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Palladium-Catalyzed Intermolecular Arylation of Functionally-Substituted Cycloalkenes by Aryl Iodides

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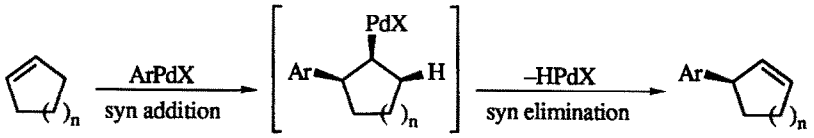
Abstract The palladium-catalyzed, intermolecular arylation of functionally-substituted cycloalkenes by aryl iodides affords a new synthetic route to a variety of arylated cyclic derivatives. The arylation of 2-cyclopenten-1-ol and 2-cyclo-hexen-1-ol provides modest yields of the corresponding 3-arylcycloalkanones, while 2-methyl-2-cyclo-penten-1-ol affords a mixture of singly and doubly arylated cyclopentanone products. 1-Acetoxycyclopentene undergoes arylation to produce the corresponding allylic aryl substitution product opening up a new route for the α-arylation of cycloalkanones. Cyclic allylic ethers undergo arylation at both ends of the C-C double bond to generate mixtures of singly arylated vinylic ethers. 1-Cyanocyclopentene reacts with aryl iodides under palladium catalysis to produce 1-cyano-5-arylcyclopentenes in high yield. 2-Methyl-2-cycloalken-1-ones afford modest yields of doubly arylated 2-cycloalken-1-ones in a single step.

INTRODUCTION

The intermolecular[1] allylic arylation of *cyclic* alkenes has been effected using palladium reagents and arylmercurials,[2] arylstannanes,[3] aryl diazonium salts,[4] aryl amines (plus nitrites),[5] aryl sulfinate salts,[6] and aryl[7] or heterocyclic[8] halides (eq 1). The arylmercury, arylstannane and aryl sulfinate reactions require stoichiometric



(1)

amounts of palladium, while coupling of the aryl diazonium salts or amines can be effected catalytically. These reactions commonly afford only low yields of mixtures of double bond regioisomers.

Clearly aryl halides are the most attractive starting materials, because they are readily available and require only catalytic amounts of palladium. Although earlier procedures employing aryl halides utilized elevated temperatures and produced isomeric mixtures, we recently reported procedures based on the use of 2.5 mol % $Pd(OAc)_2$, *n*-Bu_4NCl, and acetate bases in the presence or absence of 2.5% PPh_3, which allow these intermolecular reactions to be run at room temperature or 80 °C, accommodate a wide range of important organic functional groups, and give isomerically pure products.[9] In those examples where double bond isomerization

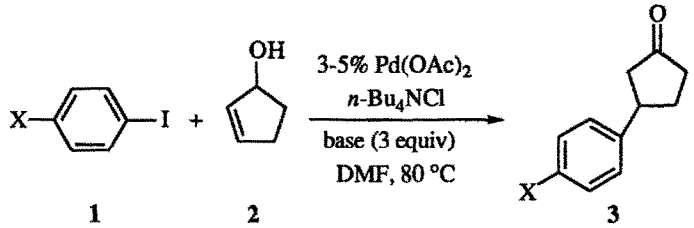
proved to be a problem, we observed that the use of 3-4% $Pd(OAc)_2$, 2 equiv of Ag_2CO_3, and 9 mol % PPh_3 in acetonitrile at 80 °C[1b,1c,9b,10] proved beneficial.

While there are several examples of the successful palladium-promoted arylation of cyclic alkenes bearing a heteroatom in the ring[2j,3,7b-d,9-12] and of carbocyclic rings bearing functional groups being arylated by arylmercurials,[2c,2d,2g,2h,2k] there are few examples in the literature of the palladium-catalyzed arylation of the latter cycloalkenes using aryl halides. Only the palladium-catalyzed arylation of 2-cyclohexen-1-ol by 2-bromothiophene[8] and 2-cyclopenten-1-ol silyl ether by iodobenzene and *p*-iodoanisole,[7e] and the conjugate addition of 2-cyclohexen-1-one by iodobenzene[13] have been reported. Although these earlier examples have given low yields of products, this type of process appears particularly promising for the preparation of a wide variety of aryl-substituted cyclic substrates, so we have undertaken a survey of this process using a variety of functionally-substituted cycloalkenes.

RESULTS AND DISCUSSION

Allylic alcohols

With others' previous success in the arylation[14] of cyclic allylic alcohols using phenyl[2c] and ferrocenyl[2g] mercurials and 2-bromothiophene,[8] we initiated our efforts by looking at the arylation of 2-cyclopenten-1-ol (**2**) by iodobenzene (**1a**) (eq 2). Our results are summarized in Table I, entries 1-11.



(2)

1 **2** **3**

a X = H
b X = OMe
c X = CO_2Et

The nature of the base and the stoichiometry appeared to be the most important factors in achieving a high yield of 3-phenylcyclopentanone (**3a**). Potassium acetate was vastly superior to sodium acetate, potassium carbonate or sodium carbonate as a base (compare entries 2 and 8-10), all of which failed to give any of the desired ketone. Triethylamine gave similar results to KOAc (compare entries 1 and 6). The addition of 5 mol % PPh_3 to the reaction generally appears to improve the overall yield, especially with Na_2CO_3 as the base (compare entries 3 and 4, 6 and 7, and 10 and 11). However, PPh_3 tends to slow down the overall reaction rate. The most dramatic improvement in yield came about when KOAc in the absence of PPh_3 was employed and a temperature of 60 °C was utilized, rather than 80°C (Table I, entry 5). A very nice 88% isolated yield of ketone **3a** could be obtained in only 16 h. This reaction provides a useful new route to 3-phenylcyclopentanone.[15]

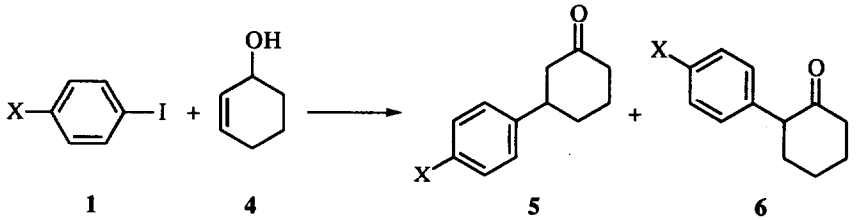
Results with substituted aryl iodides proved disappointing. Similar reactions employing *p*-iodoanisole (Table I, entries 12-16) and ethyl *p*-iodobenzoate (Table I, entries 17-20) gave much lower yields. Some slight improvement in yield was evident using acetonitrile as the solvent, but the reactions took much longer to reach completion.

Table I. Palladium-catalyzed Arylation of 2-Cyclopenten-1-ol (2) (eq. 2)

Entry	Aryl iodide	Equiv of 2	Equiv of 1	% $Pd(OAc)_2$	Base (3 equiv)	Solvent	Reaction time (d), Temp. (°C)	% Isolated yield of 3
1	**1a**	1.5	1	3	KOAc	DMF	3, 80	40
2	**1a**	2	1	3	KOAc	DMF	3, 80	55
3	**1a**	1	1.5	5	KOAc	DMF	2, 80	36
4[a]	**1a**	1	2	5	KOAc	DMF	2, 80	61
5	**1a**	1	2	5	KOAc	DMF	0.67, 60	88
6	**1a**	1.5	1	3	Et_3N	DMF	3, 80	40
7[a]	**1a**	2	1	5	Et_3N	DMF	1.5, 80	55
8	**1a**	2	1	3	NaOAc	DMF	3, 80	0
9	**1a**	2	1	3	K_2CO_3	DMF	3, 80	0
10	**1a**	2	1	3	Na_2CO_3	DMF	3, 80	0
11[a]	**1a**	2	1	5	Na_2CO_3	DMF	6, 80	52
12	**1b**	2	1	5	KOAc	DMF	1.5, 60	32
13	**1b**	2	1	5	KOAc	CH_3CN	3, 60	37
14	**1b**	2	1	5	KOAc	CH_3CN	3, 60	53[b]
15	**1b**	1	2	5	KOAc	DMF	1.2, 60	40
16	**1b**	1	2	5	KOAc	CH_3CN	3, 60	45
17	**1c**	2	1	5	KOAc	DMF	1.5, 60	34
18	**1c**	2	1	5	KOAc	CH_3CN	5, 60	37
19[b]	**1c**	2	1	5	KOAc	CH_3CN	5, 60	34
20	**1c**	1	2	5	KOAc	CH_3CN	5, 60	43

[a]5 mol % PPh_3 added. [b]The amount of solvent was doubled.

The arylation of 2-cyclohexen-1-ol was next examined and contrary to previous work on the arylation of 2-cyclohexen-1-ols,[2c,2g,8] we have observed the formation of both 3-phenylcyclohexanone (**5a**)[15d,16] and 2-phenylcyclohexanone (**6a**) in the reaction of 2-cyclohexen-1-ol and iodobenzene (eq 3). A variety of reaction conditions have been examined in an attempt to optimize the yield and the isomer ratio. The results are summarized in Table II.



(3)

1 **4** **5** **6**

a X = H
b X = OMe
c X = CO_2Et

Table II. Palladium-catalyzed Arylation of 2-Cyclohexen-1-ol (**4**) (eq. 3)

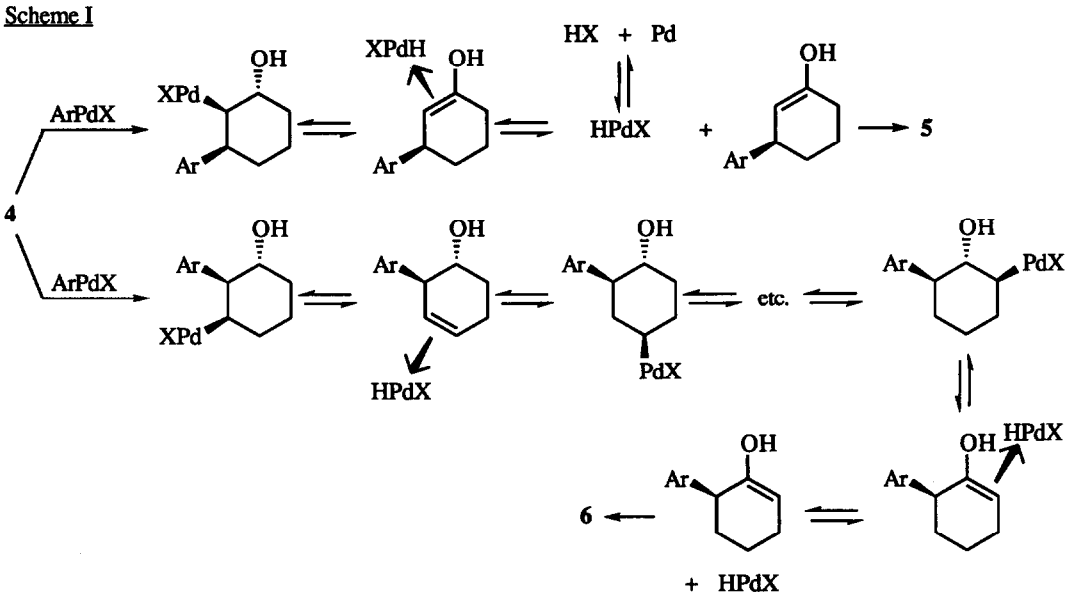
Entry	Aryl iodide	Equiv of **4**	Equiv of **1**	Base (3 equiv)	Solvent	Reaction time (d), Temp (°C)	% Isolated yield of **5** and **6**	Isomer ratio (**5**:**6**)[a]
1	**1a**	1	2	KOAc	DMF	3, 80	56	5:1
2	**1a**	1	2	KOAc	DMF	6, 60	0	–
3[b]	**1a**	1	2	KOAc	DMF	4, 80	39	5:1
4	**1a**	2	1	KOAc	DMF	3, 80	42	5:1
5[b]	**1a**	2	1	KOAc	DMF	3, 80	20	5:1
6	**1a**	1	2	Et_3N	DMF	1, 80	40	1:1
7	**1a**	1	2	Na_2CO_3	DMF	6, 80	0	–
8	**1a**	2	1	Na_2CO_3	DMF	6, 80	0	–
9[b]	**1a**	2	1	Na_2CO_3	DMF	6, 80	55	7.5:1
10[b]	**1a**	2	1	$NaHCO_3$	DMF	3, 80	25	only **5**
11[b]	**1a**	1	2	$KHCO_3$	DMF	6, 80	33	only **5**
12[b]	**1a**	1	2	K_2CO_3	DMF	6, 80	33	only **5**
13	**1a**	1	2	$KHCO_3$	DMF	6, 80	60	only **5**
14	**1a**	1	2	K_2CO_3	DMF	6, 80	56	only **5**
15	**1b**	1	2	$KHCO_3$	DMF	7, 80	5	only **5**
16	**1b**	1	2	$KHCO_3$	CH_3CN	7, 60	49	only **5**
17	**1b**	1	2	K_2CO_3	DMF	7, 80	27	only **5**
18	**1b**	1	2	K_2CO_3	CH_3CN	7, 80	33	only **5**

[a]The isomer ratio was determined by GC and ^1H NMR spectroscopy. [b]5 mol % PPh_3 added.

In the reaction of 2-cyclohexen-1-ol and iodobenzene (Table II, entries 1-14), potassium acetate again gave favorable results, but produced a 5:1 ratio of ketones **5a** and **6a** respectively. The presence of PPh_3 had no effect on the ratio of isomers and only lowered the yield. Contrary to the reactions of 2-cyclopenten-1-ol which gave a higher yield at 60 °C, rather than 80 °C, 2-cyclohexen-1-ol afforded no product at the lower temperature. The ratio of isomers was also unaffected by using either an excess of alcohol **4** or iodobenzene (**1a**) (compare entries 1 and 4, and 3 and 5 in Table II). The use of triethylamine gave a 1:1 ratio of isomers (Table II, entry 6), but better results were obtained using carbonate or bicarbonate bases (entries 9-14 in Table II). Sodium carbonate proved unreactive in the absence of PPh_3, but with PPh_3 the ratio of isomers was improved to 7.5:1 (Table II, entry 9). On the other hand, only one isomer, compound **5a**, was obtained when $NaHCO_3$, $KHCO_3$ or K_2CO_3 were employed, with or without PPh_3 (Table II, entries 10-14). Using $KHCO_3$ or K_2CO_3 in the absence of PPh_3, one can obtain 60 and 56% isolated yields of 3-phenylcyclohexanone (**5a**) respectively (Table II, entries 13 and 14). Note that K_2CO_3 completely failed when employed with 2-cyclopenten-1-ol under similar conditions, although the ratio of reactants was reversed (Table I, entry 9).

We believe that the two isomeric ketones **5** and **6** most likely arise by the mechanism depicted in Scheme I. Arylpalladium syn addition to the C-C double bond is presumed to occur predominantly, if not exclusively, from the less hindered face of the double bond anti to the alcohol group. By a series of reversible syn palladium

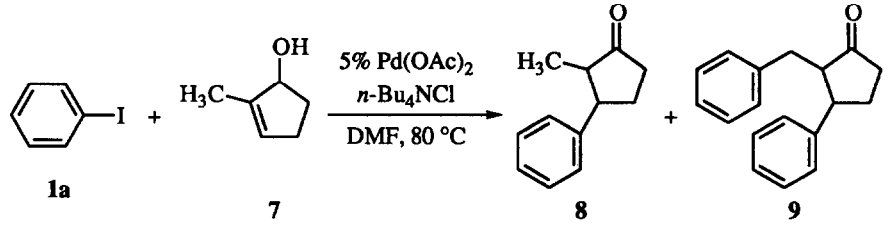
Scheme I



hydride eliminations and readditions,[17] a palladium hydride-enol complex is eventually formed which reversibly eliminates the enol,[14,18] which tautomerizes to the observed ketones **5** and **6**, thus shifting all equilibria. When the reaction of iodobenzene and 2-cyclohexen-1-ol was attempted using Ag_2CO_3 conditions[9b] to prevent palladium hydride isomerization, unfortunately no recognizable products could be identified.

Unfortunately, reduced yields of 3-arylcyclohexanone were produced when *p*-iodoanisole was employed in the reaction with 2-cyclohexen-1-ol (Table II, entries 15-18). Once again, acetonitrile gave better results as the solvent. Reactions run using ethyl *p*-iodobenzoate (**1c**) gave yields of <5% under all conditions examined.

We were curious to know what might happen if a methyl group were introduced in the 2 position of 2-cyclopenten-1-ol where palladium hydride elimination might occur towards the methyl hydrogens. The phenylation of 2-methyl-2-cyclopenten-1-ol (**7**) was examined and observed to give two major products **8** and **9** (eq 4).



(4)

Some of the results obtained using various stoichiometries, bases, and reaction conditions are summarized in Table III. Using KOAc as the base, no matter what stoichiometry or temperature, or whether PPh_3 was present or not, a 3:1 ratio of **8**:**9** was always obtained in yields up to 82% (Table III, entries 1-5). Using Na_2CO_3 or K_2CO_3 in the presence of PPh_3, no matter what the stoichiometry or temperature, a 1:1 ratio of **8**:**9** was always obtained in yields up to 86% (Table III, entries 6-9). At present, it does not appear that it is going to be possible to control this type of arylation to afford a single product in good yield.

Table III. Palladium-catalyzed Phenylation of 2-Methyl-2-cyclopenten-1-ol (7)

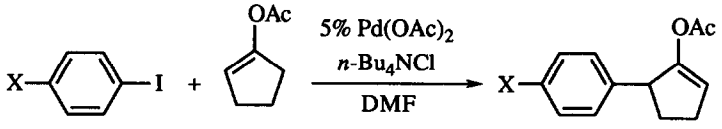
Entry	Equiv of 7	Equiv of 1a	Base (3 equiv)	Reaction conditions	% Yield[a] of 8 and 9	Product ratio (8:9)[a]
1	1	2	KOAc	80 °C, 2 d	82	3:1
2	1	2	KOAc	60 °C, 2 d	82	3:1
3[b]	1	1	KOAc	60 °C, 3 d	66	3:1
4	2	1	KOAc	60 °C, 2 d	48	3:1
5[b]	1	2	KOAc	60 °C, 3 d	24	3:1
6[b]	1	2	Na_2CO_3	80 °C, 2 d	86	1:1
7[b]	1	2	Na_2CO_3	60 °C, 2 d	80	1:1
8[b]	2	1	Na_2CO_3	60 °C, 2 d	50	1:1
9[b]	1	2	K_2CO_3	60 °C, 2 d	72	1:1

[a]The yield and product ratio was determined by GC with dodecane as an internal standard. [b]5 mol % PPh_3 added.

Compounds **8** and **9** are apparently formed by the mechanism depicted in Scheme II. While phenylpalladium addition to **7** is only expected to produce products with the palladium beta to the hydroxy group on steric grounds, two stereoisomers **10** and **11** are possible and it is not clear whether or not both are formed. Syn palladium hydride elimination of isomer **10** towards the hydroxy group eventually affords the major product **8** (the stereochemistry of **8** is unknown due to the complicated ^1H NMR spectra of the inseparable mixture). Alternatively, palladium hydride elimination in **10** towards the methyl group would afford the allylic alcohol **12** which, due to its relatively unhindered terminal double bond, would be expected to be more reactive towards further phenylpalladium addition than the starting alkene **7**. This route eventually leads to the diarylation product **9**. On the other hand, isomer **11** formed by phenylpalladium addition syn to the hydroxy group can only undergo syn palladium hydride elimination into the methyl group which eventually affords allylic alcohol **13** which in turn would be expected to undergo further arylation to eventually produce ketone **9**.

Enol ester

Since the arylation of six-membered ring enol acetates has previously proven fairly successful using arylmercurials,[2h,2k] we have examined the arylation of 1-acetoxycyclopentene (**14**) (eq 5). By varying the



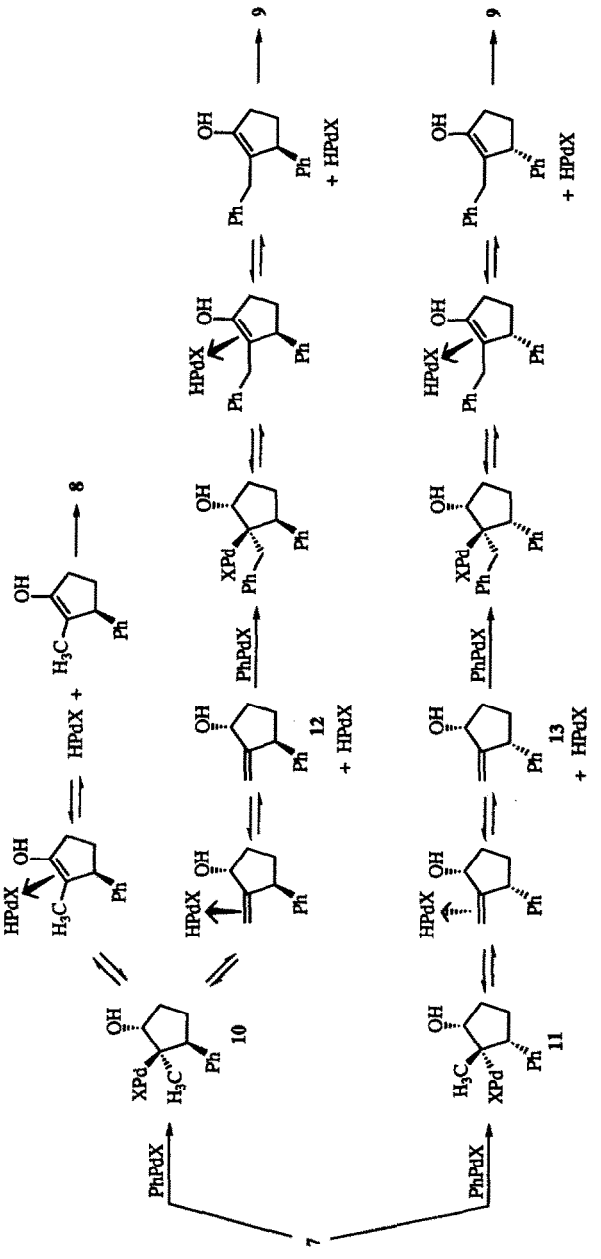
(5)

1 **14** **15**

a X = H; **b** X = OMe; **c** X = CO_2Et

stoichiometry, base, reaction time and temperature, and the presence or absence of PPh_3, we have been able to develop conditions in which we can obtain modest yields of the product **15a** (Table IV). Once again, we see a significant drop in yields when we switch to *p*-iodoanisole as the aryl iodide, and ethyl *p*-iodobenzoate affords

Scheme II



less than 5% yields under all conditions thus far examined. This process would appear to hold promise as a useful route for the α-arylation of ketones (eq 6).

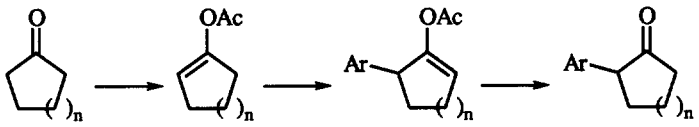


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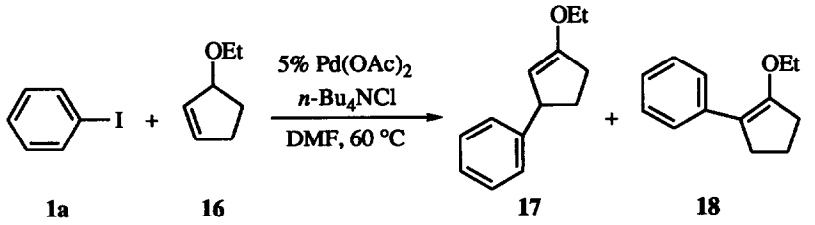
Table IV. Palladium-catalyzed Arylation of 1-Acetoxycyclopentene (**14**)

Entry	Aryl iodide	Equiv of **14**	Equiv of **1**	Base (3 equivs)	Reaction conditions	% Yield of **15**[a]
1	**1a**	3	1	KOAc	80 °C, 3 d	30
2	**1a**	3	1	KOAc	70 °C, 5 d	70
3	**1a**	3	1	KOAc	60 °C, 6 d	78
4	**1a**	3	1	KOAc	50 °C, 6 d	60
5	**1a**	3	1	Na_2CO_3	80 °C, 3 d	23
6[b]	**1a**	3	1	Na_2CO_3	80 °C, 3 d	43
7	**1a**	3	1	K_2CO_3	80 °C, 3 d	13
8	**1a**	1	2	KOAc	80 °C, 3 d	30
9[b]	**1a**	1	2	KOAc	80 °C, 3 d	29
10	**1a**	1	2	KOAc	70 °C, 5 d	43
11[b]	**1a**	1	2	KOAc	60 °C, 6 d	57
12	**1a**	1	3	KOAc	80 °C, 3 d	55
13[b]	**1a**	1	3	KOAc	80 °C, 3 d	29
14[b]	**1a**	1	2	Na_2CO_3	80 °C, 2 d	34
15	**1b**	3	1	KOAc	60 °C, 6 d	33
16	**1b**	1	2	KOAc	60 °C, 7 d	28

[a]The yield was determined by GC using dodecane as an internal standard. [b]5 mol % PPh_3 added.

Allylic ethers

There appears to be only one previous example of the palladium-catalyzed arylation of a cyclic alkene bearing an allylic ether group.[7e] Only low yields of arylation product were observed. Using 2 equiv of iodobenzene (**1a**) and 3 equiv of base per 3-ethoxycyclopentene (**16**), with or without 5 mol % PPh_3, at 60 °C, we observed what appears to be a mixture of isomers **17** and **18** (eq 7, Table V). While the yields obtained are fairly good, it proved very difficult to determine the exact ratio of the two isomers **17** and **18**, since they were inseparable by gas chromatography and there was considerable overlap of key peaks in the ^1H NMR spectra. In the reaction using KOAc as the base (Table V, entry 1), we were able to determine by GC-MS that a 2:1 ratio of **17**:**18** was present.



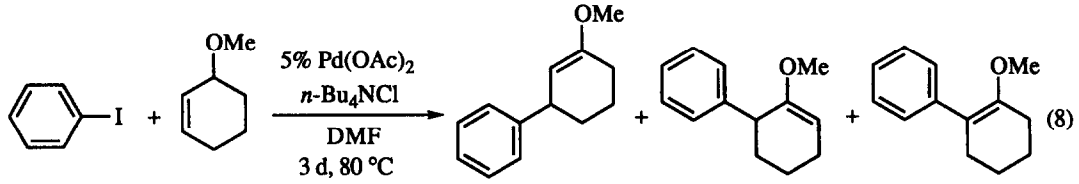
1a 16 17 18 (7)

Table V. Palladium-catalyzed Phenylation of 3-Ethoxycyclopentene (**16**)

Entry	Base	5 mol % PPh_3	Reaction time (d)	% Isolated yield of **17** + **18**
1	KOAc	–	3	65[a]
2	Na_2CO_3	–	3	0
3	Na_2CO_3	+	2	60
4	K_2CO_3	–	3	0
5	K_2CO_3	+	2	70
6	$KHCO_3$	+	3	0

[a]Isomer ratio determined to be 2:1 by GC-MS.

In a similar manner, we have examined the phenylation of 3-methoxycyclohexene (**19**) (eq 8, Table VI). This reaction afforded three isomeric products in virtually all cases. Again the products were difficult to separate



1a 19 20 21 22 (8)

and their ^1H NMR spectra overlapped substantially, but the structures **20** and **21** have been tentatively assigned based on the chemical shift of their benzylic protons. The structure of the third product, though known to be isomeric with compounds **20** and **21** by GC-MS, is pure speculation, but based on the formation of an analogous product (**18**) in the phenylation of 3-ethoxycyclopentene, the structure **22** would appear reasonable. Unfortunately, only modest overall yields could be obtained and all reactions gave bad mixtures of products.

While the yields of products from the arylation of cyclic allylic ethers are reasonable, there is little regioselectivity in the addition of the arylpalladium species to the C-C double bond and mixtures of isomeric products which are very difficult to separate are obtained in all reactions. It appears that this process is of rather limited synthetic utility.

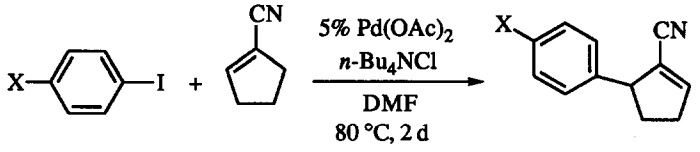
Table VI. Palladium-catalyzed Phenylation of 3-Methoxy-1-cyclohexene (**19**)

Entry[a]	Equiv of **19**	Equiv of **1a**	Base	% PPh_3	% Yield of **20-22**[b]	Isomer ratio[c] (**20**:**21**:**22**)
1	3	1	Na_2CO_3	15	47	2:1:1
2	3	1	Na_2CO_3	5	46	2:1:1
3	1	2	Na_2CO_3	–	0	–
4	1	2	Na_2CO_3	5	45	2:1:1
5	3	1	K_2CO_3	15	0	–
6	1	2	K_2CO_3	5	60	2:1:1
7	1	2	K_2CO_3	–	0	–
8	3	1	KOAc	15	15	3:1:1
9	1	2	KOAc	5	20	3:1:1
10	1	2	KOAc	–	0	–
11	3	1	NaOAc	15	66	1:1:3
12	1	2	NaOAc	5	45	1:1:3
13	3	1	CsOAc	–	0	–
14	3	1	CsOAc	15	47	1:1:0

[a]All reactions were run for 3 days at 80 °C. [b]The yield was determined by GC using dodecane as an internal standard. [c]The isomer ratio was determined by GC and ^1H NMR spectroscopy.

Cyanoalkenes

There are no previous examples of cyclic cyanoalkenes undergoing palladium-catalyzed arylation, but we have observed that this reaction can give excellent yields of the anticipated arylation product. The phenylation of 1-cyanocyclopentene (**23**) using 3 equiv of KOAc and either a 2:1 or 1:2 ratio of **1a** to **23** in the absence of PPh_3 afforded 78% and 75% yields respectively of product **24** (eq 9). On the other hand, *p*-iodoanisole affords



1 **23** **24** (9)

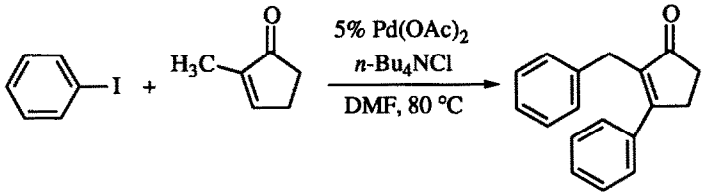
a X = H
b X = OMe
c X = CO_2Et

a 79% isolated yield when the alkene is used in a two-fold excess (18 h at 80 °C), but only a 48% yield when the aryl iodide is used in a two-fold excess (4 days at 80 °C). Under identical conditions ethyl *p*-iodobenzoate gives only 51% and 30% yields, respectively. The ease with which a cyano group can be converted to a variety of other functional groups makes this an attractive synthetic process.

Enones

Except for the palladium-catalyzed conjugate addition of iodobenzene to 2-cyclohexen-1-one mentioned earlier,[13] the intermolecular, palladium-catalyzed arylation of enones has not previously been reported, although intramolecular examples are known.[1h,1j] While simple 2-cycloalken-1-ones have no hydrogens available for eventual syn palladium hydride elimination, the arylation of 2-methyl-2-cycloalken-1-ones present interesting possibilities.

The phenylation of 2-methyl-2-cyclopenten-1-one (**25**) was first examined and found to give modest yields of a single diarylation product **26** (eq 10, Table VII). No monoarylation product could be detected, no matter



(10)

1a **25** **26**

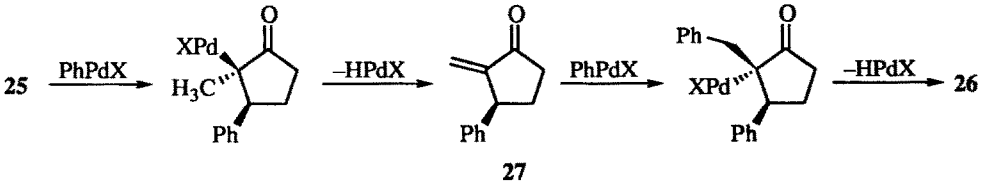
Table VII. Palladium-catalyzed Phenylation of 2-Methyl-2-cyclopenten-1-one (**25**)

Entry	Equiv of **25**	Equiv of **1a**	Base	5 mol % PPh_3	Reaction conditions	% Yield of **26**[a]
1	1	2	KOAc	–	80 °C, 3 d	42
2	1	2	KOAc	–	100 °C, 3 d	42
3	2	1	KOAc	–	80 °C, 5 d	16
4	1	2	Na_2CO_3	–	80 °C, 5 d	0
5	1	2	Na_2CO_3	+	80 °C, 5 d	48
6	1	2	Na_2CO_3	+	100 °C, 3 d	48
7	2	1	Na_2CO_3	+	80 °C, 5 d	24
8	1	2	K_2CO_3	+	80 °C, 5 d	32

[a]The yield was determined by GC using dodecane as an internal standard.

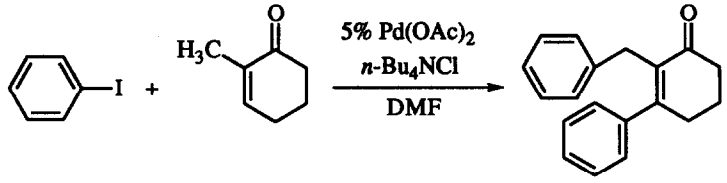
what the reaction conditions or stoichiometry employed. Apparently, the initially anticipated monoarylation product, 2-methylene-3-phenylcyclopentanone (**27**) (Scheme III), undergoes more rapid arylation than the starting material, even when an excess of starting enone **25** is available. One might also have anticipated that enone **27** might isomerize in the presence of the base and elevated temperatures employed to form 2-methyl-3-phenyl-2-cyclopenten-1-one, but none of that product has been observed either.

Scheme III



27

The analogous phenylation of 2-methyl-2-cyclohexen-1-one (**28**) using 2 equiv of iodobenzene (**1a**) per cycloalkenone has been briefly examined, and again only a diarylation product **29** is observed in low yields (eq 11). The reaction using 3 equiv of KOAc at 100 °C gave a 16% yield of enone **29**, while 3 equiv of Na_2CO_3 plus 5 mol % PPh_3 at 100 °C afforded the enone **29** in 23% yield. These enone double arylation reactions appear to be synthetically useful although the yields at this stage are not high.



(11)

1a **28** **29**

CONCLUSION

The palladium-catalyzed arylation of 2-cycloalken-1-ols by aryl iodides provides a new approach to 3-arylcycloalkanones. The analogous arylation of 2-methyl-2-cyclopenten-1-ol affords a mixture of singly and doubly arylated cyclopentanone products. The arylation of 1-acetoxycyclopentene proceeds in a reasonable yield to provide the allylic arylation product, thus offering a new route for the α-arylation of cycloalkanones. Five- and six-membered cyclic allylic ethers undergo arylation at both ends of the C-C double bond to produce mixtures of isomeric monoarylated vinylic ethers. 1-Cyanocyclopentene can be arylated in high yield. 2-Methyl-2-cycloalken-1-ones afford modest yields of doubly arylated 2-cycloalken-1-ones. Thus, the palladium-catalyzed arylation of functionally-substituted cycloalkenes affords a new synthetic route to a wide variety of arylated, functionally-substituted cyclic substrates and should prove useful in organic synthesis.

EXPERIMENTAL SECTION

Equipment

The infrared spectra were obtained on an IBM IR/98 FT spectrophotometer, and the ^1H NMR and ^{13}C NMR spectra on a Nicolet NT-300 NMR spectrometer. The GC-MS spectral data were obtained on a Finnegan 4023 GC/MS and on a Kratos MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed using a Varian 3700 gas chromatograph equipped with an OV-101 packed column.

Reagents

All chemicals were used directly as obtained commercially unless otherwise indicated. 2-Methyl-2-cyclohexen-1-one, iodobenzene, *p*-iodoanisole, ethyl *p*-iodobenzoate, 2-cyclopenten-1-one, 2-cyclohexen-1-ol, PPh_3, $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ were all purchased from Aldrich Chemical Company. *n*-Bu_4NCl was purchased from Lancaster Chemical Company. All inorganic bases used were purchased from Fisher Scientific. 1-Acetoxycyclopentene and 1-cyanocyclopentene were prepared by Dr. Baker.[19]

Preparation of starting cycloalkenes

2-Cyclopenten-1-ol was prepared using a general literature procedure.[20] 2-Cyclopenten-1-one (10 mmol) was dissolved in 25 ml of methanol containing $CeCl_3 \cdot 7H_2O$ (40 mmol), and $NaBH_4$ (10 mmol) was slowly added with stirring. The mixture was allowed to react for 1 h at room temperature, followed by hydrolysis. The mixture was extracted with two 50 ml portions of diethyl ether and the ether was dried over $MgSO_4$. The resultant colorless 2-cyclopenten-1-ol (**2**) was obtained in an 85% isolated yield after column chromatography: ^{1}H NMR ($CDCl_3$) δ 1.42 (br s, 1 H, OH), 1.64-1.74 (m, 1 H, CH_2), 2.23-2.32 (m, 2 H, CH_2), 2.46-2.55 (m, 1 H, CH_2), 4.87 (br s, 1 H, CHO), 5.82-5.85 (m, 1 H, =CH), 5.98-6.00 (m, 1 H, =CH).

2-Methyl-2-cyclopenten-1-ol (**7**) was obtained in a 90% isolated yield using the above general procedure: ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H, CH_3), 2.0 (br s, 1 H, OH), 2.17-2.60 (m, 4 H, CH_2's), 4.57-4.60 (m, 1 H, CH-O), 5.50 (t, 1 H, J = 6.0 Hz, =CH).

General procedure for the palladium-catalyzed arylation of functionally-substituted cycloalkenes

To a 1 dram vial containing a magnetic stirring bar was added: $Pd(OAc)_2$ (0.025 mmol, 3 mg), the base (1-3 equiv) and *n*-Bu_4NCl (0.5 mmol, 140 mg). The vial was sealed with a septum and purged with nitrogen. The cycloalkene (0.5 mmol), 1 ml of DMF or acetonitrile, and the aryl iodide (1.0 mmol) were then added. The mixture was stirred at the desired temperature for the time indicated. The reaction mixture was diluted with diethyl ether (10 ml) and washed with saturated aqueous NH_4Cl (2 x 10 ml), and the combined aqueous layers were backwashed with diethyl ether. The combined ether fractions were dried over anhydrous $MgSO_4$, filtered, concentrated, and purified via flash column chromatography using hexane-ethyl acetate as the eluant. The stoichiometry and reaction conditions were varied as indicated in the text and tables.

Products

The following products were obtained using the above general procedure.

3-Phenylcyclopentanone (**3a**)[15] was obtained as a yellow oil in an 88% isolated yield from iodobenzene and 2-cyclopenten-1-ol using KOAc as a base and stirring for 16 h at 60 °C (Table I, entry 5): IR (neat) 3061, 3028, 2982, 1740, 1495, 1404, 1151, 762, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.92-2.06 (m, 1 H, CH_2), 2.17-2.45 (m, 4 H, CH_2 and CH_2CO), 2.63-2.71 (dd, 1 H, J = 18.6, 8.1 Hz, CH_2CO), 3.36-3.48 (m, 1 H, ArCH), 7.16-7.31 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 31.24, 38.90, 42.35, 45.82, 126.67, 128.34, 128.58, 143.15, 218.10; HRMS calculated for $C_{11}H_{12}O$: 160.0888. Found: 160.0886.

Compound **3b**[15b-d] was obtained as a yellow oil in a 53% isolated yield from *p*-iodoanisole and 2-cyclopenten-1-ol using KOAc as a base and stirring for 2 days at 60 °C (Table I, entry 14): IR ($CDCl_3$) 2961, 1740, 1249, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.86-2.00 (m, 1 H, CH_2), 2.21-2.49 (m, 4 H, CH_2's), 2.59-2.68 (dd, 1 H, J = 18.3, 7.5 Hz, CH_2), 3.30-3.41 (m, 1 H, ArCH), 3.79 (s, 3 H, CH_3O), 6.88 (d, 2 H, J = 8.7 Hz, ArH), 7.17 (d, 2 H, J = 8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 31.40, 39.00, 41.46, 46.01, 55.29, 114.00, 127.60, 135.07, 158.28, 218.45; HRMS calculated for $C_{12}H_{14}O_2$: 190.09938. Found: 190.09885.

Compound **3c** was obtained as a yellow oil in a 43% isolated yield from ethyl *p*-iodobenzoate and 2-cyclopenten-1-ol using KOAc as a base and stirring for 5 days at 60 °C (Table I, entry 20): IR ($CDCl_3$) 2979, 1742, 1713, 1280, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, J = 7.2 Hz, CH_3), 1.93-2.07 (m, 1 H, CH_2), 2.26-2.53 (m, 4 H, CH_2's), 2.65-2.74 (dd, 1 H, J = 18.0, 7.5 Hz, CH_2), 3.42-3.55 (m, 1 H, ArCH), 4.37 (q,

2 H, J = 7.2 Hz, CH_2O), 7.32 (d, 2 H, J = 8.4 Hz, ArH), 8.02 (d, 2 H, J = 8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 14.36, 30.98, 38.72, 42.18, 45.45, 60.90, 126.69, 129.00, 129.91, 148.17, 166.27, 217.44; HRMS calculated for $C_{14}H_{16}O_3$: 232.10994. Found: 232.10933.

3-Phenylcyclohexanone (**5a**)[16] was obtained in a 60% isolated yield from iodobenzene and 2-cyclohexen-1-ol as a yellow oil using $KHCO_3$ as a base and stirring for six days at 80 °C (Table II, entry 13): IR (neat) 3063, 3030, 2937, 1711, 1497, 1450, 1250, 1225, 1030, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70-1.88 (m, 2 H, CH_2), 2.02-2.20 (m, 2 H, CH_2), 2.30-2.60 (m, 4 H, CH_2CO), 2.95-3.06 (m, 1 H, ArCH), 7.20-7.35 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 25.58, 32.86, 41.21, 44.80, 48.98, 126.59, 128.53, 128.87, 144.39, 210.81; HRMS calculated for $C_{12}H_{14}O$: 174.10447. Found: 174.10451.

Compound **5b** was obtained as a yellow oil in a 49% isolated yield from *p*-iodoanisole and 2-cyclohexen-1-ol using $KHCO_3$ as a base and stirring for 7 days at 60 °C (Table II, entry 16): IR ($CDCl_3$) 2956, 1707, 1257, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72-1.88 (m, 2 H, CH_2), 2.04-2.17 (m, 2 H, CH_2), 2.32-2.60 (m, 4 H, CH_2's), 2.91-3.00 (m, 1 H, ArCH), 3.79 (s, 3 H, CH_3O), 6.86 (d, 2 H, J = 8.7 Hz, ArH), 7.13 (d, 2 H, J = 8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 25.49, 33.00, 41.18, 43.97, 49.24, 55.26, 113.98, 127.45, 136.53, 158.20, 211.14; HRMS calculated for $C_{13}H_{16}O_2$: 204.11507. Found: 204.11580.

Compounds **8** and **9** were obtained in an 86% isolated yield from iodobenzene and 2-methyl-2-cyclopenten-1-ol as an inseparable 1:1 mixture (determined by GC and ^1H NMR spectroscopy) using Na_2CO_3 as a base and stirring for two days at 80°C (Table III, entry 6): IR (neat, 1:1 mixture) 3063, 2932, 1740, 1603, 1495, 1454, 1406, 1142, 910, 758, 733 cm^{-1}. Compound **8**: GC-MS m/z (rel. int.) 175.1 (13.5, M+1), 174.1 (100, M^+), 159.1 (14.3), 145.1 (23.4), 132.1 (17.7), 130.1 (12.6), 118.1 (49.4), 117 (96.5), 115 (34.2), 105 (24.7), 104 (39.7), 91 (42.1), 77 (12.7), 65 (8.4), 57.1 (14.0), 51 (11.8), 41.0 (6.4). ^1H NMR ($CDCl_3$) δ 1.04 (d, 3 H, J = 6.9 Hz, CH_3), 2.19-2.37 (m, 4 H, CH_2's), 2.50-2.57 (m, 1 H, CHCO), 2.81 (td, 1 H, J = 12.0, 5.4 Hz, CHAr), 7.24-7.38 (m, 5 H, ArH). Compound **9**: GC-MS m/z (rel. int.) 251.1 (2.5, M+1), 250.1 (12.2, M^+), 159.1 (12.1), 146.1 (100), 131.1 (7.8), 115.1 (13.5), 104.1 (8.4), 91 (31.5), 77.0 (5.6), 65 (5.3), 51 (3.3). ^1H NMR ($CDCl_3$) δ 1.77-1.91 (m, 1 H, CH_2), 2.01-2.14 (m, 1 H, CH_2), 2.18-2.27 (m, 1 H, CH_2) 2.49 (dd, 1 H, J = 18.3, 7.8 Hz, CH_2), 2.61-2.68 (m, 1 H, CHCO), 2.74 (dd, 1 H, J = 13.8, 6.0 Hz, CH_2Ar), 2.92 (td, 1 H, J = 11.7, 6.0 Hz, CHAr), 3.09 (dd, 1 H, J = 13.8, 4.2 Hz, CH_2Ar), 6.99-7.03 (m, 2 H, ArH), 7.13-7.27 (m, 6 H, ArH), 7.30-7.35 (m, 2 H, ArH). ^{13}C NMR spectrum was too complicated to assign chemical shifts.

1-Acetoxy-3-phenylcyclopentene (**15a**) was obtained as a yellow oil in a 78% GC yield from iodobenzene and 1-acetoxycyclopentene using KOAc as a base and stirring for 6 days at 60 °C (Table IV, entry 3): IR (neat) 3063, 3028, 2956, 1759, 1664, 1493, 1454, 1369, 1240, 1043, 760, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (s, 3 H, CH_3), 2.42-2.55 (m, 4 H, CH_2's), 4.02-4.08 (m, 1 H, ArCH), 5.67-5.68 (m, 1 H, =CH), 7.17-7.33 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.0, 27.5, 32.2, 49.4, 114.9, 126.5, 127.5, 128.5, 143.3, 151.8, 168.6; HRMS calculated for $C_{13}H_{14}O_2$: 202.09938. Found: 202.09934.

Compound **15b** was obtained as a yellow oil in a 33% isolated yield from *p*-iodoanisole and 1-acetoxycyclopentene using KOAc as a base and stirring for 7 days at 60 °C (Table IV, entry 15): IR ($CDCl_3$) 2959, 1750, 1244, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79-1.90 (m, 1 H, CH_2), 1.96 (s, 3 H, CH_3CO), 2.38-2.53 (m, 3 H, CH_2's), 3.79 (s, 3 H, CH_3O), 3.96-4.04 (m, 1 H, ArCH), 5.63-5.64 (m, 1 H, =CH), 6.84 (d, 2 H, J = 8.4 Hz, ArH), 7.10 (d, 2 H, J = 8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 21.04, 27.41, 32.33, 48.56, 55.28,

113.89, 114.60, 128.51, 135.36, 152.09, 158.23, 168.62; HRMS calculated for $C_{14}H_{16}O_3$: 232.10994. Found: 232.11011.

Compounds **17** and **18** were obtained as a 2:1 mixture of regioisomers (determined by GC-MS and ^1H NMR spectroscopy) in a 65% isolated yield from iodobenzene and 3-ethoxycyclopentene using KOAc as the base and stirring for three days at 60°C (Table V, entry 1): IR (neat, 2:1 isomeric mixture) 3063, 3030, 2934, 1742, 1495, 1404, 1254, 1136, 910, 733, 648 cm^{-1}. Compound **17**: GC-MS m/z (rel. int.) 189 (12.7, M+1), 188 (100, M^+), 159 (80.7), 144 (25.5), 143 (76.4), 141 (10.8), 131 (23.9), 117 (39.1), 115 (25.9), 111 (31.3), 103 (29.5), 91 (35.5), 83 (53.6), 77 (26.8), 65 (6.7), 55 (20.7), 51 (15.1), 43 (13.5). Compound **14**: GC-MS m/z (rel. int.) 189 (8.2, M+1), 188 (53.5, M^+), 159 (13.2), 142 (12.2), 129 (13.8), 117 (15.1), 105 (13.9), 104 (12.4), 91 (16.8), 83 (8.9), 77.0 (8.7), 55 (100), 43 (16). The ^1H and ^{13}C NMR spectra were too complicated to assign chemical shifts.

Compounds **20-22** were obtained as a 1:1:3 mixture of the three isomers respectively in approximately a 66% GC yield from iodobenzene, 3-methoxycyclohexene and 15 mol % PPh_3 using NaOAc as the base and stirring for three days at 80 °C (Table VI, entry 11): IR (neat, 1:1:3 isomeric mixture) 3063, 3023, 2934, 1668, 1603, 1495, 1452, 1377, 1271, 1213, 1163, 1018, 910, 756, 700 cm^{-1}; GC-MS m/z (rel. int.) compound **20**: 189 (14.3, M+1), 188 (100, M^+); compound **21**: 189 (11.4, M+1), 188 (100, M^+); compound **22**; 189 (9.2, M+1), 188 (73.2, M^+), 84 (100). The ^1H and ^{13}C NMR spectra were too complicated to assign chemical shifts.

1-Cyano-5-phenylcyclopentene (**24a**) was obtained as a yellow oil in a 78% isolated yield from iodobenzene and 1-cyanocyclopentene using KOAc as a base and stirring for two days at 80 °C: IR (neat) 3063, 3028, 2845, 2220, 1612, 1603, 1495, 1454, 789, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89-2.04 (m, 1 H, CH_2), 2.45-2.80 (m, 3 H, CH_2's), 4.04-4.11 (m, 1 H, ArCH), 6.84 (dd, 1 H, J = 8.4, 2.7 Hz, =CH-), 7.12-7.42 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 33.21, 33.58, 52.81, 116.34, 118.81, 127.23, 127.28, 128.92, 141.48, 148.83; HRMS calculated for $C_{12}H_{11}N$: 169.08915. Found: 169.08869.

Compound **24b** was obtained as a yellow oil in a 79% isolated yield from *p*-iodoanisole and 1-cyanocyclopentene using KOAc as a base and stirring for 18 hours at 80 °C: IR ($CDCl_3$) 2958, 2220, 1610, 1248, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83-1.96 (m, 1 H, CH_2), 2.44-2.74 (m, 3 H, CH_2's), 3.79 (s, 3 H, CH_3O), 3.99-4.06 (m, 1 H, ArCH), 6.79 (q, 1 H, J = 2.4 Hz, =CH), 6.87 (dd, 2 H, J = 8.7, 2.1 Hz, ArH), 7.15 (dd, 2 H, J = 8.7, 2.1 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 33.09, 33.60, 52.03, 55.25, 114.23, 116.34, 119.17, 128.17, 133.34, 149.25, 158.72; HRMS calculated for $C_{13}H_{13}ON$: 199.09971. Found: 199.09912.

Compound **24c** was obtained as a yellow oil in a 51% isolated yield from ethyl *p*-iodobenzoate and 1-cyanocyclopentene using KOAc as a base and stirring for 18 hours at 80 °C: IR ($CDCl_3$) 2982, 2221, 1714, 910 cm^{-1}; ^1H NMR ($CDCl_3$) 1.39 (t, 3 H, J = 7.2 Hz, CH_3), 1.99-1.87 (m, 1 H, CH_2), 2.79-2.51 (m, 3 H, CH_2's), 4.17-4.10 (m, 1 H, ArCH), 4.37 (q, 2 H, J = 7.2 Hz, OCH_2), 6.87 (q, 1 H, J = 2.4 Hz, =CH), 7.26 (d, 2 H, J = 8.1 Hz, ArH), 8.02 (d, 2 H, J = 8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 14.38, 33.21, 33.42, 52.67, 60.96, 115.94, 118.14, 127.17, 129.58, 130.21, 146.91, 150.31, 166.26; HRMS calculated for $C_{15}H_{15}O_2N$: 241.11028. Found: 241.11080.

2-Benzyl-3-phenyl-2-cyclopenten-1-one (**26**) was obtained as a yellow oil in a 42% GC yield from iodobenzene (2 equiv) and 2-methyl-2-cyclopenten-1-one using KOAc as a base and stirring for three days at 80 °C (Table VII, entry 1): IR (neat) 3061, 3028, 2924, 1695, 1622, 1495, 1445, 1358, 1333, 1178, 1032, 762, 696, 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58-2.62 (m, 2 H, CH_2), 2.98-3.01 (m, 2 H, CH_2), 3.75 (s, 2 H,

$ArCH_2$), 7.10-7.50 (m, 10 H, ArH); ^{13}C NMR ($CDCl_3$) δ 30.41, 30.70, 34.93, 126.72, 127.99, 128.99, 129.15, 129.36, 130.34, 136.85, 139.86, 139.91, 169.67, 209.85; HRMS calculated for $C_{18}H_{16}O$: 248.12019. Found: 248.12020.

2-Benzyl-3-phenyl-2-cyclohexen-1-one (**29**) was obtained as a yellow oil in a 23% GC yield from iodobenzene (2 equiv) and 2-methyl-2-cyclohexene-1-one using Na_2CO_3 with PPh_3 and stirring for three days at 100 °C: IR ($CDCl_3$) 3061, 3028, 2932, 1724, 1668, 1599, 1495, 1452, 1427, 1358, 1180, 1130, 1072, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07-2.17 (m, 2 H, CH_2), 2.50-2.57 (q, 2 H, J = 6.6 Hz, CH_2), 2.66-2.70 (t, 2 H, J = 6.0 Hz, CH_2), 3.57 (s, 2 H, $ArCH_2$), 6.94-7.50 (m, 10 H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.14, 32.13, 33.78, 38.21, 125.77, 126.77, 126.99, 128.01, 128.30, 128.48, 128.73, 135.28, 141.06, 158.60, 199.23; HRMS calculated for $C_{19}H_{18}O$: 262.13577. Found: 262.13565.

Acknowledgments

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Supplementary Material Available

^1H and ^{13}C NMR spectra for compounds **3, 5, 15, 24, 26** and **28** (41 pages). Ordering information is given on any current masthead page.

REFERENCES AND FOOTNOTES

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