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I. Asymmetric organic photochemistry; II. Palladium-catalyzed allylic arylation of cyclic alkenes

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I. Asymmetric organic photochemistry

II. Palladium-catalyzed allylic arylation of cyclic alkenes

by

Bruce Edward Baker

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DEDICATION

I would like to dedicate this work to my mother, Bernice Marie Baker, and her father, Hollis Birney Crump, in the knowledge that no one will be more proud that the Crump family had not only its first college graduate in myself in 1983, but now also has its first Ph.D. graduate in 1988.

GENERAL INTRODUCTION

The research in each section is of a completely different nature, and as such, the goals and approaches of each will be treated separately.

The primary focus of the first section is asymmetric organic photochemistry. Three different sets of experiments were performed. In the first set of experiments, the concept of a chiral electron-transfer sensitizer was tested. The operative principle is that if a sensitizer required to perform a photochemical reaction is optically active, and if it is held in close proximity to the substrate molecule during its reaction, then the product formed might be a nonracemic mixture. The likelihood and degree of chiral recognition depends upon how tightly the sensitizer is held to the substrate as the reaction takes place, and so an electron-transfer reaction was chosen. It was hoped that the radical ion-pair would be held together very tightly, and not be solvent-separated as the solvent molecule is in this case the nucleophile which attacks the substrate.

The second and third sets of experiments involve photochemically-induced π bond rotation in 1,3-diphenylallene. In 1,3-disubstituted allenes, this π bond rotation results in the interconversion of enantiomers. Therefore, an optically active sample of 1,3-diphenylallene will be prepared and its photoracemization monitored via

ORD/CD spectroscopy, to determine the quantum yield for this photoprocess. In the final set of experiments, a racemic modification of 1,3-diphenylallene will be prepared and subjected to irradiation with circularly polarized light, which is absorbed to a different degree by the two enantiomers. It is hoped, therefore, that due to this differential absorption, partial photoresolution will be observed, a phenomena which has been suggested in the literature, but which has yet to be observed.

The primary focus of the second section is palladium-catalyzed allylic arylation of cyclic alkenes. It is divided into two major parts: the first covering intermolecular reactions and the second covering intramolecular reactions. The general approach and goals of each part are very similar.

In the first part, the basic reaction conditions will be explored first, in hopes of gaining an understanding of what factors influence the rate and yield of the reaction and thereby optimizing the reaction conditions. Once that is complete, the scope and limitations of the method will be explored, with regard to olefin ring size and substitution, arene substitution and type, the effect of electron-donating/withdrawing substituents on the aromatic ring, and the use of heteroaromatics and heterocyclic cycloalkenes. In cases where isomerization of the resultant double bond

remains a problem, a different set of reaction conditions utilizing silver salts to halt isomerization will be employed.

In the final part, both sets of reaction conditions outlined in the first part will be employed in intramolecular cyclizations, again to establish the scope and limitations of the procedure. Both carbocyclic and heterocyclic rings will be formed, and various ring sizes will be tested both with regard to the ring formed in the reaction itself and also with regard to the size of the cycloalkene moiety.

SECTION I. ASYMMETRIC ORGANIC PHOTOCHEMISTRY

GOALS OF THE RESEARCH

Asymmetric organic chemistry has always been of fundamental importance in research efforts. The abundance of optically active molecules in nature has made consideration of stereospecific and stereoselective processes of paramount importance in natural product synthesis, and the use of stereochemistry as a mechanistic probe has long been recognized as a powerful tool. Photochemistry offers a number of interesting possibilities in asymmetric organic chemistry, many of which have been only peripherally examined, or in some cases only proposed, by researchers in spite of the fact that the potential applications of such research remains high.

A primary goal of the research described in this part was to find ways of generating large enantiomeric excesses through photochemical methods. The other primary goal was to explore organic photochemistry with circularly polarized light, which has to date not been well characterized.

RESULTS AND DISCUSSION

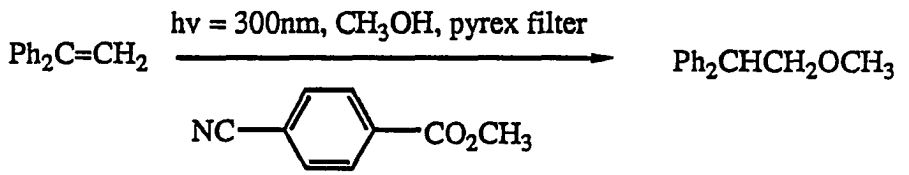
Chiral Electron-Transfer Sensitizers

In a recent review on asymmetric photochemistry in solution, Rau points out that although the theoretical potential in asymmetric sensitization is great, there has not appeared a single report of any particularly successful application of this approach; that is, one in which the enantiomeric excesses observed were greater than 5%.[1] The operative principle is a simple one: one anticipates chiral recognition to be observed when a chiral sensitizer is used to initiate the reaction, thereby resulting in the production of nonracemic product mixtures.

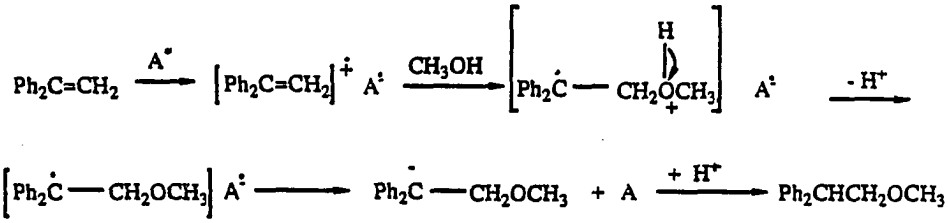
We felt that electron-transfer sensitization perhaps held the greatest potential for the induction of optical activity, as the radical ion pair formed through such a process may be held together very tightly and could thereby enhance any steric discrimination. An illustration of this process is shown in the scheme below, where A* is a chiral sensitizer and sensitizes the reaction that converts D to P, where P is a molecule with a chiral center that is formed during the sensitized reaction.

$$D + A^* \xrightarrow{\text{(electron transfer)}} {}^{\bullet}A^{\bullet}D^{+} \longrightarrow {}^{*}A^{\bullet}P^{+} \xrightarrow[\text{transfer)}]{\text{(back electron}} A^{\bullet} + P$$

A report published by Arnold and Neunteufel of an electron-transfer sensitized photoreaction provided a reaction which could be suitably modified to provide a system for study.[2] The general reaction is shown in the scheme below.



The mechanism elaborated in the report involves excitation by the sensitizer which results in the formation of a radical ion pair, the diphenylethylene radical cation and the methyl-4-cyanobenzoate radical anion. Anti-Markovnikov solvent addition then takes place, as the solvent nucleophile attacks the radical cation, which then loses a proton to become a neutral radical. At this state back electron-transfer occurs, regenerating the sensitizer and leaving the diphenylmethoxyethyl anion, which attracts a proton from the solvent to form the neutral 1,1-diphenyl-2-methoxyethane. The sensitizer apparently stays in proximity to the olefin throughout the addition of the alcohol, as back electron-transfer occurs subsequent to this addition. The mechanism described is depicted in the scheme below.

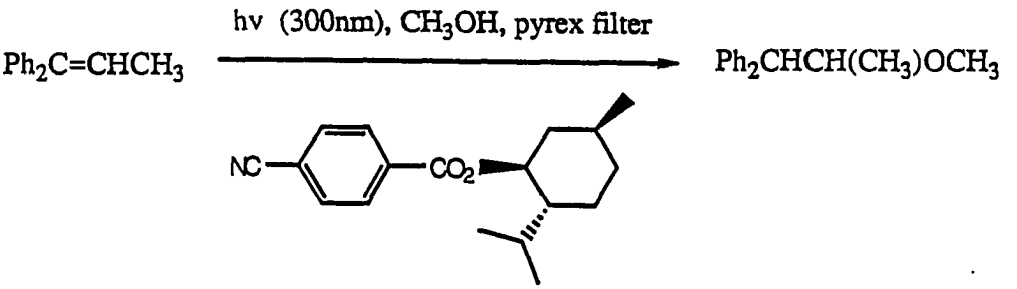


We prepared 1,1-diphenylpropene, by reacting benzophenone with an ethyl grignard reagent and dehydrating the resultant 1,1-diphenyl-1-propanol. Note that in this olefin anti-Markovnikov solvent addition will generate a chiral center at the point of nucleophilic attack. Exploratory photochemical experiments using 1,4-dicyanobenzene as sensitizer in methanol indicated rapid and efficient conversion to the expected ether photoproduct.

We wanted to determine if the use of a chiral sensitizer would result in the formation of the ether as a nonracemic mixture. As a chiral sensitizer, we decided to make the 1-menthyl ester of 4-cyanobenzoic acid. Direct esterification of the acid with 1-menthol using a Dean-Stark apparatus proved to be a slow, poor-yield process; however, a route via the acid halide was both convenient and of high yield. Subsequent UV analysis of the material indicated that it would sensitize the reaction efficiently if we irradiated with 300 nm light with a pyrex filter (>289 nm). An independent preparation of the ether we hoped to form was

accomplished by reducing 1,1-diphenylacetone with excess sodium borohydride to furnish 1,1-diphenyl-2-propanol, which was then treated with sodium hydride, and finally quenched with methyl iodide. Attempts to resolve the enantiomeric peaks of the ether using chiral NMR shift reagents were unsuccessful, but after numerous attempts the alcohol precursor was resolved. Thus, if optical activity were detected in the ether, cleavage of the product to form the alcohol and subsequent NMR analysis could then be used to determine the extent of asymmetric induction.

Irradiation of 1,1-diphenylpropene and the sensitizer in methanol at 300 nm using a pyrex filter (>289 nm) for 6.5 hours resulted in >90% conversion of the propene to 1,1-diphenyl-2-methoxypropane. The ether was isolated by chromatography on neutral alumina, and analyzed. It was optically inactive. Repetition of the experiment at conversions of approximately 50% yielded the same results. The reaction performed is shown in the scheme below.

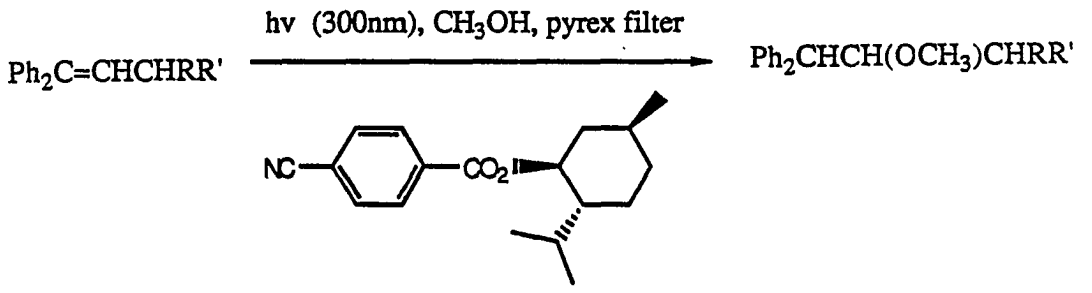


Experiments were performed that ensured the integrity of the result: an unsensitized sample of the olefin in methanol was irradiated under identical conditions for 25 hours to ensure that the reaction required the active participation of the sensitizer, and all samples were checked scrupulously to insure that no trans-esterification had taken place during the photolyses (this is critical, as we know from the previous work of Arnold and Neunteufel that the achiral methyl ester is also capable of effectively sensitizing the reaction).

One possible explanation of this result is that the ion pair is to some degree solvent-separated. This would allow for indiscriminant attack on the olefin regardless of other possible steric considerations. Reports published after completion of these experiments, however, using picosecond laser flash photolysis on similar olefin-arene electron-transfer complexes, indicate that while formation of such a solvent-separated ion pair does take place in most polar solvents, the extent of hydrogen bonding in alcohols preclude the formation of these solvent-separated ion pairs.[3] The possibility that the ion pair separates and then returns for the back electron-transfer seems remote based on statistical grounds. The results of this work indicate that in this system asymmetric sensitization is not observed; nonetheless, the concept of asymmetric

sensitization is one that bears further study and its application to other systems may yet prove fruitful.

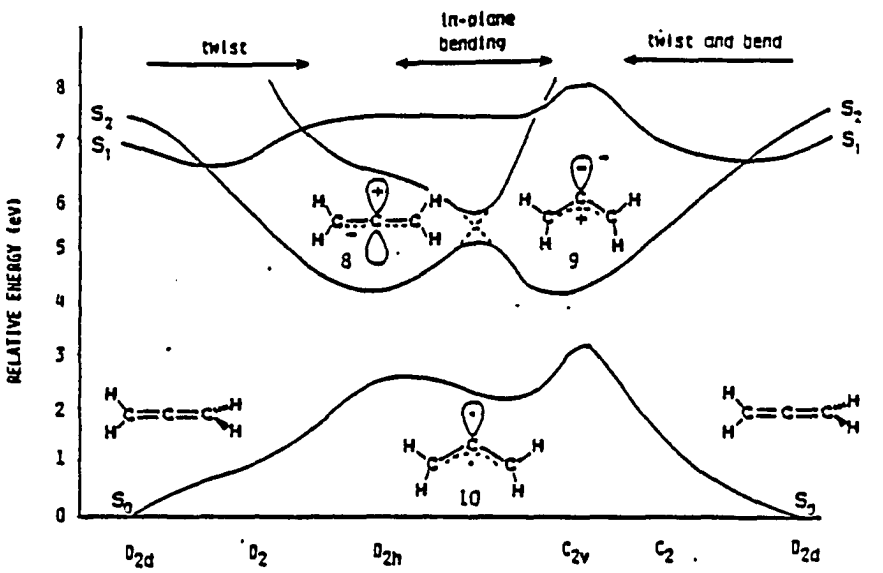
A variation on this procedure worthy of investigation, but to date untested, is to place a chiral moiety adjacent to the prochiral olefinic center, as depicted in the scheme below. Analysis of such a system becomes much more



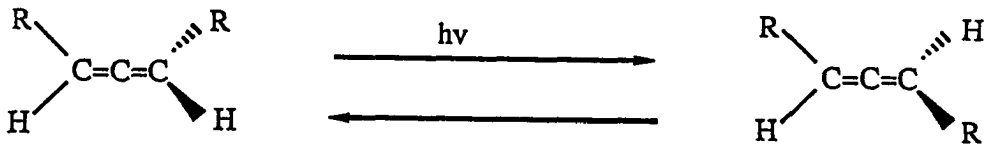
complicated, however, as more than one factor can play a role in any observed stereochemical discrimination: for example, preferential sensitization of one of the two enantiomeric olefins, or the steric influence of either the adjacent chiral center or the chiral sensitizer on the direction of nucleophilic attack. Also, two different sets of enantiomers are now possible photoproducts, and these diastereomeric pairs would require separation prior to analysis for optical activity. A control experiment would be required, using an optically inactive sensitizer, to ensure that asymmetric sensitization was responsible for any observed optical activity, and that it was not solely a result of the chirality already present in the molecule.

Photoracemization and CPL Photoresolution of 1,3-Diphenylallene

Allene photochemistry has been the subject of considerable research interest, as evidenced by the number of recent reviews which have appeared in the literature.[4] It is generally accepted that allenes have potential energy surface minima in their singlet excited state corresponding to a 90° twist in geometry: a planar structure. Recently, ab initio calculations by Lam and Johnson indicate the presence of two such minima on the allene excited state potential energy surface, as shown in the diagram below.[5]



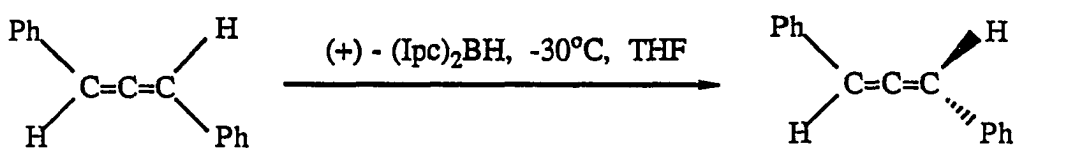
Thus, the most facile photoprocess in allenes is thought to be simple π bond rotation. This process is unobservable with most allenes; however, in the case of optically active allenes, this rotation leads to the interconversion of enantiomers, as depicted below.



Consequently, if a sample of an optically active 1,3-disubstituted allene were irradiated, one would expect to see racemization of the sample on a reasonably fast time scale. Strangely, actual examples of this process are rare. There is an unpublished report by Borden that di-t-butylallene was found to photoracemize, but attempts to quantify the process gave highly variable results.[6] 1,3-Dimethylallene has been reported to racemize in a triplet sensitized process, but no effort was made to determine the efficiency.[7] Hornback published a PRF report wherein he states that 1,3-diphenylallene photoracemizes, but here again attempts to measure its quantum efficiency yielded highly variable results.[8] Finally, Stierman and Johnson followed the photoracemization of 1,2-cyclononadiene, finding that racemization occurred in competition with a singlet rearrangement.[9] Quantification of the process was, therefore, limited to determination of the relative rates of the two photoprocesses. This study, which reported relative rates of 60-70:1 for k(rac) vs. k(rearr), clearly demonstrates the high efficiency of π bond rotation relative to other types of photoreactivity.

We sought to provide the first quantitative measure of the efficiency of π bond rotation in allenes. 1,3-Diphenylallene seemed the most appropriate choice for a number of reasons. First, its specific rotation is at least an order of magnitude greater than that of most 1,3-disubstituted allenes, allowing for greater accuracy in the experiment. Also, earlier studies in our group had shown that all other photoproduct formation had extremely low quantum efficiencies, and we were, therefore, reasonably certain that photoracemization would be complete before any other product formation was detected, and this was indeed later found to be the case. This simplifies the kinetic analysis considerably, as without a constant concentration of the allene throughout the experiment, only the relative rates can be determined, as was done earlier by Stierman and Johnson. Additionally, we had been unable to detect any fluorescence from 1,3-diphenylallene, which along with these other considerations, led us to believe that the quantum efficiency for 1,3-diphenylallene could be very high -- perhaps approaching unity. These studies on π bond rotation are new to allenes, but have long been of interest to photochemists. Stilbene, the olefinic homolog of 1,3-diphenylallene, for example, has been studied extensively with regard to its cis-trans isomerization, and entire reviews on this work are available.[10]

A number of procedures were attempted to synthesize optically active 1,3-diphenylallene. A method described by Jacobs and Danker utilizing enantioselective isomerization of 1,3-diphenylpropyne with silica gel impregnated with quinine was attempted without success.[11] Despite numerous variations, only the starting material could be recovered. Likewise, attempts to initiate the same isomerization using another chiral base, the lithio and/or potassio alkoxide of (+)-1,1-bi-2-naphthol also met with failure. Protonation of the corresponding allenyl lithium reagent at low temperatures with d-10-camphorsulfonic acid produced only racemic allene. The eventual successful approach is summarized in the scheme below: this is a modification of a previously published procedure.[12]



(+) - $(Ipc)_2BH$ = (+)-diisopinocampheylborane

R-(-)-1,3-diphenylallene

Chiral hydroboration utilizing (+)-diisopinocampheyl borane [(+)-$(Ipc)_2BH$] resulted in the isolation of 1,3-diphenylallene with a specific rotation of -122.2°, which corresponds to a 10.8% enantiomeric excess. This was sufficient for the work involved, and so this reaction was not optimized.

The kinetic treatment of the photoracemization process is explained below. Equation 1 was originally derived by Wagner for a related racemization process.[13] The same steady-state assumption applies.

$$d\alpha/dt = -S \langle k(rac) + k(prod) \rangle \langle (-)DPA \rangle I T / \langle DPA \rangle \quad \text{Eq. 1}$$

where: $d\alpha/dt$ = change in optical rotation with length of irradiation
S = proportionality constant
I = light intensity
T = lifetime of the excited state
k(rac) = rate of racemization
k(prod) = rate of product formation
<DPA> = total 1,3-diphenylallene concentration
<(-)DPA> = concentration of the excess enantiomer

The optical activity of such a solution is directly proportional to the concentration of the enantiomer in excess (eq. 2):

$$\alpha = S \langle (-)DPA \rangle \quad \text{Eq. 2}$$

Thus, dividing equation 1 by equation 2 results in, after rearrangement of the variables:

$$d\alpha/\alpha = -\langle k(rac) + k(prod) \rangle I T \, dt / \langle DPA \rangle \quad \text{Eq. 3}$$

Additionally, in the case of 1,3-diphenylallene, k(prod) = 0 for the length of the experiment. Thus, integration of equation 3 with respect to time yields:

$$\log(\alpha_t) - \log(\alpha_o) = [-\langle k(rac) \rangle T / \langle DPA \rangle] \int_o^t I dt \quad \text{Eq. 4}$$

which can be rearranged to read as follows:

$$\log(\alpha_o/\alpha_t) = [\langle k(rac)\rangle\ T/\ \langle DPA\rangle] \int_o^t I dt \qquad \text{Eq. 5}$$

Since the intensity is simply the number of photons per unit time, integration of equation 5 results in equation 6:

$$\log(\alpha_o/\alpha_t) = [\langle k(rac)\rangle\ T][\ \#\ \text{of photons absorbed}]/\langle DPA\rangle \qquad \text{Eq. 6}$$

By definition, the quantum efficiency, $\Phi(rac)$, is equal to the product of k(rac) and T, and so we finally obtain:

$$\log(\alpha_o/\alpha_t) = [\Phi(rac)][\ \#\ \text{of photons absorbed}]/\langle DPA\rangle \qquad \text{Eq. 7}$$

Thus, a plot of the logarithmic term on the left of equation 7 vs. the quotient of the number of photons absorbed divided by the total 1,3-diphenylallene concentration, should yield a straight line with a slope equal to the quantum efficiency of photoracemization, $\Phi(rac)$.

The photoracemization experiments were performed on an optical bench setup, using a 200 watt Hg-Xe lamp and a high intensity monochromator set at 250 nm and allowing a 10 nm bandpass. Light throughput was monitored by an electronic actinometer which was calibrated vs. potassium ferrioxalate. Three independent trials, varying in each case the times between racemization readings, were made. Each trial

consisted of not less than three points (not including the t = 0 point) in order to ensure accurate linear regression analysis. The progress of racemization was monitored by measuring the optical rotation at 315 nm using an ORD/CD instrument, since the rotation at the lower wavelength is significantly larger than a D-line measurement and, therefore, allows for more accurate analysis. The quantum yields for photoracemization obtained from each trial, with the correlation coefficient for each trial in parentheses following, are as follows: 0.28 (0.995), 0.32 (0.998), 0.29 (0.99996). As demonstrated by the correlation coefficients, all trials gave highly linear plots, with y-intercepts extremely close to the origin.

Irradiation of 1,3-diphenylallene, as we have already noted, results in the interconversion of enantiomers. This can be used to photoresolve as well as photoracemize, if circularly-polarized light is used. The basis for this concept is that circularly-polarized light has an inherent helicity, and is differentially absorbed by two enantiomers.[14] This difference, or circular dichroism, is what is actually measured as a function of wavelength in a CD spectrometer. Thus, if a racemic sample is irradiated with either right or left circularly-polarized light, one of the two enantiomers should absorb more of the light than the other and, assuming efficient interconversion of

enantiomers, this should result in a build-up in the relative concentration of the enantiomer with the lower molar absorptivity. This will continue until a photostationary state is reached, wherein the relative abundance of the enantiomer with the lower molar absorptivity counteracts the effect of differential absorption. The magnitude of the enantiomeric excesses achieved through such a process is dependent upon the anisotropy factor, or g factor, which is simply the ratio of the circular dichroism to the overall molar absorptivity of the solution. Since the circular dichroism and the molar absorptivity are wavelength dependent, the anisotropy factor is as well, and in most cases the maximum effect is realized by irradiation at or near the wavelength corresponding to the CD maximum for the compound: for 1,3-diphenylallene this occurs at 254 nm.[15] It is worth noting that the differential absorption is what is actually responsible for the rotation of linearly-polarized (or plane polarized) light, as linearly-polarized light may be considered the result of two circularly-polarized component beams: one left and one right. The differential absorption thus alters the displacement of the resultant beam.

In his review Rau[1] points out that there are very few examples of this resolution by photoenantiomerization process in the literature. Until 1985 there were no

examples whatsoever of this process taking place with an organic substrate, except where numerous other photodestructive processes were taking place simultaneously, making analysis complicated and, at times, questionable.[1,16] For the same reasons mentioned earlier in the photoracemization study, 1,3-diphenylallene seemed an ideal candidate to provide clear evidence of this photoprocess. Calculation of the g factor at 254 nm, as shown below, results in defining a maximum observable rotation of 2.28°.

$$G_{254} = \frac{\Delta\varepsilon}{\varepsilon} = \frac{110}{54,000} = 0.002$$

$$[\alpha]_D^{20} = 1139°;\ \alpha_{obs}(max.) = (0.002)(1139°) = 2.28°$$

The construction of a system which would provide circularly-polarized light of sufficient intensity proved to be a considerable task, as did the detection of the small rotations being generated. As such, the experiments which have been performed to date are only qualitative: further modification and optimization of the system is necessary before the process can be accurately and more readily quantified. Nonetheless, irradiation of 1,3-diphenylallene with 250 nm left circularly-polarized light (LCPL) did result in a sample with a negative rotation, the magnitude of which could not be rigorously quantified. The best result obtained was a specific rotation of -1.6° for LCPL

and a +1.4° rotation for RCPL. These results indicate that 1,3-diphenylallene is resolvable using circularly-polarized light. Allenes are not the only compounds capable of undergoing this photoresolution process. For example, exploratory photochemistry on (+)-1,1-bi-2-naphthol at 254 nm indicates that at least on an 8 hour time scale it does not form any photoproducts; but irradiation for 1 hour and 50 minutes with 254 nm light causes complete racemization. Thus, the interconversion of enantiomers takes place, and it is photostable in terms of other photoprocesses. Hence, we assume that it too will be photoresolvable using circularly-polarized light, although we have not yet conducted those experiments.

CONCLUSION

The use of l-menthyl-4-cyanobenzoate as a chiral electron-transfer sensitizer was investigated, and was found to be ineffective. Although it does sensitize the reaction, the product formed is not optically active.

Photoracemization of 1,3-diphenylallene occurs with a quantum yield of 0.30 ± 0.02. This result raises some doubt as to the previous assumption in the literature that any absorbed light in allenes not accounted for by photoproducts goes to degenerative interconversion of enantiomers. Photoresolution of 1,3-diphenylallene with circularly-polarized light also has been observed, and this result represents the first report of simple CPL photoresolution of an organic molecule.

EXPERIMENTAL SECTION

General Procedures

All ^{1}H NMR spectra were measured on a Nicolet NT 300 or a Varian 360A 60 MHz spectrometer, using $CDCl_3$ as solvent and tetramethyl silane (TMS) as reference unless otherwise indicated. ^{13}C spectra were measured on an Nicolet NT 300 MHz spectrometer using $CDCl_3$ as solvent and reference. UV spectra were measured on a Perkin-Elmer 320 spectrometer. ORD/CD measurements were measured on a JASCO ORD/UV 5 instrument, which had been upgraded to provide CD spectra as well. Melting points are uncorrected. Except where otherwise indicated, chromatographic separations were performed with quartz columns slurry-packed with Grace grade 62 silica with added green phosphor (Sylvania #2282). All solvents were distilled immediately prior to use, and the progress of component elution was monitored using a handheld UV lamp.

In all photochemical experiments, spectroquality solvents were used and samples were purged by bubbling argon through solutions immediately prior to irradiation. Where the length of irradiation warranted, argon bubbling during irradiation was also used. Quantum yield measurements were made using an optical bench setup as has been previously described.[17] The electronic actinometer was calibrated vs. potassium ferrioxalate before and after each trial, and the

average light intensity of the two calibration trials was used. All other photochemical experiments used either an immersion-well apparatus with a 450 Watt Canrad-Hanovia lamp or a Rayonett RPR-100 photoreactor.

Reagents

1,3-Diphenylpropyne

The method of Jacobs and Danker was used to synthesize 1,3-diphenylpropyne, with some modification.[11] Ethylmagnesium bromide (0.55 mol) was prepared from ethyl bromide (41.0 mL, 59.9 g, 0.55 mol) and magnesium metal (13.36 g, 0.56 mol) in dry diethyl ether (250 mL). The mixture was brought to reflux under nitrogen, and phenylacetylene (55.0 mL, 51.1 g, 0.50 mol) in diethyl ether (90 mL) was added dropwise. After 18 hours reflux, copper(I) iodide (2.0 g, 0.011 mol) and copper(II) chloride (0.20 g, 0.001 mol) were added, followed by reflux for another hour. Benzyl bromide (60 mL, 86.3 g, 0.50 mol) in diethyl ether (100 mL) was added dropwise, and the reflux was maintained for an additional 24 hours. Copper(I) iodide (1.0 g, 0.005 mol) was added, followed by another 24 hours of reflux. The mixture was then cooled to room temperature, quenched with 10% hydrochloric acid (120 mL), and filtered to remove the green-yellow insoluble salts. The organic layer was then collected, and the aqueous layer extracted

with diethyl ether (4 x 20 mL). The combined extracts and organic portion were then dried over magnesium sulfate, and concentrated in vacuo to a volume of approximately 100 mL. Distillation (.25mm Hg) yielded benzyl bromide (20.7 g) and a light yellow oil identified as 1,3-diphenylpropyne (49.8 g, 50% yield): bp 102-112°C (lit.[11] bp 140-145°C, 3 mm Hg); ^{1}H NMR δ 3.8 (s, 2 H), 7.0-7.6 (m, 10 H).

1,3-Diphenylallene

The method of Jacobs and Danker was used to synthesize 1,3-diphenylallene, with some modifications.[11] 1,3-Diphenylpropyne (5.5 g, 0.029 mol) in 4:1 hexane:ether (100 mL) was stirred over potassium hydroxide pellets (10.0 g, 0.25 mol) under nitrogen at room temperature for 48 hours. Filtration yielded an orange solution. The crude allene was absorbed onto silica gel (10 mL) by concentrating the solution in vacuo, and purified by column chromatography (3 x 60 cm, jacketed column, 200 mL silica gel) at 50°C with pentanes as eluent. Fractions were concentrated in vacuo at 0°C. White crystals (3.6 g, 65% yield) formed when the concentrated fractions were cooled in a dry ice-acetone bath: Mp 56-58°C (lit.[11] Mp 49-51°C); ^{1}H NMR δ 6.60 (s, 2 H), 7.13-7.4 (m, 10 H).

(+)-Diisopinocampheylborane

The method of Brown and Singaram was used to prepare (+)-diisopinocampheylborane.[18] The white crystals were filtered and washed with diethyl ether using Schlenk glassware in an air-free atmosphere of nitrogen, and were stored under nitrogen at -30°C.

Partial resolution of 1,3-diphenylallene

The method of Waters, Linn, and Caserio was used, with some modifications to prepare partially-resolved 1,3-diphenylallene.[12] (+)-Diisopinocampheylborane (2.24 g, 0.0078 mol) was dissolved in a minimal amount of dry THF, in a nitrogen atmosphere, and cooled to -25°C. After 30 minutes, 1,3-diphenylallene (3.0 g, 0.0156 mol) in THF (minimal) was added. The mixture was kept between -20 and -30°C for 5 hours, then allowed to slowly warm to room temperature. The THF was removed in vacuo. Elution of the concentrated mixture with pentanes (200 mL silica gel, 90 cm column) followed by crystallization as described earlier for the racemic allene yielded optically active 1,3-diphenylallene (0.79 g, 52.5% yield). The purified product had a specific rotation at 589 nm of -122.2° $\pm$ 1°. It was found that for best results the material needed to be kept under nitrogen as much as possible during the workup procedure until it was actually eluted off of the chromatography column.

1,1-Diphenylpropene

Ethylmagnesium bromide (0.054 mol) was prepared from ethyl bromide (4.0 mL, 5.84 g, 0.054 mol) and magnesium metal (1.7 g, 0.071 mol) in dry diethyl ether (80 mL). After 30 minutes of reflux under nitrogen, benzophenone (9.4 g, 0.052 mol) in diethyl ether (50 mL) was added dropwise and the solution was refluxed for an additional 17 hours. The mixture was quenched with 10% sulfuric acid (40 mL) and filtered, and the aqueous portion extracted with diethyl ether (3 x 20 mL). The combined organic portion and extracts were dried over magnesium sulfate, and the solvent was removed in vacuo to yield a white solid (1,1-diphenyl-2-propanol with a small amount of 1,1-diphenylpropene, as detected by 300 MHz NMR). The solid was placed in benzene (150 mL), p-toluenesulfonic acid (0.1 g) was added, and the solution was refluxed for 6.5 hours. Purification by silica gel chromatography using pentanes as eluent yielded white crystals (4.6g, 45% yield); ^{1}H NMR δ 7.00-7.50 (m, 10 H), 6.18 (q, 1 H), 1.55 (d, 3 H). Mp 54-55°C (lit. Mp 52°C).

1,1-Diphenyl-2-propanol

Excess sodium borohydride was added to 1,1-diphenyl-acetone (1.0 g, 0.005 mol) in methanol (25 mL). The excess borohydride was quenched with 10% sodium hydroxide (25 mL) and the mixture was extracted with diethyl ether (3 x 25 mL). The extracts were washed with a saturated sodium

chloride solution (2 x 30 mL), and the solvent was removed *in vacuo* to yield white crystals (0.88 g, 87% yield); ^{1}H NMR δ 7.00-7.50 (m, 10 H), 4.55 (m, 1 H), 3.82 (d, 1 H), 1.65 (d, 1 H), 1.2 (d, 3 H). Mp 64.5-65.5°C (lit. Mp 62°C). Splitting of the enantiomeric peaks was accomplished using 5 mg of the alcohol and 10 mg of tris[3-(trifluoromethyl-hydroxymethylene)-*d*-camphorato] europium (III). The doublet at 3.82 ppm is shifted downfield to 4.35 ppm and becomes two doublets.

1,1-Diphenyl-2-methoxypropane

Sodium hydride (0.068 g, 0.003 mol) was placed under nitrogen, and washed with hexanes and dimethoxyethane (DME) (15 mL each). DME (10 mL) was added, the mixture was cooled to 0°C, and 1,1-diphenyl-2-propanol (0.6 g, 0.003 mol) in DME (15 mL) was added dropwise. After 30 minutes methyl iodide (0.6 g, 0.004 mol, neat) was added. Following 12 hours of stirring at room temperature, the solution was quenched with 10% sodium hydroxide (20 mL) and extracted with diethyl ether (2 x 20 mL). The extracts were washed with saturated sodium chloride (20 mL) and dried over anhydrous sodium carbonate. Removal of the solvent *in vacuo* yielded a colorless liquid; ^{1}H NMR δ 7.10 to 7.50 (m, 10 H), 4.05 (m, 1 H), 3.88 (d, 1 H), 3.28 ppm (s, 3 H), 1.10 (d, 3 H). This compound has been reported in the literature before, but spectral data were not included.

4-Cyanobenzoyl chloride

Thionyl chloride (25 mL, 41.4 g, 0.348 mol) was added to 4-cyanobenzoic acid (3.0 g, 0.02 mol). After 45 minutes reflux, the mixture was cooled to 0°C and the remaining thionyl chloride was removed *in vacuo* to provide white crystals in virtually quantitative yield.

l-Menthyl-4-cyanobenzoate

A mixture of 4-cyanobenzoyl chloride (3.3g, 0.02 mol) and l-menthol (6.38g, 0.04 mol) in benzene (25 mL) was gently refluxed under nitrogen for 48 hours. Purification by column chromatography (silica gel, 1.5 x 30 cm) yielded white crystals (4.6 g, 81% yield): Mp 48.5-49.5°C; ^{1}H NMR δ 7.94 (dd, J = 1.5, 10.5 Hz), 4.95 (m), 2.3 (d), 2.10 (br m), 1.9 (br m), 1.72 (br m), 1.55 (br m), 1.45 (s), 1.28 (br m), 1.10 (d). ^{13}C NMR δ 164.161, 134.490, 131.975, 129.873, 117.788, 116.056, 75.732, 47.078, 40.731, 34.091, 31.305, 26.477, 23.543, 21.846, 20.570, 16.405. UV: (0.000123 Molar in isooctane) maxima at 237 nm(3740), 246 nm(shoulder, 2850), 280 nm(267), 289 nm(249). Minima located at 210 nm(436).

Direct irradiation of 1,1-bi-2-naphthol

A solution of racemic 1,1-bi-2-naphthol (0.050 g, 0.0002 mol) dissolved in methanol (50 mL) was irradiated in a quartz cell at 254 nm for 8 hours. No photoproducts were

detected by ^{1}H NMR or TLC analysis. Recrystallization (hexanes:ether) yielded only unreacted starting material (0.041 g). Mp 213-214.5°C (lit. Mp 210-212°C).

Photoracemization of 1,1-bi-2-naphthol

A solution of optically active 1,1-bi-2-naphthol (0.052g, 0.0002 mol, specific rotation = +34.1°) in diethyl ether (5.00 mL) was prepared. The optical rotation was measured at 365 nm using a Zeiss Polarimeter, then the sample was placed in a quartz cell, diluted with cyclohexane (40 mL) such that the alcohol remained in solution and irradiated for 1 hour and 50 minutes at 240 nm. The solution had yellowed slightly. Removal of the solvent *in vacuo* yielded 0.051 grams of material. The sample was again diluted in diethyl ether (5.00 mL) and the optical rotation measured. The sample had racemized, but was otherwise unaffected (pure starting material via ^{1}H NMR spectroscopy and TLC analysis).

Quantum yield determination for photoracemization of 1,3-diphenylallene

A solution of optically active 1,3-diphenylallene (specific rotation = -122.2°, 0.022 g) in isooctane (50 mL) was prepared. A 5.0 mL aliquot of this solution was then irradiated in a quartz cell at 250 nm, for periods of one to four hours, while monitoring the progress of racemization by ORD measurement at 315 nm (measurement here allows for much

greater accuracy than sodium D-line measurement, as the magnitude of the rotation at 315 nm is much greater). Independent runs, varying in each case the length of irradiation times between readings, resulted in a measured quantum efficiency of 0.30 ± 0.02, with at least four points (not including the zero point) taken to insure accurate linear regression analysis. The lowest linear regression of all runs recorded was 0.995.

Irradiation of 1,1-diphenylpropene with a chiral sensitizer

A solution of 1,1-diphenylpropene (0.052 g, 0.0003 mol) and l-menthyl-4-cyanobenzoate (0.080 g, 0.0003 mol) in methanol (60 mL) was irradiated at 300 nm in a pyrex cell (> 289 nm). The progress of the reaction was monitored by 300 MHz ^{1}H NMR, and after six hours the reaction was >90% complete. The mixture required chromatographic separation twice (2.5 x 10 cm neutral alumina column, hexanes as eluent) to completely separate the product from the sensitizer. Subsequent preparative runs used the following amounts: 1,1-diphenylpropene (0.400 g, 0.0021 mol), l-menthyl-4-cyanobenzoate (0.450 g, 0.0016 mol), methanol (180 mL). The purified product (1,1-diphenyl-2-methoxypropane, as verified by independent synthesis) was found to be optically inactive (no optical rotation was detected in a sample of 0.0645 g in 5.0 mL of $CHCl_3$).

Photoresolution of racemic 1,3-diphenylallene

A solution of racemic 1,3-diphenylallene (0.010 g, 0.00005 mol) in pentane (50 mL) was irradiated with 250 nm circularly polarized light for 24 hours. The samples were immediately concentrated in vacuo and diluted to a total volume of 1.0 mL to measure the D-line optical rotation. Care was taken not to concentrate the sample completely, as the material polymerizes easily, and the rotation was measured immediately after irradiation as it had been observed that 1,3-diphenylallene in solution slowly racemizes.

REFERENCES

1. Rau, H. Chem. Rev. 1983, 83, 535.

2. Arnold, D. R.; Neunteufel, R. A. J. Am. Chem. Soc. 1973, 95, 4080.

3. a) Goodman, J. L.; Petas, K. S. J. Am. Chem. Soc. 1985, 107, 1441. b) Goodman, J. L.; Petas, K. S. J. Am. Chem. Soc. 1985, 107, 6549.

4. a) Kropp, P. J. Org. Photochem. 1979, 4, 1. b) Houben-Weyl, "Methoden der Organishen Chemie," E. Muller, ed., Bank IV/5, parts I & II, Georg Thieme Verlag: Stuttgart, 1975-76. c) Specialist Periodical Reports, Photochemistry, The Chemical Society, D. Bryce Smith, ed., Burlington House: London, 1970. Vol. 1 and subsequent volumes. d) Johnson, R. P. Org. Photochem. Albert Padwa, ed., Marcel Dekker, Inc.: New York, 1985.

5. Lam, B.; Johnson, R. P. J. Am. Chem. Soc. 1983, 105, 7479.

6. Borden, W. T., Ph.D. Dissertation, Harvard University, 1968.

7. Rodriguez, O.; Morrison, H. Chem. Commun. 1971, 679.

8. Hornback, J. M.; 17th annual report on research under sponsorship of the Petroleum Research Fund, American Chemical Society, 1972, 121.

9. Stierman, T. J.; Johnson, R. P. J. Am. Chem. Soc. 1985, 107, 3971.

10. a) Doany, F. E.; Greene, B. I.; Liang, Y.; Negus, D. K.; Hochstrasser, R. M. Springer Ser. Chem. Phys. 1980, 14 (picosecond Phenom. 2), 259. b) Searle, R.; Williams, J. L. R.; Doty, J. C.; DeMeyer, D. E.; Merrill, S. H.; Laakso, T. M. Makromol. Chem. 1967, 107, 246. c) Hammond, G. S.; Saltiel, J.; Lamola, A. A.; Turro, N. J.; Bradshaw, J. S.; Cowan, D. O.; Counsell, R. C.; Vogt, V.; Dalton, C. J. Am. Chem. Soc. 1964, 86, 3197, and references therein. d) Wagner, P. J.; Hammond, G. S. Adv. in Photochem., 1968, 5, 21. e) Saltiel, J., Ph.D. Dissertation, California Institute of Technology, 1964.

11. Jacobs; Danker, J. Org. Chem. 1957, 22, 1424.

12. Waters, W. L.; Linn, W. S.; Caserio, M. C. J. Am. Chem. Soc. 1968, 90, 6741.

13. Wagner, P. J. Am. Chem. Soc. 1972, 94, 7480.

14. Gordon, A. J.; Ford, R. A. The Chemist's Companion, J. Wiley & Sons, Inc.: New York, 1972.

15. Mason, S. F.; Vane, G. W. Tetrahedron Lett. 1965, 1593.

16. Radziszewski, J. G.; Downing, J. W.; Jawdosiuk, M.; Kovacic, P.; Michl, J. J. Am. Chem. Soc. 1985, 107, 594.

17. Zimmerman, H. E.; Cutler, T. P.; Fitzgerald, V. R.; Weigt, T. J. Molec. Photochem. 1977, 8, 379.

18. Brown, H. C.; Singaram, B. J. Org. Chem. 1984, 49, 945.

SECTION II. PALLADIUM-CATALYZED ALLYLIC ARYLATION OF CYCLIC ALKENES

PART I. INTERMOLECULAR ARYLATION OF CYCLOALKENES

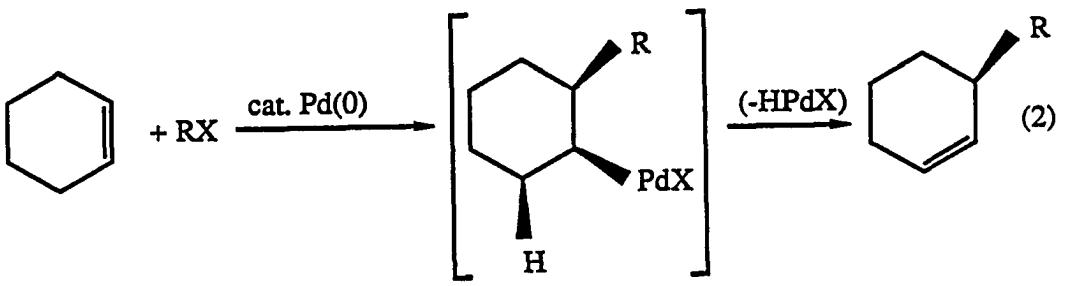
INTRODUCTION

The development of synthetic methods which utilize palladium has become an important area in organic synthesis since initial reports of its use by Heck in 1967.[1] The recent publication of two books devoted entirely to the subject attest to the rapid growth in this field.[2] Two important reasons for the growth in this area are the ability of palladium-based methodology to accommodate an enormous variety of important organic functional groups and the ability of the metal to catalytically affect a number of novel synthetic transformations.[2,3]

In 1967, R. F. Heck reported the very valuable reaction of acyclic alkenes with arylpalladium intermediates.[1] The reaction proceeds via cis addition onto the alkene and subsequent cis beta hydride elimination to afford vinyl hydrogen substitution products (eq. 1).[4] The lack of free

$$RX + H_2C{=}CHR^1 \xrightarrow{\text{cat. Pd(0)}} \left[RCH_2{-}CHR^1PdX\right] \longrightarrow RCH{=}CHR^1 + HPdX \quad (1)$$

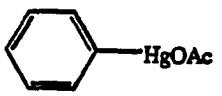
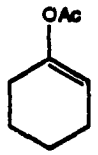
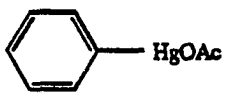
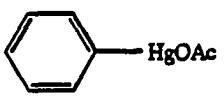
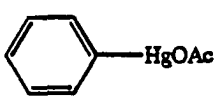
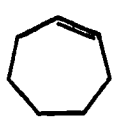
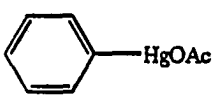
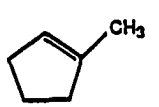
carbon-carbon bond rotation in cyclic alkenes, however, requires that cis elimination proceed to yield only the allylic isomer (eq. 2).



Many examples of coupling reactions between arylpalladium reagents and cyclic alkenes exist in the literature, and will be discussed in detail. These reactions suffer from a large number of disadvantages, including the need for reaction temperatures in excess of 100°C, low product yields, isomeric product mixtures, the need for stoichiometric amounts of palladium salts, and the use of toxic and/or difficult to prepare starting materials. Two types of palladium reagents have been used for this purpose, palladium(II) and palladium(0) salts. Palladium(II) salts, which in all but one case involve transmetallation, will be discussed first.

The use of palladium(II) salts in the coupling of arylpalladium reagents with cyclic alkenes is well-represented in the literature. Table 1 summarizes all published reports of Pd(II) couplings, including pertinent experimental details. It should be noted that in each case the reaction was stoichiometric in palladium, making these reactions quite expensive. Additionally, all entries except

Table 1. Pd(II)-mediated arylation of cyclic alkenes

Entry	Arene	Alkene	Palladium Source	Solvent
1			$Pd(OAc)_2$	CH_3CN
2			$Pd(OAc)_2$	HOAc
3			$Pd(OAc)_2$	CH_3CN
4			$Pd(OAc)_2$	CH_3CN
5			$Pd(OAc)_2$	CH_3CN

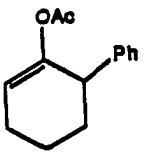
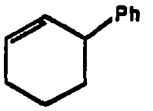
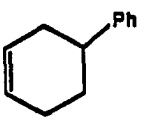
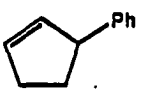
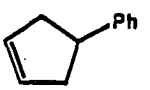
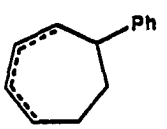
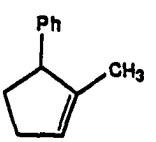
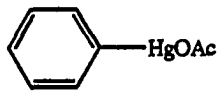
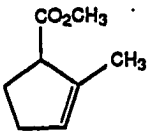
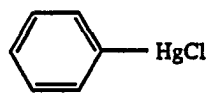
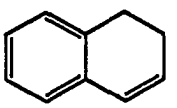
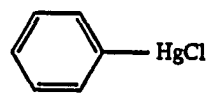
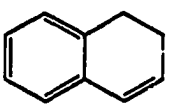
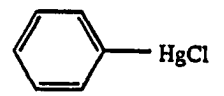
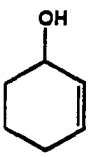
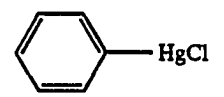
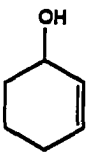
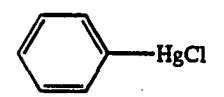
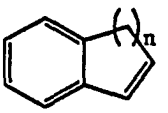
Temp(°C)	Product(s)	% Yield	Ref.
25		32	5
25		40	6
		10	
25		47	7
		29	
25	 (2.9 : 2.1 : 1.0)	60	7
25		83	7

Table 1. Continued

Entry	Arene	Alkene	Palladium Source	Solvent
6			$Pd(OAc)_2$	CH_3CN
7			Li_2PdCl_4	t-BuOH
8			Li_2PdCl_4	acetone
9			$CuCl_2$, Li_2PdCl_3	CH_3CN
10[a]			$CuCl_2$, Li_2PdCl_3	CH_3CN
11		 n = 1, 2	Li_2PdCl_4	HOAc

[a]Dicyclohexylethylamine was also added.

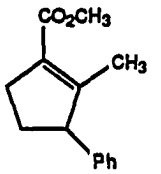
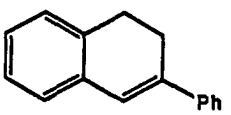
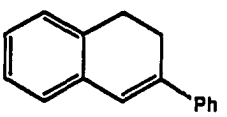
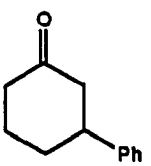
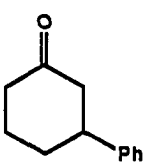
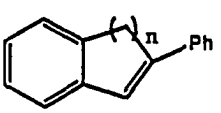
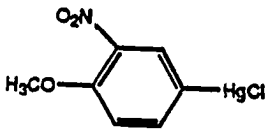
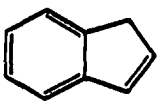
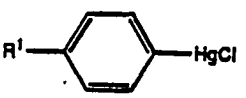
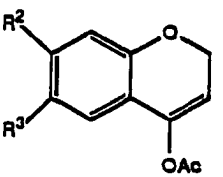
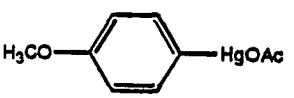
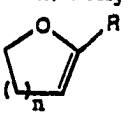
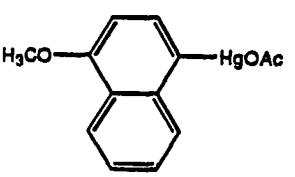
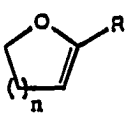
Temp(°C)	Product(s)	% Yield	Ref.
25		63	7
25		57	8
25		57	8
25		26	1b
25		25	1b
25	 n = 1, 2	40-72	9

Table 1. Continued

Entry	Arene	Alkene	Palladium Source	Solvent
12			Li_2PdCl_4	HOAc
13	 R^1 = H, Cl, Ph, CH_3, OCH_3	 $R^2 = R^3$ = H, OCH_3	$Pd(OAc)_2$	HOAc
14		 n = 1, 2 R = H, CH_3	$Pd(OAc)_2$	CH_3CN
15		 n = 1, 2 R = H, CH_3	$Pd(OAc)_2$	CH_3CN

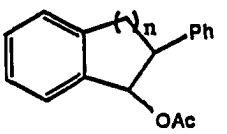
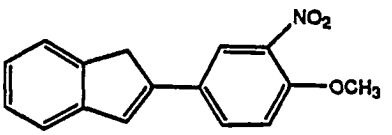
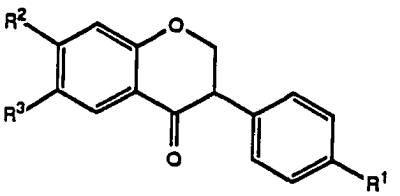
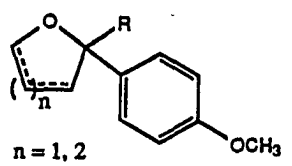
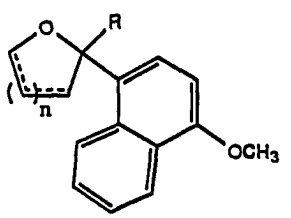
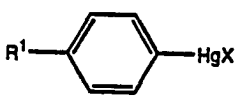
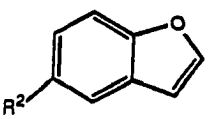
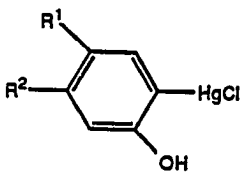
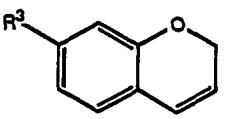
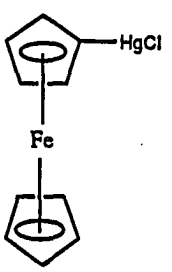
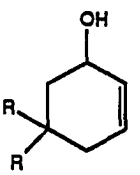
Temp(°C)	Product(s)	% Yield	Ref.
	 n = 1, 2		
25		10	1a
25		60-72	10
25	 n = 1, 2	55-100	11
25	 n = 1, 2	27-100	11

Table 1. Continued

Entry	Arene	Alkene	Palladium Source	Solvent
16	 X = Cl, OAc; R^1 = H, CH_3, OCH_3	 R^2 = H, CH_3	$Pd(OAc)_2$	EtOH
17	 $R^1 = R^2 = H$ or R^1-R^2 = O-CH_2-O	 R^3 = H, OCH_3	Li_2PdCl_4	CH_3CN, HOAc or acetone
18		 R = H, CH_3, Ph	Li_2PdCl_4	CH_3CN

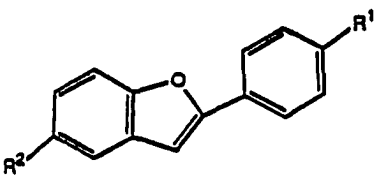
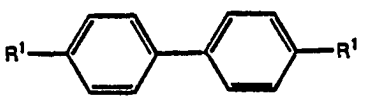
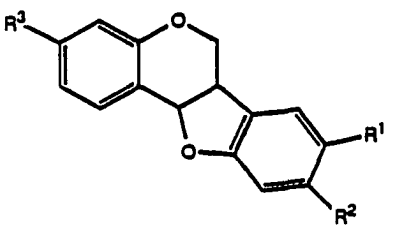
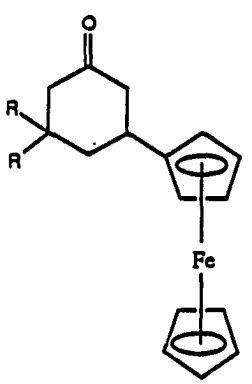
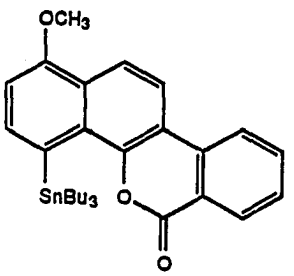
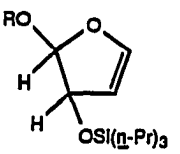
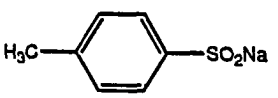
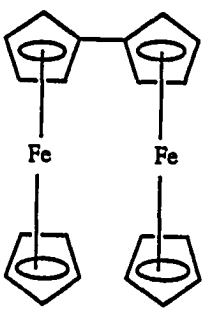
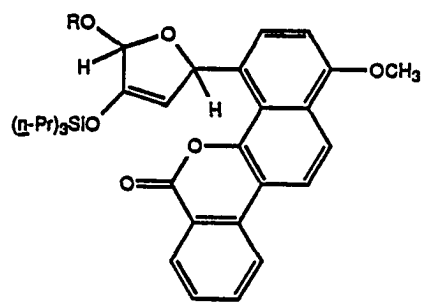
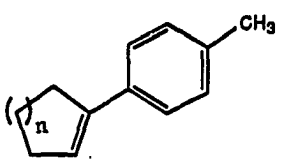
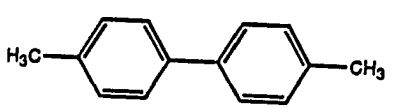
Temp(°C)	Product(s)	% Yield	Ref.
25		60-80	12
		5-10	
25		36-85	13
25		12-14	14

Table 1. Continued

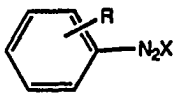
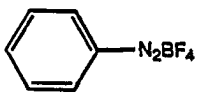
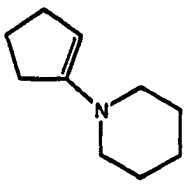
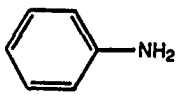
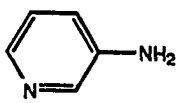
Entry	Arene	Alkene	Palladium Source	Solvent
19		 R = CH_2OCH_3 or Si (n-Pr)$_3$	$Pd(OAc)_2$	CH_3CN
20		 n = 1, 2	Na_2PdCl_4	EtOH

Temp(°C)	Product(s)	% Yield	Ref.
		10-12	
25		28-66	15
58-71	 "and isomers" n = 1, 2	22-28	16
		traces	

19 and 20 required mercurials as starting materials, which are toxic and generally not commercially available. Yields are low to fair, with only a few exceptions, and the products formed are either isomeric mixtures of products or not the desired allylicly-substituted product. The best results obtained using this approach were reported by R. F. Heck in 1971 (entries 5 and 6). Good yields of the appropriate coupling products are obtained at room temperature using trisubstituted cyclic alkenes. Attempts by the authors to apply the same method to disubstituted systems (entries 3 and 4) resulted in product mixtures arising from isomerization of the double bond. Thus, the reaction does not appear to be very general.

The use of palladium(0) catalysts in the coupling of arylpalladium reagents with cyclic alkenes has been much less prevalent. Table 2 summarizes all published reports of Pd(0) couplings, including pertinent experimental details. While most reactions utilized halides as the starting arene, there has been one report published which used aryl diazonium salts (entries 1 and 2) and another which used aromatic amines (entries 3 and 4). Unlike the previously reported Pd(II) results, these reactions are catalytic in palladium. The amount of catalyst employed varied from 0.1-20.0 mol %. As before, yields are low to fair, with exceptions, and the product obtained was either an isomeric

Table 2. Pd(0)-catalyzed arylation of cyclic alkenes

Entry	Arene	Alkene	Palladium Source	Solvent
1[a]	 X = Cl, BF_4, OAc; R = H, CH_3, OCH_3, NO_2, Cl, Br, F	 n = 1-4	$PdCl_2$ or $Pd(dba)_2$ (1-20)	CH_3CN or CH_2Cl_2
2[a]			$Pd(dba)_2$ (20)	CH_2Cl_2
3[b]		 n = 1-3	$Pd(dba)_2$ (5-10)	HOAc or HOAc/ $ClCH_2CO_2H$
4[b]			$Pd(dba)_2$ (10)	HOAc/ $ClCH_2CO_2H$

[a]Sodium acetate was also added.

[b]t-Butyl nitrite was also added.

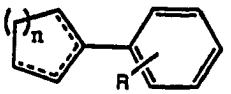
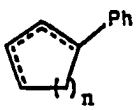
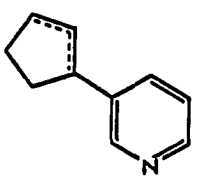
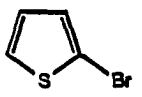
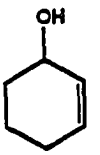
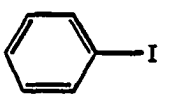
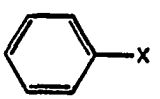
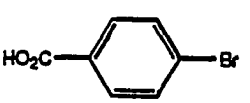
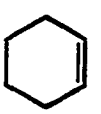
Temp(°C)	Product(s)	% Yield	Ref.
25	 n=1-4	18-78	17
25	---	---	17
50	 n=1-3	43-81	18
25		traces 32	18

Table 2. Continued

Entry	Arene	Alkene	Palladium Source	Solvent
5[c]			$Pd(OAc)_2$ (1)	HMPA
6			$Pd(OAc)_3(PPh_3)_2$	Et_3N
7[d]	 X = Br, I		$Pd(OAc)_2$ (1)	Et_3N
8[d]			$Pd(OAc)_2$ (1)	Et_3N

[c]Sodium iodide, triphenylphosphine, and sodium bicarbonate were also added.

[d]$P(\underline{o}\text{-tol})_3$ or $P(2,5\text{-}\underline{i}\text{-}Pr_2C_6H_3)_3$ was also added.

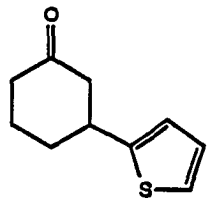
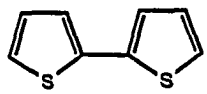
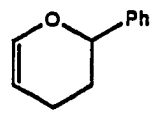
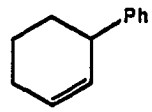
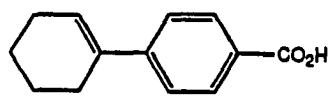
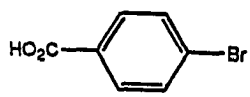
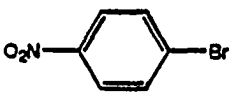
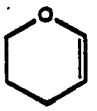
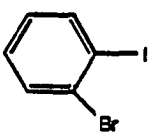
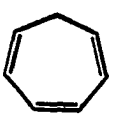
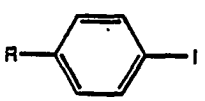
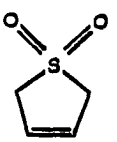
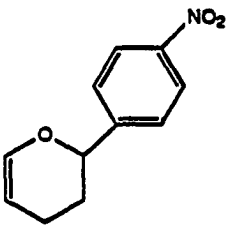
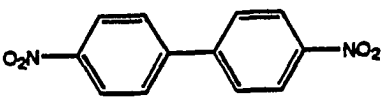
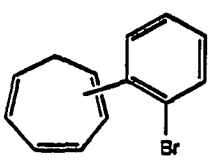
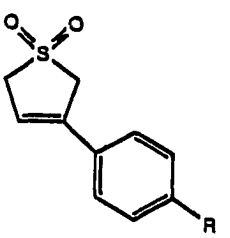
Temp(°C)	Product(s)	% Yield	Ref.
120		65	19
		29	
	Unidentified	6	
100		63	20
100-125		56-72	21
125		16	21
		60	

Table 2. Continued

Entry	Arene	Alkene	Palladium Source	Solvent
9[e]			Pd/C or $Pd(PPh_3)_4$ (1)	CH_3CN
10			$Pd(OAc)_2$ (5)	$(n\text{-}Bu)_3N$
11[f]	 R = H, CH_3, OCH_3, Br, OAc, CO_2CH_3		$Pd(OAc)_2$ (5)	Benzene

[e]Triethylamine was also added.

[f]Triethylamine and $(n\text{-}Bu)_4NBr$ were also added.

Temp(°C)	Product(s)	% Yield	Ref.
100		16	22
		trace	
not specified		45	23
not specified		50-70	24

mixture of two or more products (entries 1-4, 10) or not the desired allylicly-substituted product (entries 6, 8, 9, 11). In one instance (entry 5), isomerization difficulties were averted by having the initially generated double bond an enol, which then rapidly tautomerized to the carbonyl, and did not undergo further reaction. Dimerization of the starting aryl halide was a significant side reaction in this report. By far the best results obtained were reported by Cortese and coworkers in 1978 (entry 7), wherein good yields of allylicly-substituted products were obtained using only 1.0 mol % palladium acetate. The reaction was sluggish, however, requiring relatively high temperatures (100-125°C) and the addition of phosphines. Also, the only attempt made by the authors to use a substituted aryl halide (entry 8) went in very poor yield, did not produce the allylicly-substituted isomer, and left more than half of the starting aryl bromide unreacted. As such, the reaction does not appear to be very general.

Recently, Jeffrey reported palladium(0)-catalyzed addition reactions done under solid-liquid phase transfer conditions,[25] based in part on an earlier study reported by Spencer.[26] The reaction consists of treating a vinyl or aryl iodide with an olefin in the presence of catalytic amounts of palladium acetate (1 or 2 mole %), a base (potassium carbonate or sodium bicarbonate) and

tetra-n-butylammonium chloride (phase transfer reagent) in N,N-dimethylformamide (DMF) at or near room temperature. A typical reaction done under these conditions is shown below (eq. 3). Notably, virtually all olefins employed were

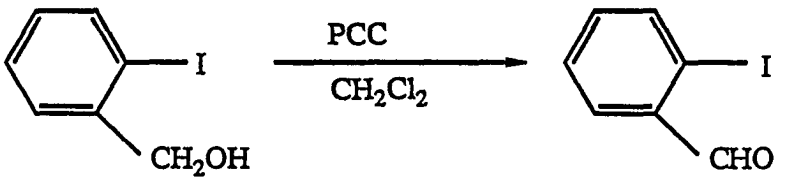
$$PhI + H_2C{=}CHCO_2CH_3 \xrightarrow[(n\text{-}Bu)_4NCl,\ DMF]{Pd(OAc)_2,\ Et_3N} PhCH{=}CHCO_2CH_3 \quad (3)$$

97%

monosubstituted and electron-deficient, enhancing their reactivity. Nonetheless, the high yields of products obtained in these reactions, in addition to the mild temperatures and small amounts of catalyst used, make this an attractive synthetic procedure. Employing the same solid-liquid phase transfer conditions with cyclic alkenes, in theory, should provide the allylicly-substituted products under very mild conditions. Also, for two reasons it was believed that this procedure might alleviate the double bond isomerization which has interfered with previous similar procedures. First, the lower temperatures employed might reduce the isomerization. Secondly, since the intermediate palladium hydride species is believed to be responsible for causing the isomerization, using a smaller amount of palladium catalyst might result in a smaller amount of palladium hydride throughout the course of the reaction, and as such reduce the amount of isomerization.

RESULTS AND DISCUSSION

Most of the starting aryl halides were commercially available, and were used directly as purchased. 2-Iodobenzaldehyde was prepared by treating 2-iodobenzyl alcohol with pyridinium chlorochromate (PCC) in methylene chloride (eq. 4). It was prepared immediately prior to use,

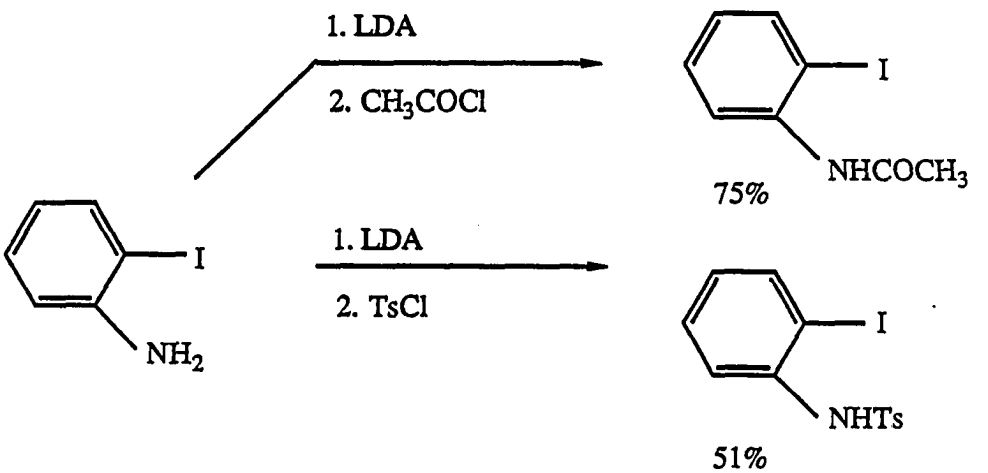


(4)

100%

as it was found to slowly oxidize to the corresponding carboxylic acid upon standing.

N-Acetyl-2-iodoaniline was prepared by treating 2-iodoaniline with lithium diisopropylamide (LDA), followed by acetyl chloride (eq. 5). N-Tosyl-2-iodoaniline was



prepared in analogous fashion, substituting tosyl chloride (TsCl) for acetyl chloride (eq. 6).

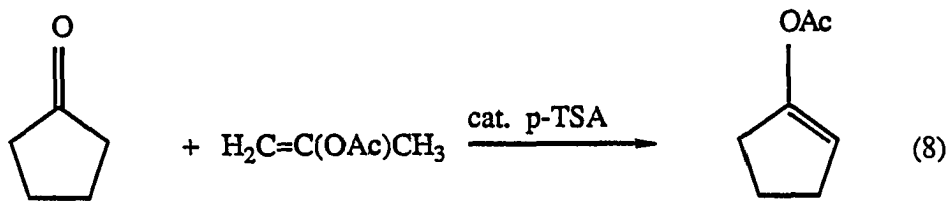
2-Iodobenzamide and N,N-dimethyl-2-iodobenzamide were prepared by treating 2-iodobenzoic acid with thionyl chloride, followed by the addition of either aqueous ammonia or dimethylamine (eq. 7).

(7)

R= H 91%

R= CH_3 95%

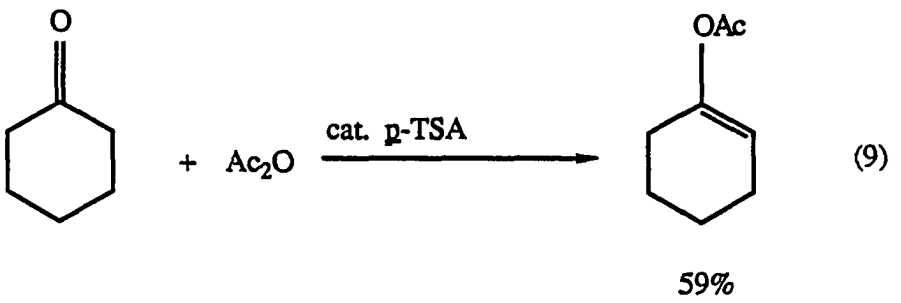
Similarly, most of the starting cycloalkenes used were commercially available, and were used directly as purchased. 1-Acetoxycyclopentene was prepared by treating cyclopentanone with isopropenyl acetate in the presence of catalytic amounts of p-toluenesulfonic acid (p-TSA) (eq. 8).



(8)

80%

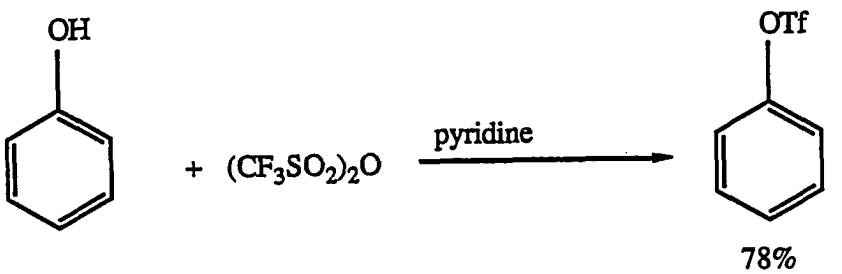
1-Acetoxycyclohexene was prepared from cyclohexanone and acetic anhydride, as shown below (eq. 9).



(9)

59%

Finally, phenyl trifluoromethanesulfonate was prepared from phenol and trifluoromethanesulfonic anhydride, in the presence of pyridine (eq. 10).



(10)

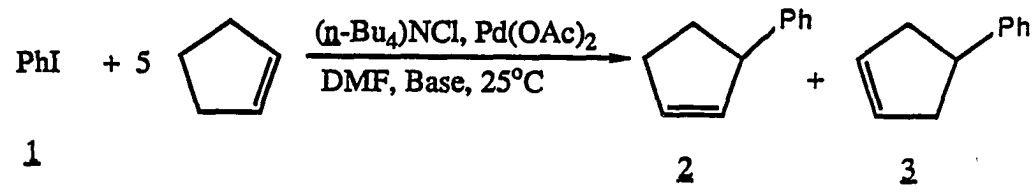
78%

Initial studies were directed at gaining an understanding of what variables most influenced the reaction, as the previously mentioned work varied conditions without explanation, especially with regard to the selection of the base. Therefore, a detailed study of the base was undertaken, using a wide variety of commercially available carbonates, bicarbonates, and acetates, as well as two common amine bases, triethylamine and tetramethylethylenediamine (TMEDA).

The reaction of cyclopentene and iodobenzene was examined first, and the results of this study are summarized

in Table 3. All results are optimized by monitoring the course of the reaction by gas chromatography with an internal standard. As a general rule, acetates outperformed all other bases (entries 12, 13, 15), except when a hydrate was utilized (entry 14). The dramatic reduction in yield using the hydrate of sodium acetate instead of anhydrous, fused sodium acetate was also observed when potassium acetate powder was used instead of the crystalline material. Our results with acetates indicate that crystalline bases function better than their powder counterparts, except that sodium acetate trihydrate crystals perform worse than any other acetate base. Cesium acetate (entry 12), available only as a "semi-crystalline" solid, performs well, although somewhat slower than the other acetate bases. Thus, a non-hydrate crystalline base is the preferred form of base whenever available. This may be a result of the phase transfer process, since the function of the quaternary ammonium salt is most likely to solubilize the base.[27] Certainly solubility of the base must play a role, as the completely insoluble bases magnesium oxide and barium oxide (entries 1 and 2) were totally ineffective. An experiment wherein tetra-n-butylammonium acetate was substituted for both the base and the phase transfer reagent (entry 16) was successful, supporting this hypothesis.

Table 3. Effect of bases on the palladium-catalyzed reaction of iodobenzene and cyclopentene[a]



1 2 3

Entry	Base	Time(days)	% Yield 2[b]	% Yield 3[b]
1	MgO	6	0	0
2	BaO	6	0	0
3	TMEDA	7	0	0
4	Et_3N	6	72	0
5	NaO_2CPh	1.5	1	trace
6	NaO_2CEt	1.5	3	0
7	Na_2CO_3	2	86	trace
8	K_2CO_3	5	22	48
9	Cs_2CO_3	1	64	11
10	$NaHCO_3$	3	26	6
11	$KHCO_3$	4	74	9
12	CsOAc	2.5	92	trace
13	NaOAc	5	94	0
14	$NaOAc \cdot 3H_2O$	1.5	16	0
15	KOAc	2	100	0
16	$(n\text{-}Bu)_4NOAc$[c]	1.5	72	3

[a]Actual amounts of reagents used were as follows: 0.5 mmol iodobenzene, 2.5 mmol cyclopentene, 0.5 mmol $(n\text{-}Bu)_4NCl$, 0.0125 mmol $Pd(OAc)_2$, 1 ml DMF, 1.5 mmol base. Reactions were run under a nitrogen atmosphere at room temperature.

[b]Optimized yield determined by gas chromatography using n-tetradecane as an internal standard.

[c]In this experiment, 0.75 mmol $(n\text{-}Bu)_4NOAc$ was substituted for both the base and $(n\text{-}Bu)_4NCl$, using amounts of all other reagents as before.

Notably, sodium benzoate and sodium propionate (entries 5 and 6), which are structurally similar to the acetates, performed very poorly. Additional experiments performed with sodium acetate wherein varying amounts of water or acetic acid were added to the reaction mixture indicated little or no effect upon the rate or the yield of the reaction unless several equivalents were added. Another experiment wherein the strictest anhydrous procedures were employed (predried solvent and reagents, including a rigorous drying procedure for the hygroscopic quaternary ammonium salt, weighed and run under glove box conditions) found both the rate and the yield of the reaction dropped considerably. It may be concluded, therefore, that the reaction is not particularly moisture-sensitive, and special drying procedures beyond the use of dried, distilled DMF are not required.

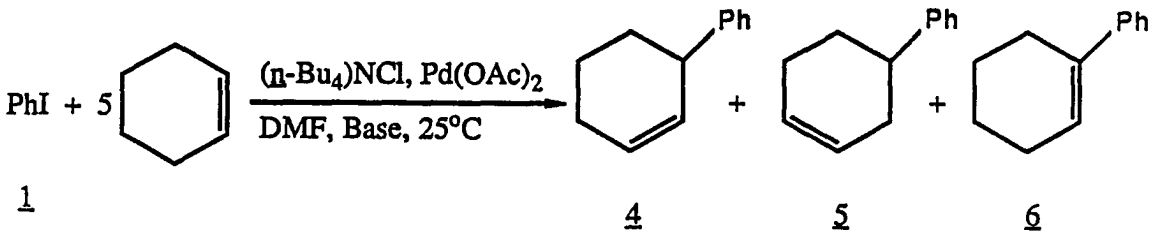
If an acetate base is not practical, triethylamine and sodium carbonate (entries 4 and 7) also performed well, although the amine proceeds at a much slower rate. Using potassium bicarbonate (entry 11) as base resulted in a high yield, but also gave rise to isomerization of the double bond. The use of potassium carbonate (entry 8) gave a predominance of the isomerized product; this, however, was later found not to be general for other cycloalkenes. The use of carbonate bases (entries 7-9) also caused at least

some isomerization. Finally, tetramethylethylenediamine (TMEDA) was completely ineffective (entry 3); its capacity to function as a ligand on the palladium catalyst is believed to be responsible for its failure.

The reaction of cyclohexene and iodobenzene was studied next, using only those bases which proved most effective in the previous study. The literature published to date has either omitted cyclohexene completely or reported very poor yields and/or isomeric mixtures of products, as shown in the earlier literature review. This is particularly unfortunate given the prevalence of six membered rings in organic chemistry. Table 4 summarizes the results obtained from this study. As anticipated, the reaction was far more sluggish than the previous cyclopentene/iodobenzene system. Only three bases yielded over fifty percent of a product: sodium carbonate, sodium acetate, and potassium acetate (entries 2, 7, 8). The use of potassium acetate caused isomerization of the double bond; fortunately, this was later found not to be general for other cycloalkenes.

In general, the preferred bases are sodium acetate, potassium acetate, and sodium carbonate. If these bases result in a high overall yield, but cause isomerization of the double bond, then other acetate bases or triethylamine may be desirable. Hydrates perform quite poorly, yet the reaction is not moisture-sensitive. Of particular note is

Table 4. Effect of bases on palladium-catalyzed reaction of iodobenzene and cyclohexene[a]



1 4 5 6

Entry	Base	Time(days)	% Yield 4[b]	% Yield 5[b]	% Yield 6[b]
1	Et_3N	6	7	0	0
2	Na_2CO_3	5	66	0	0
3	K_2CO_3	7	0	0	0
4	Cs_2CO_3	6	0	0	0
5	$KHCO_3$	6	0	0	0
6	CsOAc	4	12	15	7
7	NaOAc	6	88	0	0
8	KOAc	6	63	28	12
9	$(n\text{-Bu})_4NOAc$[c]	4	6	4	3

[a]Actual amounts of reagents used were as follows: 0.5 mmol iodobenzene, 2.5 mmol cyclopentene, 0.5 mmol $(n\text{-Bu})_4NCl$, 0.0125 mmol $Pd(OAc)_2$, 1 ml DMF, 1.5 mmol base. Reactions were run under a nitrogen atmosphere at room temperature.

[b]Optimized yield determined by gas chromatography using n-dodecane as an internal standard.

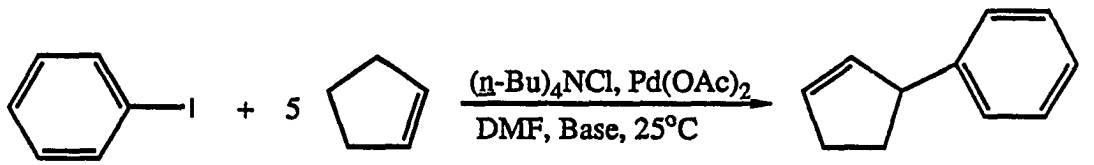
[c]In this experiment, 0.75 mmol $(n\text{-Bu})_4NOAc$ was substituted for both the base and $(n\text{-Bu})_4NCl$, using amounts of all other reagents as before.

that the hygroscopic phase transfer reagent may be used directly from the bottle without drying. Most important, excellent yields of the allylicly-arylated cycloalkenes were obtained, without isomers, at room temperature.

While monitoring the results of various bases by gas chromatography, it was found that the use of biphenyl as an internal standard caused the reaction to fail completely. This result proved reproducible, and as such, work was undertaken to discover the nature of this interference. No literature precedent for the interference of simple arenes in palladium-catalyzed reactions could be found. Since halides are used as starting materials and simple alkylated arenes are the products of these reactions, it was believed that the source of the interference must be simple, unsubstituted arenes, and Tables 5 and 6 summarize the results of all experiments performed to gain an understanding of this observation.

In the absence of a potentially interfering arene, the reaction of cyclopentene and iodobenzene goes to completion in one and a half days at room temperature. If either benzene or biphenyl are added, however, no product is formed after four and a half days at room temperature. Subsequent trials at 80°C yielded the same result. Experiments were then performed wherein the addition of the arene took place after the reaction had successfully begun, and these results

Table 5. Effect of simple arenes on the reaction of iodobenzene and cyclopentene



1 2

Arene Added	Reaction Time (Days)	% Yield 2	% Recovery 1
---	1.5	100	0
benzene	4.5	0	100
biphenyl	4.5	0	100

are shown in Table 6. If the observed interference was in fact hindering the initial reduction of the palladium acetate to zerovalent palladium, then no interference with the progress of the reaction should be noted in these experiments. This is obviously not the case. As a second issue, the size of the alkyl chain was increased, to note its effect upon the production of the coupling product. As shown, the addition of benzene after 19 hours reaction time brought an immediate halt to the progress of the reaction and to the consumption of iodobenzene in the reaction mixture. The same result was observed with toluene as well. The result obtained with t-butylbenzene and 1-phenylcyclohexene seem to indicate not only a halt to the progress of the reaction, but also a reduction in the yield of the product. Also, in these reactions iodobenzene continued to be consumed after the addition of the arene. This would suggest that a second addition of iodobenzene to the already substituted cycloalkene ring may be occurring, and raises the possibility of multiple arylation. No general conclusions regarding the origin and nature of this phenomenon have been deduced from these results; however, it is clear that care must be taken with any starting materials to separate them completely from potential interferences utilized in their preparation.

Table 6. Effect of substituted arenes on the reaction of iodobenzene and cyclopentene

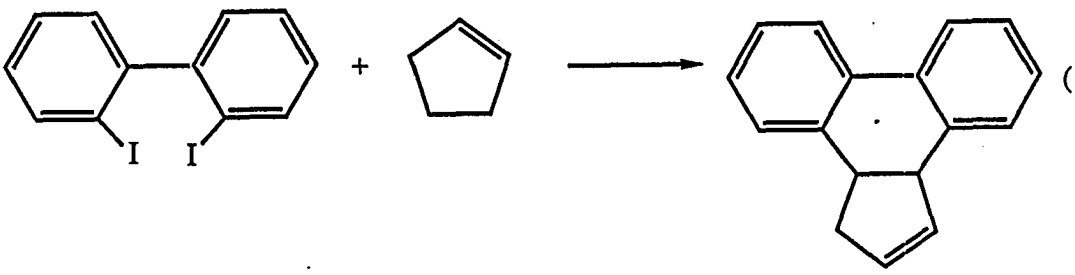
Arene Added	Time of Arene Addition (Hours)	Reaction Time (Hours)	% Yield 2	Consumption of 1
benzene	19	19	80	yes
		43	80	no
		93	80	no
toluene	19	19	43	yes
		48	44	no
		90.5	40	no
		124	40	no
t-butylbenzene	22	22	39	yes
		41.5	22	yes[a]
		60	22	---
1-phenylcyclo-hexene	22	22	34	yes
		41.5	20	yes[a]
		60	23	---

[a]All iodobenzene was consumed at this point in the reaction.

The possibility of multiple arylation, as suggested previously, was examined briefly. An experiment was performed wherein a five to one ratio of iodobenzene to cyclopentene was employed, and the experiment was monitored via gas chromatography. A large number of products were detected by gas chromatography-mas spectrometry (GC-MS), including biphenyl and two different phenylcyclopentene isomers. However, five major products, each with molecular weights corresponding to diarylation, were observed. A trace amount of a product with a molecular weight corresponding to diphenylcyclopentadiene was detected as well. Further work in this area in currently being undertaken by another student within our research group, using allylicly-substituted cycloalkenes as starting materials.

The possibility of multiple olefination was also examined briefly by reacting o-diiodobenzene with five equivalents of cyclopentene. As before, the reaction was monitored by gas chromatography. GC-MS results indicated small amounts of o-diiodobenzene and (o-iodophenyl)-cyclopentene were present, as well as a trace of 1-phenylcyclopentene. The three major products, however, each had molecular weights corresponding to the desired product, o-di(cyclopentenyl)-benzene, with two of the three isomers comprising 80% of the total amount of all products

found. No further investigation in this area was attempted; however, based upon this single experiment, multiple olefination is also possible using these basic conditions. Based upon the potential indicated by the results of the multiple arylation and multiple olefination experiments, another student in our research group is currently investigating an interesting intramolecular variation (eq. 11).



(11)

Attempts to use nickel instead of palladium were made. Substitution of palladium acetate with nickel(II) acetate tetrahydrate proved disastrous; no evidence of product was found at room temperature or at 80°C, and all of the iodobenzene remained (as determined by GC) after two and a half days at 80°C.

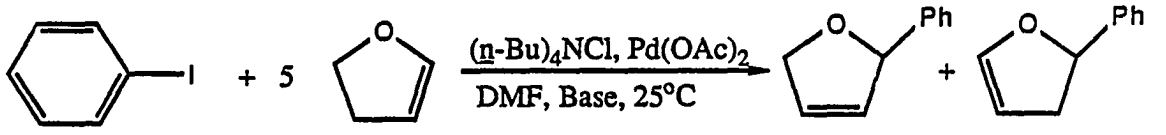
The nature of the phase transfer reagent was examined. Other quaternary ammonium phase transfer reagents such as tetra-n-butylammonium hydrogen sulfate, tri-n-octylmethylammonium chloride, and tetra-n-butylammonium bromide were not attempted, as previous researchers had reported that tetra-n-butylammonium chloride was more effective.[25a,26]

The use of tetra-n-butylammonium acetate has already been discussed. Tetra-n-butylphosphonium chloride was also used, and a comparison of the results obtained using the ammonium and phosphonium reagents is shown in Table 7. Yields and isomer ratios are very similar; the two reagents function comparably well.

Having gained an understanding of what factors influence the reaction, the scope and limitations of the arylation procedure were then explored. The optimized results of this work may be found in Table 8. In each case arylation was attempted using the three most effective bases (sodium acetate, potassium acetate, and sodium carbonate); whenever these provided isomeric mixtures, arylations using other acetate bases and/or triethylamine were also examined. If poor yields were obtained using the three initial bases, however, no further attempts were made.

Entries 1-4 were performed specifically to determine the various cycloalkene ring sizes which were reactive under these conditions. Very good to excellent yields of one product only were obtained at room temperature using every cycloalkene ring attempted; in each case except one, the product obtained was the desired allylicly-substituted product. With cycloheptene (entry 3), however, the homoallylic isomer is the sole product. The tendency of seven membered cycloalkenes to isomerize when other ring

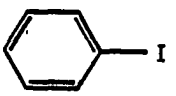
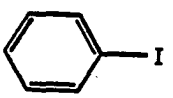
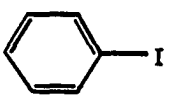
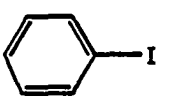
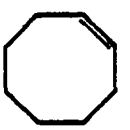
Table 7. Comparison of quaternary ammonium and phosphonium salts in the reaction of iodobenzene and 2,3-dihydrofuran



1 7 8

Base	Phase Transfer Catalyst	Reaction Time (d)	% Yield 7	% Yield 8
KOAc	n-Bu_4NCl	4	53	27
KOAc	n-Bu_4PCl	4	60	31
NaOAc	n-Bu_4NCl	5	15	85
NaOAc	n-Bu_4PCl	5	24	43

Table 8. Pd-catalyzed arylation of cyclic alkenes using $(n\text{-Bu})_4NCl$[a]

Entry	Arene	Cycloalkene	Base[b]
1			KOAc
2			NaOAc
3			KOAc
4			CsOAc

[a]Actual amounts of reagents used were as follows: 0.5 mmol iodobenzene, 2.5 mmol cyclopentene, 0.5 mmol $(n\text{-Bu})_4NCl$, 0.0125 mmol $Pd(OAc)_2$, 1 ml DMF, 1.5 mmol base. Reaction conditions were optimized first using gas chromatography with an appropriate hydrocarbon as an internal standard.

[b]In entries where more than one base is listed, results of separate trials using each base yielded an identical result.

[c]All products gave appropriate spectral data, and assignments are based on previously published literature spectra, mechanistic arguments, and assignment made by others on identical or very similar compounds, and are tentative.

[d]Regioisomer ratios are reported with indicated allylic isomer on the left, followed by homoallylic isomer, and then other isomers. If no ratio is reported, then the product is essentially pure.

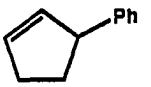
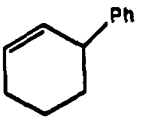
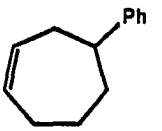
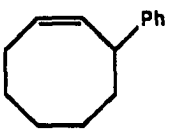
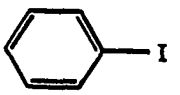
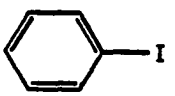
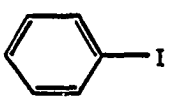
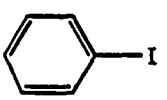
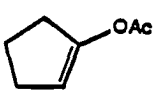
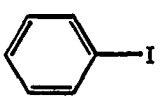
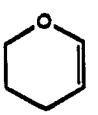
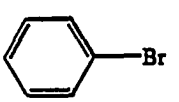
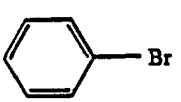
Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
1.5d, 25°C		100 (89)
5d, 25°C		88 (70)
6d, 25°C		99 (95)
2d, 25°C		100 (85)

Table 8. Continued

Entry	Arene	Cycloalkene	Base[b]
5			NaOAc
6			NaOAc
7			CsOAc
8			KOAc
9			NaOAc
10			KOAc/NaOAc/Na_2CO_3
11			KOAc/NaOAc/Na_2CO_3

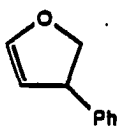
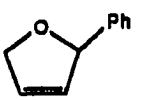
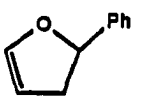
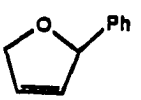
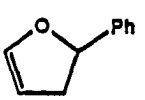
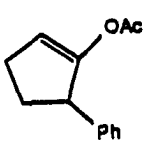
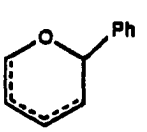
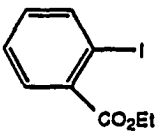
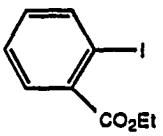
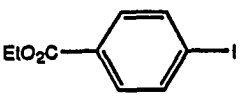
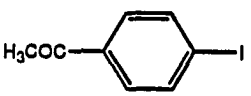
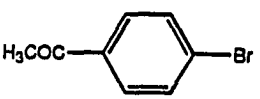
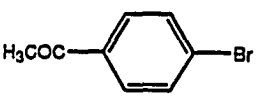
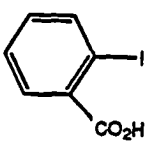
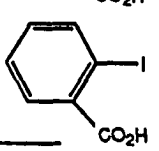
Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
4d, 25°C		91 (78)
5d, 25°C		15
		85
6d, 25°C		77
		23
6.5d, 25°C		(16)
6d, 25°C	 (3.9 : 1.0 : 1.0)	(71)
7d, 25°C	---	---
5d, 80°C	---	---

Table 8. Continued

Entry	Arene	Cycloalkene	Base[b]
12			KOAc
13[e]			KOAc
14			KOAc
15			KOAc
16			KOAc
17			KOAc
18			KOAc/NaOAc/Na_2CO_3
19			KOAc/NaOAc/Na_2CO_3

[e]This reaction was run on a scale 20 times the others in the table, and purified by vacuum distillation rather than by column chromatography, as in entry 12.

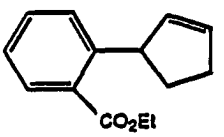
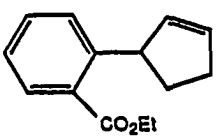
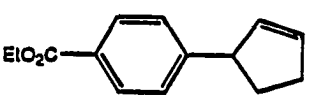
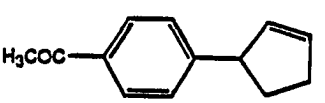
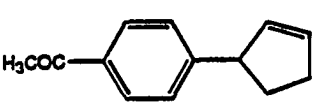
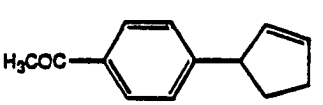
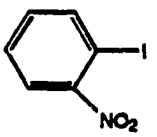
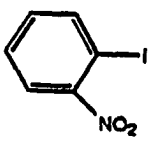
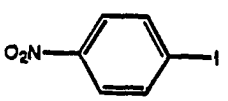
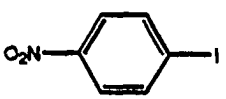
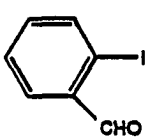
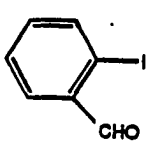
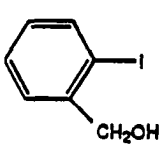
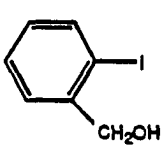
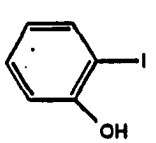
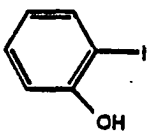
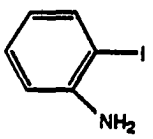
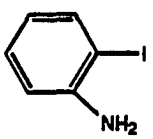
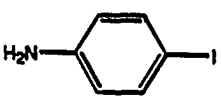
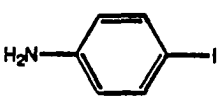
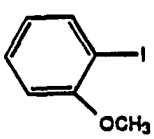
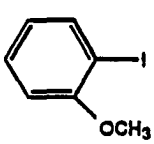
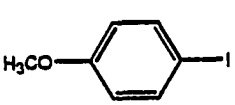
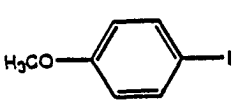
Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
0.5d, 25°C		77 (74)
1.0d, 25°C		(90)
3.5d, 25°C		90 (85)
4.5d, 25°C		96 (94)
7d, 25°C		11
2d, 80°C		87
6d, 25°C	---	---
5d, 80°C	---	---

Table 8. Continued

Entry	Arene	Cycloalkene	Base[b]
20			KOAc/NaOAc
21			KOAc/NaOAc
22			KOAc/NaOAc
23			KOAc/NaOAc
24			KOAc/NaOAc
25			KOAc/NaOAc
26			KOAc
27			KOAc
28			KOAc/NaOAc

Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
7d, 25°C	- - -	---
4d, 80°C	- - -	---
7d, 25°C	- - -	---
4d, 80°C	- - -	---
7d, 25°C	- - -	---
4d, 80°C	- - -	---
5.5d, 25°C	- - -	---
5d, 80°C	- - -	---
5.5d, 25°C	- - -	---

Table 8. Continued

Entry	Arene	Cycloalkene	Base[b]
29			NaOAc
30			KOAc/NaOAc
31			KOAc/NaOAc
32			KOAc/NaOAc
33			KOAc
34			KOAc/NaOAc/Na_2CO_3
35			KOAc
36			KOAc/NaOAc/Na_2CO_3
37			KOAc

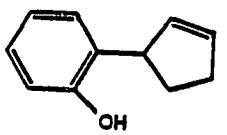
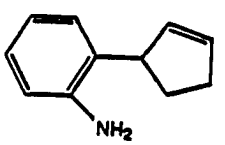
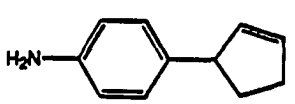
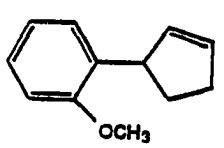
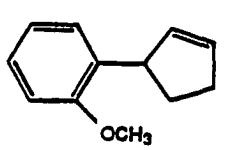
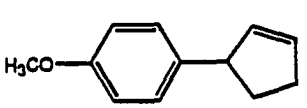
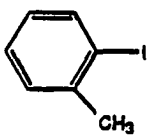
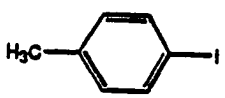
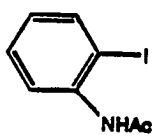
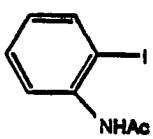
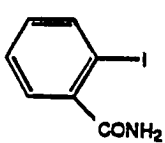
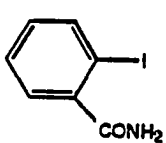
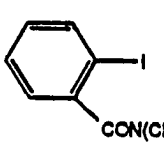
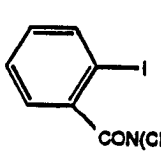
Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
5.5d, 80°C		34 (27)
7d, 25°C	- - -	---
4.5d, 80°C		6/6
7d, 25°C	- - -	--
5.5d, 80°C		38 (32)
7d, 25°C		trace
1d, 80°C		(78)
7d, 25°C	- - -	---
3d, 80°C		(67)

Table 8. Continued

Entry	Arene	Cycloalkene	Base[b]
38			KOAc
39			KOAc
40			KOAc
41			KOAc
42			KOAc/NaOAc/Na_2CO_3
43			KOAc/NaOAc/Na_2CO_3
44[f]			KOAc
45			KOAc/NaOAc

[f]Twenty-six percent of the starting iodide was recovered from this reaction.

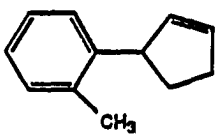
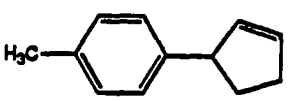
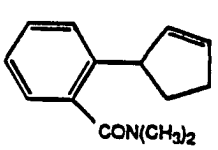
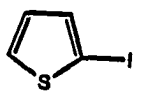
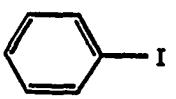
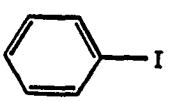
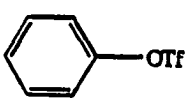
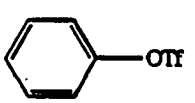
Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
7d, 25°C		(72)
7d, 25°C		(75)
6d, 25°C	- - -	---
2d, 80°C	- - -	---
6d, 25°C	- - -	---
4d, 80°C	- - -	---
6d, 25°C		(74)
4d, 80°C	- - -	---

Table 8. Continued

Entry	Arene	Cycloalkene	Base[b]
46[g]			KOAc
47[h]			KOAc
48[i]			KOAc
49			KOAc/NaOAc/Na_2CO_3
50			KOAc/NaOAc/Na_2CO_3

[g]An additional 1% $Pd(OAc)_2$ was added at 5 days to drive the reaction to completion.

[h]This reaction was run on a scale 10 times the others in the table, and the product isolated by column chromatography.

[i]This reaction was run on a scale 100 times the others in the table and isolated by vacuum distillation.

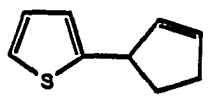
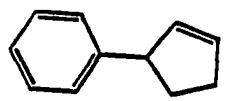
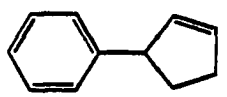
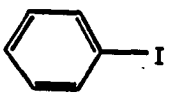
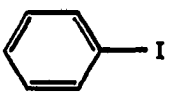
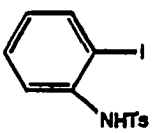
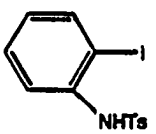
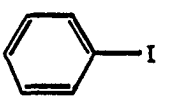
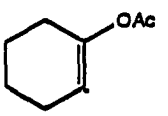
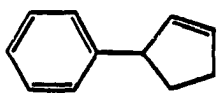
Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
7d, 25°C		(80)
1.5d, 25°C		(89)
2.5d, 25°C		(87)
7d, 25°C	- - -	---
4d, 80°C	- - -	---

Table 8. Continued

Entry	Arene	Cycloalkene	Base[b]
51[j]			NaO_2CH
52[k]			KOAc
53			KOAc
54			KOAc
55			KOAc/NaOAc/Na_2CO_3

[j]The ratio shown here is the exo:endo isomer ratio.

[k]In this trial only 0.75 mmol of cyclopentene was added.

Reaction Conditions	Product(s)[c] (Isomer Ratio)[d]	% GC Yield (Isolated Yield)
2d, 25°C	 (4.3 : 1.0)	(76)
2.5d, 25°C		(81)
6d, 25°C	- - -	---
3d, 80°C	- - -	---
6.5d, 80°C	- - -	---

sizes did not had already been observed in palladium-catalyzed chemistry, both independently and within our own research group.[28] Notably, this is the only report of quantitative conversion to the isomerized product; isomeric mixtures are usually obtained. Cyclohexene gave a higher yield and no isomerized product when sodium acetate was used as base (entry 2), and cyclooctene gave a cleaner reaction when cesium acetate was used as base (entry 4) than when sodium or potassium acetate were employed. Under identical reaction conditions using potassium acetate as the base, the relative reactivities of the cycloalkenes were observed to be: cyclopentene > cyclooctene > cycloheptene > cyclohexene. It is also of note that although an excess of the cycloalkene was utilized, one can employ lesser amounts with satisfactory results. As an example, when the amount of cyclopentene was reduced from five equivalents to one and a half equivalents (entries 1 and 52), the optimized GC yield dropped only from 100% to 81%.

Heterocyclic alkenes were employed with equal success, as demonstrated by the use of dihydrofurans and dihydropyran (entries 5-7, 9). Again, yields were very good to excellent; however, double bond isomerization in the product became a problem when the initial isomer formed did not have the resultant double bond adjacent to the oxygen. This isomerization of the double bond to the position

adjacent to the oxygen is well-precedented in the palladium literature, as evidenced in the literature review.

Entries 8 and 55 represent the only trisubstituted alkenes in the table; reactions with trisubstituted olefins, as expected, were slower than with the less sterically hindered disubstituted olefins. Thus, steric hindrance on the olefin is believed to exert an effect on these reactions, and elevated temperatures (80°C) are required to react trisubstituted or tetrasubstituted alkenes.

Some aryl bromides were also reactive under these conditions although to a much lesser extent than their corresponding aryl iodides. While simple bromobenzene (entries 10 and 11) proved unreactive, aryl bromides activated by an electron-withdrawing group in the para position do react (entries 16 and 17) in very good yield at 80°C. Comparison of p-bromoacetophenone and p-iodoacetophenone (entries 15-17) demonstrates the magnitude of the reduction in reactivity of the aromatic bromide; this observation is well supported in the literature.[29] Aryl trifluoromethanesulfonates (triflates) were also examined as potential starting materials, since aryl triflates have been reported to react with palladium catalysts under the appropriate conditions;[30] phenyl triflate was inert under our reaction conditions, however, either at room temperature or at 80°C (entries 49 and 50),

and no further investigation using triflates has been undertaken.

A wide variety of aryl halides were employed in these arylation reactions. In contrast to the conclusion obtained concerning steric hindrance on the alkene, steric hindrance on the aryl halide apparently had little effect upon the reaction rate or yield, as throughout the table comparison of ortho and para substituted aryl iodides indicated that the ortho compounds perform as well or better at comparable or faster rates relative to their para analogues (entries 12-14). Noteworthy, however, is the fact that most of the examples in the table wherein both an ortho and its corresponding para-substituted aryl iodide reacted well had an oxygen in the substituent. The oxygen can coordinate to the palladium, and thereby facilitate the reaction.[31] The ortho- and para-tolyl iodides (entries 38 and 39) represent an instance where this potential interference is not present, and reacting these two compounds under identical conditions for an identical length of time resulted in an almost identical isolated yield. Thus, steric hindrance on the aromatic ring is believed to have little effect upon these reactions. This is in contrast to the recent report of Harrington and DiFiore,[24] where he states that substituents adjacent to the iodide retard the reaction rate. His conclusion, however, is based only upon the

result obtained using 2,3,4-trimethoxyiodobenzene. Electron-donating groups, as will be discussed later, retard the reaction rate, and this may well explain the apparent disparity.

Also in contrast to the report of Harrington and DiFiore, electron-withdrawing substituents, whether in the ortho or para positions, did not particularly deactivate the arene towards the addition (entries 12-17); indeed, exactly the opposite was found to be the case when aryl bromides were used. Harrington appears to have based his conclusion primarily upon a result obtained with one electron-withdrawing substitutent, the para nitro group, which he found to be completely unreactive. We also found nitro groups to be unreactive, and believe that they are incompatible with the reaction conditions (entries 20-23), which are virtually identical with those used by Harrington. Notably, he reports that the reaction of ethyl 4-iodobenzoate proceeds in comparable yield to, as an example, 4-iodoanisole. There is ample literature precedent for the interference of nitro groups in palladium-catalyzed reactions.[32]

The failure of some aryl iodides bearing electron-withdrawing substituents in the ortho position to react is worthy of mention. 2-Iodobenzoic acid (entries 18 and 19) may form a stable chelate with the palladium catalyst, thus

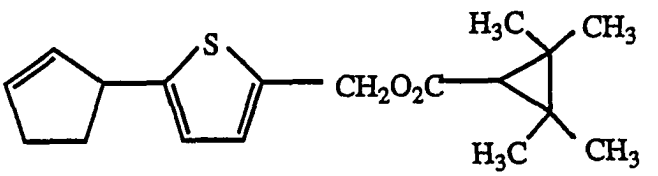
explaining its failure to react. Heck has suggested a similar explanation for the failure of 2-bromobenzoic acid to react with methyl acrylate.[33] Heck noted that the methyl ester reacts well under identical conditions; a similar result was obtained by us using the ethyl ester of 2-iodobenzoic acid (entries 12 and 13). The presence of a hydrogen on the heteroatom must be critical, although whether this is simply for steric reasons or some other reason is not known. This hypothesis would also explain the fact that 2-iodobenzamide (entries 42 and 43) fails to react, while N,N-dimethyl 2-iodobenzamide (entries 44 and 45) reacts in good yield. With this latter compound the desired product was formed at elevated temperatures as well (entry 45), as determined by GC-MS, but owing to substantial amounts of decomposition, products could not be isolated. 2-Iodobenzaldehyde (entries 24 and 25) also failed to react, presumably because it was oxidized to the corresponding benzoic acid, which as noted before does not react. We have observed that 2-iodobenzaldehyde slowly autooxidizes to the corresponding acid upon standing if it is not kept at 0°C. o-Iodobenzyl alcohol fails to give any of the desired product. Primary, secondary, and benzylic alcohols have recently been reported to oxidize under conditions virtually identical to ours, although the reaction produced benzaldehyde rather than benzoic acid when benzyl alcohol

was used.[34] Reactions were monitored by GC, and the authors make no comment as to whether further oxidation of the aldehyde was observed. Other examples of the oxidation of alcohols using palladium catalysts have been reported.[35]

Electron-donating substituents on the aryl halide were found to slow the rate of reaction (entries 38 and 39), and higher reaction temperatures are required to obtain a high yield if the substituent is strongly electron-donating (entries 34-37). Electron-donating substituents containing a heteroatom with an available hydrogen proved to be a significant limitation (entries 26-33, 40, 41). Heck notes similar difficulties in his reactions of bromoanilines, bromophenols, bromorescorcinols, and bromohydroquinones,[33] although his explanation is not applicable to this system. He noted that acetylation of p-bromoaniline doubled the yield of its reaction with methyl acrylate under his conditions; this was not the case under our conditions (entries 40 and 41). Also noteworthy, however, is that the reaction of 2-iodophenol under his conditions proceeded in 95% yield.

Heteroaromatic iodides are equally reactive, as evidenced by entry 46. The success of 2-iodothiophene is of particular note given that sulfur-containing compounds have been reported to interfere with palladium-catalyzed reactions, either by tying up the catalyst in the form of a

complex or by precipitating out the catalyst.[36] Sota et al.[37] synthesized the product of this reaction, 2-(3-cyclopentenyl)-thiophene, in 43% yield as an intermediate in the synthesis of 5-alk-2-enyl substituted 2-thienyl chrysanthemates, which demonstrated potent insecticidal activity. One of these compounds, shown below, was shown to have ten times the potency of allethrin. Our synthesis of this intermediate goes in almost twice the yield of what is the only published route to this molecule.



Another important result is that the reaction may be scaled up with only a slight increase in reaction time or temperature required (entries 1, 12, 13, 47, 48). Thus, cyclopentene and iodobenzene react in 1.5 days in 89% column isolated yield on a 0.5 mmol scale, or in 2.5 days in 87% distilled isolated yield on a 50.0 mmol scale. Similarly, ethyl 2-iodobenzoate and cyclopentene react to afford the expected product in 0.5 days in 74% column isolated yield on a 0.5 mmol scale, or in 1.0 day in 90% distilled isolated yield on a 10.0 mmol scale. The observed difference in isolated yields of the ester is a direct result of the increase in reaction time. The increase in reaction time

allowed the large scale reaction to go to completion (the small scale had not), and isolation on a small scale by column chromatography was difficult owing to the very similar Rfs of the starting aryl iodide and the product.

The generation of the allylicly-substituted isomer, as previously discussed, is contingent upon the fact that the only beta hydrogen cis to the palladium in the intermediate organopalladium species is in the appropriate position to yield that isomer. In norbornylene (entry 51), however, no such cis beta hydrogen is present. Attempts to isolate the intermediate were not undertaken, as this would have required a stoichiometric amount of the metal; rather, reduction of the organopalladium intermediate (yielding the saturated coupling product) and thereby regeneration of the catalyst in situ was performed by adding sodium formate.[38] The formate can also function as the base, and so no additional base was added in this trial. A good yield of 2-phenyl norbornane was obtained, which by GC-MS and ^{1}H NMR spectroscopy was a 4:1 mixture favoring the exo isomer. No further work to improve this result was attempted.

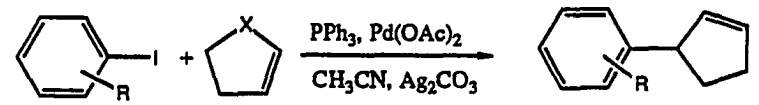
Throughout the course of this work, the emphasis was on developing a general catalytic method which would provide high yields of only the allylicly-substituted isomer under mild reaction conditions. Although our approach had proven effective under most circumstances, it failed to stop

isomerization with three olefins: 2,3-dihydrofuran, 3,4-dihydropyran, and cycloheptene. It had been reported that the presence of silver ions had reduced or eliminated isomerization in other palladium-catalyzed reactions,[39] and investigations were therefore undertaken to see the effect of adding silver ions to our reactions. Using the reaction of cycloheptene and iodobenzene as a model system, silver acetate, silver nitrate, and silver carbonate were added in separate trials. Silver acetate completely halted the reaction; silver nitrate and silver carbonate slowed the rate of reaction dramatically. Subsequent trials with these two silver salts using each of the three alkenes mentioned above all met with the same result: reactions could not be brought to completion, even if additional amounts of palladium(II) acetate were added during the course of the reaction.

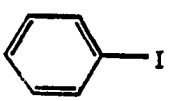
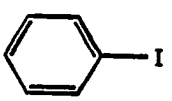
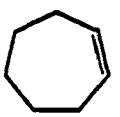
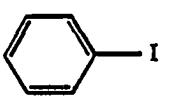
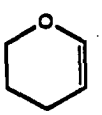
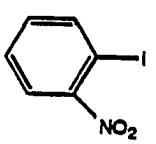
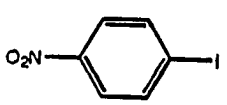
A recent report by Abelman and co-workers used silver nitrate and silver carbonate in a palladium-catalyzed intramolecular cyclization of aryl and vinyl halides;[28b] two different sets of conditions were employed. Both systems were examined for their potential in cases where our previous conditions had been unsuccessful, and in every case silver carbonate proved to be superior.

Table 9 summarizes the results obtained using the conditions outlined in Overman's report. The first result

Table 9. Pd-catalyzed arylation of cyclic alkenes using silver carbonate[a]



R = H, CO_2H, CHO, NO_2 X = O, OCH_2, $CH_2CH_2CH_2$

Entry	Arene	Cycloalkene
1		
2		
3		
4		
5		

[a]Reactions were run using amounts of reagents as follows: 0.5 mmol aryl halide, 0.0375 mmol PPh_3, 2.5 mmol cycloalkene, 1.0 mmol silver carbonate, 6 mL CH_3CN. If the reaction appeared to slow down or stop completely, an additional 0.0042 mmol $Pd(OAc)_2$ and 0.0125 mmol PPh_3 were added, as needed.

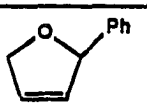
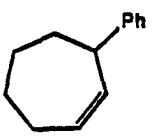
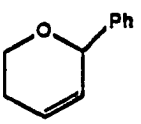
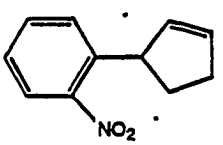
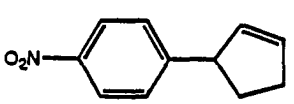
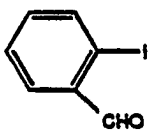
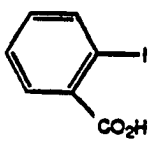
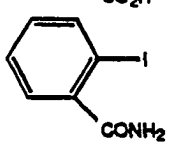
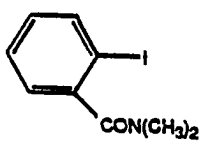
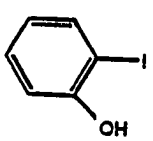
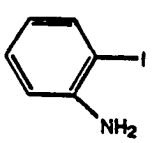
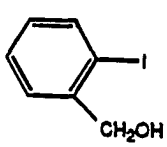
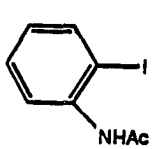
Total % $Pd(OAc)_2$	Reaction Conditions	Product	% Isolated Yield
2.5	2d, 80°C		98
2.5	1d, 80°C		98
2.5	2d, 80°C		96
2.5	2d, 80°C		70
2.5	2d, 80°C		52

Table 9. Continued

Entry	Arene	Cycloalkene
6		
7		
8		
9		
10		
11		
12		
13		

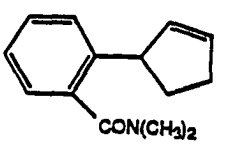
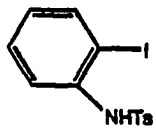
Total % $Pd(OAc)_2$	Reaction Conditions	Product	% Isolated Yield
2.5	5d, 80°C	- - -	--
3.5	5d, 80°C	- - -	--
3.5	5d, 80°C	- - -	--
2.5	2d, 80°C		73
3.5	5d, 80°C	- - -	--
3.5	5d, 80°C	- - -	--
3.5	5d, 80°C	- - -	--
3.5	5d, 80°C	- - -	--

Table 9. Continued

Entry	Arene	Cycloalkene
14		

Total % $Pd(OAc)_2$	Reaction Conditions	Product	% Isolated Yield
3.5	5d, 80°C	- - -	--

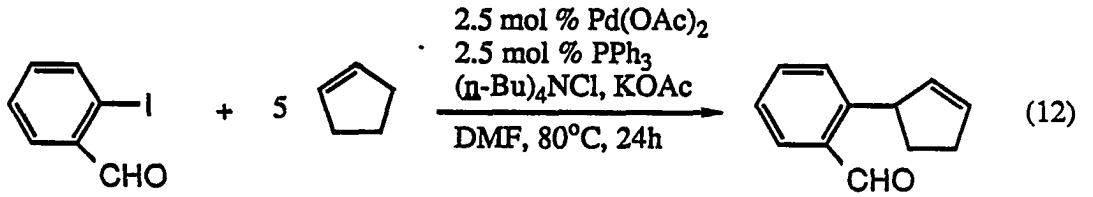
obtained was with cycloheptene (entry 2); notably, however, attempts under similar conditions at room temperature all met with poor yields. When subsequent trials using dihydrofuran and dihydrophyran also failed to proceed at room temperature, all subsequent reactions were run at 80°C. Evidently the presence of the silver ions slows the reaction under these conditions as well. Nonetheless, excellent yields of only the allylicly-substituted cycloalkene were obtained using 2,3-dihydrofuran (entry 1), cycloheptene (entry 2), and 3,4-dihydropyran (entry 3). In the latter case, 2-D ^{1}H COSY NMR was required to conclusively prove that the isomer obtained was the desired one (see experimental section for details). The success of the two heterocyclic alkenes is of great importance, as applications to nucleoside and glycoside chemistry can be envisioned. Based upon the success of these initial trials, other experiments were conducted. Unlike our earlier reaction conditions, nitro groups on the aromatic ring do not interfere with this reaction (entries 4 and 5). It should be noted, however, that this does not represent the only report of the tolerance of the nitro group in palladium-catalyzed reactions.[40]

The effect of electron-donating and electron-withdrawing groups on the aromatic ring was not investigated, as the previous, milder conditions had proven effective under most

circumstances; instead, only those situations in which the previous conditions had proven unacceptable were investigated. 2-Iodobenzoic acid and 2-iodobenzamide, which were believed to chelate in the previous work, also failed under these conditions (entries 7 and 8). N,N-Dimethyl 2-iodobenzamide, formed the desired product in very good yield after only two days at 80°C (entry 9). Thus, chelation appears to interrupt the course of these reactions also. 2-Iodobenzaldehyde was also examined, in hopes that under these conditions oxidation to the carboxylic acid would not take place (entry 6). No reaction occurred, except for the slow, incomplete oxidation of the aldehyde to 2-iodobenzoic acid, as determined by TLC analysis during the course of the reaction and crude ^{1}H NMR spectroscopic analysis of the final mixture.

The earlier problems encountered when substituents containing a heteroatom with an available hydrogen were present on the aromatic ring also continued to interfere: 2-iodophenol, 2-iodoaniline, 2-iodobenzyl alcohol, N-acetyl 2-iodoaniline, and N-tosyl 2-iodoaniline all were completely unreactive (entries 10-14). Recently, however, we have observed that the presence of triphenylphosphine in reactions using the quaternary ammonium salt improves yields in some intramolecular cyclizations of this sort. Based upon this result, another student in our research group is

currently reexamining these substrates. Only preliminary data are available; however, 2-iodophenol, 2-iodobenzyl alcohol, and 2-iodobenzaldehyde all react with cyclopentene under these conditions in very good yield, as illustrated below (eq. 12).



(12)

87%

CONCLUSION

The palladium-catalyzed intermolecular arylation of cyclic alkenes presented in this part provides a valuable route to allylicly-arylated compounds, without the presence of regioisomeric products found in previously published procedures. Alkene rings of five to eight members each react in good yield, at room temperature if simple aryl iodides are employed, or at 80°C if electron-donating groups are present in the aryl iodide. In cases where isomerization of the double bond is particularly stubborn, a different set of reaction conditions employing silver carbonate eliminates isomerization. Certain function groups on the aromatic ring (OH, NHR, CO_2H, $C(O)NH_2$, CH_2OH, CHO) inhibit the reaction however.

EXPERIMENTAL SECTION

Equipment

NMR Spectra were recorded on a Nicolet NT-300 (operating at 300 MHz for proton nuclei and 75 MHz for carbon nuclei) spectrometer. Infrared spectra were obtained on either an IBM IR/98 FT-IR spectrophotometer or on a Beckman-42050 spectrophotometer. Mass spectral data were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with a 3% OV-101 on Chromasorb W packed column.

Reagents

All chemicals were used directly as obtained unless otherwise noted, and were obtained from Aldrich Chemical Co. unless otherwise noted. Ethyl ether, acetonitrile, and N,N-dimethylformamide (DMF) were distilled over calcium hydride, the latter at reduced pressure. Tetrahydrofuran was distilled over a mixture of sodium metal and benzophenone. 4-Iodotoluene, 4-iodoaniline, and iodobenzene were purchased from Eastman Kodak Chemicals, Inc. 2-Iodophenol and tetra-n-butylammonium chloride (TBAC) were obtained from Lancaster Synthesis, Inc. Sodium acetate, potassium acetate, triethylamine, and bromobenzene were

obtained from Fischer Scientific Co. Palladium acetate was generously supplied by Johnson Matthey, Inc.

The following compounds were prepared by literature procedures: 1-acetoxycyclopentene,[41] 1-acetoxycyclohexene,[42] 2-iodobenzaldehyde,[43] N-acetyl-2-iodoaniline,[44] phenyl triflate.[45] N-Tosyl-2-iodoaniline, generously supplied by Norman Berrios-Pena, was prepared in a fashion similar to that mentioned earlier for N-acetyl-2-iodoaniline. N,N-Dimethyl-2-iodobenzamide and 2-iodobenzamide were prepared and provided by L. Wayne Harrison, the former according to a literature procedure[46] and the latter in similar fashion using ammonium hydroxide in place of dimethylamine.

Preparation of 3-arylcycloalkenes using TBAC

The following procedure for the preparation of 3-phenylcyclopentene is representative of that used for the other compounds. In cases where the compound obtained was identical with previously reported literature, only spectral data absent from previous reports is included.

To an oven-dried 5 mL roundbottom flask containing a magnetic stirrer and fitted with a rubber septa were added the following reagents: palladium acetate (3.0 mg, 2.5 mol %), tetra-n-butylammonium chloride (140 mg, 0.5 mmol), anhydrous crystalline potassium acetate (147 mg, 1.5 mmol), and DMF (1.0 mL). The flask was then purged with nitrogen

for five minutes with stirring. Cyclopentene (0.30 mL, 2.5 mmol) and iodobenzene (0.056 mL, 0.5 mmol) were then added via syringe, followed by a similar addition of n-tetradecane (0.10 mL) for use as an internal standard if GC analysis was performed. The mixture was then stirred at room temperature, shielded from light, for 36 hours. The reaction mixture turns black within fifteen minutes after the addition of all reagents. Preparatory runs were performed in a similar manner, typically using a tenfold increase in the amounts of each reagent. After the reaction was complete, the mixture was diluted with ethyl ether (10 mL), washed with saturated aqueous ammonium chloride solution (2 X 10 mL), and the combined aqueous portions backwashed with ethyl ether (2 X 10 mL). All ether portions were then combined, dried over magnesium sulfate, vacuum-filtered through Celite, and concentrated at reduced pressure to yield 3-phenylcyclopentene in 89% isolated yield. In some cases charcoal was added to remove colored impurities while drying, and some products required purification via flash chromatography (silica gel, 6" X 10 mm). The ^{1}H and ^{13}C NMR spectra were identical with previously reported literature.[17,47] IR (neat) 3050 (phenyl), 3010 (C=C), 1595 (C=C), 695 (C=C) cm^{-1}.

3-Phenylcyclohexene

Obtained in 70% isolated yield (88% GC) from iodobenzene and cyclohexene as a colorless oil, using sodium acetate as base and stirring for five days at room temperature.[48]

4-Phenylcycloheptene

Obtained in 77% isolated yield (99% GC) from iodobenzene and cycloheptene as a colorless oil, using potassium acetate as base and stirring for six days at room temperature.[18] IR (neat) 3015 (phenyl), 2920 (C=C), 1595 (C=C), 700 (C=C) cm^{-1}.

3-Phenylcyclooctene

Obtained in 85% isolated yield (100% GC) from iodobenzene and cyclooctene as a colorless oil, using cesium acetate as base and stirring for two days at room temperature.[49]

3-Phenyl-2,3-dihydrofuran

Obtained in 78% isolated yield (91%) GC) from iodobenzene and 2,5-dihydrofuran as a colorless oil, using sodium acetate as base and stirring for four days at room temperature.[50] IR (neat) 3030 (phenyl), 3010 (C=C), 1060 (C-O), 700 (C=C) cm^{-1}.

2-Phenyl-2,3-dihydrofuran

Obtained in 85% GC yield from iodobenzene and 2,3-dihydrofuran as a colorless oil, and separated from its isomer, 2-phenyl-2,5-dihydrofuran, by flash chromatography (silica gel, hexane), using sodium acetate as base and stirring for five days at room temperature.[51] Isolated yield not determined.

2-Phenyl-2,5-dihydrofuran

Obtained in 15% GC yield from iodobenzene and 2,3-dihydrofuran as a colorless oil, and separated, as indicated above. ^{1}H NMR spectra compares favorably with a similar compound, 2-(p-anisyl)-2,5-dihydrofuran.[11] ^{1}H NMR ($CDCl_3$) δ 4.2-4.5 (2 H, m, OCH_2), 5.2-5.6 (3 H, m, OCH and olefinic), 7.2-7.4 (5 H, m, phenyl); IR (neat) 3035 (phenyl), 3020 (C=C), 1065 (C-O), 690 (C=C) cm^{-1}; Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.07; H, 7.09.

Phenyldihydropyrans

Obtained in 71% isolated yield from iodobenzene and dihydropyran, as a 4:1:1 mixture of three isomers (determined by GC-MS analysis), using sodium acetate as base and stirring for six and a half days at room temperature.[19,20,52] Further separation and analysis was not performed.

Ethyl o-(3-cyclopentenyl)-benzoate

Obtained in 74% isolated yield (77% GC) from ethyl o-iodobenzoate and cyclopentene as a colorless oil, using potassium acetate as base and stirring for twelve hours at room temperature. A subsequent run on a 10 mmol reaction scale resulted in a 90% distilled isolated yield after one day at room temperature. ^{1}H NMR ($CDCl_3$) δ 1.35-1.44 (3 H, t, J = 7.0 Hz, CH_3), 1.58-1.74 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.33-2.63 (3 H, m, CHArC<u>H</u>(H) cis to aryl and $C=CCH_2$), 4.30-4.41 (2 H, q, J = 7.2 Hz, OCH_2), 4.54-4.67 (1 H, m, CHAr), 5.70-5.78 (1 H, m, CHArCH=C<u>H</u>), 5.91-6.01 (1 H, m, CHArC<u>H</u>=CH), 7.17-7.32 (2 H, m, aromatic), 7.37-7.47 (1 H, d, J = 7.2 Hz, aromatic ortho to cyclopentene ring), 7.74-7.81 (1 H, d, J = 7.5 Hz, aromatic ortho to carboxylate); IR (neat) 3053 (phenyl), 1718 (C=O), 1600 (C=C), 1575 (C=C), 754 (phenyl), 733 (phenyl), 714 (C=C) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.55 (CH_3), 32.54 (CH_2), 34.17 (allylic CH_2), 47.93 (OCH_2), 61.08 (CH), 125.87, 127.89, 130.01, 130.33, 131.96, 132.52, 134.18, 147.51 (aromatics and vinylics), 168.31 (C=O); Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.87; H, 7.09.

Ethyl p-(3-cyclopentenyl)-benzoate

Obtained in 85% isolated yield (90% GC) from ethyl p-iodobenzoate and cyclopentene as a colorless oil, using potassium acetate as based and stirring for three and a half

days at room temperature. ^{1}H NMR ($CDCl_3$) δ 1.30-1.38 (3 H, t, J = 7.1 Hz, CH_3), 1.58-1.78 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.29-2.60 (3 H, m, CHArC<u>H</u>(H) cis to aryl and C=CCH_2), 3.83-3.97 (1 H, m, CHAr), 4.27-4.38 (2 H, q, J = 7.1 Hz, OCH_2), 5.70-5.77 (1 H, m, CHArCH=C<u>H</u>), 5.90-5.99 (1 H, m, CHArC<u>H</u>=CH), 7.18-7.25 (2 H, d, J = 8.4 Hz, aromatics meta to carboxylate), 7.88-7.97 (2 H, d, J = 8.1 Hz, aromatics ortho to carboxylate); IR (neat) 3055 (phenyl), 1717 (C=O), 1610 (C=C), 1576 (C=C), 771 (phenyl), 730 (phenyl), 706 (C=C) cm^{-1}; ^{13}C NMR δ 14.60 (CH_3), 32.72 (CH_2), 33.87 (allylic CH_2), 51.53 (OCH_2), 60.94 (CH), 127.33, 128.53, 129.93, 132.82, 133.68, 152.03 (aromatics and vinylics), 166.78 (C=O); Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.52; H, 7.11.

<u>p-(3-Cyclopentenyl)-acetophenone</u>

Obtained in 94% isolated yield (96% GC) from <u>p</u>-iodoacetophenone and cyclopentene as a colorless oil, using potassium acetate as base and stirring for four and a half days at room temperature. ^{1}H NMR ($CDCl_3$) δ 1.59-1.75 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.28-2.57 (6 H, m with 3 H singlet embedded, C(O)CH_3, CHArC<u>H</u>(H) cis to aryl, and C=CCH_2), 3.82-3.95 (1 H, m, CHAr), 5.66-5.75 (1 H, m, CHArCH=C<u>H</u>), 5.86-5.96 (1 H, m, CHArC<u>H</u>=CH), 7.14-7.24 (2 H, d, J = 8.1 Hz, aromatics meta to carbonyl), 7.77-7.86 (2 H, d, J = 8.4 Hz, aromatics ortho to carbonyl); IR (neat) 3047

(phenyl), 1680 (C=O), 1607 (C=C), 1570 (C=C), 829 (phenyl), 735 (C=C), 648 (C=C) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 26.74 (CH_3), 3272 (CH_2), 33.80 (allylic CH_2), 51.49 (CH), 127.54, 128.78, 132.92, 133.53, 135.41, 152.43 (aromatics and vinylics), 197.89 (C=O); Anal. Calcd for $C_{13}H_{14}O$: C, 83.34; H, 7.54. Found: C, 82.99; H, 7.02.

2-(3-Cyclopentenyl)-phenol

Obtained in 27% isolated yield (34% GC) from o-iodophenol and cyclopentene as a colorless oil, using sodium acetate as base and stirring for five and a half days at 80°C. Compound identical with previously reported literature.[53]

3-Phenyl-2-acetoxycyclopentene

Obtained in 16% GC yield from iodobenzene and 1-acetoxycyclopentene, using potassium acetate as base and stirring for six and a half days at room temperature. ^1H NMR ($CDCl_3$) δ 1.8-2.2 (5 H, br m with 3 H singlet embedded, $CH_3C(O)$ and $CHPhC\underline{H}_2$), 2.4-2.6 (2 H, m, $C=CCH_2$), 4.0-4.1 (1 H, m, CHPh), 5.65-5.70 (1 H, d, J = 1.5 Hz, C=CH), 7.15-7.35 (5 H, m, phenyl). Irradiation of the peak at δ 4.0-4.1 causes the doublet at δ 5.65-5.70 to collapse to a singlet at δ 5.675. Irradiation of the multiplet at δ 2.4-2.6 does not affect the doublet at δ 5.65-5.70.

2-(3-Cyclopentenyl)-aniline

Obtained in 6% GC yield from o-iodoaniline and cyclopentene, using either sodium or potassium acetate as the base and stirring for four and a half days at 80°C. Too little material present to isolate and characterize completely. Identity is based on GC-MS (shows molecular ion peak at 159) and GC retention time (relative to 4-(3-cyclopentenyl)-aniline). Also, presence of peak at δ 3.67 in crude ^{1}H NMR indicates that product was the allylicly-substituted isomer.

4-(3-Cyclopentenyl)-aniline

Obtained in 32% isolated yield (38% GC) from p-iodoaniline and cyclopentene as a straw yellow oil, using potassium acetate as base and stirring for five and a half days at 80°C. ^{1}H NMR ($CDCl_3$) δ 1.50-1.70 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.15-2.50 (3 H, m, CHArC<u>H</u>(H) cis to aryl and C=CCH_2), 3.20-3.55 (2 H, br s, NH_2), 3.65-3.75 (1 H, m, CHAr), 5.65-5.70 (1 H, m, CHArCH=C<u>H</u>), 5.80-5.85 (1 H, m, CHArC<u>H</u>=CH), 6.55 (2 H, d, J = 8.4 Hz, aromatics meta to NH_2), 6.90 (2 H, d, J = 8.4 Hz, aromatics ortho to NH_2); ^{13}C NMR δ 32.41 (CH_2), 33.86 (allylic CH_2), 50.52 (CH), 115.25, 127.92, 131.23, 134.83, 136.63, 144.36 (aromatics and vinylics).

2-(3-Cyclopentenyl)-anisole

Obtained in 78% isolated yield from o-iodoanisole and cyclopentene as a colorless oil, using potassium acetate as base and stirring for one day at 80°C.[17,47] ^{1}H NMR ($CDCl_3$) δ 1.45-170 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.10-2.53 (3 H, m, CHArC<u>H</u>(H) cis to aryl and C=CCH_2), 3.75 (3 H, s, OCH_3), 4.13-4.25 (1 H, m, CHAr), 5.65-5.70 (1 H, m, CHArCH=C<u>H</u>), 5.80-5.90 (1 H, m, CHArC<u>H</u>=CH), 6.73-6.92 (2 H, m, aromatics meta to OCH_3), 7.00-7.20 (2 H, m, aromatics ortho to OCH_3).

4-(3-Cyclopentenyl)-anisole

Obtained in 67% isolated yield from p-iodoanisole and cyclopentene as a colorless oil, using potassium acetate as base and stirring for three days at 80°C.[17,47] ^{1}H NMR ($CDCl_3$) δ 1.60-1.75 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.30-2.55 (3 H, m, CHArC<u>H</u>(H) cis to aryl and C=CCH_2), 3.77 (3 H, s, OCH_3), 3.78-3.90 (1 H, m, CHAr), 5.67-5.77 (1 H, m, CHArCH=C<u>H</u>), 5.84-5.92 (1 H, m, CHArC<u>H</u>=CH), 6.82 (1 H, d, J = 13.8 Hz, aromatics meta to OCH_3), 7.08 (1 H, d, <u>J</u> = 13.8 Hz, aromatics ortho to OCH_3).

2-(3-Cyclopentenyl)-toluene

Obtained in 72% isolated yield from o-iodotoluene and cyclopentene as a colorless oil, using potassium acetate as base and stirring for seven days at room temperature.[17,47]

^{1}H NMR ($CDCl_3$) δ 1.30-1.50 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.37 (3 H, s, CH_3), 2.40-2.50 (3 H, m, CHArC<u>H</u>(H) cis to aryl and C=CCH_2), 4.05-4.15 (1 H, m, CHAr), 5.75-5.80 (1 H, dddd, <u>J</u> = 2.1, 2.1, 2.1, 6.3 Hz, CHArCH=C<u>H</u>), 5.84-6.00 (1 H, dddd, <u>J</u> = 2.1, 2.1, 2.1, 6.3 Hz, CHArC<u>H</u>=CH), 7.05-7.20 (4H, m, aromatic); IR (neat) 3060 (phenyl), 2953 (C=C), 1487 (C=C), 663 (C=C) cm^{-1}.

<u>4-(3-Cyclopentenyl)-toluene</u>

Obtained in 75% isolated yield from <u>p</u>-iodotoluene and cyclopentene as a colorless oil which becomes a white solid if cooled to -2°C, using potassium acetate as base and stirring for seven days at room temperature.[17,47] ^{1}H NMR ($CDCl_3$) δ 1.65-1.80 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.34 (3 H, s, CH_3), 2.35-2.60 (3 H, m, CHArC<u>H</u>(H) cis to aryl and C=CCH_2), 3.80-3.95 (1 H, m, CHAr), 5.70-5.77 (1 H, m, CHArCH=C<u>H</u>), 5.80-5.95 (1 H, m, CHArC<u>H</u>=CH), 6.88-6.92 (2 H, d, J = 8.1 Hz, aromatics ortho to CH_3), 7.53-7.57 (2 H, d, J = 8.1 Hz, aromatics meta to CH_3); IR (neat) 3051 (phenyl), 2924 (C=C), 1512 (C=C) cm^{-1}.

<u>2-(3-Cyclopentenyl)-thiophene</u>

Obtained in 80% isolated yield from 2-iodothiophene and cyclopentene as a colorless oil, using potassium acetate as base and stirring for seven days at room temperature.[37] A slightly different workup procedure was employed, as under

the original procedure a black tar was obtained. After the ether extractions, an excess of charcoal was added, along with magnesium sulfate, and this mixture was stirred for 24 hours before filtering through Celite. One milliliter of hexanes was added, and the solution was then concentrated to a volume of approximately one milliliter and immediately placed on a silica gel flash column and eluted with hexanes. ^{1}H NMR ($CDCl_3$) δ 1.74-1.83 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.27-2.49 (3 H, m, CHArC<u>H</u>(H) cis to aryl and C=CCH_2), 4.05-4.15 (1 H, m, CHAr), 5.72-5.78 (1 H, m, CHArCH=C<u>H</u>), 5.82-5.88 (1 H, m, CHArC<u>H</u>=CH), 6.73 (1 H, d, J = 3.3 Hz, 3-thienyl H), 6.82-6.86 (1 H, dd, J = 3.3, 3.9 Hz, 4-thienyl H), 7.03 (1 H, d, J = 3.9 Hz, 5-thienyl H); IR (neat) 2961 (C=C), 2905, 1439 (C=C), 1412, 1259, 1076, 1038, 1009, 912, 851, 822, 756, 725 (C=C) cm^{-1}; ^{13}C NMR δ 32.11 (CH_2), 34.077 (allylic CH_2), 46.12 (CHAr), 122.65, 122.91, 126.62, 131.98, 133.83, 150.47 (aromatics and vinylics); m/z calcd for $C_9H_{10}S$ 150.05032; found 150.05001 (2.1 ppm error). Measuring M-1 peak, calcd for C_9H_9S 149.04249; found 149.04222 (1.8 ppm error).

2-phenyl norbornanes

Obtained in 76% crude isolated yield from iodobenzene and norbornene as a 4:1 mixture of the exo:endo isomers (determined by ^{1}H NMR spectral integration), using sodium formate as base and stirring for two days at room

temperature. Compounds were identical with previous literature reports.[54]

Preparation of 3-arylcycloalkenes using silver carbonate

The following procedure used for the preparation of 3-phenylcycloheptene is representative of that used for the other compounds. As before, only spectral data absent from the literature is provided.

To an oven dried 25 mL roundbottom flask containing a magnetic stirrer and fitted with a rubber septa were added the following reagents: palladium acetate (3.6 mg, 3 mol %), triphenylphosphine (11.8 mg, 9 mol %), silver carbonate (275.75 mg, 1.0 mmol) and acetonitrile (6 mL). The flask was then purged with nitrogen for five minutes with stirring. Cycloheptene (0.30 mL, 2.5 mmol) and iodobenzene (0.056 mL, 0.5 mmol) were then added via syringe, and the septa was then covered with Parafilm and secured to the flask with copper wire. The mixture was then stirred at 80°C, shielded from light, for one day. The reaction mixture turned black within twenty minutes at the elevated temperature. Reactions were monitored via GC, and when warranted by a reduction in the rate of reaction, an additional 1% $Pd(OAc)_2$ and 3% PPh_3 were added, and the flask purged with nitrogen and resealed as before. After the reaction was complete, a workup identical to the TBAC procedure was employed, with only minor alterations.

Charcoal was added to the magnesium sulfate during the drying stages, and flash chromatography (silica gel, 6" X 10 mm) was required for purification of each compound listed below. 3-Phenylcycloheptene was obtained in 99% isolated yield; ^{1}H and ^{13}C NMR spectra were identical with previously reported literature.[18,49]

2-Phenyl-5,6-dihydropyran

Obtained in 96% isolated yield from iodobenzene and 3,4-dihydropyran as a colorless oil, stirring for two days at 80°C. ^{1}H NMR ($CDCl_3$) δ 2.00-2.16 (1 H, m, allylic), 2.30-2.45 (1 H, m, allylic), 3.75-3.87 (1 H, ddd, J = 4.2, 8.7, 11.25 Hz, OCH(H)), 3.97-4.07 (1 H, m, OCH(H)), 5.12-5.19 (1 H, s with fine coupling, OCHPh), 5.80-5.87 (1 H, dq, J = 1.8, 10.2 Hz, CHPhCH=CH), 5.95-6.05 (1 H, dp, J = 2.55, 10.2 Hz, CHPhCH=CH), 7.25-7.42 (5 H, m, aromatic). COSY 2D ^{1}H NMR indicates that the OCH_2 is not coupled with the CHPh or either vinyl proton, but is coupled with the allylic CH_2, consistent with only this double bond isomer. IR (neat) 1493, 1450, 1279, 1259, 1178, 1084, 1061, 906, 864, 843, 756, 700, 675 cm^{-1}; ^{13}C NMR δ 25.15 (allylic CH_2), 63.10 (OCH_2), 76.03 (OCHPh), 125.14, 127.41, 127.73, 128.37, 129.44, 141.26 (vinylic and aromatic); m/z calcd for $C_{11}H_{12}O$ 160.08882; found 160.08902 (1.2 ppm error); Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.42; H, 7.61.

2-(3-Cyclopentenyl)-nitrobenzene

Obtained in 70% isolated yield from o-iodonitrobenzene and cyclopentene as a colorless oil, stirring for two days at 80°C.[17,47] ^{1}H NMR ($CDCl_3$) δ 1.65-1.78 (1 H, dddd, J = 6.3, 6.5, 7.4, 14.9 Hz, CHArCH(H) trans to aryl), 2.41-2.53 (2 H, m, allylic CH_2), 2.54-2.69 (1 H, m, CHArCH(H) cis to aryl), 4.28-4.39 (1 H, m, CHAr), 5.67-5.72 (1 H, ddt, J = 2.1, 6.0, 4.2 Hz, CHArCH=CH), 6.01-6.07 (1 H, ddt, J = 2.1, 4.5, 2.1 Hz, CHArCH=CH), 7.27-7.34 (1 H, dt, J = 1.5, 6.9 Hz, aromatic para to cyclopentene ring), 7.33-7.36 (1H, dd, J = 1.2, 7.8 Hz, aromatic ortho to cyclopentene ring), 7.48-7.51 (1H, dt, J = 1.2, 7.5 Hz, aromatic para to nitro), 7.76-7.80 (1 H, dd, J = 1.2, 8.1 Hz, aromatic ortho to nitro); IR (neat) 1607, 1576, 1526 (C=C), 1475 (C=C), 1352, 1292, 1013, 916, 852, 785, 744, 706 (C=C), 658 cm^{-1}; ^{13}C NMR δ 32.23 (CH_2), 33.51 (allylic CH_2), 48.35 (CHAr), 123.88, 126.73, 128.95, 132.40, 132.70, 133.65, 140.79 (vinylic and aromatic), 149.43 (CNO_2); m/z calcd for $C_{11}H_{11}NO_2$ minus OH (mol. ion weak) 172.07624; found 172.07629 (0.3 ppm error); Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86. Found: C, 69.35; H, 5.27.

4-(3-Cyclopentenyl)-nitrobenzene

Obtained in 52% isolated yield from p-iodo nitrobenzene and cyclopentene as a colorless oil, stirring for two days at 80°C.[17,47] ^{1}H NMR ($CDCl_3$) δ 1.65-1.79 (1 H, m, CHArCH(H)

trans to aryl), 2.39-2.60 (3 H, m, CHArC<u>H</u>(H) cis to aryl and allylic CH_2), 3.95-4.05 (1 H, m, CHAr), 5.73-5.78 (1 H, ddt, J = 1.8, 5.4, 2.1 Hz, CHArCH=C<u>H</u>), 6.00-6.05 (1 H, ddt, J = 2.4, 5.4, 2.1 Hz, CHArC<u>H</u>=CH), 7.80-7.85 (2 H, d, J = 8.7 Hz, aromatic meta to nitro), 8.12-8.15 (2 H, d, J = 9.0 Hz, aromatic ortho to nitro); IR (neat) 2941 (C=C), 2853, 1599, 1518 (C=C), 1458 (C=C), 1348, 1178, 1109, 1015, 916, 854, 820 (phenyl), 752 (phenyl), 727 (C=C) cm^{-1}; ^{13}C NMR δ 32.44 (CH_2), 33.59 (allylic CH_2), 51.16 (CHAr), 123.66, 127.60, 127.92, 132.66, 133.44 (vinylic and aromatic), 154.28 (CNO_2); m/z calcd for $C_{11}H_{11}NO_2$ 189.07898; found 189.07018 (1.1 ppm error); Anal. Calcd for $C_{11}H_{11}NO_2$: C, 68.93; H, 5.86. Found: C, 69.66; H, 5.52.

<u>N,N</u>-Dimethyl 2-(3-cyclopentenyl)-benzamide

Obtained in 73% isolated yield from <u>N,N</u>-dimethyl <u>o</u>-iodobenzamide and cyclopentene as a colorless oil, stirring for two days at 80°C. ^1H NMR ($CDCl_3$) δ 1.60-1.80 (1 H, m, CHArC<u>H</u>(H) trans to aryl), 2.26-2.62 (3 H, m, CHArC<u>H</u>(H) cis to aryl and allylic CH_2), 2.79-2.84 (3 H, s, NCH_3), 3.10-3.14 (3 H, s, NCH_3), 3.69-4.05 (1 H, m, CHAr), 5.63-5.73 (1 H, br s, CHArCH=C<u>H</u>), 5.86-5.99 (1 H, br s, CHArC<u>H</u>), 7.05-7.14 (1 H, m, aromatic para to cyclopentene ring), 7.17-7.24 (2 H, m, aromatic ortho to cyclopentene ring and aromatic para to $C(O)N(CH_3)_2$), 7.24-7.33 (1 H, m, aromatic ortho to C(O) $N(CH_3)_2$); ^{13}C NMR δ 32.30 (CH_2),

34.32 (allylic CH_2), 38.62 (NCH_3), 47.67 (NCH_3), 60.06 (CHAr), 125.31, 125.81, 127.02, 128.82, 133.37, 133.46, 135.82, 142.52 (aromatic and vinylic), 171.22 (C=O).

REFERENCES

1. (a) Heck, R. F. J. Am. Chem. Soc. 1968, 90, 5518.
(b) Heck, R. F. J. Am. Chem. Soc. 1968, 90, 5526.
(c) Heck, R. F. J. Am. Chem. Soc. 1968, 90, 5535.
(d) Heck, R. F. J. Am. Chem. Soc. 1968, 90, 5538.
(e) Heck, R. F. J. Am. Chem. Soc. 1968, 90, 5542.
(f) Heck, R. F. J. Am. Chem. Soc. 1968, 90, 5546.

2. (a) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer Verlag: New York, 1980.
(b) Heck, R. F. "Palldium Reagents in Organic Synthesis"; Academic Press: New York, 1985.

3. Maitlis, P. M. "The Organic Chemistry of Palladium"; Academic Press: New York, 1973; Vols. 1 & 2.

4. Heck, R. F. Organic Reactions 1982, 27, 345.

5. Heck, R. F. Organomet. Chem. Synth. 1972, 1, 455.

6. Henry, P. M.; Ward, G. A. J. Am. Chem. Soc. 1972, 94, 673.

7. Heck, R. F. J. Am. Chem. Soc. 1971, 93, 6896.

8. Horino, H.; Arai, M.; Inoue, N. Bull. Chem. Soc. Jpn. 1974, 47, 1683.

9. Horino, H.; Inoue, N. Bull. Chem. Soc. Jpn. 1971, 44, 3210.

10. Saito, R. -I.; Isumi, T.; Kasahara, A. Bull. Chem. Soc. Jpn. 1973, 46, 1776.

11. Lee, T. D.; Daves, D. G., Jr. J. Org. Chem. 1983, 48, 399.

12. Kasahara, A.; Isumi, T.; Yodono, M.; Saito, R. -I.; Takeda, T.; Sugawara, T. Bull. Chem. Soc. Jpn. 1973, 46, 1220.

13. Horino, H.; Inoue, N. J. Chem. Soc., Chem. Commun. 1976, 500.

14. Kasahara, A.; Isumi, T.; Saito, G.; Yodono, M. Bull. Chem. Soc. Jpn. 1972, 45, 895.

15. Outten, R. A.; Daves, G. D., Jr. J. Org. Chem. 1987, 52, 5064.

16. Garves, K. J. Org. Chem. 1970, 35, 3273.

17. Kikukawa, K. Nagira, F.; Wada, F.; Matsuda, T. Tetrahedron 1981, 37, 31.

18. Kikukawa, K.; Maemura, K.; Kiseki, Y.; Wada, F.; Matsuda, T. J. Org. Chem. 1981, 46, 4885.

19. Tamaru, Y.; Yamada, Y.; Yoshida, Z. -I. Tetrahedron 1979, 35, 329.

20. Arai, I.; Daves, G. D., Jr. J. Org. Chem. 1979, 44, 21.

21. Cortese, N. A.; Ziegler, C. B., Jr.; Hrnjez, B. J.; Heck, R. F. J. Org. Chem. 1978, 43, 2952.

22. Andersson, C. -M.; Hallberg, A.; Daves, D. G., Jr. J. Org. Chem. 1987, 52, 3529.

23. Yamamura, K.; Nakatsu, K.; Nakao, K.; Nakazawa, T.; Murata, I. Tetrahedron Lett. 1979, 4999.

24. Harrington, P. J.; DiFiore, K. A. Tetrahedron Lett. 1987, 28, 495.

25. (a) Jeffrey, T. J. Chem. Soc., Chem. Commun. 1984, 1287. (b) Jeffrey, T. Tetrahedron Lett. 1985, 26, 2667. (c) Jeffrey, T. Synthesis 1987, 70.

26. Spencer, A. J. Organomet. Chem. 1983, 258, 101.

27. (a) Rabinovitz, M.; Cohen, Y.; Halpern, M. Angew. Chem., Int. Ed. Engl. 1986, 25, 960 and references cited therein. (b) Halpern, M., Dow Chemical Company, Midland, Mich., personal communication, 1988.

28. (a) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. Tetrahedron Lett. 1988, 29, 2919. (b) Abelman, M. M.; Oh, T.; Overman, L. E. J. Org. Chem. 1987, 52, 4130.

29. (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. J. Org. Chem. 1980, 45, 2709. (b) Heck, R. F. J. Org. Chem. 1978, 43, 2952.

30. (a) Kowalski, M. H.; Stang, P. J. Organometallics 1986, 5, 2392. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. Synthesis 1982, 85. (c) Scott, W. J.; Crisp, G. T.; Stille, J. K. J. Am. Chem. Soc. 1984, 106, 4630. (d) Scott, W. J.; Crisp, G. T.; Stille, J. K. J. Am. Chem. Soc. 1986, 108, 3033. (e) Echavarren, A. M.; Stille, J. K. J. Am. Chem. Soc. 1988, 110, 1557. (f) Echavarren, A. M.; Stille, J. K. J. Am. Chem. Soc. 1987, 109, 5478. (g) Andersson, C.-M.; Hallberg, A. J. Org. Chem. 1988, 53, 2112. (h) Cacchi, S.; Ciattini, P. G.; Morera, E.; Otar, G. Tetrahedron Lett. 1986, 27, 3931. (i) Chen, Q.-Y.; Yang, Z.-Y.; Tetrahedron Lett. 1986, 27, 1171. (j) Cacchi, S.; Ciattini, P. G.; Morera, E.; Otar, G. Tetrahedron Lett. 1986, 27, 5541. (k) Subramanian, L. R.; Martinez, A. G.; Fernandez, A. H.; Alvarez, R. M. Synthesis 1984, 481. (l) Chen, Q.-Y.; He, Y.-B.; Yang, Z.-Y. J. Chem. Soc., Chem. Commun. 1986, 1452.

31. Backvall, J. -E.; Nordberg, R. E.; J. Am. Chem. Soc. 1981, 103, 4959 and references cited therein.

32. (a) Cacchi, S.; Ciattini, P. G.; Morera, E.; Otar, G. Tetrahedron Lett. 1986, 27, 3921. (b) Baillargeon, V. P.; Stille, J. K. J. Am. Chem. Soc. 1986, 108, 452. (c) Baillargeon, V. P.; Stille, J. K. J. Am. Chem. Soc. 1983, 105, 7175. (d) Echavarren, A. M.; Stille, J. K. J. Am. Chem. Soc. 1988, 110, 1557.

33. Heck, R. F. Pure Appl. Chem. 1978, 50, 691.

34. Choudary, B. M.; Reddy, N. P.; Kantam, M. L.; Jamil, Z. Tetrahedron Lett. 1985, 26, 6257.

35. (a) Blackburn, T. F.; Schwartz, J. J. Chem. Soc., Chem. Commun. 1977, 157. (b) Tamaru, Y.; Yamamoto, Y.; Yamanda, Y. Tetrahedron Lett. 1981, 22, 1171.

36. (a) Auburn, P. R.; Whelan, J.; Bosnich, B. J. Chem. Soc., Chem Commun. 1986, 146. (b) Trost, B. M.; Scanlan, T. S. Tetrahedron Lett. 1986, 27, 4141.

37. Sota, K.; Hayashi, A.; Noda, K.; Aida, M. Botyu Kagaku 1973, 38, 106.

38. (a) Larock, R. C.; Babu, S. Tetrahedron Lett. 1987, 28, 5241. (b) Pri-Bar, I.; Buchman, O. J. Org. Chem. 1986, 51, 734. (c) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Worakun, T. Tetrahedron Lett. 1988, 29, 4329. (d) Burns, B.; Grigg, R.; Sridharan, V.; Warakun, T. Tetrahedron Lett. 1988, 29, 4325.

39. Oertle, K. CIBA-GEIGY Corporation, Geneva, personal communication, 1987.

40. (a) Bumagin, N. A.; Bumagina, I. G.; Nashin, A. N.; Beletskaya, I. P. Dokl. Akad. Nauk SSSR 1981, 261, 1141. (b) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. Tetrahedron Lett. 1985, 26, 4819.

41. Goodman, L.; Benitez, A.; Anderson, C. D.; Baker, B. R. J. Am. Chem. Soc. 1958, 80, 6582.

42. Bezoukian, P. J. Am. Chem. Soc. 1945, 67, 1430.

43. Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 2647.

44. Harrison, L. W. Ph.D. Thesis, Iowa State University, 1984.

45. Creary, X.; Benage, B.; Hilton, K. J. Org. Chem. 1983, 48, 2887.

46. Fong, C. W.; Lincoln, S. F.; Williams, E. H. Aust. J. Chem. 1978, 31, 2623.

47. Andrist, H. A.; Kalynchuk, D. G. Spectroscopic Lett. 1978, 11, 133.

48. (a) Murato, K.; Yatsunami, T.; Iwasaki, S. Helv. Chim. Acta 1980, 63, 588. (b) Nakagawa, K.; Sawai, M.; Ishii, Y.; Ogawa, M. Bull. Chem. Soc. Jpn. 1977, 50, 2487.

49. Cope, A. C.; Hecht, S. S. J. Am. Chem. Soc. 1967, 89, 6920.

50. Chalk, A. J.; Magennis, S. A. J. Org. Chem. 1976, 41, 273.

51. Scribe, P.; Wieman, J. Bull. Chim. Soc. Fr. 1971, 2268.

52. Descotes, G.; Giroud-Abel, B.; Martin, J. -C. Bull. Chim. Soc. Fr. 1967, 2472.

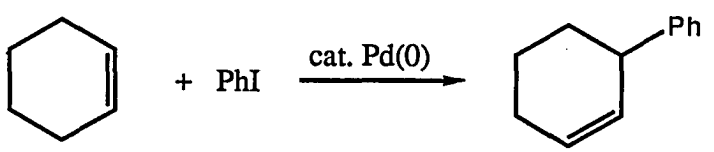
53. Dai, S. H.; Lin, C. Y.; Rao, D. V.; Stuber, F. A.; Carleton, P. S.; Ulrich, H. J. Org. Chem. 1985, 50, 1722.

54. Kropp, P. J. J. Am. Chem. Soc. 1973, 95, 4611.

PART II. INTRAMOLECULAR ARYLATION OF CYCLOALKENES

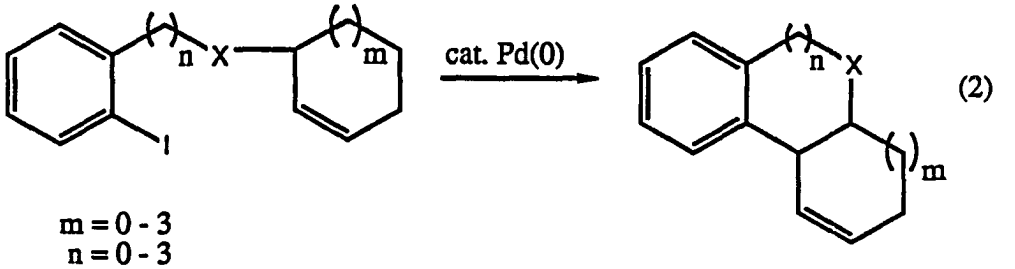
INTRODUCTION

The palladium-catalyzed arylation of alkenes, known as the Heck reaction, has proven to be a valuable method for carbon-carbon bond formation.[1] As discussed in Part I, the majority of these reactions involve intermolecular carbopalladation of an acyclic alkene followed by palladium-hydride elimination to form a Heck product.[1a-b] When cyclic alkenes are used, the resultant product is not the Heck product, but rather the allylic cross-coupling product (eq. 1).



(1)

In Part I, a mild, catalytic procedure for allylic cross-coupling of aryl halides with cyclic alkenes was examined. This procedure proved to be applicable to a wide variety of cyclic alkenes and aryl halides and circumvented the tendency of earlier procedures to afford product mixtures of double bond isomers. During the course of this work it was recognized that an analogous intramolecular process could provide a valuable new route to a wide variety of polycyclic compounds, both carbocyclic and heterocyclic (eq. 2).



(2)

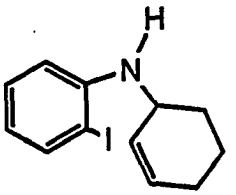
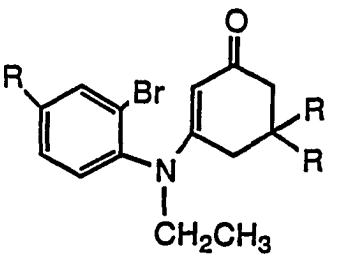
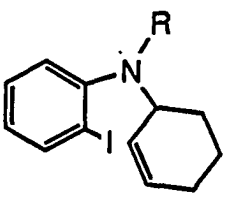
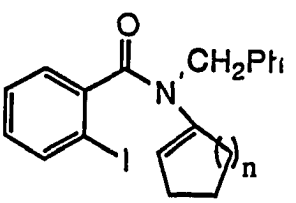
m = 0-3
n = 0-3
X = C, O, N

At the time our investigation began, only three reports of such an intramolecular process existed in the literature. During the course of our work, however, three additional reports have been published by other groups. Representative examples of these results are shown in Table 1, and will be discussed in detail, in the order they appeared in the literature.

The first report (entry 1) was published in 1980 by Odle et al., as part of an overall study directed toward the synthesis of indole ring systems.[2] While a large number of 2-halo-N-allylanilines did react in fair to good yield, the only compound containing a cyclic alkene resulted only in recovery of the starting material. No explanation for the failure of the compound to react was given, and the authors concluded from this result that the synthesis of carbazoles by this method was not possible.

Later in 1980, however, Iida et al. reported the first successful synthesis of carbazoles involving arylpalladium complexes (entry 2).[3] Both stoichiometric and catalytic

Table 1. Palladium-catalyzed intramolecular arylation with cyclic alkenes

Entry	Substrate	Palladium Source (mol %)	Solvent
1		$Pd(OAc)_2$ (3)	CH_3CN
2	 R = H, CH_3	$Pd(OAc)_2(PPh_3)_2$ (1-2)	DMF
3	 R = H, CH_3	$Pd(OAc)_2$ (3)	DMF
4	 n = 1 - 4	$Pd(OAc)_2$ (10)	CH_3CN

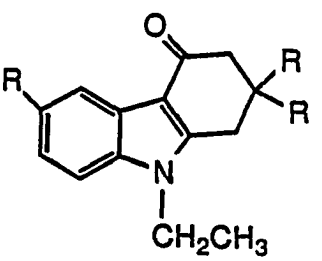
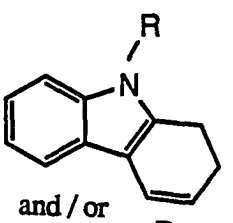
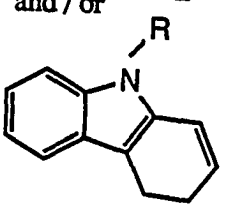
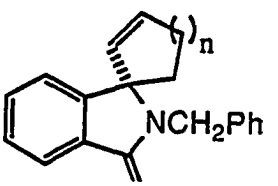
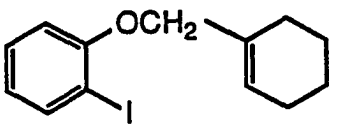
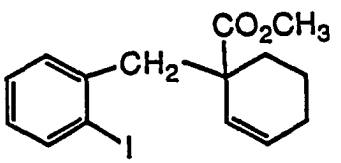
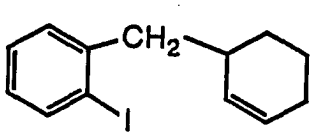
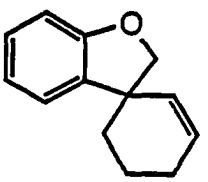
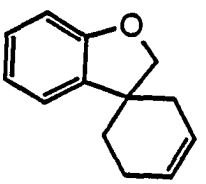
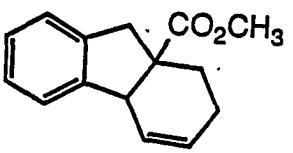
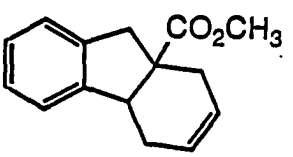
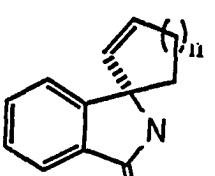
	Temp (°C)	Additional Reagents	Product(s)	% Yield	Ref.
1	110	Et_3N	- -	--	2
2	120-130	$NaHCO_3$		8-36	3
3	80	$(\underline{n}\text{-Bu})_4NCl$ [Et_3N or NaOAc or Na_2CO_3]	 and/or 	0-29	4
4	80	PPh_3, K_2CO_3, Et_4NCl	 "and double bond isomers"	60-87	5

Table 1. Continued

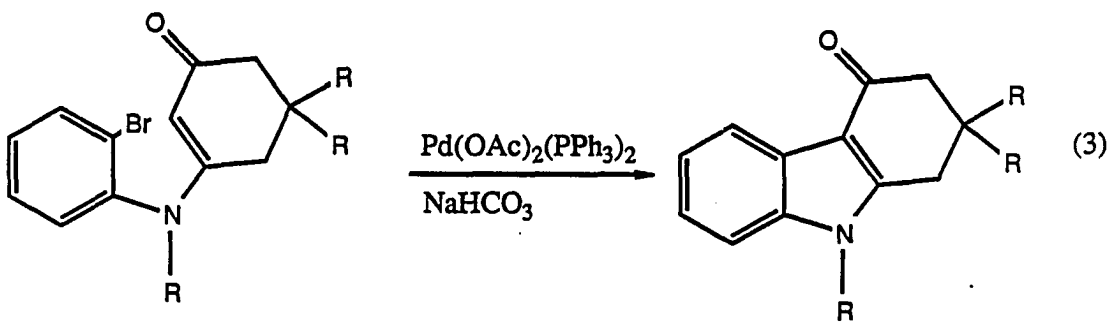
Entry	Substrate	Palladium Source (mol %)	Solvent
5		$Pd(OAc)_2$ (8)	CH_3CN
6[a]		$Pd(OAc)_2$ (5)	CH_3CN
7		$Pd(PPh_3)_4$ (3.5)	THF

[a]Both products were 90-95% cis.

Temp	(°C)	Additional Reagents	Product(s)	% Yield	Ref.
5	25	Ag_2CO_3		55	6
				16	
6	25	Ag_2CO_3		83	6
				3	
7	70	CH_3CN, Et_3N	 "and double bond isomers"	72	7
				8	

palladium(0) complexes were employed, with catalyst ratios reaching as low as one or two mole percent. Though this report at first seems attractive, upon closer examination of the results one finds that the reaction suffers from significant drawbacks. Yields were poor: three of the eight substrates reacted went in yields of 32-36%, and the rest were less than 15%. Reaction temperatures were high: in all cases between 120 and 130°C. Recovery of unreacted starting material was poor as well: with the exception of three substrates mentioned earlier, product yields based on recovered starting material were less than 40%. Finally, the choice of substrates used in the study was such that it is impossible to draw a conclusion as to whether or not isomeric mixtures would be obtained, as each substrate chosen contained a proximate carbonyl which affected the position of the resultant double bond.

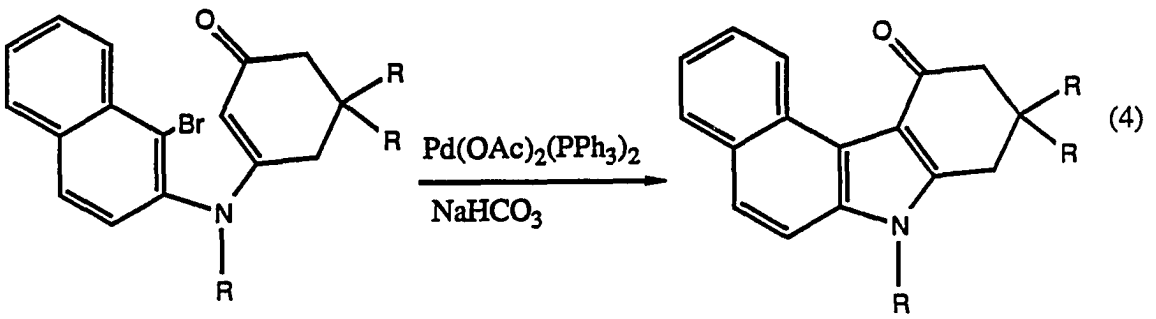
An interesting aspect of this work can be seen from the results shown below (eqs. 3 and 4). Replacement of the



(3)

R = H 9%

R = Et 32%



(4)

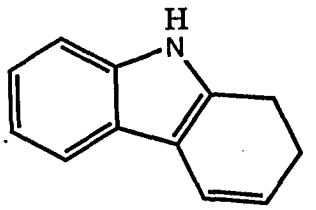
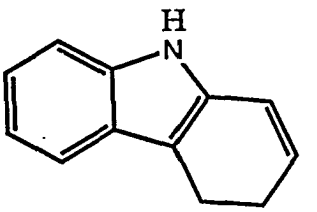
R = H 8%

R = Et 36%

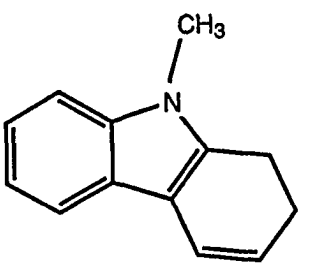
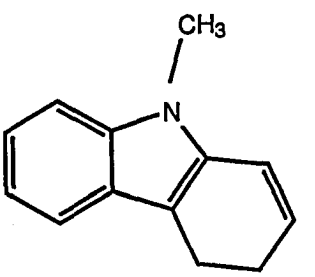
available hydrogens on the aniline nitrogen has a significant positive effect upon the yield. This parallels the results obtained earlier in our intermolecular study, and suggests a possible explanation for the earlier report by Hegedus that 2-iodo-N-(cyclohex-2-enyl)aniline fails to cyclize.

The only other report in the literature at the time our study was undertaken was by a member of our own research group (entry 3).[4] Babu attempted to cyclize the same substrate Hegedus had examined earlier, 2-iodo-N(cyclohex-2-enyl)aniline, as well as the N-methyl derivative. Under most conditions only recovery of the starting material was observed, in yields of 69-76%, and all cases involving the N-methyl derivative either resulted in no isolated products or many products. However, when either sodium acetate or triethylamine were used as the base, a cyclization product was obtained in 29 and 22% yield, respectively. The product

could not be purified and completely characterized, but was found to be one of the two dihydrocarbazoles shown below.

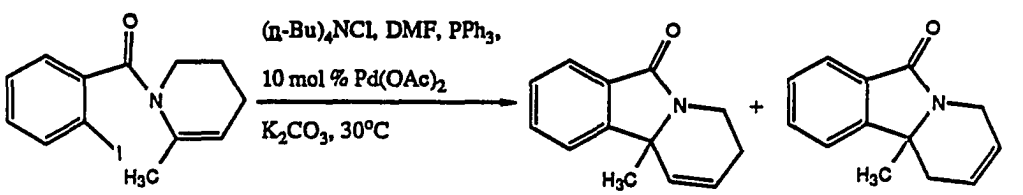
Evidently, dehydrogenation of the product takes place after cyclization. GC/MS analysis of the product mixture from cyclization of the N-methyl derivative indicated that the two major products of the reaction were the dihydrocarbazole and tetrahydrocarbazole shown below (or olefinic isomers of

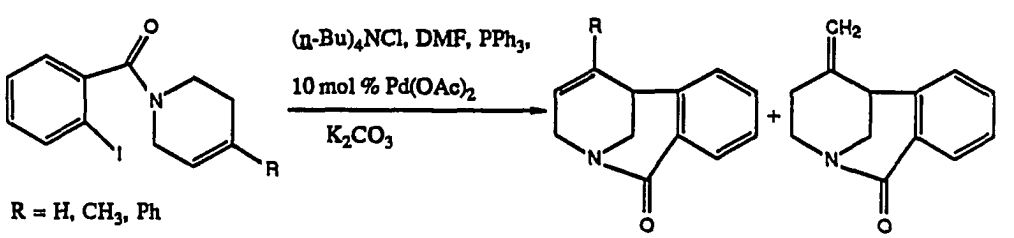
these compounds), though neither compound could be successfully isolated. Thus, yield comparisons of the secondary and tertiary aniline cyclizations cannot be made.

Three additional reports of intramolecular arylpalladation of cycloalkenes appeared at or near the time of our initial publication. The first report, by Grigg et al., appeared in 1986 (entry 4).[5] The authors cyclized 18

different cyclic enamides to form spirocyclic and bridged polycyclic compounds. Notably, di-, tri-, and tetrasubstituted cycloalkenes were each employed with success, although the author noted that double bond isomerization occurs under some conditions. Yields are fair to good, and a catalyst ratio of ten mole percent was required. Unfortunately, only tertiary amides were reported, and so no comparison of reactivity of fully substituted and partially substituted or unsubstituted amides can be made. The two systems most closely related to those in our investigation are shown below (eqs. 5 and 6).



(5)



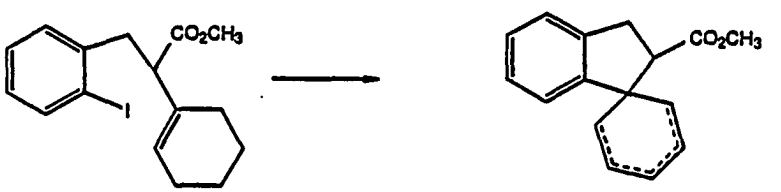
(6)

R = H	30°C	88%	-
R = Ph	80°C	55%	-
R = CH_3	110°C	14%	56%

Abelman and co-workers published a palladium-catalyzed intramolecular arylation procedure in 1987.[6] They studied systems that involved the synthesis of polycyclic compounds with quaternary centers (entries 5 and 6). A wide variety of substrates were employed, including enamides, enanilines, and phenolic alkenes. The only carbocyclic example attempted is shown in entry 2. Isomeric product mixtures were observed in about two-thirds of the cyclizations, although in many cases isomer ratios as high as twenty or thirty to one were obtained. Reactions were performed either at room temperature or at eighty degrees Celsius.

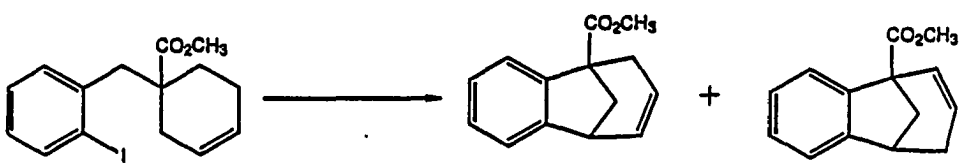
It was found that the addition of silver salts dramatically reduced double bond isomerization in the cyclization products. The authors maintain that this is the result of the silver ion trapping out the hydrohalic acid produced, thus reducing readdition-reelimination of the palladium hydride species and hence double bond isomerization. Each of the following salts were screened to determine the salt most effective at reducing isomerization, and the latter two proved to be the most effective: lead(II) nitrate, cadmium(II) carbonate, barium(II) carbonate, calcium carbonate, sodium carbonate, lithium carbonate, potassium carbonate, silver oxide, silver sulfate, silver trifluoromethanesulfonate, silver nitrate, and silver carbonate.

Negishi and co-workers published a report simultaneous to our own, in which a variety of carbocyclic compounds were prepared by intramolecular cyclization of vinyl and aryl iodides using 3-5 mole percent tetrakis(triphenylphosphine)-palladium as catalyst (entry 7).[7] Yields of approximately 80%, which included ten to thirty percent of the regioisomeric product as well as the desired compound, were reported. All seven reactions were run at eighty degrees Celsius. In addition to the one shown in entry 7, two other aromatic substrates were cyclized; these are shown in equations 7 and 8.



(7)

mixture of 3 - 4 isomers,
80% combined yield

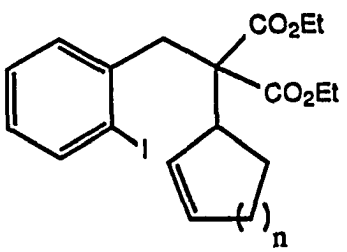


(8)

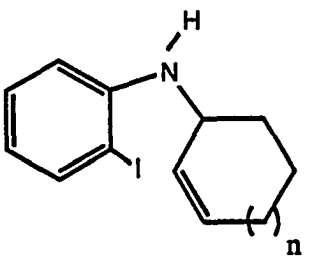
57% 24%

RESULTS AND DISCUSSION

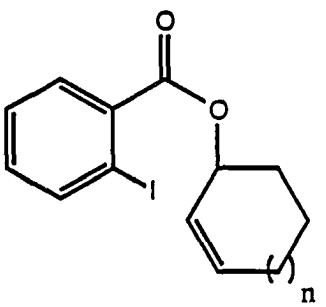
The following compounds 1-14 were considered for cyclization. The preparation of compounds 1-3 involved



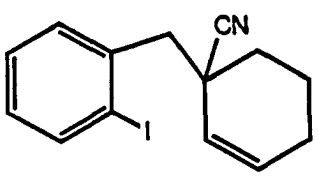
1 n=1
2 n=2
3 n=3



4 n=1
5 n=2



6 n=1
7 n=2



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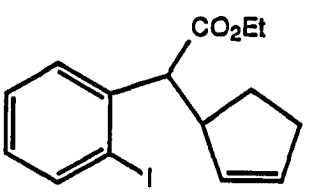
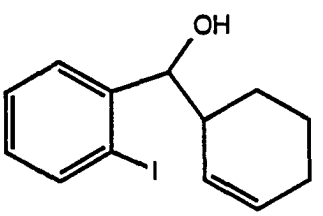
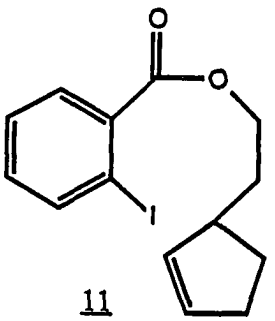


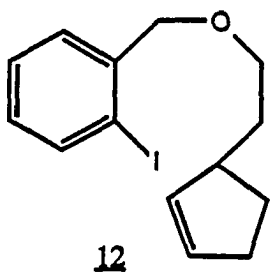
9



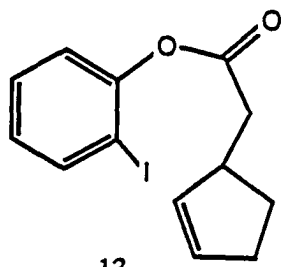
10



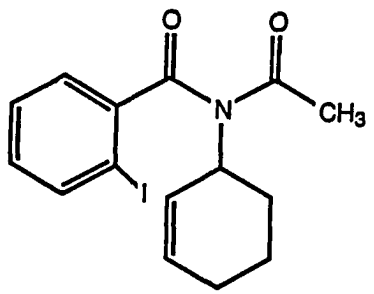
11



12

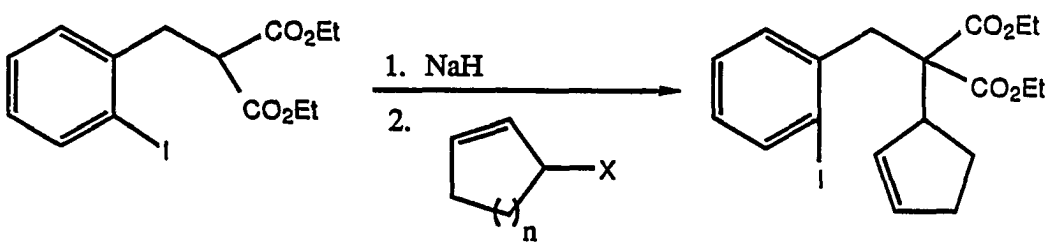


13



14

treatment of diethyl o-iodobenzyl malonate with sodium hydride, followed by quenching with 3-chlorocyclopentene, 3-bromocyclohexene, and 3-bromocycloheptene, respectively (eq. 9). Compounds 4 and 5 were prepared by treatment



(9)

n = 1, R = Cl

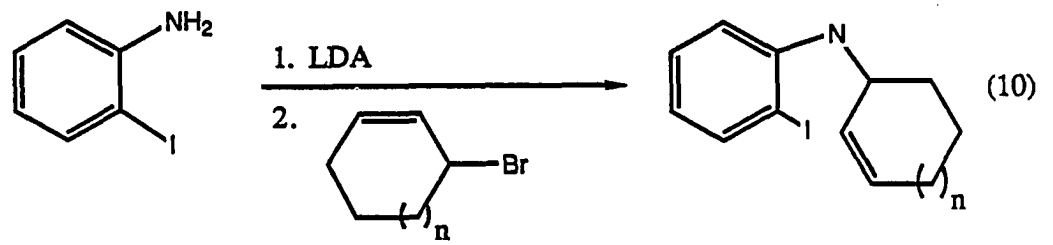
n = 2, 3 R = Br

1 n = 1 78%

2 n = 2 73%

3 n = 3 99%

of o-iodoaniline with lithium diisopropylamide, followed by quenching with 3-bromocyclohexene and 3-bromocycloheptene, respectively (eq. 10). Compounds 6 and 7 were prepared



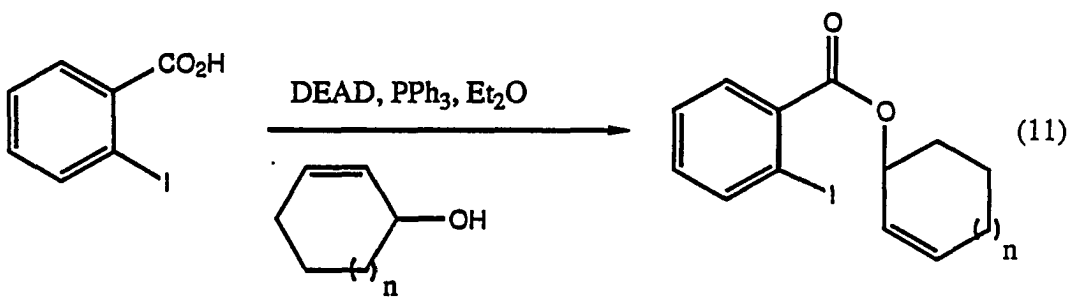
(10)

n = 1, 2

4 n = 1 84%

5 n = 2 84%

by coupling o-iodobenzoic acid with cyclohexen-3-ol and cyclohepten-3-ol, respectively, using triphenylphosphine and diethyl diazodicarboxylate (DEAD) (eq. 11). Compound 8 was



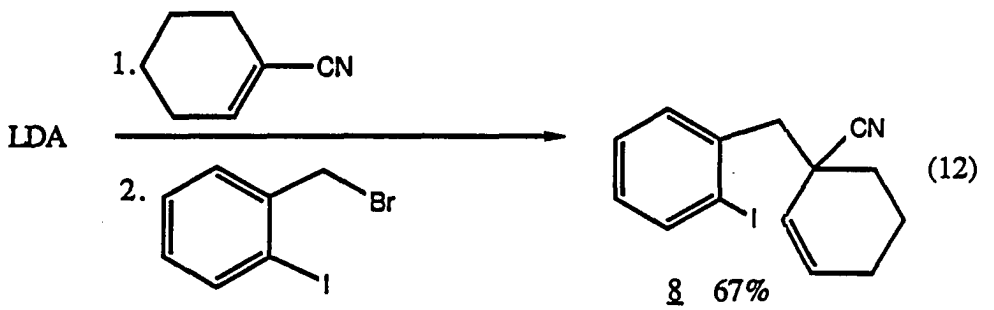
(11)

n = 1, 2

6 n = 1 100%

7 n = 2 47%

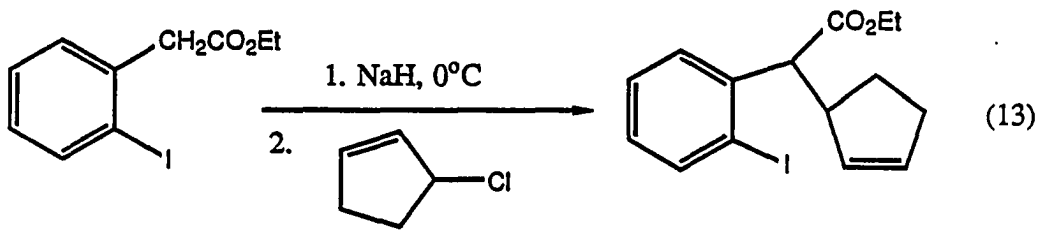
prepared by treating 1-cyanocyclohexene with lithium diisopropylamide to generate an "extended enolate", followed by quenching with o-iodobenzyl bromide (eq. 12). Analogous



(12)

8 67%

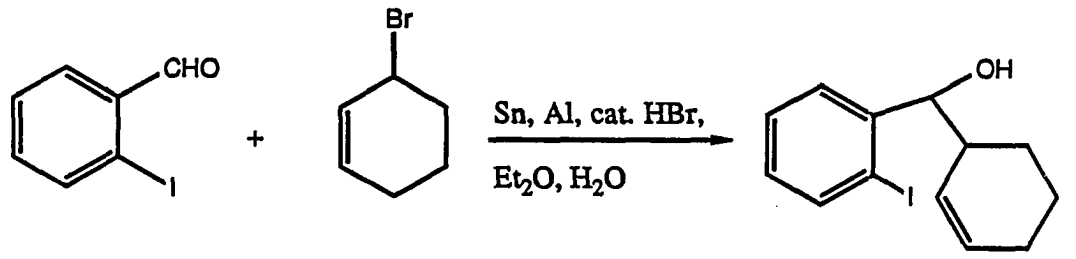
reactions using 1-carboethoxycyclohexene and 1-cyanocyclopentene in place of 1-cyanocyclohexene resulted in mixtures of alpha and gamma alkylation products which were inseparable, and, therefore, not subjected to cyclization. Compound 9 was prepared by treating the ethyl ester of o-iodophenylacetic acid with sodium hydride, followed by quenching with 3-chlorocyclopentene (eq. 13). Compound 10



(13)

9 54%

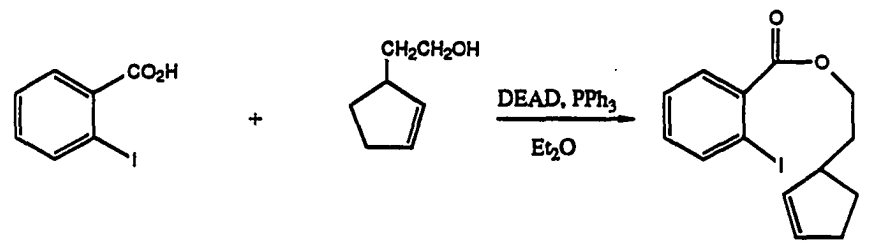
was prepared using the general procedure of Nokami, et al, in poor yield (eq. 14).[8] The starting aldehyde was obtained from oxidation of the corresponding alcohol with pyridinium



(14)

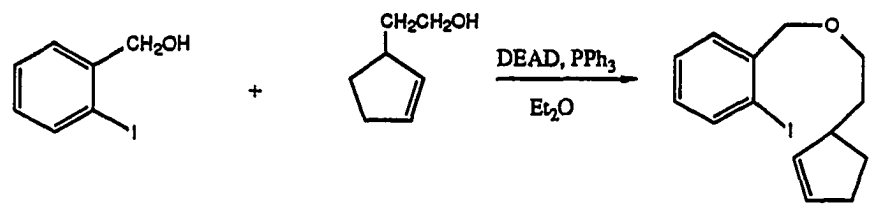
10 17%

chlorochromate (PCC). Compounds 11-13 were prepared by essentially the same method as were compounds 6 and 7, with the poor yield of the ether 12 owing to the fact that neither of the starting alcohols has an acidic hydrogen (eqs. 15-17). A similar coupling reaction using



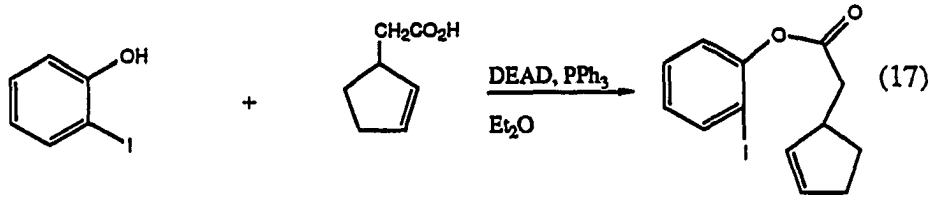
(15)

11 83%



(16)

12 26%

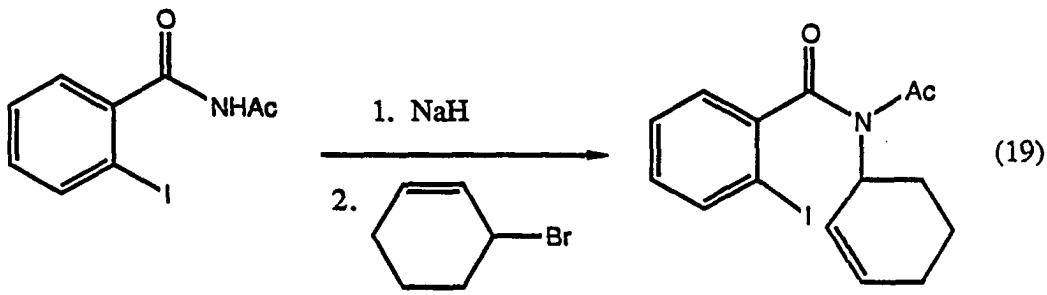


(17)

13 55%

(18)

2-(cyclopent-2-enyl)ethanol and o-iodophenol was unsuccessful (eq. 18). Compound 14 was prepared by acetylation of o-iodobenzamide, followed by treatment with sodium hydride and subsequent quenching with 3-bromocyclohexene (eq. 19).

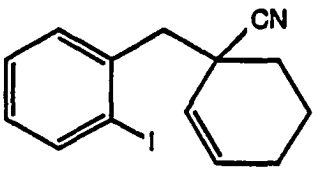
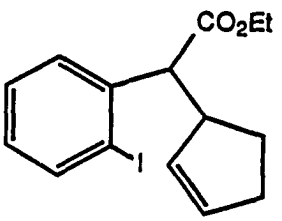


(19)

14 8%

The results of the cyclizations of these compounds are summarized in Tables 2 and 3. Table 2 contains the results for all compounds except 6 and 7, which are in Table 3. In

Table 2. Palladium-catalyzed cyclization of compounds 1-5 and 8-14

Entry	Organic Halide	Procedure[a]	Total % Pd
			
	8		
1		A	3
2		B	4
			
	9		
3		A	3
4		B	4

[a]Procedure A: 0.5 mmol organic halide, 1.0 ml DMF, 2.5 or 3.0 mol % $Pd(OAc)_2$, 0.5 mmol $(n\text{-}Bu)_4NCl$, 1.5 mmol KOAc. Procedure B: 0.5 mmol organic halide, 6.0 ml CH_3CN, 1.0 mmol Ag_2CO_3, 3.0 mol % $Pd(OAc)_2$, 9.0 mol % PPh_3.

[b]Regioisomer ratios, unless otherwise noted, are reported with the allylic isomer indicated on the left and the homoallylic isomer on the right. If no ratio is reported, the product is essentially pure.

Footnotes continue on next page.

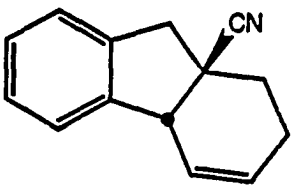
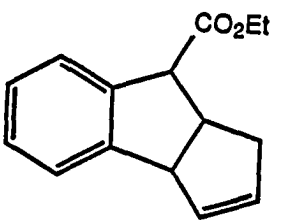
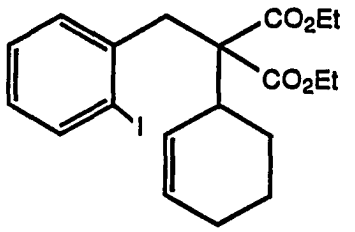
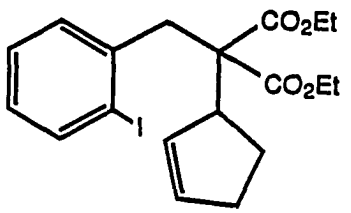
Reaction Conditions	Product[b] (Isomer Ratio)	% Isolated[c] Yield
		
	15	
1d, 25°C	(1.0:5.3)	77
3d, 80°C		62
		
	16	
0.75d, 80°C	(1.0:1.0)	92[d]
3d, 80°C		72[e]

Table 2. Continued

Entry	Organic Halide	Procedure[a]	Total % Pd
			
	2		
5		A	3
6		B	4
			
	1		
7		A	3
8		B	5

[c]All yields refer to chromatographically purified products.

[d]13.0:1.0 diastereomeric ratio.

[e]1.2:1.0 diastereomeric ratio.

[f]Twenty-three percent starting material was recovered from this reaction.

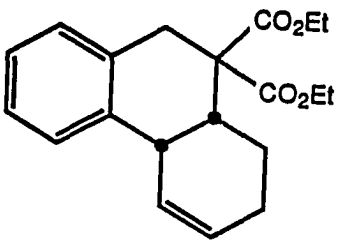
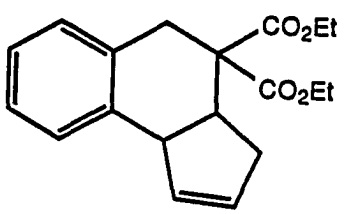
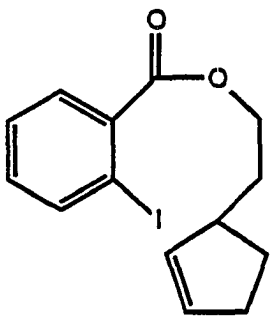
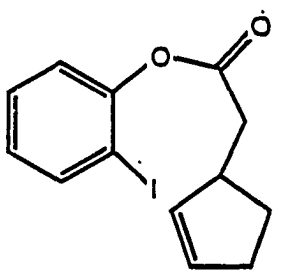
Reaction Conditions	Product[b] (Isomer Ratio)	% Isolated[c] Yield
		
	17	
2d, 80°C	(1.0:5.1)	64
4d, 80°C		72
		
	18	
6d, 25°C	(1.0:1.0)	46[f]
7d, 80°C		61

Table 2. Continued

Entry	Organic Halide	Procedure[a]	Total % Pd
			
	11		
9		A	6
10		B	6
11		A	3
			
	13		
12		A	5
13		B	6
14		A[h]	3

[g]It was not possible to determine the isomer ratio in this reaction.

[h]Triethylamine was used instead of potassium acetate.

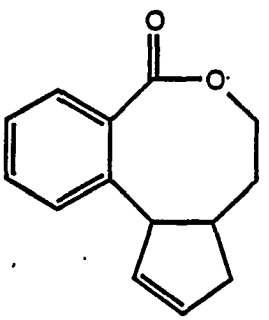
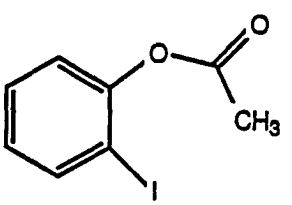
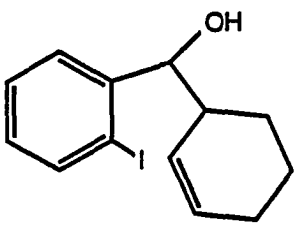
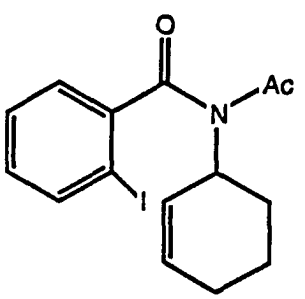
Reaction Conditions	Product[b] (Isomer Ratio)	% Isolated[c] Yield
		
	19	
7d, 25°C	(2 isomers)[g]	15
7d, 80°C		13
3d, 80°C	many products	--
		
	20	
6d, 25°C		11
6d, 80°C	--	--
3d, 80°C	many products	--

Table 2. Continued

Entry	Organic Halide	Procedure[a]	Total % Pd
			
	10		
15		A	4
16		B	10
			
	14		
17		B	5

[i]Two percent starting material was recovered from this reaction. Only one diastereomer was formed, as evidenced by ^{1}H and ^{13}C NMR, but its exact identity could not be determined.

[j]Twenty-three percent starting material was recovered from this reaction. Only one diastereomer was formed, as evidenced by ^{1}H and ^{13}C NMR, but its exact identity could not be determined.

[k]This reaction was run using only 0.37 mmol organic halide, with the amounts of the other reagents adjusted accordingly. Also, it was not possible to determine the ring fusion of this compound.

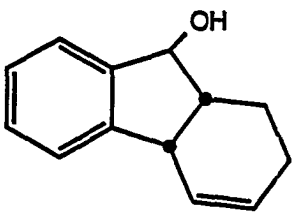
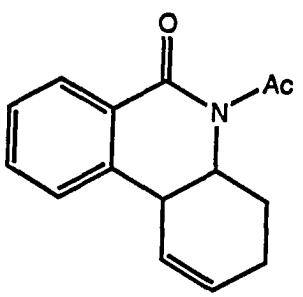
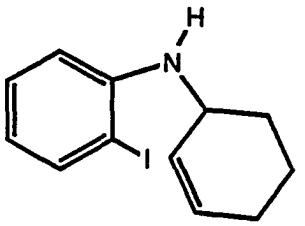
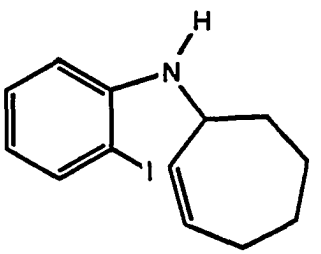
Reaction Conditions	Product[b] (Isomer Ratio)	% Isolated[c] Yield
		
	21	
5d, 25°C	(1.5:1.0)	81[i]
7d, 80°C		73[j]
		
	22	
5d, 80°C		28[k]

Table 2. Continued

Entry	Organic Halide	Procedure[a]	Total % Pd
			
18	4	A	3
19		B	3
			
	5		
20		A	5
21		B	5
22		A	4

[1]The regioisomer ratio in this reaction is as follows: the left number represents the indicated indole, the right number is a roughly (1:1:1) ratio of three other isomers. The indole was isolated separately, in 58% yield (entry 20) and 40% (entry 22).

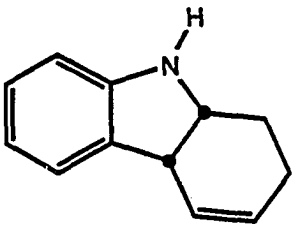
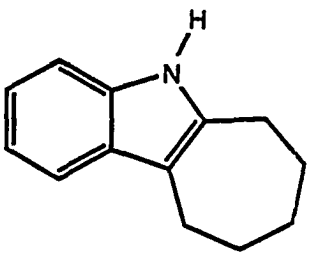
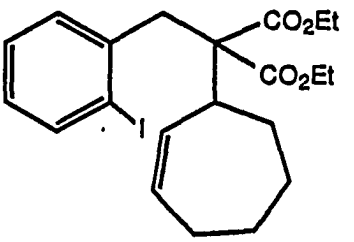
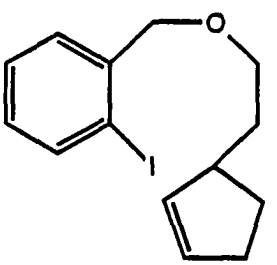
Reaction Conditions	Product[b] (Isomer Ratio)	% Isolated[c] Yield
		
3d, 80°C	<u>23</u>	53
3d, 80°C	--	--
		
	<u>24</u>	
7.5d, 25°C	(2.9:1.0)[1]	78
7.5d, 80°C	--	--
4.5d, 80°C	(1.2:1.0)[1]	73

Table 2. Continued

Entry	Organic Halide	Procedure[a]	Total % Pd
			
	3		
23		A	4
24		B	4
			
25		A	3
26		B	3

[m]The regioisomer ratio in this reaction is as follows: the left number represents the indicated isomer, the right number is a (1:1) ratio of two other isomers. The isomer shown was isolated separately, in 66% yield (entry 23) and 23% yield (entry 24).

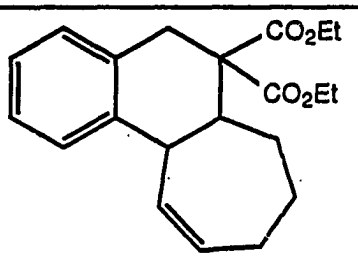
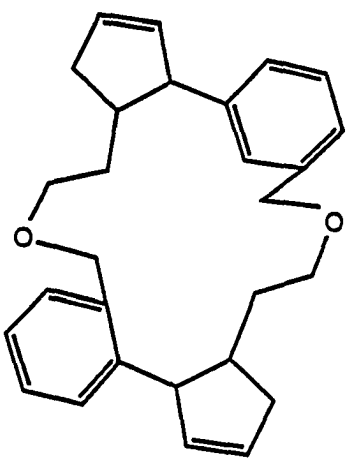
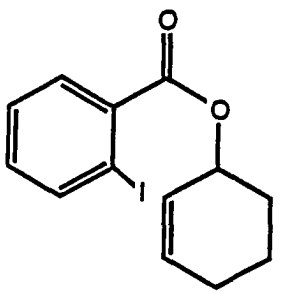
Reaction Conditions	Product[b] (Isomer Ratio)	% Isolated[c] Yield
		
	25	
6d, 80°C	(2.9:1.0)[m]	89
7d, 80°C	(1.8:1.0)[m]	36
		
	26	
1d, 80°C	--	--
2d, 80°C		13

Table 3. Palladium-catalyzed cyclization of compounds 6 and 7

Entry	Organic Halide	Procedure[a]	mmol NaO_2CH
	 6		
1		A	--
2		B	--
3		A	2

[a] Procedure A: 0.5 mmol organic halide, 1.0 ml DMF, 2.5 or 3.0 mol % $Pd(OAc)_2$, 0.5 mmol $(n\text{-}Bu)_4NCl$, 1.5 mmol KOAc. Procedure B: 0.5 mmol organic halide, 6.0 ml CH_3CN, 1.0 mmol Ag_2CO_3, 3.0 mol % $Pd(OAc)_2$, 9.0 mol % PPh_3.

[b] Regioisomer ratios, unless otherwise noted, are reported with the indicated allylic isomer on the left and the homoallylic isomer on the right. If no ratio is reported, the product is essentially pure.

[c] All yields refer to chromatographically purified products.

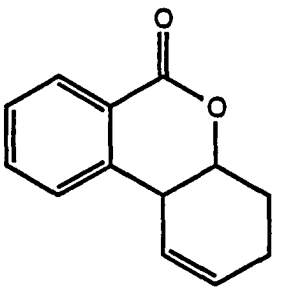
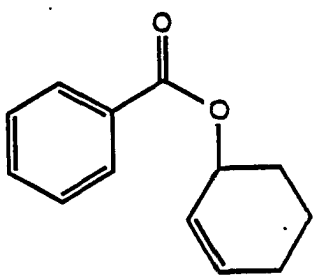
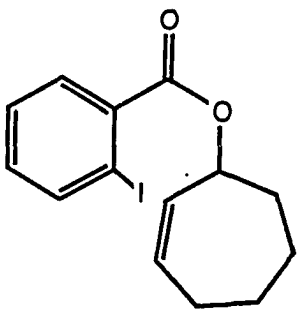
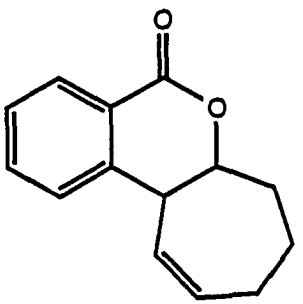
Total % $Pd(OAc)_2$-PPh_3	Reaction Conditions	Product (Isomer Ratio)[b]	% Isolated Yield[c]
			
		27	
4-0	5d, 80°C	(1.0:10.0)	40
4-12	7d, 80°C	(12.0:1.0)	13
			
3-0	2d, 25°C	28	100

Table 3. Continued

Entry	Organic Halide	Procedure[a]	mmol NaO_2CH
4		B	3
5		A	1
6		A	--
7	 7	A	--
8		A	--
9[d]		B	--
10		A	--

[d]Fifty percent of the starting material was recovered from this reaction.

[e]Product was not completely pure, and only partial spectral data on the desired compound were obtained.

Total % $Pd(OAc)_2$-PPh_3	Reaction Conditions	Product (Isomer Ratio)[b]	% Isolated Yield[c]
		27	
3-9	2d, 80°C	(1.0:5.3)	20
3-0	0.25d, 25°C	(1.0:2.5)	37
3-3	1.25d, 80°C	(1.0:3.7)	51
3-9	1.75d, 80°C	(1.0:3.8)	52
			
		29	
4-0	5d, 80°C	many products	--
4-12	7d, 80°C	(2.5:1.0)	27[e]
3-3	4d, 80°C	many products	--

both tables, the product shown is the desired isomer. When mixtures are obtained, the first number presented in the isomer ratio is the illustrated product; the second number is the isomer wherein the double bond has migrated one position away from the arene moiety, unless otherwise noted (entries 20-24).

A number of general conclusions can be drawn from the results in Table 2. First, some comparisons between the two sets of conditions outlined in the previous chapter can be made. Under quaternary ammonium salt conditions, reaction times are typically shorter, and reaction temperatures are the same or lower than when the silver carbonate conditions are employed on the same compound. However, under the former conditions mixtures of regioisomers are obtained, typically favoring the undesired isomer; under the latter conditions, usually only the desired compound is obtained. Product yields are slightly higher under the quaternary ammonium salt conditions, with three exceptions (entries 3-6, 25 and 26), and this procedure tends to work even in cases where the other one does not (entries 12, 13, 18-22). It may be concluded therefore that if a mixture of regioisomers is acceptable (if, for example, the double bond is to be hydrogenated after cyclization), then the quaternary ammonium salt conditions will be more apt to succeed, will proceed in higher yield, and will react under

milder conditions. If, however, the specific regioisomer is required, the silver carbonate conditions will be more apt to provide the isomerically pure product.

Both sets of conditions cyclize onto five, six, and seven membered alkene rings effectively (entries 5-8, 23, and 24). Since all other factors are equal in these trials, they also provide some measure of relative reactivities of the ring sizes under both sets of conditions. Under the quaternary ammonium salt conditions, the observed relative reactivity is five > six > seven; under silver carbonate conditions the observed relative reactivity is six > five > seven.

Another feature of note with respect to these entries is the tendency for isomerization. Five and six membered rings do not yield regioisomeric mixtures under silver carbonate conditions; seven member rings do. This is in concert with our earlier findings from the intermolecular study, wherein it was found that the seven membered alkene ring had the strongest tendency to provide isomeric product mixtures. Interestingly, there is also no observed isomerization when the quaternary ammonium salt conditions was used on compound 4 (entry 18), which contains a six membered alkene ring, but a great deal of isomerization in the corresponding seven membered compound 5 is observed (entries 20, 22).

Given the failure of compounds containing a hydrogen-abstractable moiety on the arene to react in the intermolecular reaction, it is worth noting that this does not seem to be true with the intramolecular reaction (entries 15, 16, 18-22). These reactions do proceed at a slower pace than most, and require more palladium catalyst additions (note that entry 16 requires nearly twice as much total percent palladium catalyst as any other entry in the table), but this may be in part due to the electron-donating effect of these groups, an effect which was also seen in the intermolecular reaction.

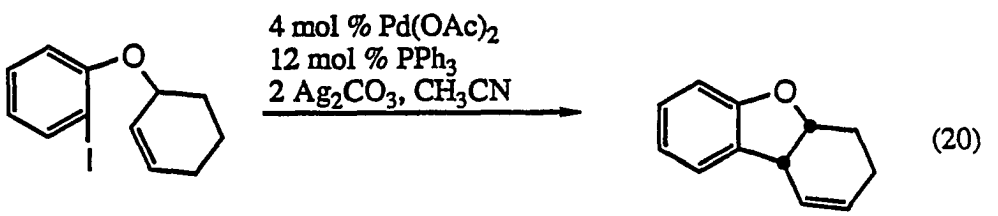
One example each containing a five and six membered alkene ring were attempted in which the presence of a benzylic functional group allowed for the formation of diastereomer as well as regioisomers, and the results obtained for each are quite different. In the first case (entries 3 and 4), the presence of diastereomers is observed: a 1:1 mixture under silver carbonate conditions, and a 13:1 mixture under quaternary ammonium salt conditions. In the other case (entries 15 and 16), however, no evidence of a diastereomeric mixture is found. As these examples are not identical, any number of good explanations can be suggested which might explain this anomaly, and further study is required to determine if this effect is in fact a function of the ring size of the alkene moiety.

As per ring sizes which may be formed by this cyclization, it would appear from the results obtained to date to be limited to the formation of five and six membered rings. The only attempt at forming a seven membered ring (entries 12-14) met with complete failure. A degradation product, o-iodophenyl acetate, was the only recognizable product found (entry 12). Two attempts were made at forming an eight membered ring (entries 9-11, 25 and 26); in the first instance, only small amounts of product were obtained, and in the second case a dimerization took place instead, in poor yield.

The cis or trans nature of the ring fusion is also of interest. In all cases where enough material was obtained to determine whether the ring fusion was cis or trans, and where experimental techniques allowed for a determination to be made, all ring fusions were found to be cis. Only those determined to be cis are drawn as such in the table: the rest are drawn as unspecified.

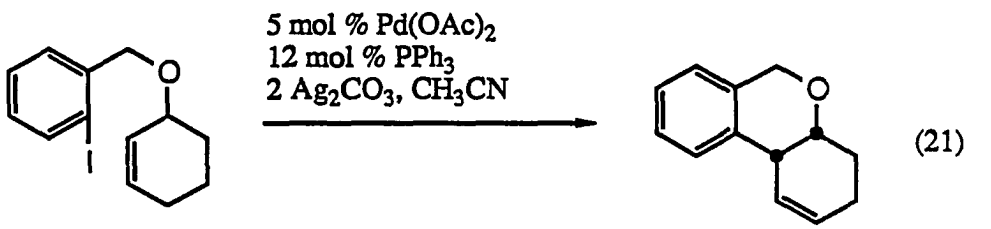
Carbocyclic rings are formed in good yields. While esters 11 and 13 do not cyclize in good yield, as results in Table 3 show, lactone 6 does react in good yield. The addition of sodium formate to the reaction mixture resulted only in deiodination of the starting material; addition of triphenylphosphine under quaternary ammonium salt conditions, did improve the yield of lactone 27, but

decomposition in entries 8 and 10 made it difficult to ascertain whether this effect was general. The imide 14 did not react in good yield under silver carbonate conditions, and too little material was obtained to examine it sufficiently to determine if this result could be improved upon. The only ether attempted, 12, failed primarily because it involved formation of an eight membered ring; from the result obtained, it is anticipated that cyclic ethers can be formed in good yield using this methodology. Recently, two members of our research group have in fact synthesized and cyclized the compounds shown below, and they do in fact proceed in good yield (eqs. 20 and 21). Cyclic



(20)

89%



(21)

73%; (7 : 1)

amines can also be formed using this methodology, as demonstrated by the cyclization of compounds 4 and 5 (entries 18-22). Cyclization of amine 4 yielded the desired tetrahydrocarbazole, which other groups, as mentioned earlier, had failed to obtain. Cyclization of compound 5 yielded cycloheptenoindole as the major product.

Indoles and carbazoles have very diverse biological activity. Skatole, or 3-methylindole, for example, has antidiuretic[9] and tuberculoclastic[10] activity. Likewise, tryptophan, a naturally occurring amino acid and an indole, inhibits the growth of tuberculosis,[11] and indole acetic acid is a major growth hormone.[12] Given the potential importance of a new route to these compounds and the success achieved in the two systems studied, further studies may be undertaken in this area.

CONCLUSION

The palladium-catalyzed intramolecular arylation of cyclic alkenes presented in this part provides a valuable new route to a variety of polycyclic compounds. Lactones, lactams, carbazoles, indoles, and carbocyclic compounds have all been synthesized using this approach, which appears to be most effective in the formation of five and six membered rings. Cyclization onto five, six, and seven membered alkene rings all proceed smoothly, and no interfering functional groups were noted throughout the course of this study.

EXPERIMENTAL SECTION

Equipment

NMR Spectra were recorded on a Nicolet NT-300 (operating at 300 MHz for proton nuclei and 75 MHz for carbon nuclei) spectrometer, or on a Brucker WM-200 spectrometer. Infrared spectra were obtained either on an IBM IR/98 FT-IR spectrophotometer or on a Beckman-42050 spectrophotometer. Mass spectral data were obtained on a Kratos high resolution mass spectrometer. GC/MS data were obtained on a Finnigan MS-50 mass spectrometer. Gas chromatographic analyses were obtained using a Varian 3700 gas chromatograph equipped with a 3% OV-101 on Chromasorb W packed column.

Reagents

All chemicals were used directly as obtained from Aldrich Chemical Co. unless otherwise noted either here or in the previous chapter. Acetyl chloride was purchased from Fisher Chem. Co., and distilled prior to use. 3-Bromocyclohexene was used as purchased from Fluka Chemical Co. Sodium hydride was used as purchased from J. T. Baker Chemical Co. The following compounds were prepared according to previously published procedures: 3-chlorocyclopentene,[13] 3-bromocycloheptene,[14] 2-cyclohepten-1-ol,[15] o-iodobenzyl bromide,[16] 1-cyanocyclohexene,[17] 1-cyanocyclopentene,[16] 1-carboethoxycyclohexene,[18] 2-(2'-cyclopentenyl)-

ethanol,[19] 2-(2'-cyclopentenyl)ethyl methanesulfonate.[19] N-Acetyl o-iodobenzamide, generously supplied by Norman Berrios-Pena, was prepared according to a previously published procedure.[20] The ethyl ester of o-iodophenylacetic acid and o-iodobenzyl malonate, generously provided by Colleen Fried, were each prepared according to literature procedures. The ester was prepared by thallation-iodination of phenylacetic acid,[21] followed by esterification with a catalytic amount of sulfuric acid in ethanol.[22] The malonate was prepared by the general procedure of Ciufolini and Browne, by treating diethyl malonate with sodium hydride and quenching with o-iodobenzyl bromide.[23]

Preparation of Compounds 1-3, 9 and 14

Compounds 1-3, 9 and 14 were prepared, in 78%, 73%, 99%, 54%, and 8% isolated yields, respectively, according to the general procedure of Ciufolini and Browne.[23]

Compound 1

^{1}H NMR ($CDCl_3$) δ 1.00 - 1.12 (dt, 6 H, J = 0.9, 7.2 Hz, CH_3), 1.75 - 1.95 (m, 1 H, aliphatic), 1.95 - 2.13 (m, 1 H, aliphatic), 2.18 - 2.36 (br m, 2 H, aliphatic), 3.33 - 3.44 (s, 2 H, benzylic), 3.44 - 3.57 (br m, 1 H, C=C-CH), 3.92 - 4.21 (m, 4 H, OCH_2), 5.73 - 5.86 (s, 2 H, vinyl), 6.75 - 6.86 (t, 1 H, J = 7.5 Hz, aromatic), 7.12 - 7.22 (t, 1 H, J = 7.5 Hz, aromatic), 7.35 - 7.42 (d, 1 H, J = 7.5 Hz,

aromatic), 7.70 - 7.79 (d, 1 H, J = 7.8 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 13.818, 25.637, 31.954, 41.735, 41.827, 51.107, 61.025, 61.119, 61.946, 103.074, 127.785, 128.088, 130.648, 131.289, 132.551, 139.388, 140.700, 170.439 (C=O), 170.531 (C=O); IR 3018 (C=C), 2980, 1732 (br), 1470 (C-O), 1367, 1190, 1163, 1074, 1038, 1011, 748 cm^{-1}; HRMS calcd for m/z 442.0673, found m/z 442.06412.

Compound 2

^1H NMR ($CDCl_3$) δ 0.73 - 0.85 (m, 1 H, aliphatic), 0.94 - 1.07 (dt, 6 H, J = 15.6, 7.2 Hz, CH_3's), 1.16 - 1.98 (m, 6 H, aliphatic), 2.95 - 3.06 (m, 1 H, C=C-CH), 3.37 - 3.43 (s, 2 H, benzylic), 3.85 - 4.09 (m, 4 H, OCH_2), 5.65 - 5.75 (m, 1 H, C=C<u>H</u>CH), 5.75 - 5.85 (m, 1 H, C=C<u>H</u>CH_2), 6.73 - 6.82 (dt, 1 H, J = 1.5, 7.5 Hz, aromatic), 7.09 - 7.18 (t, 1 H, J = 7.2 Hz, aromatic), 7.34 - 7.41 (dt, 1 H, J = 1.5, 7.8 Hz, aromatic), 7.67 - 7.73 (dd, 1 H, J = 0.9, 8.1 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 13.738, 13.812, 22.477, 24.769, 24.973, 41.457, 41.496, 61.064, 61.100, 62.052, 103.109, 127.766, 127.990, 128.084, 130.587, 139.314, 140.995, 170.146 (C=O), 170.238 (C=O); IR 2980, 2935, 1730 (br), 1470 (C-O), 1248, 1186, 1096, 1076, 1034 cm^{-1}; HRMS calcd for m/z 456.08043, found m/z 456.07977.

Compound 3

^{1}H NMR ($CDCl_3$) δ 1.05 - 1.19 (dt, 6 H, J = 7.2, 18.3 Hz, CH_3), 1.20 - 1.42 (m, 2 H, aliphatic), 1.62 - 1.85 (m, 3 H, aliphatic), 1.95 - 2.05 (m, 1 H, aliphatic), 2.12 - 2.20 (m, 2 H, aliphatic), 3.07 - 3.15 (dd with fine coupling, 1 H, J = 2.7, 10.5 Hz, C=C-CH), 3.35 - 3.42 (d, 1 H, J = 14.4 Hz, benzylic), 3.53 - 3.59 (d, 1 H, J = 14.4 Hz, benzylic), 4.00 - 4.20 (symm m, 4 H, OCH_2), 5.85 - 5.90 (d, 2 H, J = 4.2 Hz, vinylic), 6.80 - 6.90 (dt, 1 H, J = 1.5, 10.8 Hz, aromatic), 7.18 - 7.25 (dt, 1 H, J = 1.2, 7.5 Hz, aromatic), 7.37 - 7.41 (dd, 1 H, J = 1.8, 7.8 Hz, aromatic), 7.75 - 7.81 (dd, 1 H, J = 1.2, 7.8 Hz, aromatic); ^{13}C NMR δ 13.500, 13.616, 25.750, 27.729, 30.168, 31.370, 42.105, 44.277, 60.768, 62.094, 102.896, 127.362, 127.818, 130.450, 131.397, 133.387, 139.037, 140.195, 169.763 (C=O), 170.025 (C=O) (note: missing one aromatic or vinyl peak -- probable overlap); IR 2980, 2930, 1728 (br), 1470 (C-O), 1445 (C-O), 1367, 1298, 1246, 1188, 1043, 1011, 910, 748, 733 cm^{-1}; HRMS calcd for m/z 470.09545, found m/z 470.09542.

Compound 9

^{1}H NMR ($CDCl_3$) δ 1.14 - 1.24 (dt, 3 H, J = 2.4, 7.2 Hz, CH_3), 1.24 - 1.43 (m, 1 H, aliphatic), 1.55 - 1.77 (m, 1 H, aliphatic), 2.09 - 2.50 (m, 3 H, C=C-CH and $C=C-CH_2$), 3.86 - 3.90 (d, J = 10.5 Hz, diastereomeric benzylic), 3.90 - 3.98 (d, J = 10.5 Hz, diastereomeric benzylic), 3.99 - 4.26 (m, 2

H, OCH_2), 5.68 - 5.89 (m, 2 H, vinylic), 6.86 - 6.97 (t, 1 H, J = 7.5 Hz, aromatic), 7.28 (t, 1 H, J = 7.5 Hz, aromatic), 7.48 - 7.51 (dd, 1 H, J = 1.5, 7.8 Hz, aromatic), 7.83 - 7.86 (dd, 1 H, J = 0.6, 7.8 Hz, aromatic); IR 1736 (C=O), 1466 (C-O), 1259, 1225, 1194, 1026, 1011, 746 cm^{-1}; HRMS calcd for m/z 356.02770, found m/z 356.02733.

Compound 14

^1H NMR ($CDCl_3$) δ 1.4 - 2.15 (m, 6 H, aliphatic), 2.20 (s, 3 H, $COCH_3$), 4.6 (br s, 1 H, NCH), 5.52 - 5.56 (m, 1 H, C=C<u>H</u>CH), 5.65 - 5.70 (m, 1 H, C=C<u>H</u>CH_2), 7.01 - 7.08 (dt, 1 H, J = 1.2, 15.3 Hz, aromatic), 7.16 - 7.22 (dd, 1 H, J = 1.5, 13.5 Hz, aromatic), 7.30 - 7.36 (dt, 1 H, J = 0.6, 15.9 Hz, aromatic), 7.76 - 7.79 (d, 1 H, J = 7.8 Hz, aromatic); ^{13}C NMR δ 22.103, 23.900, 27.085, 27.751 (aliphatics), 55.531 (<u>C</u>HN), 92.007, 127.458, 127.718, 128.110, 128.189, 131.069, 139.702, 142.091 (vinyls and aromatics), 172.725 (C=O), 173.154 (C=O); IR 1693 (C=O), 1670 (C=O), 1394, 1367, 1333, 1234, 1161, 1030, 1016, 775, 750, 631 cm^{-1}; HRMS calcd for m/z 369.02271, found m/z 369.02258.

Preparation of Compounds <u>4</u> and <u>5</u>

Compounds <u>4</u> and <u>5</u> were prepared, each in 84% isolated yield, according to the method of Odle, et al.[2]

Compound 4

^{1}H NMR ($CDCl_3$) δ 0.81 - 0.94 (m, 1 H, $CH_2C\underline{H}_2CH_2$), 1.24 - 1.36 (m, 1 H, $CH_2C\underline{H}_2CH_2$), 1.58 - 1.80 (m, 2 H, $CH_2C\underline{H}_2CH$), 2.00 - 2.18 (m, 2 H, C=C-CH), 3.96 - 4.06 (br s, 1 H, N<u>H</u>), 4.14 - 4.22 (m, 1 H, NCH), 5.70 - 5.80 (m, 1 H, C=C<u>H</u>CH), 5.85 - 5.95 (m, 1 H, C=C<u>H</u>CH_2), 6.35 - 6.46 (dt, 1 H, J = 1.2, 7.5 Hz, aromatic), 6.57 - 6.66 (dd, 1 H, J = 1.2, 7.5 Hz, aromatic), 7.13 - 7.22 (dt, 1 H, J = 1.2, 7.5 Hz, aromatic), 7.61 - 7.69 (dd, 1 H, J = 1.2, 7.5 Hz, aromatic); IR 3393 (NH), 3067 (aromatic), 3029 (C=C), 2935, 2860, 1587, 1501, 1450, 1425, 1313, 1279, 1171, 1090, 1005, 741, 727 cm^{-1}; HRMS calcd for m/z 299.01726, found m/z 299.01720.

Compound 5

^{1}H NMR ($CDCl_3$) δ 0.76 - 2.20 (m, 8 H, aliphatic), 3.95 - 4.06 (br s, 1 H, NH), 4.10 - 4.23 (s with fine coupling, 1 H, CHN), 5.50 - 5.62 (dd with fine coupling, 1 H, J = 1.2, 14.4 Hz, C=C<u>H</u>CH_2), 6.25 - 6.35 (dt, 1 H, J = 1.2, 7.5 Hz, aromatic), 6.38 - 6.45 (dd, 1 H, J = 0.6, 8.4 Hz, aromatic), 7.05 - 7.10 (dt, 1 H, J = 0.9, 7.8 Hz, aromatic), 7.50 - 7.58 (dd, 1 H, J = 1.5, 7.8 Hz, aromatic); ^{13}C NMR δ 26.589, 28.513, 33.516, 54.190, 65,780, 111.297, 118.272, 129.161, 131.748, 133.521, 136.568, 138.999, 146.099; IR 3584, 3391 (NH), 3065 (C=C), 3018 (aromatic), 2922, 1587, 1502, 1450, 1425, 1315, 1281, 1082, 1003, 739 cm^{-1}; HRMS calcd for m/z 313.03284, found m/z 313.03275.

Preparation of Compounds 6, 7, 11 and 13

Compounds 6, 7, 11 and 13 were prepared in 100%, 47%, 83%, and 55% isolated yields, respectively, according to the general procedure of Mitsonobu.[24]

Compound 6

^{1}H NMR ($CDCl_3$) δ 1.55 - 2.25 (m, 6 H, aliphatic), 5.40 - 5.50 (dd with fine coupling, 1 H, J = 1.5, 3.3 Hz, OCH), 5.75 - 5.82 (dddd, 1 H, J = 2.1, 2.1, 3.6, 8.4 Hz, C=CHCH), 5.90 - 6.00 (dt, 1 H, J = 3.6, 9.9 Hz, C=CHCH$_2$), 7.00 - 7.10 (dt, 1 H, J = 1.5, 9.0 Hz, aromatic), 7.25 - 7.35 (dt, 1 H, J = 7.6, 0.9 Hz, aromatic), 7.65 - 7.71 (dd, 1 H, J = 1.5, 7.8 Hz, aromatic), 7.85 - 7.90 (dd, 1 H, J = 0.9, 8.4 Hz, aromatic); ^{13}C NMR δ 18.864, 24.917, 28.286, 69.623 (OCH), 93.822, 125.206, 127.771, 130.744, 32.277, 133.106, 135.785, 141.074, 166.231 (C=O); IR 2941, 1720 (C=O, sharp), 1583, 1286, 1250, 1132, 1099, 1042, 1015, 912, 743, 681, 665 cm^{-1}; HRMS calcd for m/z 327.99563, found m/z 327.99603.

Compound 7

^{1}H NMR ($CDCl_3$) δ 1.37 - 1.46 (m, 1 H, aliphatic), 1.64 - 2.40 (m, 7 H, aliphatic), 5.62 - 5.73 (d with fine coupling, 1 H, J = 8.7 Hz, OCH), 5.73 - 5.96 (m, 2 H, vinylic), 7.08 - 7.18 (t with fine coupling, 1 H, J = 7.5 Hz, aromatic), 7.35 - 7.44 (t with fine coupling, 1 H, J = 7.5 Hz, aromatic), 7.73 - 7.83 (d with fine coupling, 1 H, J = 7.8 Hz,

aromatic), 7.93 - 8.02 (d with fine coupling, 1 H, J = 7.8 Hz, aromatic); ^{13}C NMR δ 26.617, 28.858, 31.598, 32.762 (aliphatics), 75.825 (OCH), 93.907, 127.809, 130.751, 131.959, 132.373, 133.021, 139.692, 141.162 (aromatics and vinyls), 165.930 (C=O); IR 3064 (C=C), 3030 (aromatic), 2928, 2856, 1724 (C=O), 1583, 1464 (C-O), 1445 (C-O), 1323, 1286, 1256, 1134, 1101, 1043, 1016, 975, 784, 743, 682, 638 cm^{-1}; HRMS calcd for m/z 342.01167, found m/z 342.01168.

Compound 11

^{1}H NMR ($CDCl_3$) δ 1.40 - 1.55 (dddd, 1 H, J = 6.6, 6.6, 9.0, 12.9 Hz, aliphatic), 1.65 - 1.83 (dddd, 1 H, J = 6.9, 6.9, 6.9, 14.1 Hz, $OCH_2C\underline{H}_2$), 1.83 - 2.00 (dddd, 1 H, J = 6.9, 6.9, 6.9, 13.5 Hz, $OCH_2C\underline{H}_2$), 2.00 - 2.20 (ddt, 1 H, J = 5.1, 17.4, 8.4 Hz, aliphatic), 2.20 - 2.50 (m, 2 H, $C=C-CH_2$), 2.75 - 3.00 (m, 1 H, C=C-CH), 4.25 - 4.50 (m, 2 H, OCH_2), 5.60 - 5.73 (m, 1 H, $C=C\underline{H}CH$), 5.73 - 5.80 (m, 1 H, $C=C\underline{H}CH_2$), 7.05 - 7.20 (dt, 1 H, J = 1.8, 7.5 Hz, aromatic), 7.33 - 7.50 (dt, 1 H, J = 0.9, 7.5 Hz, aromatic), 7.70 - 7.85 (dd, 1 H, J = 1.8, 7.8 Hz, aromatic), 7.90 - 8.01 (dd, 1 H, J = 0.9, 7.8 Hz, aromatic); ^{13}C NMR δ 29.697, 31.902, 34.549, 42.283, 64.614 (OCH_2), 93.919, 127.749, 130.704, 130.994, 132.368, 133.932, 135.333, 141.128, 166.451 (C=O); IR 2951, 2849, 1728 (C=O), 1583, 1464 (C-O), 1429 (C-O), 1288, 1250, 1134, 1105, 1043, 1016, 741, 721, 638 cm^{-1}; HRMS calcd for m/z 342.01149, found m/z 342.01168.

Compound 13

^{1}H NMR ($CDCl_3$) δ 1.38 - 1.67 (m, 1 H, aliphatic), 2.07 - 2.55 (m, 3 H, aliphatic and C=C-CH_2), 2.54 - 2.75 (dddd, 2 H, J = 3.9, 15.4, 15.4, 15.4 Hz, $COCH_2$), 3.20 - 3.36 (m, 1 H, C=C-CH), 5.64 - 5.76 (m, 2 H, vinylic), 6.90 - 6.97 (dt, 1 H, J = 1.0, 7.5 Hz, aromatic), 7.76 - 7.82 (d, 1 H, J = 7.8 Hz, aromatic); ^{13}C NMR δ 29.731, 31.818, 40.361, 41.757, 90.410 (aromatic C with ester), 122.949, 127.374, 129.238, 131.723, 133.301, 139.253, 151.073 (other aromatics and vinyls), 170.236 (C=O); IR 2937, 1763 (C=O), 1466 (C-O), 1441 (C-O), 1258, 1231, 1175, 1121, 1036, 1018, 754, 729, 642 cm^{-1}; HRMS calcd for m/z 327.99600, found m/z 327.99603.

Preparation of Compound 8

Compound 8 was prepared in 67% isolated yield, according to the general procedure of Cargill, Bushey, and Good.[25]

Compound 8

^{1}H NMR ($CDCl_3$) δ 1.75 - 1.90 (m, 3 H, aliphatic), 2.00 - 2.15 (m, 3 H, aliphatic), 3.10 - 3.15 (d, 1 H, J = 13.8 Hz, benzylic), 3.18 - 3.24 (d, 1 H, J = 13.8 Hz, benzylic), 5.54 - 5.58 (d with fine coupling, 1 H, J = 9.75 Hz, C=CHC(CN)), 5.91 - 5.97 (dt, 1 H, J = 3.7, 9.9 Hz, C=C<u>H</u>CH_2), 6.93 - 6.99 (dt, 1 H, J = 1.8, 7.65 Hz, aromatic), 7.32 - 7.37 (dt, 1 H, J = 0.9, 7.5 Hz, aromatic), 7.53 - 7.56 (dd, 1 H, J = 1.8, 7.8 Hz, aromatic), 7.86 - 7.89 (dd, 1 H, J = 1.2, 8.1 Hz,

aromatic); ^{13}C NMR δ 19.150, 24.451 (C-CN), 32.771, 38.569 (C=C-C), 47.923 (PhC-CH_2), 122.771 (C≡N), 102.849, 125.628, 128.969, 129.009, 130.868, 131.678, 138.941, 139.927 (aromatics and vinyls); IR 3028 (aromatic), 2933, 2864, 2835, 2229 (C≡N), 1647, 1585, 1562, 1465, 1447, 1435, 1389, 1346, 1321, 1267, 1231, 1201, 1184, 1163, 1120, 1047, 1012, 989, 960, 872, 762, 741, 698, 669, 648 cm^{-1}; HRMS calcd for m/z 323.01681, found m/z 323.01710.

Preparation of Compound 10

Compound 10 was prepared in 17% isolated yield, according to the general procedure of Nokami et al.[8]

Compound 10

^1H NMR ($CDCl_3$) δ 0.80 - 0.95 (m, 1 H, aliphatic), 1.40 - 1.55 (m, 2 H, aliphatic), 1.73 - 1.83 (m, 1 H, aliphatic), 1.90 - 1.95 (d, 1 H, J = 2.7 Hz, OH), 1.96 - 2.10 (m, 2 H, allylic), 2.60 - 2.75 (m, 1 H, CHOH-CH-C=C), 4.85 - 4.95 (dd, 1 H, J = 3.6, 6.0 Hz, CHOH), 5.45 - 5.55 (dd with fine coupling, 1 H, J = 2.1, 9.9 Hz, vinylic closest to OH), 5.75 - 5.90 (dq with fine coupling, 1 H, J = 10.5, 3.0 Hz, vinylic furthest from OH), 6.90 - 7.00 (dt, 1 H, J = 7.8, 1.8 Hz, aromatic), 7.30 - 7.40 (dt, 1 H, J = 7.5, 1.2 Hz, aromatic), 7.45 - 7.52 (dd, 1 H, J = 1.8, 7.8 Hz, aromatic), 7.79 - 7.83 (dd, 1 H, J = 1.2, 7.8 Hz, aromatic); ^{13}C NMR δ 21.180, 22.597, 25.037, 40.855, 65.675, 98.163, 127.895,

127.993, 128.044, 128.823, 130.625, 139.007, 144.172; IR 3414 (OH), 3020 (aromatic), 3018 (aromatic), 2930, 2860, 1462 (C-O), 1435 (C-O), 1074, 1009, 885, 758, 735, 692 cm^{-1}; HRMS calcd for m/z 314.01684, found m/z 314.01677.

Preparation of Compound 12

Compound 12 was prepared in 26% isolated yield, by treating o-iodobenzyl alcohol with sodium hydride at 0°C in THF, stirring for 30 minutes, followed by quenching by dropwise addition of 2-(2'-cyclopentenyl)ethyl methanesulfonate.

Compound 12

^1H NMR ($CDCl_3$) δ 1.38 - 1.56 (m, 1 H, aliphatic), 1.60 - 1.73 (m, 1 H, aliphatic), 1.73 - 1.88 (apparent heptet, 1 H, J = 3.6 Hz, aliphatic), 2.01 - 2.16 (m, 1 H, aliphatic), 2.19 - 2.44 (m, 2 H, $C=C-CH_2$), 2.74 - 2.91 (m, 1 H, C=C-CH), 3.57 - 3.65 (t, 2 H, J = 6.9 Hz, OCH_2), 4.49 (s, 2 H, benzylic), 5.65 - 5.77 (m, 2 H, vinylic), 6.92 - 7.02 (dt, 1 H, J = 1.5, 7.5 Hz, aromatic), 7.30 - 7.40 (dt, 1 H, J = 0.9, 7.5 Hz, aromatic), 7.44 - 7.50 (d, 1 H, J = 7.5 Hz, aromatic), 7.81 - 7.83 (d, 1 H, J = 7.8 Hz, aromatic); ^{13}C NMR δ 29.732, 29.968, 31.942, 35.945, 42.535, 69.809, 97.634, 128.129, 128.575, 128.955, 130.447, 134.776, 139.056, 140.826; IR 3053 (aromatic), 2926, 2853, 1566, 1462

(C-O), 1437 (C-O), 1377, 1121, 1045, 746, 719, 656 cm^{-1}; HRMS calcd for m/z 328.03243, found m/z 328.03242.

Cyclization of Compounds 1-14

The cyclization reactions were run using the procedures listed in Tables 2 (see footnote a) and 3 (see footnote a). Any variation from the procedure is noted in the table in which it appears. The following compounds were obtained from the cyclization reactions.

Compound 15

^1H NMR ($CDCl_3$) δ 1.55 - 1.70 (ddd, 1 H, J = 4.8, 11.4, 13.2 Hz, aliphatic), 1.88 - 1.96 (ddd, 1 H, J = 3.0, 4.8, 13.5 Hz, aliphatic), 2.00 - 2.13 (d with fine coupling, 1 H, J = 18.3 Hz, allylic), 2.30 - 2.47 (m, 1 H, allylic), 3.01 - 3.07 (d, 1 H, J = 15.6 Hz, benzylic), 3.51 - 3.57 (d, 1 H, J = 15.9 Hz, benzylic), 4.0 (br s, 1 H, methine), 5.90 - 6.00 (m, 1 H, C=C<u>H</u>CH), 6.07 - 6.17 (m, 1 H, C=C<u>H</u>CH_2), 7.17 - 7.30 (br s with fine coupling, 4 H, aromatic); ^{13}C NMR δ 21.976, 27.956, 39.373, 43.202, 43.202, 49.033, 123.831, 124.031, 124.992, 125.544 (C≡N), 127.189, 127.350, 127.473, 138.032, 142.853; IR 3028, 2926, 2851, 2235 (CN), 1479, 1460, 1440, 762, 741, 720, 700 cm^{-1}; HRMS calcd for m/z 195.10470, found m/z 195.10480.

Compound 16

Major Diastereomer ^{1}H NMR ($CDCl_3$) δ 1.28 - 1.33 (t, 1 H, J = 7.2 Hz, CH_3), 2.27 - 2.38 (dddd, 1 H, J = 2.4, 2.4, 4.8, 17.1 Hz, aliphatic), 2.73 - 2.84 (dddd, 1 H, J = 2.1, 4.2, 8.6, 16.8 Hz, aliphatic), 3.45 - 3.60 (m, 1 H, $C\underline{H}CHCO_2Et$), 4.10 - 4.25 (m, 1 H, C=C-C$\underline{H}$), 4.10 - 4.30 (m, 2 H, OCH_2) 4.27 - 4.29 (d, 1 H, J = 3.9 Hz, $CHCO_2Et$), 5.65 - 5.71 (ddd, 1 H, J = 2.1, 4.5, 5.6 Hz, C=C$\underline{H}$CH), 5.76 -5.85 (ddd, 1 H, J = 2.1, 4.2, 5.7 Hz, C=C$\underline{H}CH_2$), 7.06 - 7.26 (m, 4 H, aromatic).

Minor Diastereomer ^{1}H NMR ($CDCl_3$) δ 1.28 - 1.34 (t, 1 H, J = 7.2 Hz, CH_3), 2.08 - 2.20 (dddd, 1 H, J = 2.4, 4.8, 7.1, 17.0 Hz, aliphatic), 2.47 - 2.59 (dddd, 1 H, J = 2.1, 2.1, 9.6, 17.4 Hz, aliphatic), 3.45 - 3.60 (m, 1 H, $C\underline{H}CHCO_2Et$), 3.81 - 3.84 (d, 1 H, J = 5.1 Hz, $C\underline{H}CO_2Et$), 4.10 - 4.30 (m, 2 H, OCH_2), 4.25 - 4.40 (m, 1 H, C=C-CH), 5.63 - 5.73 (m, 1 H, C=C$\underline{H}$CH), 5.96 - 6.02 (m, 1 H, C=C$\underline{H}CH_2$), 7.06 - 7.26 (m, 4 H, aromatic).

For Mixture ^{13}C NMR δ 14.314, 35.170, 39.305, 44.187, 44.728, 46.299, 52.291, 55.603, 57.014, 57.654, 60.400, 60.795, 123.981, 124.231, 124.948, 126.503, 126.642, 126.724, 127.499, 127.604, 127.832, 129.578, 131.158, 132.101, 138, 798, 139.835, 144.751, 145.074, 172.811 (C=O), 173.902 (C=O); IR 3051 (aromatic), 2966, 2932, 1734 (C=O),

1720 (C=O), 1178 cm^{-1}; HRMS calcd for m/z 228.11493, found m/z 228.11503.

Compound 17

^{1}H NMR ($CDCl_3$) δ 1.08 - 1.14 (t, 3 H, J = 7.2 Hz, CH_3), 1.25 - 1.31 (t, 3 H, J = 7.2 Hz, CH_3), 1.45 - 1.60 (m, 1 H, aliphatic), 1.75 - 2.20 (m, 3 H, aliphatic), 2.82 - 2.94 (dd with fine coupling, 1 H, J = 3.9, 12.9 Hz, $CHC(CO_2Et)_2$), 3.25 - 3.31 (d, 1 H, J = 1.7 Hz, benzylic), 3.35 - 3.42 (d, 1 H, J = 16.8 Hz, benzylic), 3.69 - 3.79 (br s, 1 H, C=C-CH), 4.04 - 4.12 (q, 2 H, J = 7.2 Hz, OCH_2), 4.20 - 4.28 (q, 2 H, J = 7.2 Hz, OCH_2), 5.76 - 5.85 (m, 1 H, C=C<u>H</u>CH), 6.17 - 6.28 (m, 1 H, C=C<u>H</u>CH_2), 7.02 - 7.16 (m, 4 H, aromatic); ^{13}C NMR δ 13.841, 14.049, 21.458, 25.571, 30.390, 35.588, 36.889, 57.613, 61.295 (OCH_2), 61.436 (OCH_2), 125.468, 126.371, 127.125, 127.633, 128.824, 128.998, 131.845, 137.533, 170.158 (C=O), 170.413 (C=O); IR 2970, 2932, 1734 (C=O), 1254, 1232, 1180, 1045 cm^{-1}; HRMS calcd for m/z 328.16772, found m/z 328.16747.

Compound 18

^{1}H NMR ($CDCl_3$) δ 0.95 - 1.00 (t, 3 H, J = 6.9 Hz, CH_3), 1.23 - 1.31 (dt, 3 H, J = 0.9, 7.2 Hz, CH_3), 2.21 - 2.32 (m, 1 H, aliphatic), 2.41 - 2.51 (m, 1 H, aliphatic), 3.17 (s, 2 H, benzylic), 3.52 - 3.61 (dd, 1 H, J = 8.7, 17.7 Hz, $CHC(CO_2Et)_2$), 3.91 - 4.00 (q, 2 H, J = 7.2 Hz, OCH_2), 4.18 -

4.28 (dq, 2 H, J = 1.2, 6.9 Hz, OCH_2), 4.28 - 4.35 (m, 1 H, C=C-CH), 5.60 - 5.64 (m, 1 H, C=C<u>H</u>CH), 5.71 - 5.74 (m, 1 H, C=C<u>H</u>CH_2), 7.04 - 7.15 (m, 4 H, aromatic); ^{13}C NMR δ 13.789, 14.015, 31.186, 34.513, 39.119, 48.979, 57.493, 61.117 (OCH_2), 61.373 (OCH_2), 125.595, 126.327, 127.795, 128.220, 129.060, 132.073, 134.723, 138.370, 170.569 (C=O), 170.803 (C=O); IR 2932, 2914, 1734 (C=O), 1715 (C=O), 1256, 1229, 1182, 1061, 733 cm^{-1}; HRMS calcd for m/z 314.15187, found m/z 314.15181.

<u>Compound 19</u>

<u>Isolated as a mixture of two isomers</u> ^1H NMR ($CDCl_3$) δ 1.22 - 2.93 (m, 11 H, aliphatic), 4.25 - 4.42 (m, 4 H, OCH_2), 4.50 - 4.57 (t, 1 H, J = 6.6 Hz, C=C-CH-Ar), 5.50 - 5.55 (m, 1 H, vinylic), 5.65 - 5.80 (m, 2 H, vinylic), 5.85 - 5.95 (m, 1 H, vinylic), 7.00 - 7.45 (m, 6 H, aromatic), 7.75 - 7.81 (m, 1 H, aromatic), 7.90 - 8.04 (m, 1 H, aromatic).

<u>Compound 20</u>

^1H NMR ($CDCl_3$) δ 2.36 (s, 3 H, $COCH_3$), 6.90 - 7.00 (dt, 1 H, J = 1.5, 7.5 Hz, aromatic), 7.07 - 7.15 (dd, 1 H, J = 1.5, 7.8 Hz, aromatic), 7.32 - 7.40 (dt, 1 H, J = 1.5, 7.5 Hz, aromatic), 7.80 - 7.84 (dd, 1 H, J = 1.5, 7.8 Hz, aromatic); HRMS calcd for m/z 261.94880, found m/z 261.94910.

Compound 21

^{1}H NMR ($CDCl_3$) δ 1.5 - 1.9 (m, 3 H, aliphatic and OH), 2.0 - 2.1 (br s, 2 H, allylic), 2.45 - 2.55 (m, 1 H, C(OH)C<u>H</u>), 3.76 - 3.86 (m, 1 H, C=C-CH), 4.95 - 5.00 (d, 1 H, J = 4.5 Hz, C<u>H</u>OH), 5.70 - 5.80 (m, 1 H, C=C<u>H</u>-CH_2), 5.80 - 5.95 (m, 1 H, CH-C<u>H</u>=C), 7.20 - 7.30 (m, 3 H, aromatic), 7.35 - 7.45 (d, 1 H, J = 6.6 Hz, aromatic); ^{13}C NMR δ 22.338, 42.209, 47.802, 76.578, 78.633 (CHOH), 124.321, 124.918, 126.957, 127.202, 127.918, 128.659, 143.480; IR 3327 (OH), 3022, 2922, 1475 (C-O), 1458 (C-O), 1053, 1020, 910, 754, 735, 683 cm^{-1}; HRMS calcd for m/z 186.10475, found m/z 186.10447.

Compound 22

^{1}H NMR ($CDCl_3$) δ 1.42 - 1.67 (m, 1 H, aliphatic), 1.70 - 1.85 (m, 1 H, aliphatic), 2.04 - 2.20 (m, 1 H, allylic), 2.25 - 2.40 (m, 1 H, allylic), 2.68 (s, 3 H, $COCH_3$), 3.73 - 3.81 (m, 1 H, C=CCH), 4.89 - 5.00 (ddd, 1 H, J = 3.0, 5.6, 9.3 Hz, NCH), 5.87 - 5.95 (m, 1 H, C=C<u>H</u>CH), 6.21 - 6.29 (m, 1 H, C=C<u>H</u>CH_2), 7.28 - 7.66 (m, 4 H, aromatic); IR 1691 (C=O), 1398, 1367, 1283, 1242, 1074, 1030, 797, 760, 731, 660 cm^{-1}; HRMS calcd for m/z 241.11021, found m/z 241.11028.

Compound 23

^{1}H NMR ($CDCl_3$) δ 1.88 - 1.92 (t, 1 H, J = 5.7 Hz, aliphatic), 1.85 - 1.92 (m, 3 H, aliphatic), 3.30 - 3.45 (m,

2 H, C=C-CH and NH), 4.15 - 4.22 (d with fine coupling, 1 H, J = 8.1 Hz, C<u>H</u>NH), 5.60 - 5.70 (d with fine coupling, 1 H, J = 10.0 Hz, C=C<u>H</u>CH), 5.85 - 5.98 (m, 1 H, C=C<u>H</u>CH_2), 6.64 - 6.67 (d, 1 H, J = 7.8 Hz, aromatic), 6.73 - 6.78 (dt, 1 H, J = 0.6, 7.5 Hz, aromatic), 7.01 - 7.06 (t, 1 H, J = 7.8 Hz, aromatic), 7.08 - 7.11 (d, 1 H, J = 7.2 Hz, aromatic); ^{13}C NMR δ 26.567, 28.470, 33.478, 54.146, 85.800, 111.288, 118.246, 129.140, 131.706, 136.529, 138.977, 146.065; IR 3391 (NH), 3065 (aromatic), 3018 (C=C), 2922, 1587, 1504, 1450, 1425, 1317, 1281, 1005, 741, 689, 650 cm^{-1}; HRMS calcd for m/z 171.10480, found m/z 171.10498.

<u>Compound 24</u>

^{1}H NMR ($CDCl_3$) δ 1.72 - 1.86 (m, 6 H, aliphatic), 1.86 - 1.98 (m, 4 H, allylic), 7.05 - 7.15 (m, 2 H, aromatic), 7.22 - 7.29 (dt, 1 H, J = 4.5, 3.3 Hz, aromatic), 7.57 - 7.69 (br s, 1 H, NH), 7.45 - 7.53 (t, 1 H, J = 4.5 Hz, aromatic); ^{13}C NMR δ 24.879, 27.542, 28.558, 28.736, 31.798, 110.120, 113.708, 117.587, 118.966, 120.569, 129.278, 134.297, 137.321; IR 3391 (NH), 3053 (aromatic), 3028 (C=C), 2914, 2838, 2245, 1663, 1466, 1439, 1317, 1279, 1007, 908, 739 cm^{-1}; HRMS (M^{+}) calcd for m/z 185.11994, found m/z 185.12045; HRMS (M^{-1}) calcd for m/z 184.11271, found m/z 184.11262.

Compound 25

^{1}H NMR ($CDCl_3$) δ 1.04 - 2.55 (m, 7 H, aliphatic), 1.23 - 1.37 (t, 6 H, J = 7.1 Hz, CH_3's), 3.21 - 3.26 (m, 2 H, benzylic), 3.85 - 4.34 (m, 5 H, OCH_2's and C=C-CH), 5.66 - 5.81 (ddd, 1 H, J = 1.8, 4.5, 10.8 Hz, C=C<u>H</u>-CH), 5.81 - 5.95 (m, 1 H, C=C<u>H</u>-CH_2), 6.96 - 7.24 (m, 4 H, aromatic); ^{13}C NMR δ 13.754, 14.105, 28.179, 31.574, 33.867, 39.052, 42.857, 48.214, 60.466 (O-C), 61.343 (O-C), 125.564, 126.984, 128.282, 128.543, 132.106, 133.263, 139.058, 140.576 (aromatics and vinyls), 169.727 (C=O), 172.056 (C=O); IR 3020 (C=C), 2980, 2932, 2854, 1728 (C=O, br), 1445 (C-O), 1367, 1258, 1234, 1184, 1117, 1074, 748 cm^{-1}; HRMS calcd for m/z 342.18265, found m/z 342.18312.

Compound 26

HRMS calcd for m/z 400.23963, found m/z 400.24024.

Compound 27

Allylic Isomer ^{1}H NMR ($CDCl_3$) δ 1.80-2.00 (m, 1 H, aliphatic), 2.00 - 2.50 (m, 3 H, aliphatic), 3.52 - 3.60 (d, 1 H, J = 2.4 Hz, C=C-CH), 4.92 - 4.98 (t with fine coupling, 1 H, J = 4.5 Hz, OCH), 5.40 - 5.50 (d with fine coupling, 1 H, J = 10.2 Hz, C=C<u>H</u>CH), 5.80 - 5.90 (m, 1 H, C=C<u>H</u>CH_2), 7.25 - 7.33 (d, 1 H, J = 7.8 Hz, aromatic), 7.35 - 7.45 (dt, 1 H, J = 1.2, 7.8 Hz, aromatic), 7.55 - 7.65 (dt, 1 H, J = 1.5, 7.5 Hz, aromatic), 8.07 - 8.22 (dd, 1 H, J = 0.9, 7.2 Hz,

aromatic); IR 3050 (aromatic), 2961, 2349, 1724 (C=O), 1605, 1458, 1360, 1273, 1244, 1121, 1088, 1022, 800 cm^{-1}; HRMS calcd for m/z 200.08338, found m/z 200.08373.

Homoallylic Isomer ^1H NMR ($CDCl_3$) δ 1.65 - 2.15 (m, 2 H, ArCH-C$\underline{H}_2$), 2.15 - 2.35 (m, 1 H, OCHC$\underline{H}_2$), 2.45 - 2.50 (s with fine coupling, 1 H, OCHC$\underline{H}_2$), 2.85 - 3.00 (ddd, 1 H, J = 3.0, 6.3, 13.2 Hz, ArCH), 4.70 - 4.80 (dd, 1 H, J = 3.0, 6.0 Hz, OCH), 5.60 - 5.70 (ddd, 1 H, J = 3.0, 6.0, 13.2 Hz, C=C$\underline{H}$CH_2CHAr), 5.70 - 5.80 (ddd, 1 H, J = 2.4, 4.8, 9.9 Hz, C=C$\underline{H}$CH_2CHO), 7.15 - 7.25 (d, 1 H, J = 7.2 Hz, aromatic), 7.28 - 7.40 (dt, 1 H, J = 1.2, 7.5 Hz, aromatic), 7.42 - 7.55 (dt, 1 H, J = 1.2, 7.5 Hz, aromatic), 8.00 - 8.06 (d, 1 H, J = 7.8 Hz, aromatic); ^{13}C NMR δ 28.514 (allylic), 29.911 (allylic), 35.440 (benzyl), 74.944 (OCH), 122.659, 122.800, 124.181, 125.619, 127.658, 130.646, 133.597 (aromatics and vinyls), 145.022 (aromatic with C=O attached), 165.825 (C=O); IR 3032 (C=C), 2920, 1722 (C=O), 1657, 1605, 1460 (C-O), 1269, 1231, 1115, 1088, 1026, 758, 700, 660 cm^{-1}; HRMS calcd for m/z 200.08338, found m/z 200.08373.

Compound 28

^1H NMR ($CDCl_3$) δ 1.65 - 2.20 (m, 6 H, aliphatic), 5.45 - 5.55 (dddd, 1 H, J = 2.1, 3.6, 3.6, 6.6 Hz, OCH), 5.80 - 5.90 (dddd, 1 H, J = 2.18, 2.1, 3.6, 9.9 Hz, C=C$\underline{H}$CH_2), 5.95 - 6.10 (ddt, 1 H, J = 0.9, 9.9, 3.6 Hz, C=C$\underline{H}$CH), 7.40 - 7.46 (m, 2 H, aromatics meta to carbonyl), 7.50 - 7.60 (tt, 1 H,

J = 1.2, 7.5 Hz, aromatic para to carbonyl), 8.01 - 8.08 (m, 2 H, aromatic ortho to carbonyl); ^{13}C NMR δ 18.98 ($CH_2\underline{C}H_2CH_2$), 24.98 ($\underline{C}H_2CH$), 28.45 ($\underline{C}H_2C{=}C$), 68.57 (OCH), 125.73, 128.10, 128.21, 129.50, 129.56, 130.80, 132.68, 132.75 (aromatics and vinyls), 166.15 (C=O); IR 2937, 2868, 1715 (C=O), 1452 (C-O), 1337, 1313, 1271, 1177, 1111, 1070, 1051, 918, 710 cm^{-1}; GC/MS shows only one peak, with a mass at m/e 202 ($C_{13}H_{14}O_2$).

Compound 29

^1H NMR ($CDCl_3$) δ 1.40 - 2.30 (m, 6 H, aliphatic), 3.92 - 4.00 (s with fine coupling, 1 H, Ar$\underline{C}H$-C=C), 4.60 - 4.75 (ddd, 1 H, J = 3.6, 3.6, 7.2 Hz, OCH), 5.30 - 5.50 (dd, 1 H, J = 5.1, 11.4 Hz, ArCH$\underline{C}H$=C), 5.95 - 6.08 (dddd, 1 H, J = 1.8, 6.3, 6.3, 12.0 Hz, C=$\underline{C}HCH_2$), 7.25-7.32 (m, 1 H, aromatic), 7.35-7.43 (dt, 1 H, J = 0.9, 7.5 Hz, aromatic), 7.50-7.62 (dt, 1 H, J = 1.5, 7.5 Hz, aromatic), 8.05-8.12 (dd, 1 H, J = 0.9, 7.5 Hz, aromatic).

REFERENCES

1. (a) Heck, R. F. "Palladium Reagents in Organic Synthesis," Academic Press Inc., New York, 1985. (b) Heck, R. F. Org. Reactions 1982, 27, 345. (c) Tsuji, J. "Organic Synthesis with Palladium Compounds," Springer-Verlag, New York, 1980.

2. Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. J. Org. Chem. 1980, 45, 2709.

3. Iida, H.; Yuasa, Y.; Kibayashi, C. J. Org. Chem. 1980, 45, 2938.

4. Babu, S., Ph.D. Thesis, Iowa State University, 1987.

5. Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. J. Chem. Soc., Chem. Commun. 1986, 1697.

6. Abelman, M. M.; Oh, T.; Overman, L. E. J. Org. Chem. 1987, 52, 4133.

7. Negishi, E.; Zhang, Y.; O'Connor, B. Tetrahedron Lett. 1988, 29, 2915.

8. Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. Organometallics 1983, 2, 191.

9. Erspamer, V. Nature (London) 1952, 170, 281.

10. Abdel Kader, M. M.; Zaki, O.; Shams El Din Moustafa, M. Jpn J. Tuberc. 1961, 9, 65; Chem. Abstr. 1962, 57, 6555h.

11. (a) Abdel Kader, M. M.; Zaki, O. Experientia 1958, 14, 455. (b) Abedel Kader, M. M.; Zaki, O. Jpn J. Tuberc. 1960, 8, 1; Chem. Abstr. 1961, 55, 5663b.

12. Leopold, A. C. In "The Hormones", Pincus, G.; Thimann, K. V.; Astwood, E. B., Eds.; Academic Press: New York, 1964; Vol. 4, pp 1-66.

13. Moffett, R. B. Org. Synth., Coll. Vol. IV 1963, 238.

14. Vogel, A. "Vogel's Textbook of Practical Organic Chemistry", 4th ed.; Longman Group Limited: London, 1978; pp 400-402.

15. Luche, J.-L. J. Am. Chem. Soc. 1978, 100, 2226.

16. Hooz, J.; Gilani, S. S. H. Can. J. Chem. 1968, 46, 86.

17. Ruzicka, L.; Brugger, W. Helv. Chim. Acta 1926, 9, 319.

18. Vogel, A. "Vogel's Textbook of Practical Organic Chemistry", 4th ed.; Longman Group Limited: London, 1978, pp 513-514.

19. Song, H., Ph.D. Thesis, Iowa State University, 1988.

20. Polya, J. B.; Spotswood, T. M. Rec. Trav. Chim. 1948, 67, 927.

21. McKillop, a.; Hunt, J. D.; Zelesko, M. J.; Fowler, J. S.; Taylor, E. C.; McGillivray, G.; Kienzle, F. J. Am. Chem. Soc. 1971, 93, 4841.

22. Harrison, L. W., Ph.D. Thesis, Iowa State University, 1984.

23. Ciufolini, M. A.; Browne, M. E. Tetrahedron Lett. 1987, 28, 1171.

24. Mitsonobu, O. Synthesis 1981, 1.

25. Cargill, R. L.; Bushey, D. F.; Good, J. J. Tetrahedron Lett. 1973, 2433.

GENERAL SUMMARY

In the first section of this work, the topic of asymmetric organic photochemistry was explored. The concept of a chiral electron-transfer sensitizer, which when used would generate optically active products from molecules with a prochiral center, was tested. Results from the model system developed indicated that while the reaction continued to be effectively sensitized by the modified sensitizer, no chiral recognition was observed. The quantum yield for photoracemization of 1,3-diphenylallene was determined to be 0.30 ± 0.02. This result represents the first absolute measurement of allene π-bond rotation in the literature, and raises some doubt about the previous assumption in the literature that all absorbed light in allenes not accounted for by either the formation of photoproducts or fluorescence goes to the degenerate interconversion of enantiomers. Partial photoresolution of 1,3-diphenylallene with circularly polarized light (CPL) has also been observed, and this result represents the first literature report of simple CPL photoresolution.

In the second section of this work both the intermolecular and intramolecular palladium-catalyzed allylic arylation of cyclic alkenes was explored, and a general synthetic method for this transformation was established. In cases where isomerization of the double

bond was particularly difficult to control, a different procedure involving the use of silver carbonate was found to eliminate isomerization in almost every case.

In the intermolecular study, olefin ring sizes of five to eight members all worked well, and both electron-donating and electron-withdrawing substituents are permissible on the aromatic iodide, although in the former case higher temperatures are required. Activated aryl bromides were found to react at higher temperatures; aryl trifluoromethanesulfonates were found to be unreactive.

In the intramolecular study, the general result appears to be that the conditions using the quaternary ammonium salt are faster and work under comparatively milder conditions, but typically afford isomeric, product mixtures. The conditions utilizing silver carbonate typically provide isomerically pure product, but are more sluggish and require the addition of phosphines and higher temperatures. Both sets of conditions are effective primarily in cyclizations which form five and six membered rings, and alkene rings of five to seven members functioned well in these cyclizations. Both heterocyclic and carbocyclic rings can be formed using this general procedure.

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