147.1, 139.9, 132.6, 123.5, 118.8, 109.8; IR (KBr) 1585, 1510, 1435, 1335, 1235, 1110, 860, 825, 730, 650 cm^{-1}. Anal. Calcd for $C_6H_3I_2NO_2$: C, 19.22; H, 0.81; N, 3.74. Found: C, 19.04; 0.86; N, 3.70.

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4,5-Dimethoxy-1,2-diiodobenzene. 4,5-Dimethoxy-2-aminobenzoic acid (13.8 g, 70 mmol) in dioxane (200 mL) was added over 1 h to a refluxing solution of iodine (38 g, 150 mmol), isoamyl nitrite (21 g, 180 mmol), and chloroform (1000 mL) and treated as above. After concentration the residue was diluted with ligroin, passed through a pad of silica gel, and concentrated. The residue was recrystallized from heptane to give 2.5 g product (9%): mp 130–132 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 2), 3.79 (s, 6); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 149.3, 121.6, 96.8, 55.8; IR (KBr) 1490, 1430, 1330, 1315, 1245, 1205, 1180, 1020, 850, 780, 630 cm^{-1}. Anal. Calcd for $C_8H_8I_2O_2$: C, 24.64; H, 2.07. Found: C, 24.75; H, 2.08.

4-Methyl-1,2-diiodobenzene. 5-Methyl-2-aminobenzoic acid (50 g, 330 mmol) in dioxane (600 mL) was added over several hours to a refluxing solution of iodine (92.5 g, 360 mmol), isoamyl nitrite (58 g, 500 mmol), and chloroform (1200 mL) and treated as above. The product was purified by fractional distillation to give 26.4 g (8%): bp 260 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (m, 2), 6.84 (dd, J = 7.7, 1.2 Hz, 2), 2.25 (s, 3); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 139.8, 139.3, 138.7, 130.2, 107.7, 103.6, 20.5; IR (neat) 1450, 1375, 1255, 1090, 1000, 870, 815, 805, 660 cm^{-1}. Anal. Calcd for $C_7H_6I_2$: C, 24.45; H, 1.76. Found: C, 24.74; H, 1.88.

2,3-Diiodonaphthalene. 3-Amino-2-naphthoic acid (25 g, 133 mmol) in dioxane (1500 mL) was added over several hours to a refluxing solution of iodine (35 g, 138 mmol), isoamylnitrite (25 g, 215 mmol), and chloroform (2000 mL) and allowed to react for 18 h. After this time the reaction mixture was neutralized with 10 L of 10% NaOH. The product was extracted with ethyl acetate (2 × 1000 mL), treated with a $Na_2S_2O_3$ solution, and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was dissolved in ligroin and then passed through a column of silica gel, eluting with 1:1 ligroin–dichloromethane. The product was isolated and recrystallized from ethanol to give 1.9 g (0.5%): mp 115.5–117 °C; ^{1}H NMR (DMSO-d_6) δ 8.55 (s, 2), 7.81 (m, 2), 7.52 (m, 2); ^{13}C NMR (DMSO-d_6) {^{1}H} δ 137.9, 133.4, 127.2, 126.6, 105.1; IR (KBr) 1480, 1395, 1300, 1130, 935, 870, 840, 755 cm^{-1}. Anal. Calcd for $C_{10}H_6I_2$: C, 31.61; H, 1.59. Found: C, 31.35; H, 1.63.

Preparation of Imides. For these preparative-scale reactions the following general conditions were used: 3% $PdCl_2L_2$, 2.4 equiv of DBU, DMAc (0.2 M), 115 °C, 90–95 psi of CO, and 1.0–1.1 equiv of *o*-diiodobenzene unless otherwise noted. The following is a representative example. Isolation and characterization data for previously reported phthalimides can be found in the supplementary material.

***N*-(4-Carbomethoxyphenyl)phthalimide (8d).** 4-(Aminomethyl)benzoate (517 mg, 3.42 mmol), *o*-diiodobenzene (500 μL, 3.82 mmol), $PdCl_2L_2$ (72 mg, 0.102 mmol), DMAc (17 mL), and DBU (1.23 mL, 8.20 mmol) were allowed to react at 115 °C under 95 psi CO for 5.5 h. After this time the reaction mixture was concentrated. The solid which crystallized was isolated by filtration and washed with methanol to give 470 mg (49%) of product. The filtrate was concentrated and slurried with methanol, and the solid formed was isolated by filtration and again washed with methanol to give 110 mg more product. The filtrate was again concentrated, dissolved in $CHCl_3$ (50 mL), washed with water (3 × 50 mL), dried over Na_2SO_4, filtered, concentrated, and then subjected to chromatotron purification (3:1, hexanes–ethyl acetate) to give 40 mg more product: total yield 62%; mp 179–180 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 2), 7.94 (m, 2), 7.80 (m, 2), 7.58 (d, J = 8.5 Hz, 2), 3.93 (s, 3); ^{13}C NMR ($CDCl_3$) {^{1}H} δ 166.7, 166.2, 135.8, 134.6, 131.4, 130.3, 129.2, 125.8, 123.8, 52.2; IR (KBr) 2950, 1785, 1715, 1605, 1380, 1275, 1115, 720 cm^{-1}. Anal. Calcd for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 67.96; H, 4.07; N, 4.97.

4-Methyl-*N*-phenylphthalimide (8l): mp 199–201 °C; ^{1}H NMR (DMSO-d_6) δ 7.82 (d, J = 7.6 Hz, 1), 7.77 (s, 1), 7.68 (d, J = 7.6 Hz, 1), 7.48 (m, 2), 7.41 (m, 3), 2.49 (s, 3); ^{13}C NMR (DMSO-d_6) {^{1}H} δ 167.1, 167.0, 145.7, 135.1, 132.0, 131.9, 128.8, 128.0, 127.4, 123.8, 123.4, 21.4; IR (KBr) 1770, 1705, 1490, 1375, 1100, 750, 735 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.00; H, 4.75; N, 5.87.

4,5-Dimethoxy-*N*-phenylphthalimide (8p): mp 242–243.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.47 (m, 4), 7.40 (m, 3), 3.94 (s, 6). ^{13}C NMR (DMSO-d_6) {^{1}H} δ 149.3, 121.6, 96.8, 55.8; IR (KBr) 1775, 1705, 1595, 1500, 1375, 1315, 1220, 1090, 1065, 990, 760 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.43; H, 4.66; N, 4.94.

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Supplementary Material Available: A full description of experimental procedures and physical and spectral properties of all phthalimides synthesized as well as mass spectral data of the products in Scheme II (9 pages). Ordering information is given on any current masthead page.

Cyclodextrin-Induced Conformational Enantiomerism of Dinaphthylmethanes

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Pamoic acid (4,4′-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid]) included in the γ-cyclodextrin (γ-CDx) cavity shows an extremely strong, bisignate Cotton effect on its circular dichroism (CD) spectrum, suggesting that (*R*)-helix pamoic acid is selectively bound to γ-CDx. 2,2′-Dihydroxy-1,1′-dinaphthylmethane also exhibits the (+) to (−) bisignate CD signals in aqueous γ-CDx solution but the CD intensities are much weaker than those of pamoic acid–γ-CDx complex. The CD intensities are correlated with the stabilities of the inclusion complexes. A larger binding constant for the pamoic acid–γ-CDx complex (K = 4100 dm^3 mol^{-1}) may be ascribed to a hydrogen-bonding interaction between a carboxylate anion of the guest and a secondary hydroxyl group of the host. The ^{1}H NMR spectroscopic measurements suggest a plausible structure of the pamoic acid–γ-CDx complex where a naphthalene moiety of pamoic acid is situated inside of the γ-CDx cavity and another naphthalene ring is located at the rim of the primary hydroxyl group side of the γ-CDx cavity. Although the hydrogen-bonding interaction is not essential for conformational enantiomerism of dinaphthylmethane derivatives, it seems to enhance the chiral recognition by cyclodextrins.

Introduction

Cyclodextrins (CDx) are cyclic oligosaccharides composed of several glucopyranose units and can include organic compounds and inorganic anions into their hydrophobic cavities.[1] Since cyclodextrins are chiral host molecules, attempts have been made to achieve optical resolution using CDxs. Sulfinyl compounds,[2] phenyl-

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