1998

Palladium-catalyzed synthesis of heterocycles and highly functionalized polycyclics

Xiaojun Han
Iowa State University

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UMI
Palladium-catalyzed synthesis of heterocycles and highly functionalized polycyclics

by

Xiaojun Han

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry
Major Professor: Richard C. Larock

Iowa State University
Ames, Iowa
1998
Graduate College
Iowa State University

This is to certify that the Doctoral dissertation of

Xiaojun Han

has met the dissertation requirement of Iowa State University

Signature was redacted for privacy.

Major Professor
Signature was redacted for privacy.

For the Major Program
Signature was redacted for privacy.

For the Graduate College
To my wife, Ling
and our son, Gregory
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<tr>
<th>Abbreviation</th>
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</tr>
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ABSTRACT

Palladium catalyzes the regio- and stereoselective annihilation of allenes by vinylic halides bearing tertiary alcohol and p-toluenesulfonamide groups to produce a variety of 5- and 6-membered ring heterocycles containing a 1,3-diene moiety. In addition, the palladium-catalyzed reaction of N-(2-iodo-2-alkenyl)-p-toluenesulfonamides with diphenylacetylene or 4,4-dimethyl-2-pentyne affords pyrolidine derivatives containing a 1,3-diene moiety, or unexpected 2-alkenyl substituted α,β-unsaturated aldehydes. These synthetically useful intermediates are difficult to prepare or are inaccessible by other existing methodology.

A number of 3,4,6-tri- and 3,4,5,6-tetrasubstituted α-pyrones have been prepared in good yields by the reaction of vinylic iodides or triflates bearing an ester functionality with internal alkynes in the presence of a palladium catalyst. The methodology provides an especially simple, convenient, and regioselective route to α-pyrones containing aryl, silyl, tert.-alkyl and other hindered groups. This methodology is important due to the fact that α-pyrones occur as structural subunits in numerous natural products that exhibit a wide range of biological activity, and very recently, low molecular weight α-pyrones have been shown to be potent HIV-1 protease inhibitors.

2,5-Cyclohexadienyl-substituted aryl and vinylic iodides have been reacted with carbon nucleophiles (diethyl malonate, 2-methyl-1,3-cyclohexanedione), nitrogen nucleophiles (morpholine, potassium phthalimide, N-benzyl tosylamide, di-tert.-butyl iminodicarboxylate, lithium azide and anilines), a sulfur nucleophile (sodium benzenesulfinate), and oxygen nucleophiles (lithium acetate and phenols) in the presence of a palladium catalyst to afford products of cyclization and subsequent cross-coupling in good to excellent yields. In most cases, this process is highly diastereoselective and the products are formed as single
diastereoisomers. The structures of the representative compounds have been
determined by $^1$H NMR, $^{13}$C NMR, COSY, HMQC, and NOESY spectroscopy. This
methodology has potential applications in natural product synthesis, and may
provide quick access to a library of compounds with different skeletons and
functionality.
GENERAL INTRODUCTION

The palladium-catalyzed hetero- and carboannulation of unsaturated cyclopropanes and cyclobutanes, 1,2-dienes, 1,3-dienes, and alkynes by functionally-substituted aromatic halides have been studied by the Larock group and others. This provides a valuable route to a variety of arene-containing heterocycles and carbocycles. In this dissertation, vinylic halides or triflates bearing additional functionality are utilized to annulate allenes and internal alkynes to produce heterocycles containing a 1,3-diene moiety and α-pyrones.

The Larock group has recently shown that aryl halides, non-conjugated dienes, and carbon nucleophiles or amines can be readily coupled in high yields using a Pd(0) catalyst. In this dissertation, aryl and vinylic iodides bearing a 2,5-cyclohexadienyl moiety readily undergo sequential intramolecular/intermolecular Pd-catalyzed cross-coupling with carbon and heteroatom nucleophiles to produce a wide variety of diastereomerically pure polycyclic products in good to excellent yields. The author of this manuscript was the primary investigator and author for each of the papers reported in this dissertation.

Dissertation Organization

This dissertation is divided into three chapters. Each chapter is written by following the format of a full paper in the Journal of Organic Chemistry.

Chapter 1 describes the synthesis of five- and six-membered ring heterocycles containing a 1,3-diene moiety by the palladium-catalyzed annulation of allenes and internal alkynes using functionally-substituted vinylic iodides. It is interesting to note that the reaction of some of these vinylic iodides with 4,4-dimethyl-2-pentyne affords unexpected α,β-unsaturated aldehydes. A mechanism for this latter transformation is proposed.
Chapter 2 examines the synthesis of a number of 3,4,6-tri- and 3,4,5,6-tetrasubstituted α-pyrones by the reaction of vinylic iodides or triflates bearing ester functionality with internal alkynes in the presence of a palladium catalyst. The reaction is believed to proceed through a seven-membered palladacyclic salt in which the regiochemistry of the reaction is controlled by steric factors.

Chapter 3 presents the synthesis of highly functionalized polycyclics via Pd-catalyzed intramolecular coupling of aryl and vinylic halides, non-conjugated dienes and nucleophiles. The reaction is believed to proceed via (1) oxidative addition of the aryl or vinylic iodide to Pd(0), (2) organopalladium addition to one of the carbon-carbon double bonds, (3) palladium migration along the carbon chain on the same face of the ring to form a π-allylpalladium intermediate, and (4) nucleophilic displacement of the palladium either through backside nucleophilic attack, or nucleophilic attack on the palladium, followed by reductive elimination.

Finally, following general conclusions, all of the 1H and 13C NMR spectra of the palladium-catalyzed reaction products are compiled in appendices A-C of this dissertation. The COSY, HMQC, and NOESY spectra of some palladium-catalyzed reaction products in chapter 3 can also be found in appendix C.
CHAPTER 1. PALLADIUM-CATALYZED ANNULATION OF ALLENES AND INTERNAL ALKYNES USING FUNCTIONALLY-SUBSTITUTED VINYLC HALIDES

A portion of a paper submitted to the Journal of Organic Chemistry
Richard. C. Larock and Xiaojun Han

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Abstract

Palladium catalyzes the regio- and stereoselective annulation of allenes by vinylic iodides bearing tertiary alcohol and p-toluenesulfonamide groups to produce a variety of 5- and 6-membered heterocycles containing a 1,3-diene moiety. The reaction appears to proceed by vinylic palladium formation and addition to the allene, followed by intramolecular nucleophilic displacement of the palladium in the resulting π-allylpalladium intermediate. 6-Membered rings are formed more readily than 5-membered rings. The regioselectivity is high with vinylic iodides bearing an alcohol group affording predominantly the product of intramolecular attack on the more substituted end of the π-allylpalladium intermediate. Vinylic iodides bearing tosylamides afford mixtures of regioisomers, where the predominant 6-membered ring products arise by attack on the less substituted end of the allene, while 5-membered ring products involve addition to the more substituted end of the allene. In addition, the palladium-catalyzed reaction of \(N\)-(2-iodo-2-alkenyl) p-toluenesulfonamides with diphenylacetylene or
4,4-dimethyl-2-pentyne afford either pyrrolidine derivatives containing a 1,3-diene moiety, or unexpected 2-alkenyl substituted α,β-unsaturated aldehydes.

**Introduction**

π-Allylpalladium intermediates have proven extraordinarily useful in organic synthesis.\(^1\) One important route to such compounds is addition of organopalladium compounds to allenes (eq. 1).\(^2\) This approach to π-allylpalladium compounds is finding increasing utility in organic synthesis. Thus, aryl and vinylic halides or triflates are allowed to react with allenes and nucleophiles to afford products containing all three moieties (eq. 2).\(^3\) In an analogous manner, allenes bearing internal carbon nucleophiles react with aryl or vinylic halides to form carbocyclic products.\(^4\) The intermolecular and intramolecular alkoxy-, amido- and aminopalladation of allenes and subsequent carbon monoxide or alkene insertion also provides a useful route to a variety of allene addition products.\(^5\)

Y. He and W. Leung, former members of the Larock research group, have reported that vinylic halides bearing primary alcohol, amine, carboxylic acid and
amide groups, as well as carbanion-stabilizing groups react regio- and stereoselectively with allenes to produce 5- and 6-membered ring heterocycles and carbocycles in good yields (eq. 3). The objective of this report is to further expand the scope of this synthetically useful process.

M. Doty, a former member of the Larock research group, reports that the reaction of vinylic iodide 1, which contains a neighboring hydroxyl group, with internal alkynes affords bicyclic furans 3 in good yields in the presence of 5% Pd(OAc)2, 4 equiv of NaOAc, and 1 equiv of LiCl in DMF at 100 °C, while the reaction of vinylic iodide 2, which contains a neighboring sulfonamide functionality, with internal alkynes affords pyrrolidine derivatives 4 in good yields under the same reaction conditions, except that 2 equiv of Na2CO3 are used as the base (eq. 4).

A second objective of this work is to extend this process to vinylic iodides, such as 5, which contain a neighboring sulfonamide functionality, to produce...
pyrrole derivatives 7, by the isomerization of intermediates 6 due to the presence of the unstable exocyclic carbon-carbon double bond (eq. 5).7

\[
\begin{array}{c}
\text{R}^1 \ \text{NHTs} \\
\text{R}^2 \\
\text{I} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\end{array}
\begin{array}{c}
\text{NHTs} \\
\text{NHTs} \\
\text{NHTs} \\
\end{array}
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^3 \\
\text{R}^4 \\
\end{array}
\begin{array}{c}
+ 2.5 \text{ R}^3 \text{C} = \text{CR}^4 \\
cat. \text{ Pd}(0) \\
\rightarrow \\
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\end{array}
\begin{array}{c}
\text{NHTs} \\
\text{NHTs} \\
\text{NHTs} \\
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\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
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\text{NHTs} \\
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\text{NHTs} \\
\end{array}
\end{array}
\] (5)

### Results and Discussions

The starting materials used in this study (Figure 1) are readily prepared. For example, iodide 8 was prepared by sequential treatment of (propene)Ti(O\(\text{Pr}^\text{t}\))\(_2\) (formed \textit{in situ} from Ti(O\(\text{Pr}^\text{t}\))\(_4\) and \(\text{tPrMgCl}\)) with diphenylacetylene, acetone and I\(_2\) according to a literature procedure.8 Tosylamides 11, 13, 17, 19, 28, and 30 were prepared by the Mitsunobu reaction of the corresponding alcohols with TsNHBoc, followed by cleavage with trifluoroacetic acid in CH\(_2\)Cl\(_2\).9 (Z)-3-Iodo-2-methyl-2-propen-1-ol, the precursor to iodide 11, was prepared through the copper-catalyzed addition of MeMgl to propargyl alcohol, followed by an iodine

![Figure 1. The functionally-substituted vinylic iodides.](image-url)
quench using a literature procedure.\textsuperscript{10} (Z)-3-iodo-1,2,3-triphenyl-2-propen-1-ol, the precursor to iodide 13, was prepared by sequential treatment of Cp$_2$ZrEt$_2$ (formed \textit{in situ} from Cp$_2$ZrCl$_2$ and EtMgBr) with diphenylacetylene, benzaldehyde, and I$_2$ using a literature procedure.\textsuperscript{11} 2-Iodo-2-propen-1-ol, the precursor to iodide 17, was prepared by the reaction of propargyl alcohol with NaI, Me$_3$SiCl, and water in acetonitrile according to a literature procedure.\textsuperscript{12} 2-Iodo-3-methyl-2-butenol and (Z)-2-iodo-3-phenyl-2-butenol, the precursors to iodides 19 and 28, were prepared by the DIBAL reduction\textsuperscript{13} of ethyl 2-iodo-3-methyl-2-butenoate and ethyl (Z)-2-iodo-3-phenyl-2-butenoate, respectively.\textsuperscript{14} The alcohol precursor to tosylamide 30 was prepared by the NaBH$_4$ reduction of cyclohexylideneiodoacetaldehyde\textsuperscript{15} in the presence of CeCl$_3$.

The results of the palladium-catalyzed annulation of allenes by these vinylic iodides are summarized in Table 1. Y. He and W. Leong have found that vinylic halides bearing functional groups as diverse as primary alcohols, amines, and even carboxylic acids and amides undergo annulation with allenes successfully. We have found that vinylic iodides, which contain a tertiary hydroxyl group or sulfonamide functionality, can also be used for this process to produce the corresponding pyran (entries 1 and 2), piperidine (entries 3-5) or pyrrolidine (entries 6-8) derivatives. It is worth mentioning that pyrrolidine derivatives can be formed in fair to good yields (entries 6-8), because Y. He noticed that 5-membered ring oxygen-containing heterocycles were formed in only relatively low yields.\textsuperscript{6}

These reactions are believed to proceed through palladium acetate reduction to palladium(0), oxidative addition of the vinylic halide to palladium(0), and vinylic palladium addition to the allene to initially produce a sigma allylpalladium intermediate. The sigma allylpalladium intermediate rapidly equilibrates to \textit{syn} (23) and/or \textit{anti} (24) $\pi$-allylpalladium intermediates, which
Table 1. Palladium-catalyzed annulation of allenes by vinylc iodides.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>vinylic halide</th>
<th>allene</th>
<th>time (h)</th>
<th>product(s)(^b)</th>
<th>% isolated yield (isomer ratio)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>(n)-C(_3)H(_7)CH=CH(-n)-C(_3)H(_7)</td>
<td>24</td>
<td>(9a) + (9b)</td>
<td>53 (56 : 44)</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>(n)-C(_8)H(_17)CH=CH(_2)</td>
<td>41</td>
<td>(10)</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>(H_3)C(_{18})NHTs</td>
<td>20</td>
<td>(12)</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>(H_3)C(_{18})NHTs</td>
<td>27</td>
<td>(14a : 14b : 14c : 14d)</td>
<td>80 (59 : 21 : 14 : 6)</td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
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<tr>
<th>entry</th>
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<th>allene</th>
<th>time (h)</th>
<th>product(s)$^b$</th>
<th>% isolated yield (isomer ratio)$^c$</th>
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<td>Ph Ph H NHTs</td>
<td>Ph</td>
<td>13</td>
<td>27</td>
<td>Ph Ph H NHTs + Ph Ph H NHTs</td>
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<tr>
<td>6</td>
<td>NHTs</td>
<td>n-C8H17CH=C=CH2</td>
<td>31</td>
<td>=NTs</td>
<td>n-C8H17 CH=C=CH2 =NTs + n-C8H17 CH=C=CH2 =NTs</td>
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<td>H3C H3C NHTs</td>
<td>Ph</td>
<td>19</td>
<td>31</td>
<td>H3C H3C NHTs + H3C H3C NHTs</td>
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<td>19</td>
<td>n-C8H17CH=C=CH2</td>
<td>22</td>
<td>=NTs</td>
<td>n-C8H17 CH=C=CH2 =NTs + n-C8H17 CH=C=CH2 =NTs</td>
</tr>
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</table>

$^a$ See the text for the experimental detail. $^b$ All of the products gave satisfactory $^1H$, $^{13}C$ NMR, IR and HRMS data. $^c$ The isomer ratios were determined by $^1H$ NMR spectroscopy.
subsequently undergo intramolecular nucleophilic displacement to provide the observed products and regenerate the palladium(0) catalyst (Scheme 1). The regio- and stereoselectivity of this process arises from the \( \pi \)-allylpalladium displacement step.

**Scheme 1**

The reaction of iodide 8 with 4,5-nonadiene gave the desired pyran derivatives 9a and 9b in 53% yield as an inseparable 56:44 mixture of two stereoisomers (entry 1), while the reaction of (Z)-3-iodo-2-methyl-2-propenol with
the same allene afforded the desired product as just one stereoisomer derived from the syn $\pi$-allylpalladium intermediate. The formation of a mixture of two stereoisomers is probably due to the equilibrium existing between syn $\pi$-palladium intermediate 23 and anti $\pi$-palladium intermediate 24, since the steric hindrance between $R^2 (R^2 = \text{Ph})$ and $R^3$ would force the formation of anti-24 from syn-23. When an unsymmetrical allene, 1,2-undecadiene, was used, the regiochemistry of the product formed is the same as that of the product formed from (Z)-3-iodo-2-methyl-2-propenol and the same allene, in which the oxygen nucleophile attacks the more substituted end of the $\pi$-allylpalladium intermediate.

Tosylamide derivatives have proven quite successful in this annulation chemistry. Compound 12 is formed from the syn $\pi$-allylpalladium intermediate derived from the reaction of vinylic iodide 11 and 1,2-cycloctadecadiene. The structure of compound 12 was confirmed by the NOESY spectrum, since there is a strong NOE interaction between the vinylic hydrogen exocyclic to the 6-membered ring and its allylic counterpart at the ring junction. The reaction of vinylic iodide 13 with 1,2-cycloctadecadiene afforded piperidine derivatives 14 as an inseparable four diastereoisomers in the ratio of 59 : 21 : 14 : 6. The formation of $E$ and $Z$ carbon-carbon double bond isomers is also probably due to the presence of a sterically hindered phenyl group (see Scheme 4, $R^2 = \text{Ph}$, intermediates 23 and 24). Similar to the annulation of allenes with aromatic iodides containing a tosylamide functionality, six-membered ring products are formed by preferential attack at the less hindered end of the allene (entry 5), while five-membered ring products come preferentially from attack at the more hindered end of the allene (entries 6-8).
In conclusion, palladium-catalyzed annulation of allenes has been extended to vinylic iodides containing a tertiary hydroxyl group or sulfonamide functionality. The results obtained from this study further support the proposed mechanism.

These same functionalized tosylamides have also been reacted with alkynes in the presence of a palladium catalyst. The reaction of acyclic sulfonamides 19, 28 and 30 afforded the expected products 27, 29 and 31 in 77, 61 and 58% yields, respectively, when reacted with diphenylacetylene under reaction conditions similar to those previously reported for cyclic sulfonamides (eq. 6).7

\[
\begin{align*}
R^1 & \quad NHTs \quad + \quad 2 \; \text{PhC} = \text{CPh} \quad \xrightarrow{5 \% \; \text{Pd(OAc)}_2, \; 2 \; \text{Na}_2\text{CO}_3, \; 1 \; \text{LiCl}, \; 100 \, ^{\circ} \text{C}} \quad R^1 \quad \text{NTs} \\
19 & \quad R^1 = R^2 = \text{Me} \quad 10 \; \text{h} \quad 27 \quad 77\% \\
28 & \quad R^1 = \text{Me}, \; R^2 = \text{Ph} \quad 10 \; \text{h} \quad 29 \quad 61\% \\
30 & \quad R^1, \; R^2 = -(\text{CH}_2)_5- \quad 8 \; \text{h} \quad 31 \quad 58\%
\end{align*}
\]

Interestingly, the reaction of sulfonamides 19, 28 and 30 with 4,4-dimethyl-2-pentyne afforded unsaturated aldehydes 32-34 in 56, 73 and 55% yields as inseparable 89:11, 57:18:17:8, and 84:16 mixtures of all possible stereoisomers about the two double bonds (eq. 7). No attempt was made to identify each isomer.

\[
\begin{align*}
R^1 & \quad NHTs \quad + \quad 5 \; \text{MeC} = \text{CMe}_3 \quad \xrightarrow{5 \% \; \text{Pd(OAc)}_2, \; 2 \; \text{Na}_2\text{CO}_3, \; 1 \; \text{LiCl}, \; 100 \, ^{\circ} \text{C}} \quad R^1 \quad \text{CHO} \\
19 & \quad R^1 = R^2 = \text{Me} \quad 20 \; \text{h} \quad 32 \quad 56\% \; (89 : 11) \\
28 & \quad R^1 = \text{Me}, \; R^2 = \text{Ph} \quad 18 \; \text{h} \quad 33 \quad 73\% \; (57 : 18 : 17 : 8) \\
30 & \quad R^1, \; R^2 = -(\text{CH}_2)_5- \quad 24 \; \text{h} \quad 34 \quad 55\% \; (84 : 16)
\end{align*}
\]
The mechanism of this latter transformation is rather interesting. The reactions of sulfonamides 19, 28 and 30 with diphenylacetylene or 4,4-dimethyl-2-pentyne presumably afford intermediate 35 by a sequence involving (1) reduction of Pd(OAc)$_2$ to the actual Pd(0) catalyst, (2) oxidative addition of the starting halide to Pd(0), (3) vinylpalladium coordination to the alkyne and subsequent insertion of the alkyne to form a new vinylpalladium intermediate, and (4) attack of the negatively charged nitrogen nucleophile on the vinylpalladium intermediate to form the six-membered palladacycle 35 (Scheme 2). Apparently, when $R^3 = R^4 = \text{Ph}$, intermediate 35 undergoes reductive elimination to afford products 27, 29 and 31. However, when $R^3 = \text{Me}$ and $R^4 = \text{CMe}_3$, intermediate 35 apparently undergoes $\beta$-hydride elimination to afford intermediate 36, which upon subsequent reductive elimination affords products 32-34. The reason for this difference is not clear. However, this is consistent with the fact that our previous yields from the annulation of internal alkynes by functionally-substituted aryl halides are consistently high.

**Scheme 2**
when diphenylacetylene is employed, presumably due to the easy reductive elimination of intermediates like 35. Since the addition of organopalladium intermediates to 4,4-dimethyl-2-pentyne is generally highly regioselective, the mixtures of isomers 32-34 observed are probably formed by either (1) base-catalyzed isomerization of the \( \alpha,\beta \)-unsaturated aldehydes formed, and/or (2) non-stereospecific reductive elimination of intermediate 36. We have not attempted to ascertain which path is involved.

Due to the instability of compounds 27, 29, and 31, they could not be fully characterized. Therefore, compound 27 was converted to 1,2,3,4-tetrasubstituted pyrrole 37, which was fully characterized, in 72% yield by an ene reaction with DEAD (eq 8).  

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Me} & \quad \text{Me} \\
\text{NTs} & \\
\text{27} & \\
\end{align*}
\begin{align*}
+ & \quad \begin{array}{c}
\text{EtO}_2\text{CN}=\text{NCO}_2\text{Et}
\end{array} \\
\text{PhMe, 85 °C} & \\
\text{Me} & \quad \text{Me} \\
\text{NHCOC}_2\text{Et} & \quad \text{NHCOC}_2\text{Et} \\
\text{Ph} & \quad \text{Ph} \\
\text{37} & \\
\end{align*}
\]

In conclusion, the reaction of acyclic sulfonamides 19, 28 and 30 with diphenylacetylene afforded the anticipated pyrrolidine derivatives, as previously reported for cyclic sulfonamides. Unexpectedly, the reaction of sulfonamides 19, 28 and 30 with 4,4-dimethyl-2-pentyne affords the potentially useful \( \alpha,\beta \)-unsaturated aldehydes 32-34.

**Experimental Section**

**General.** All \(^1\)H and \(^13\)C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography (TLC) was performed using commercially
prepared 60 mesh silica gel plates (Whatman K6F), and visualized with short
wavelength UV light (254 nm), and basic KMnO₄ solution [3g KMnO₄ + 20g K₂CO₃ +
5 ml NaOH (5%) + 300 ml H₂O].

Reagents. All reagents were used directly as obtained commercially
unless otherwise noted. Tetra-n-butylammonium chloride monohydrate was
purchased from Aldrich Chemical Co. Vinylidene cyclohexane was prepared from
(1-chlorocyclohexyl)acetylene using a literature procedure.¹⁹ 1,2-Undecadiene
and 4,5-nonadiene were prepared by treating the corresponding 1,1-
dibromocyclopropanes with methyllithium according to a literature procedure.²⁰
Iodides 8, 11, 13, 17, 19, 28 and 30 were prepared as follows.

(Z)-4-Iodo-2-methyl-3,4-diphenyl-3-buten-2-ol (8). A 2 M ethereal
solution of ‘PrMgCl (15 ml, 30 mmol) was added to a solution of Ti(O’Pr)₄ (4.43 ml,
4.26 g, 15 mmol) and diphenylacetylene (2.67 g, 15 mmol) in ether (160 ml) at -78
°C. The resulting yellow homogeneous mixture was warmed to -50 °C over 45 min
to give a brown solution, which was stirred at -50 °C for 2.5 h. After the reaction
mixture was recooled to -78 °C, acetone (0.78 ml, 0.62 g, 10.7 mmol) was added to
the reddish brown mixture and stirred at -78 °C for 2 h, followed by the addition of a
THF (10 ml) solution of I₂ (7.61 g, 30 mmol) at -78 °C. The mixture was stirred at
-78 °C for 30 min, then quenched with satd. aq. NH₄Cl (90 ml) and brine (100 ml),
followed by warm-up to room temperature. After filtration, the mixture was washed
with satd. aq. Na₂S₂O₃ (100 ml). The organic layer was dried over Na₂SO₄ and
then evaporated to provide a residue. Flash chromatography of this residue using
1:9 ethyl acetate/hexanes as eluent afforded iodide 8 as an off-white solid in 77%
yield: mp 85-87 °C; ¹H NMR (CDCl₃) δ 1.55 (s, 6H), 2.99 (s, 1H), 6.89-7.06 (m,
10H); ¹³C NMR (CDCl₃) δ 29.4, 74.0, 94.6, 126.5, 126.6, 127.4, 127.5, 128.4, 129.1,
139.4, 146.4, 153.9; IR (CHCl₃) 3541, 3440, 3077, 3058, 2976 cm⁻¹.
(Z)-N-(3-ido-1,2,3-triphenyl-2-propenyl)-p-toluenesulfonamide (13). **Representative Procedure.** N-BOC p-toluenesulfonamide (1.78 g, 6.52 mmol) was dissolved in 36 ml of THF and PPh₃ (3.44 g, 13.1 mmol) was added. The solution was stirred under argon and 1,2,3-triphenyl-2-propen-1-ol¹¹ (1.8 g, 4.37 mmol) was added, followed by the addition of diethyl azodicarboxylate (1.73 ml, 1.9 g, 10.9 mmol). The mixture was stirred at room temperature for 50 h. Silica gel was added to the above solution, which was then evaporated to provide a residue. Chromatography of the latter on silica gel, using 1:9 ethyl acetate/hexanes as eluent yielded 2.20 g of the desired N-BOC sulfonamide (76% yield): Rₗ = 0.14 (1:9 EtOAc/hexanes); 'H NMR (CDCl₃) δ 0.58 (s, 9H), 2.51 (s, 3H), 6.95-7.36 (m, 16H), 7.42 (d, J = 8.4 Hz, 2H), 8.13 (dd, J = 6.6, 1.5 Hz, 2H); ^1³C NMR (CDCl₃) δ 21.7, 26.8, 71.7, 83.4, 107.2, 126.4, 126.8, 126.9, 127.2, 127.4, 128.5, 129.0, 129.2, 129.4, 131.01, 131.02, 136.4, 136.9, 137.3, 144.2, 144.55, 144.60, 149.7.

The N-BOC-sulfonamide (2.07 g, 3.10 mmol) was dissolved in CH₂Cl₂ (50 ml) and trifluoroacetic acid (1.07 ml, 1.59 g, 14.0 mmol) was added. The resulting slight yellow solution was stirred at room temperature for 45 h. Silica gel was added to the solution, which was then evaporated to provide a residue. Chromatography of the latter on silica gel, using 1:7 and 1:1 ethyl acetate/hexanes as eluent, afforded 1.01 g of sulfonamide 13 as an off-white solid (58 % yield): mp 190-192 °C; Rₗ = 0.18 (1:5 EtOAc/hexanes); 'H NMR (CDCl₃) δ 2.50 (s, 3H), 4.74 (d, J = 10.2 Hz, 1H), 6.20 (d, J = 7.2 Hz, 2H), 6.25 (d, J = 10.2 Hz, 1H), 6.85 - 6.90 (m, 3H), 6.95 - 7.05 (m, 5H), 7.32 - 7.42 (m, 5H), 7.58 (d, J = 7.2 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H); ^1³C NMR (CDCl₃) δ 21.6, 66.3, 104.9, 126.3, 127.5, 127.6, 127.68, 127.74, 127.8, 128.0, 128.7, 128.9, 129.6, 129.7, 134.9, 137.76, 137.79, 143.6, 143.7, 146.0; IR (CHCl₃) 3296, 3069, 2985, 1340, 1160 cm⁻¹.
**N-[(Z)-3-ido-2-methyl-2-propenyl]-p-toluenesulfonamide (11).** (Z)-3-ido-2-methyl-2-propen-1-ol$^{10}$ was used instead of 1,2,3-triphenyl-2-propen-1-ol in the above general procedure (95% yield). Mp 82-84 °C; $^1$H NMR (CDCl$_3$) δ 1.86 (d, J = 1.5 Hz, 3H), 2.43 (s, 3H), 3.67 (d, J = 6.0 Hz, 2H), 5.14 (t, J = 6.0 Hz, 1H), 5.98 (t, J = 0.9 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 21.4, 22.1, 50.1, 77.4, 127.1, 129.6, 136.5, 142.5, 143.5; IR (CHCl$_3$) 3306, 3062, 3026, 2917, 1342, 1158 cm$^{-1}$.

**N-(2-ido-2-propenyl)-p-toluenesulfonamide (17).** 2-ido-propenol$^{12}$ was used instead of 1,2,3-triphenyl-2-propen-1-ol in the above general procedure (83% yield). Mp 58-60 °C; $^1$H NMR (CDCl$_3$) δ 2.43 (s, 3H), 3.81 (s, 2H), 5.27-5.30 (m, 1H), 5.76 (d, J = 1.2 Hz, 1H), 6.26 (td, J = 3.0, 1.2 Hz, 1H), 7.31 (d, J = 7.5 Hz, 2H), 7.75 (d, J = 7.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 21.5, 54.4, 104.6, 127.2, 127.4, 129.7, 136.8, 143.8; IR (CHCl$_3$) 3288, 3097, 3029, 2867, 1328, 1158 cm$^{-1}$.

**N-(2-ido-3-methyl-2-butenyl)-p-toluenesulfonamide (19).** 2-ido-3-methyl-2-buten-1-ol (prepared by the DIBAL reduction of ethyl 2-ido-3-methyl-2-butenoate,$^{14}$ see chapter 3) was used instead of 1,2,3-triphenyl-2-propen-1-ol in the above general procedure (67% yield). Mp 95-97 °C; $^1$H NMR (CDCl$_3$) δ 1.76 (s, 3H), 1.81 (s, 3H), 2.42 (s, 3H), 4.00 (d, J = 6.0 Hz, 2H), 4.90 (t, J = 6.0 Hz, 1H), 7.28 (d, J = 7.5 Hz, 2H), 7.74 (d, J = 7.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 19.1, 21.5, 31.3, 51.2, 95.9, 127.2, 129.4, 137.2, 141.8, 143.4; IR (CHCl$_3$) 3284, 3068, 2923, 1328, 1158 cm$^{-1}$.

**N-[(Z)-2-ido-3-phenyl-2-butenyl]-p-toluenesulfonamide (28).** (Z)-2-ido-3-phenyl-2-buten-1-ol (prepared by the DIBAL reduction of ethyl (Z)-2-ido-3-phenyl-2-butenoate,$^{14}$ see chapter 3) was used instead of 1,2,3-triphenyl-2-propen-1-ol in the above general procedure (70% yield). Mp 132-134 °C; $^1$H NMR (CDCl$_3$) δ 2.07 (s, 3H), 2.47 (s, 3H), 4.18 (d, J = 6.0 Hz, 2H), 5.05 (t, J = 6.0 Hz, 1H),
6.76 (dd, J = 9.0, 3.0 Hz, 2H), 7.24-7.31 (m, 3H), 7.33 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H); 13C NMR (CDCl$_3$) δ 21.5 (2 C), 50.9, 98.4, 126.9, 127.2, 127.4, 128.2, 129.6, 137.5, 143.6, 146.6, 146.8; IR (CHCl$_3$) 3263, 3076, 3061, 1323, 1151 cm$^{-1}$.

**N-(2-Cyclohexylidene-2-iodoethyl)-p-toluenesulfonamide (30).**

2-Cyclohexylidene-2-iodoethyl alcohol (prepared by the NaBH$_4$ reduction of cyclohexylideneiodoacetaldehyde$^{15}$ in the presence of CeCl$_3$, see chapter 3) was used instead of 1,2,3-triphenyl-2-propen-1-ol in the above general procedure (59% yield). Mp 103-105 °C; $^1$H NMR (CDCl$_3$) δ 1.40-1.48 (m, 6H), 2.19 (t, J = 5.4 Hz, 2H), 2.71 (t, J = 5.7 Hz, 2H), 2.42 (s, 3H), 4.04 (d, J = 6.0 Hz, 2H), 5.11 (t, J = 5.7 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H); 13C NMR (CDCl$_3$) δ 21.4, 26.0, 27.1, 27.5, 31.1, 41.8, 50.6, 93.4, 127.2, 129.4, 137.1, 143.3, 149.0; IR (CHCl$_3$) 3384, 3070, 2935, 1330, 1158 cm$^{-1}$.

**General Procedure for the Palladium-Catalyzed Annulation of Allenes.** After stirring Pd(OAc)$_2$ (5 mol %), PPh$_3$ (5 mol %), n-Bu$_4$NCl (1 equiv, Aldrich Chemical Co., monohydrate), Na$_2$CO$_3$ (5 equivs), and the organic halide (0.25 mmol) in 1 mL of anhydrous DMF for two minutes, the allene (1.25 mmol) was added to the mixture. The vial was then capped and suspended in an oil bath at 80 °C for the appropriate period of time. When the reaction was considered complete as determined by TLC analysis, it was allowed to cool to room temperature and diluted with saturated NH$_4$Cl and extracted with ether. The extracts were dried over Na$_2$SO$_4$ and concentrated prior to chromatography. The desired products were collected and the solvents were removed by rotary evaporation. When necessary, the isomeric ratio of the products was determined by employing $^1$H NMR spectral analysis. Most products were sufficiently unstable as to prevent us from obtaining elemental analyses to ascertain purity. The following products were synthesized by using this procedure.
(E)-5-Butylidene-5,6-dihydro-2,2-dimethyl-3,4-diphenyl-6-n-propyl-2H-pyran (9a) and (Z)-5-butylidene-5,6-dihydro-2,2-dimethyl-3,4-diphenyl-6-n-propyl-2H-pyran (9b) (Table 1, entry 1). Compounds 9a and 9b (9a : 9b = 56 : 44, inseparable mixture): pale yellow oil; Rf = 0.70 (9:1 hexanes/EtOAc). Compound 9a: 1H NMR (CDCl3) δ 0.59 (t, J = 7.2 Hz, 3H), 0.84-1.17 (m, 1H), 1.03 (t, J = 7.2 Hz, 3H), 1.24-1.36 (m, 1H), 1.31 (s, 3H), 1.38 (s, 3H), 1.42-2.08 (m, 6H), 4.30 (t, J = 6.1 Hz, 1H), 5.35 (td, J = 7.2, 0.9 Hz, 1H), 6.88-7.10 (m, 10H). Compound 9b: 1H NMR (CDCl3) δ 0.84 (t, J = 7.2 Hz, 3H), 0.84-1.17 (m, 1H), 1.02 (t, J = 7.2 Hz, 3H), 1.18 (s, 3H), 1.24-1.36 (m, 1H), 1.42-2.08 (m, 6H), 1.52 (s, 3H), 4.86-4.93 (m, 2H), 6.88-7.10 (m, 10H). Additional spectral data for the product mixture: 13C NMR (CDCl3) δ 13.6, 13.9, 14.2, 14.3, 18.7, 19.2, 22.6 (2 C), 26.3, 28.3, 28.8, 29.2, 30.0, 30.5, 36.1, 38.6, 71.0, 74.0, 74.4, 75.7, 125.6, 125.8, 125.9, 126.1, 127.1, 127.2, 127.7, 128.2, 129.9, 130.37, 130.40, 130.43, 130.7, 134.2, 134.9, 135.6, 137.7, 139.5, 139.8, 139.9, 141.2, 142.1, 144.8; IR (CHCl3) 3077, 3057, 1073 cm\(^{-1}\); HRMS m/z 360.2455 (calcd for C\(_{26}\)H\(_{32}\)O 360.2453).

5,6-Dihydro-2,2-dimethyl-5-methylene-6-n-octyl-3,4-diphenyl-2H-pyran (10) (Table 1, entry 2). Colorless oil; Rf = 0.75 (9:1 hexanes/EtOAc); 1H NMR (CDCl3) δ 0.89 (t, J = 6.8 Hz, 3H), 1.30-1.52 (m, 11H), 1.31 (s, 3H), 1.46 (s, 3H), 1.65-1.77 (m, 2H), 1.90-1.97 (m, 1H), 4.47-4.50 (m, 1H), 4.51 (s, 1H), 5.00 (d, J = 0.9 Hz, 1H), 6.91-7.09 (m, 10H); 13C NMR (CDCl3) δ 14.1, 22.7, 24.2, 25.5, 28.9, 29.4, 29.7, 31.9, 32.5, 69.8, 75.1, 110.3, 125.9, 126.1, 127.1, 127.2, 130.0, 130.4, 135.4, 138.9, 139.3, 145.0, 145.5; IR (CHCl3) 3054, 1633, 1094 cm\(^{-1}\); HRMS m/z 388.2769 (calcd for C\(_{28}\)H\(_{36}\)O 388.2766).

(E)-1,2,5,6-Tetrahydro-3-methyl-1-toluenesulfonyl-6,7,8,9,10,11,12,13,14,15-decahydrocyclotrideca[b]pyridine (12) (Table 1, entry 3). Pale yellow, viscous oil; Rf = 0.35 (9:1 hexanes/EtOAc); 1H

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1. Compounds 9a and 9b (9a : 9b = 56 : 44, inseparable mixture): pale yellow oil; Rf = 0.70 (9:1 hexanes/EtOAc).
2. Compound 9a: 1H NMR (CDCl3) δ 0.59 (t, J = 7.2 Hz, 3H), 0.84-1.17 (m, 1H), 1.03 (t, J = 7.2 Hz, 3H), 1.24-1.36 (m, 1H), 1.31 (s, 3H), 1.38 (s, 3H), 1.42-2.08 (m, 6H), 4.30 (t, J = 6.1 Hz, 1H), 5.35 (td, J = 7.2, 0.9 Hz, 1H), 6.88-7.10 (m, 10H).
3. Compound 9b: 1H NMR (CDCl3) δ 0.84 (t, J = 7.2 Hz, 3H), 0.84-1.17 (m, 1H), 1.02 (t, J = 7.2 Hz, 3H), 1.18 (s, 3H), 1.24-1.36 (m, 1H), 1.42-2.08 (m, 6H), 1.52 (s, 3H), 4.86-4.93 (m, 2H), 6.88-7.10 (m, 10H).
4. Additional spectral data for the product mixture: 13C NMR (CDCl3) δ 13.6, 13.9, 14.2, 14.3, 18.7, 19.2, 22.6 (2 C), 26.3, 28.3, 28.8, 29.2, 30.0, 30.5, 36.1, 38.6, 71.0, 74.0, 74.4, 75.7, 125.6, 125.8, 125.9, 126.1, 127.1, 127.2, 127.7, 128.2, 129.9, 130.37, 130.40, 130.43, 130.7, 134.2, 134.9, 135.6, 137.7, 139.5, 139.8, 139.9, 141.2, 142.1, 144.8; IR (CHCl3) 3077, 3057, 1073 cm\(^{-1}\); HRMS m/z 360.2455 (calcd for C\(_{26}\)H\(_{32}\)O 360.2453).

5. Compound 10: 1H NMR (CDCl3) δ 0.89 (t, J = 6.8 Hz, 3H), 1.30-1.52 (m, 11H), 1.31 (s, 3H), 1.46 (s, 3H), 1.65-1.77 (m, 2H), 1.90-1.97 (m, 1H), 4.47-4.50 (m, 1H), 4.51 (s, 1H), 5.00 (d, J = 0.9 Hz, 1H), 6.91-7.09 (m, 10H); 13C NMR (CDCl3) δ 14.1, 22.7, 24.2, 25.5, 28.9, 29.4, 29.7, 31.9, 32.5, 69.8, 75.1, 110.3, 125.9, 126.1, 127.1, 127.2, 130.0, 130.4, 135.4, 138.9, 139.3, 145.0, 145.5; IR (CHCl3) 3054, 1633, 1094 cm\(^{-1}\); HRMS m/z 388.2769 (calcd for C\(_{28}\)H\(_{36}\)O 388.2766).

6. Compound 12: Pale yellow, viscous oil; Rf = 0.35 (9:1 hexanes/EtOAc); 1H
NMR (CDCl$_3$) δ 1.08-1.56 (m, 18H), 1.67 (s, 3H), 1.68-1.78 (m, 1H), 2.06-2.14 (m, 1H), 2.38 (s, 3H), 3.72 (d, J = 18.9 Hz, 1H), 4.00 (d, J = 18.9 Hz, 1H), 4.18 (dd, J = 10.5, 3.0 Hz, 1H), 5.17 (dd, J = 10.5, 4.6 Hz, 1H), 5.85 (s, 1H), 7.18 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 20.5, 21.4, 23.4, 24.4, 24.8, 24.9, 25.2, 25.6, 26.3 (2 C), 28.0, 32.1, 45.6, 58.3, 117.6, 127.2, 127.6, 128.9, 130.1, 131.3, 136.7, 142.8; IR (CHCl$_3$) 1650, 1598, 1337, 1161 cm$^{-1}$; HRMS m/z 401.2392 (calcd for C$_{24}$H$_{35}$NO$_2$S 401.2388).

1,2,5,6-Tetrahydro-2,3,4-triphenyl-1-toluenesulfonyl-6,7,8,9,10,11,12,13,14,15-decahydrocyclotrideca[b]pyridine (14a-d) (Table 1, entry 4). Inseparable mixture of four diastereomers (6 : 21 : 59 : 14); yellow oil; R$_f$ = 0.39 (9:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$) δ 0.76-1.77 (m, 45.8H), 2.05-2.22 (m, 4H), 2.28 (s, 1.1H), 2.29 (s, 3H), 2.32 (s, 0.72H), 2.39 (s, 0.30H), 2.61-2.74 (m, 2H), 4.52 (d, J = 7.6 Hz, 0.35H), 4.66-4.70 (m, 1.14H), 4.98-5.02 (m, 0.08H), 5.09-5.11 (m, 0.42H), 5.17-5.20 (m, 0.29H), 5.18 (dd, J = 2.8, 10.4 Hz, 0.29H), 5.29 (dd, J = 3.6, 9.2 Hz, 0.24H), 5.34 (s, 0.24H), 5.39 (s, 1H), 5.62 (dd, J = 3.8, 11.0 Hz, 1.12H), 5.91 (s, 0.35H), 6.14 (s, 0.10H) 6.43 (d, J = 6.8 Hz, 0.48H), 6.48 (d, J = 6.8 Hz, 2.04H), 6.60 (d, J = 7.2 Hz, 0.66H), 6.77-6.79 (m, 0.63H), 6.86-7.26 (m, 34.2H), 7.58-7.63 (m, 1.8H), 7.85 (d, J = 8.0 Hz, 0.43H); $^{13}$C NMR (CDCl$_3$) δ 143.0, 141.6, 141.5, 140.5, 140.3, 140.1, 139.8, 139.6, 139.5, 139.3, 139.2, 139.0, 138.5, 138.2, 138.0, 137.6, 137.1, 136.4, 135.2, 135.0, 134.9, 134.7, 134.0, 133.5, 133.3, 132.2, 131.5, 130.6, 130.4 (2 C), 130.2, 130.0, 129.8, 129.7, 129.5, 129.3, 129.2 (2 C), 128.9, 128.6, 128.5 (2 C), 128.0, 127.8 (2 C), 127.7 (2 C), 127.6, 127.5 (2 C), 127.4, 127.3, 127.2 (2 C), 127.1, 126.6, 126.5 (3 C), 126.4, 126.3, 126.1, 63.7, 63.6, 63.5, 63.0, 62.9, 62.8, 62.4, 60.8, 60.1, 58.4, 54.7, 53.0, 35.6 (2 C), 34.3, 34.2, 33.6, 31.9, 29.7, 29.6, 28.3 (2 C), 28.2, 28.0, 27.8, 27.5, 27.4, 27.3, 27.1, 28.67, 26.7, 26.5, 26.3, 26.0, 25.4 (2 C), 25.3 (2 C), 25.2, 24.3,
24.2, 24.0, 23.9, 23.3, 22.6, 21.4, 21.3; IR (CHCl₃) 3019, 1653, 1558, 1215 cm⁻¹; HRMS m/z 615.3183 (calcd for C₄₁H₄₅NO₂S 615.3171).

**6-Spiro-cyclohexane-1,2,5,6-tetrahydro-5-methylidene-2,3,4-triphenyl-1-toluenesulfonylpyridine (15)** and **5-cyclohexylidene-1,2,5,6-tetrahydro-2,3,4-triphenyl-1-toluenesulfonylpyridine (16)** (Table 1, entry 5). Compound 15: white wax; Rᶠ = 0.36 (9:1 hexanes/EtOAc); ¹H NMR (CDCl₃) δ 0.95-1.04 (m, 2H), 1.28-1.67 (m, 4H), 1.76-1.84 (m, 1H), 1.95-2.07 (m, 1H), 2.27 (s, 3H), 2.69-2.78 (m, 1H), 2.85-2.91 (m, 1H), 4.39 (s, 1H), 5.04 (s, 1H), 6.45 (s, 1H), 6.71-6.74 (m, 2H), 6.92-7.25 (m, 13H), 7.66-7.69 (m, 4H); ¹³C NMR (CDCl₃) δ 21.3, 22.7, 22.9, 25.7, 34.6, 38.7, 61.6, 64.1, 115.9, 126.6, 126.67, 126.72, 127.63, 127.65, 127.76, 127.80, 128.8 (2 C), 129.6, 130.8, 134.1, 138.3, 138.8, 139.5, 139.6, 140.4, 142.7, 148.4; IR (CHCl₃) 3058, 1658, 1598, 1330, 1160 cm⁻¹; HRMS m/z 545.2401 (calcd for C₃₆H₃₅NO₂S 545.2388).

Compound 16: colorless oil; Rᶠ = 0.36 (9:1 hexanes/EtOAc); ¹H NMR (CDCl₃) δ 0.63-0.73 (m, 1H), 0.88-1.26 (m, 5H), 1.39-1.58 (m, 2H), 1.81-1.91 (m, 1H), 2.18-2.31 (m, 1H), 2.30 (s, 3H), 4.00 (d, J = 13.2 Hz, 1H), 4.39 (d, J = 13.2 Hz, 1H), 5.69 (s, 1H), 6.61 (dt, J = 6.6, 1.2 Hz, 2H), 6.84-6.88 (m, 2H), 6.96-7.07 (m, 8H), 7.23-7.34 (m, 3H), 7.50 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 7.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.4, 26.0, 26.6, 27.5, 31.1, 32.6, 44.7, 61.8, 123.1, 126.4, 126.5, 126.7, 127.2, 127.3, 127.5, 127.8, 128.0, 128.2, 128.9, 129.3, 129.7, 136.2, 136.5, 139.5, 140.0, 140.4, 140.8, 142.8, 143.3; IR (CHCl₃) 3077, 3051, 1598, 1367, 1160 cm⁻¹; HRMS m/z 545.2396 (calcd for C₃₆H₃₅NO₂S 545.2388).

**3,4-Dimethylidene-2-n-octyl-1-toluenesulfonylpyrrolidine (18a)** and **(E)-4-methylidene-3-n-nonylidene-1-toluenesulfonylpyrrolidine (18b)** (Table 1, entry 6). Compounds 18a and 18b (18a : 18b = 7 : 1, inseparable mixture): colorless oil; Rᶠ = 0.38 (9:1 hexanes/EtOAc). Compound
18a: $^1$H NMR (CDCl$_3$) δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.22-1.40 (m, 12H), 1.60-1.78 (m, 2H), 2.40 (s, 3H), 4.03-4.17 (m, 2H), 4.34-4.38 (m, 1H), 4.79 (s, 1H), 4.85 (t, $J = 1.8$ Hz, 1H), 5.29 (s, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.66 (d, $J = 8.0$ Hz, 2H). Additional spectral data for the product mixture: $^{13}$C NMR (CDCl$_3$) δ 14.1, 21.5, 22.6, 24.3, 29.3, 29.5 (2 C), 31.8, 36.4, 52.3, 65.0, 105.2, 105.4, 127.4, 129.5, 135.1, 141.8, 143.3, 146.0; IR (CHCl$_3$) 1658, 1558, 1342, 1160 cm$^{-1}$; HRMS m/z 361.2083 (calcd for C$_{21}$H$_{31}$NO$_2$S 361.2076).

2-Spiro-cyclohexane-4-isopropylidene-3-methylidene-1-toluenesulfonylpyrrolidine (20) and 3-cyclohexylidene-4-isopropylidene-1-toluenesulfonylpyrrolidine (21) (Table 1, entry 7). Compound 20: pale yellow solid; mp 94 - 96 °C; $R_f = 0.41$ (9:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$) δ 1.23-1.35 (m, 1H), 1.40-1.50 (m, 2H), 1.61-1.71 (m, 5H), 1.71 (3H), 1.90 (s, 3H), 2.32-2.42 (m, 2H), 2.40 (s, 3H), 4.07 (s, 2H), 5.05 (s, 1H), 5.36 (s, 1H), 7.24 (d, $J = 8.2$ Hz, 2H), 7.71 (d, $J = 8.2$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 21.4, 21.9, 22.3, 23.5, 24.9, 33.6, 50.6, 70.6, 109.8, 126.7, 127.2, 129.0, 129.3, 139.9, 142.6, 150.7; IR (CHCl$_3$) 1642, 1598, 1327, 1155 cm$^{-1}$; HRMS m/z 345.1768 (calcd for C$_{20}$H$_{27}$NO$_2$S 345.1762). Compound 21: pale yellow oil; $R_f = 0.34$ (9:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$) δ 1.41-1.53 (m, 3H), 1.53 (s, 3H), 1.59 (s, 3H), 1.63 (s, 3H), 1.91 (t, $J = 6.0$ Hz, 2H), 2.05 (t, $J = 6.0$ Hz, 2H), 2.42 (s, 3H), 3.88 (s, 4H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.71 (d, $J = 8.1$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 21.5, 21.8, 23.4, 26.2, 27.3, 27.5, 32.5, 32.9, 50.3, 50.7, 124.6, 127.5, 127.6, 127.7, 129.7, 134.5, 135.6, 143.2; HRMS m/z 345.1759 (calcd for C$_{21}$H$_{31}$NO$_2$S 345.1763).

4-Isopropylidene-3-methylidene-2-n-octyl-1-toluenesulfonylpyrrolidine (22a) and (E)-3-isopropylidene-4-n-nonylidene-1-toluenesulfonylpyrrolidine (22b) (Table 2, entry 8).
Compounds 22a and 22b (22a : 22b = 6 : 1, inseparable mixture): colorless oil; 
$R_f = 0.36$ (9:1 hexanes/EtOAc). Compound 22a: $^1$H NMR (CDCl$_3$) $\delta$ 0.88 (t, $J = 6.8$ Hz, 3H), 1.20-1.36 (m, 12H), 1.60-1.72 (m, 2H), 1.68 (s, 3H), 1.78 (s, 3H), 2.39 (s, 3H), 4.03 (s, 2H), 4.29 (t, $J = 6.0$ Hz, 1H), 4.88 (s, 1H), 4.94 (s, 1H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.66 (d, $J = 7.8$ Hz, 2H). Additional spectral data for the product mixture: $^1$C NMR (CDCl$_3$) $\delta$ 14.0, 21.4, 21.8, 22.6, 23.3, 24.6, 29.2, 29.3, 29.4, 31.8, 36.6, 51.6, 66.5, 108.7, 127.27, 127.31, 129.4, 130.7, 135.3, 143.0, 145.8; IR (CHCl$_3$) 1734, 1653, 1599, 1370, 1161 cm$^{-1}$; HRMS m/z 389.2392 (calcd for C$_{23}$H$_{35}$NO$_2$S 389.2388).

**General Procedure for the Palladium-Catalyzed Annulation of Internal alkynes.** Pd(OAc)$_2$ (3 mg, 0.013 mmol), Na$_2$CO$_3$ (0.50 mmol), DMF (5 ml), LiCl (10.6 mg, 0.25 mmol), the vinylic iodide (0.25 mmol), and the alkyne (0.5 or 1.25 mmol) were placed in a 2 dram vial in the above order. After the vial was flushed with argon and capped, it was heated in an oil bath at 100 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with saturated NH$_4$Cl, dried over anhydrous Na$_2$SO$_4$, and decanted. The solvent was evaporated under reduced pressure and the product was isolated by chromatography (hexanes/EtOAc) on a silica gel column. The following products were synthesized using this procedure.

4,5-Dihydro-4-isopropylidene-2,3-diphenyl-1-p-toluenesulfonylpyrrole (27) (eq 6). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield compound 27 as an off-white solid: $^1$H NMR (CDCl$_3$) $\delta$ 1.05 (t, $J = 2.1$ Hz, 3H), 1.60 (s, 3H), 2.44 (s, 3H), 4.58 (t, $J = 2.1$ Hz, 2H), 6.82-6.86 (m, 2H), 7.10-7.16 (m, 8H), 7.27 (dd, $J = 8.4$, 0.9 Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 20.1, 21.6, 23.4, 55.2, 122.1, 126.9, ...
127.0, 127.4, 127.9, 128.1, 128.3, 128.9, 129.3, 130.06, 130.12, 130.6, 130.8, 131.9, 135.8, 143.7. The mp, IR and HRMS could not be obtained due to the compound’s instability.

4,5-Dihydro-4-[([Z]-1-phenylethylidene)-2,3-diphenyl-1-p-toluenesulfonylpyrrole (29) (eq 6). The reaction mixture was chromatographed using 1:12 EtOAc/hexanes to yield compound 29 as an off-white solid: $^1$H NMR (CDCl$_3$) $\delta$ 1.97 (t, $J = 1.8$ Hz, 3H), 2.45 (s, 3H), 4.78 (q, $J = 1.8$ Hz, 2H), 6.30 (dd, $J = 8.1$, 1.4 Hz, 2H), 6.51 (dd, $J = 8.1$, 1.4 Hz, 2H), 6.62 (t, $J = 7.5$, 1.4 Hz, 2H), 6.67-6.79 (m, 4H), 7.05-7.20 (m, 5H), 7.27 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 8.1$ Hz, 2H). The mp, HRMS, IR and $^{13}$C NMR spectra could not be obtained due to the compound’s instability.

4,5-Dihydro-4-cyclohexylidene-2,3-diphenyl-1-p-toluenesulfonylpyrrole (31) (eq 6). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield compound 31 as an off-white solid: $^1$H NMR (CDCl$_3$) $\delta$ 1.03-1.11 (m, 2H), 1.35-1.42 (m, 4H), 1.45-1.54 (m, 2H), 1.98 (t, $J = 6.0$ Hz, 2H), 2.45 (s, 3H), 4.63 (s, 2H), 6.83-6.87 (m, 2H), 7.11-7.16 (m, 8H), 7.28 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 8.1$ Hz, 2H); $^{13}$C NMR (acetone-d$_6$) $\delta$ 31.2, 32.5, 32.8, 34.7, 35.0, 38.4, 59.8, 132.1, 132.3, 132.9, 133.2, 133.4, 133.8, 134.6, 134.8, 134.9, 135.0, 136.8, 137.1, 138.1, 138.3, 141.4, 149.3. The mp, HRMS and IR spectrum could not be obtained due to the compound’s instability.

2-Isopropyldiene-3,5,5-trimethyl-3-hexenal (32) (eq 7). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield compound 32 as a light yellow liquid consisting of an inseparable 89:11 mixture of isomers 32a and 32b. Compound 32a (major isomer): $^1$H NMR (CDCl$_3$) $\delta$ 1.21 (s, 9H), 1.59 (s, 3H), 1.90 (s, 3H), 2.01 (d, $J = 1.2$ Hz, 3H), 5.94 (dq, $J = 8.4$, 1.2 Hz, 1H), 9.55 (d, $J = 8.4$ Hz, 1H). Compound 32b (minor isomer): $^1$H NMR (CDCl$_3$) $\delta$
1.18 (s, 9H), 1.58 (s, 3H), 1.85 (s, 3H), 2.22 (d, J = 1.2 Hz, 3H), 5.67 (dq, J = 8.4, 1.2 Hz, 1H), 10.03 (d, J = 8.4 Hz, 1H). Additional spectral data for the product mixture: $^{13}$C NMR (CDCl$_3$) δ 22.0, 24.4, 26.8, 30.9, 31.0, 34.2, 128.4, 128.9, 129.0, 139.4, 168.0, 194.4; IR(CHCl$_3$) 1670 cm$^{-1}$; HRMS m/z 180.1516 (calcd for C$_{12}$H$_{20}$O 180.1514).

2-[(Z)-1-Phenylethylidene]-3,5,5-trimethyl-3-hexenal (33) (eq 7). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield compound 33 as a light yellow liquid consisting of an inseparable 57:18:17:8 mixture of isomers: $^1$H NMR (CDCl$_3$) δ 0.93 (s, 0.72H), 0.96 (s, 1.53H), 1.30 (s, 1.62H), 1.32 (s, 5.13H), 1.82 (s, 0.24H), 1.84 (s, 0.51H), 1.85 (d, J = 1.5 Hz, 1.71H), 1.95 (d, J = 1.5 Hz, 0.54H), 2.13 (s, 0.54H), 2.17 (s, 1.71H), 2.19 (d, J = 1.2 Hz, 0.51H), 2.39 (d, J = 1.2 Hz, 0.24H), 5.54-5.60 (m, 0.74H), 5.89 (dq, J = 8.4, 1.2 Hz, 0.08H), 6.04 (dq, J = 8.4, 1.2 Hz, 0.18H), 6.92-6.96 (m, 1.14H), 6.98-7.02 (m, 0.36H), 7.12-7.35 (m, 3.5H), 9.66 (d, J = 8.1 Hz, 0.18H), 9.74 (d, J = 8.4 Hz, 0.57H), 9.83 (d, J = 8.4 Hz, 0.17H), 10.11 (d, J = 8.1 Hz, 0.08H); $^{13}$C NMR (CDCl$_3$) δ 23.7, 27.55, 27.60, 30.8, 31.8, 32.0, 34.5, 125.9, 126.0, 126.1, 126.3, 126.9, 127.0, 127.2, 127.4, 127.8, 127.9, 128.0, 128.2, 129.1, 129.2, 130.6, 135.3, 142.2, 145.8, 165.8, 166.8, 191.0, 193.8, 194.0; IR(CHCl$_3$) 1660 cm$^{-1}$; HRMS m/z 242.1676 (calcd for C$_{17}$H$_{22}$O 242.1671).

2-Cyclohexylldene-3,5,5-trimethyl-3-hexenal (34) (eq 7). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield compound 34 as a light yellow liquid consisting of an inseparable 84:16 mixture of 34a and 34b. Compound 34a (major isomer): $^1$H NMR (CDCl$_3$) δ 1.21 (s, 9H), 1.44-1.63 (m, 6H), 1.95-2.01 (m, 2H), 2.00 (d, J = 1.2 Hz, 3H), 2.30-2.51 (m, 2H), 5.96 (dq, J = 8.4 Hz, 1.2 Hz, 1H), 9.63 (d, J = 8.4 Hz, 1H). Compound 34b (minor isomer): $^1$H NMR (CDCl$_3$) δ 1.18 (s, 9H), 2.21 (d, J = 1.2 Hz, 3H), 5.67 (dq, J = 8.4,
1.2 Hz, 1H), 10.02 (d, J = 8.4 Hz, 1H), the other peaks are obscured by those of the major isomer 34a. Additional spectral data for the product mixture: IR(CHCl₃) 1675 cm⁻¹; HRMS m/z 220.1824 (calcld for C₁₅H₂₄O 220.1827).

4-[1-Methyl-1-N-(diethyl hydrazinedicarboxylate)-ethyl]-2,3-diphenyl-1-p-toluenesulfonylpyrrole (37) (eq 8). Compound 27 (75mg, 0.181 mmol) and 4 ml of toluene were added to a 2 dram vial equipped with a stirring bar, followed by DEAD (0.06 ml, 0.0662g, 0.38 mmol). After flushing with argon, the reaction mixture was heated at 85 °C for 4.5 h and chromatographed using EtOAc/hexanes (1:2.5 and 1:1.5) to yield compound 37 as a colorless liquid, 76.5 mg (72 % yield): Rf = 0.21 (1:3 EtOAc/hexanes); ¹H NMR (CDCl₃) δ 1.09-1.28 (m, 6H), 1.34 (s, 3H), 1.90 (s, 0.84H), 1.95 (s, 2.16H), 2.38 (s, 3H), 3.97-4.13 (m, 4H), 4.52 (s, 0.28H), 4.76 (s, 0.72H), 6.85-6.91 (m, 4H), 7.02-7.27 (m, 10H), 7.38 (s, 1H); NMR (CDCl₃) δ 14.4, 21.5, 27.0, 29.9, 60.1, 61.5, 61.7, 118.32, 118.33, 126.8, 127.0, 127.2, 127.7, 127.9, 129.3, 129.9, 130.5, 130.6, 132.0, 132.9, 133.6, 134.8, 135.9, 144.4, 156.7; IR(CHCl₃) 1730, 1705, 3410 cm⁻¹; HRMS m/z 589.2258 (calcld for C₃₂H₃₅N₃O₆S 589.2246).

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References


CHAPTER 2. SYNTHESIS OF α-PYRONES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKynes

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Abstract

A number of 3,4,5,6-tetrasubstituted α-pyrones have been prepared in good yields by the reaction of vinylic iodides or triflates bearing an ester functionality with internal alkynes in the presence of a palladium catalyst. The methodology provides a simple, convenient, and regioselective route to α-pyrones containing aryl, silyl, tert.-alkyl and other hindered groups. The reaction is believed to proceed through a seven-membered palladacyclic complex in which the regiochemistry of the reaction is controlled by steric factors.

Introduction

α-Pyrones are useful intermediates in the synthesis of a variety of important hetero- and carbocyclic molecules and occur as structural subunits in numerous natural products that exhibit a wide range of biological activity. Very recently, low molecular weight α-pyrones have been shown to be potent HIV-1 protease inhibitors.

Approaches to the synthesis of α-pyrones have been diverse. Pertinent to the present work, α-pyrones have been synthesized by the cyclization of open
chain 2,4-pentadienoic acids using lithium chloropalladate or formed as unstable multiple-insertion products from the reaction of palladium complexes with internal alkynes.

We have previously reported that the reaction of methyl 2-iodobenzoate with internal alkynes affords isocoumarins in the presence of a palladium catalyst (eq 1). We have also shown that the palladium-catalyzed reaction of cyclic vinylic bromides or triflates with internal alkynes affords \( \alpha \)-pyrones (eq 2). Since preliminary data suggested that this annulation methodology may be limited to cyclic vinylic halides, we were interested in exploring the scope of this annulation methodology. Indeed, we have now extended this chemistry to acyclic vinylic iodides and triflates and wish to report on reaction conditions for the synthesis of a variety of 3,4,5,6-tetrasubstituted \( \alpha \)-pyrones as well as extension of this process to double annulation reactions.

\[
\begin{align*}
\text{OMe} & + R^1\equiv R^2 \xrightarrow{5\% \text{ Pd(OAc)}_2, 1 \text{ Na}_2\text{CO}_3, 1 \text{ LiCl}, 100 \, ^\circ\text{C}} \text{R}^1\text{R}^2 \\
\text{R}^1\equiv R^2 & \xrightarrow{5\% \text{ Pd(OAc)}_2, 1 \text{ Na}_2\text{CO}_3, 1 \text{ LiCl}, 100 \, ^\circ\text{C}} \text{R}^1\text{R}^2
\end{align*}
\]

\( n = 0-2, \ X = \text{Br, OTf} \)
Results and Discussion

The starting materials for our α-pyrone synthesis, β-iodo substituted propenoates, were synthesized by the reactions shown in Scheme 1. (Z)-β-Iodo substituted 2-propenols were synthesized by the Cul-catalyzed Grignard addition across the triple bond of a propargylic alcohol, and subsequent quenching by I₂. Alcohol 6 was prepared by the reaction of 3-phenyl-2-propyn-1-ol with Red-Al, followed by quenching with I₂. Oxidation of the (Z)-β-iodo-substituted 2-propenols with 20 equiv of MnO₂ in CH₂Cl₂ at room temperature afforded the corresponding
aldehydes. The resulting (Z)-β-iodo-substituted 2-propenals were subjected to a second oxidation by 20 equiv of MnO₂, 5.2 equiv of NaCN, 1.5 equiv of AcOH in MeOH at room temperature to provide the (Z)-methyl β-iodo-substituted 2-propenoates.

The triflates 19 and 20 were synthesized from the corresponding β-keto ester (eq 3). The stereochemistry of the triflates 19 and 20 was assigned by ¹H NMR spectral analysis based on the downfield chemical shift of a methyl group cis to an ester group due to the deshielding effect of an ester group.

The diiodide 21 was synthesized in 88% yield according to a literature procedure (eq 4).

Methyl (Z)-3-bromo-3-iodo-2-phenyl-propenoate 22 was prepared according to the reactions shown in Scheme 2.
From Table 1, we can make the following observations. (1) Methyl (Z)-3-iodo-2-phenyl-2-propenoate (entries 4-8) gives slightly higher yields than methyl (Z)-3-iodo-2-methyl-2-propenoate (entries 1-3). Both give a mixture of regioisomers. (2) Methyl (Z)-3-iodo-2,3-diphenyl-2-propenoate (entries 9-13) gives high yields of just one regioisomer. (3) Ethyl (Z)-3-iodo-2-propenoate (entries 14-16) gives only very low yields of products. (4) Methyl (Z)-3-iodo-2-methyl-3-phenyl-2-propenoate (entries 17-18) gives lower yields of products and a slower reaction rate compared with the first two esters. (5) Trialkylsilyl-substituted α-pyrones in which C-Si bonds are available for further functionalization can be obtained in modest yields (entries 8, 12 and 13). (6) The triflate 19, which is easily prepared, gives the desired product in low yield (entry 21).
Table 1. Synthesis of α-pyrones via annulation of internal alkynes (eq 5).\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>alkyne</th>
<th>time (h)</th>
<th>product(s)\textsuperscript{b}</th>
<th>yield (%)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{CH}_3\text{COOCH}_3)</td>
<td>(\text{C} = \text{C(CH}_3)_3)</td>
<td>28</td>
<td>(\text{H}_3\text{C}\text{O}) (\text{C}_2\text{H}_5\text{CO}) (\text{C} = \text{C(CH}_3)_3) (\text{H}_3\text{C}\text{O}) (\text{C}_2\text{H}_5\text{CO}) (\text{C} = \text{C(CH}_3)_3)</td>
<td>69 : 31</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Ph} = \text{C(CH}_3)_2\text{OH})</td>
<td>(\text{Ph} = \text{C(CH}_3)_2\text{OH})</td>
<td>5</td>
<td>(\text{H}_3\text{C}\text{O}) (\text{C}_2\text{H}_5\text{CO}) (\text{Ph} = \text{C(CH}_3)_2\text{OH}) (\text{Ph} = \text{C(CH}_3)_2\text{OH}) (\text{Ph} = \text{C(CH}_3)_2\text{OH})</td>
<td>50 + 10</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ph} = \text{C(CH}_3)_3)</td>
<td>(\text{H}_3\text{C}\text{O}) (\text{C}_2\text{H}_5\text{CO}) (\text{Ph} = \text{C(CH}_3)_3) (\text{H}_3\text{C}\text{O}) (\text{C}_2\text{H}_5\text{CO}) (\text{Ph} = \text{C(CH}_3)_3)</td>
<td>40 + 25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: eq 5.

\textsuperscript{b} product(s) are shown in the table.

\textsuperscript{c} yield is given in percent.
<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>alkyne</th>
<th>time (h)</th>
<th>product(s)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Ph(\equiv)C(CH(_3))(_2)OH</td>
<td>Ph(\equiv)C(CH(_3))(_2)OH</td>
<td>10</td>
<td>(\overset{5a}{\text{5a 40%}}) + (\overset{5a + \text{Ph} = \text{SiEt}_3}{22% 37 : 63})</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>HO(CH(_3))(_2)O(\equiv)C(CH(_3))(_2)OH</td>
<td>HO(CH(_3))(_2)O(\equiv)C(CH(_3))(_2)OH</td>
<td>10</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Ph(\equiv)Ph</td>
<td>Ph(\equiv)Ph</td>
<td>10</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>Ph(\equiv)SiEt(_3)</td>
<td>Ph(\equiv)SiEt(_3)</td>
<td>22</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>entry</td>
<td>ester</td>
<td>alkyne</td>
<td>time (h)</td>
<td>product(s)</td>
<td>yield (%)</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>----------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>9</td>
<td>Ph(\text{OCH}_3)Ph</td>
<td>Ph(\equiv)Ph</td>
<td>15</td>
<td><img src="image" alt="Product 9" /></td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>H(\text{CH}_3)(\equiv)C((\text{CH}_3)_3)</td>
<td>H(\equiv)C((\text{CH}_3)_3)</td>
<td>9</td>
<td><img src="image" alt="Product 10" /></td>
<td>70</td>
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<tr>
<td>11</td>
<td>Ph(\equiv)C((\text{CH}_3)_2\text{OH})</td>
<td>Ph(\equiv)C((\text{CH}_3)_2\text{OH})</td>
<td>15</td>
<td><img src="image" alt="Product 11" /></td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>H(\text{CH}_3)(\equiv)Si((\text{CH}_3)_3)</td>
<td>H(\equiv)Si((\text{CH}_3)_3)</td>
<td>22</td>
<td><img src="image" alt="Product 12" /></td>
<td>30</td>
</tr>
<tr>
<td>entry</td>
<td>ester</td>
<td>alkyne</td>
<td>time (h)</td>
<td>product(s)(^b)</td>
<td>yield (%)(^c)</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>----------------</td>
<td>----------</td>
<td>---------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>13</td>
<td>Ph = SiEt(_3)</td>
<td>22</td>
<td></td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>31</td>
</tr>
<tr>
<td>14</td>
<td>H(_2)OEt</td>
<td>H(_3)C = C(CH(_3))(_3)</td>
<td>28</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>69 : 31</td>
</tr>
<tr>
<td>15</td>
<td>Ph = C(CH(_3))(_2)OH</td>
<td>28</td>
<td></td>
<td><img src="image4" alt="Chemical structure" /></td>
<td>10</td>
</tr>
<tr>
<td>16</td>
<td>HO(CH(_3))(_2)O = C(CH(_3))(_2)OH</td>
<td>6</td>
<td></td>
<td><img src="image5" alt="Chemical structure" /></td>
<td>10</td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>alkyne</th>
<th>time (h)</th>
<th>product(s) (^b)</th>
<th>yield (%) (^c)</th>
</tr>
</thead>
</table>
| 17    | H₃C⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁃ | H₃C⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁺ | H₃C⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻ relu}
Table 1. (continued)

<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>alkyne</th>
<th>time (h)</th>
<th>product(s)$^b$</th>
<th>yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>H$_3$C[\backslash\backslash]OCH$_3$</td>
<td>Ph[\equiv]Ph</td>
<td>9</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>12</td>
</tr>
</tbody>
</table>

$^a$ All of the reactions were run at 100 °C, except the reactions in entries 17 and 18. $^b$ A colon (:) indicates that the products were inseparable and a plus (+) indicates that they were separated. $^c$ Yields refer to isolated compounds purified by chromatography. All of these compounds gave satisfactory $^1$H NMR, $^{13}$C NMR, HRMS and IR spectra. $^d$ This reaction was run in the presence of 2.5 equiv. of LiCl. $^o$ This reaction was run in the presence of 3 equiv. of LiCl.
From the above findings, we conclude that the substrates with a non-hydrogen substituent in the 2-position give α-pyrones in good yields (entries 1-13). Second, the presence of a hydrogen beta to the iodide in the starting material lowers the yields of the palladium reactions, presumably due to β-hydrogen elimination in the vinylic palladium intermediate, although we have no solid evidence that this is the source of the problem. For example, all three esters used in this study, which have a β-hydrogen, namely ethyl (Z)-3-iodo-2-propenoate and esters 17 and 19, gave α-pyrone in low yields (entries 14-16 and 19-21). Third, esters with a phenyl group adjacent to the iodo group gave α-pyrones in poor yields. For example, ester 16 gave only low yields of products (entries 17 and 18) and ester 18 failed to give any α-pyrones. These observations might be explained by the above mentioned β-hydride elimination reaction (for ester 18) and/or steric hindrance about the C-I bond, which retards the oxidative addition reaction and subsequent insertion of internal alkynes. It should be pointed out that we did not observe any methyl 3-phenylpropynoate, the β-hydride elimination product of the vinylic palladium intermediate from ester 18, despite careful chromatography of the products from the reactions of ester 18 and diphenylacetylene or 4,4-dimethyl-2-pentyne. However, ester 15, which has a phenyl group adjacent to the iodo group, gave α-pyrone in good yields, perhaps due to activation by the phenyl group in the 2-position during the oxidative addition step. Finally, an alkyl or aryl substituent in the 3-position increases the regioselectivity during the carbopalladation step, resulting, in most cases, in the formation of just one regioisomer (entries 10-13, 18 and 20).

The regiochemistry was established for the products of entries 4 and 5 of Table 1 by NOESY spectroscopy. For the minor product of entry 4, there was an NOE interaction between C₄-H and C₅-C(CH₃)₃ and no interaction between C₄-H
and C₆-CH₃. This compound was therefore assigned the structure shown in Table 1. The major product of entry 5 was assigned the structure shown in Table 1 due to the lack of an observable NOE interaction between C₄-H and the methyl hydrogens. The above assignments are consistent with our previous work, i.e. the bulkier group of the alkyne ends up bonded to the carbon atom to which the palladium species was originally attached. The rest of the products in Table 1 have been assigned by analogy with the above observations.

Based on the above results and our previous work, we believe that this annulation process proceeds as shown in Scheme 3 by a sequence involving (1) reduction of Pd(OAc)₂ to the actual Pd(0) catalyst, (2) oxidative addition of the starting iodide or triflate to Pd(0), (3) vinylpalladium coordination to the alkyne and subsequent insertion of the alkyne to form a vinylpalladium intermediate, (4) attack of the carbonyl oxygen on the vinylpalladium intermediate to form a seven-membered palladacyclic salt, and (5) regeneration of the Pd(0) catalyst by reductive elimination and formation of the salt. Loss of the R group of the ester is
thought to occur either during the reaction by either an S_N1 or S_N2 process or during the aqueous workup, but the real path for this step is unclear.

To extend the above chemistry to a double annulation process, dihalo-substituted esters 21 and 22 were prepared (eq 4 and Scheme 2). When

\[
\text{\begin{align*}
21 + 4 \text{Ph} \equiv \text{Ph} & \xrightarrow{10\% \text{Pd(OAc)}_2, 2 \text{Et}_3\text{N}, 2 \text{LiCl}, 75^\circ\text{C}, 22 \text{h}} \text{Ph} \equiv \text{Ph} \text{Ph} \\
& \text{Ph} \equiv \text{Ph} \\
& \text{Ph} \equiv \text{Ph}
\end{align*}}
\]

(6)

\[
\text{\begin{align*}
21 + 10 \text{H}_3\text{C} \equiv \text{C(CH}_3\text{)}_3 & \xrightarrow{32 \text{h}} \text{CH}_3 \equiv \text{CH}_3 \\
& \text{CH}_3 \equiv \text{CH}_3
\end{align*}}
\]

(7)

\[
\text{\begin{align*}
22 + 4 \text{Ph} \equiv \text{Ph} & \xrightarrow{22 \text{h}} \text{Ph} \equiv \text{Ph} \\
& \text{Ph} \equiv \text{Ph}
\end{align*}}
\]

(8)

compounds 21 or 22 were reacted with diphenylacetylene or 4,4-dimethyl-2-pentyne in the presence of 10% Pd(OAc)_2, 2 equiv of Et_3N and 2 equiv of LiCl at 75 °C for 22 to 32 h, the double annulation products 23-25 were formed in 17 -19% yields (eqs 6-8) with the formation of four new carbon-carbon bonds.
The formation of compounds 23 - 25 can be explained by the reactions shown in Scheme 4. The oxidative addition of Pd(0) to compound 21 or 22 affords vinylpalladium intermediate 26 in which the halogen trans to the carbonyl group undergoes preferential insertion. This is consistent with the known reactivity of such halogens towards Pd oxidative addition. Vinylpalladium intermediate 26 undergoes insertion of a molecule of internal alkyne and subsequent substitution onto the adjacent phenyl ring to form intermediate 27. Vinylpalladium intermediate 28 is then formed by oxidative addition of Pd(0) to compound 27 and
subsequent insertion of a second molecule of internal alkyne. When
diphenylacetylene is employed, compound 23 or 25 is obtained. When 4,4-
dimethyl-2-pentyne is used, compound 24 is produced. The formation of
compounds 23 and 25 indicates that the production of aromatic rings is easier
than that of α-pyrones.

In conclusion, a variety of 3,4,5,6-tetrasubstituted α-pyrones have been
prepared in low to good yields by the reaction of vinylic iodides bearing ester
functionality with internal alkynes in the presence of a palladium catalyst. The
above chemistry has also been extended to a double annulation process by
employing geminal dihalo-substituted esters.

EXPERIMENTAL SECTION

General. All ′H and ′3C NMR spectra were recorded at 300 and 75.5 MHz
respectively. Thin-layer chromatography (TLC) was performed using commercially
prepared 60 mesh silica gel plates (Whatman K6F), and visualized with short
wavelength UV light (254 nm), and basic KMnO₄ solution [3 g KMnO₄ + 20 g K₂CO₃
+ 5 ml NaOH (5%) + 300 ml H₂O].

Reagents. All reagents were used directly as obtained commercially
unless otherwise noted. Anhydrous Na₂CO₃ and LiCl were purchased form Fisher
Scientific. Pd(OAc)₂ was donated by Johnson Matthey, Inc. and Kawaken Fine
Chemicals Co., Ltd. Ethyl (Z)-3-iodo-2-propenoate was synthesized according to a
literature procedure. The other vinylic esters used in this study were prepared as
follows.

General Procedure to Prepare (Z)-β-iodo-substituted 2-
Propenols. Into a dry 250 ml three-necked flask equipped with an Ar inlet, a gas
outlet tube and maintained under a positive pressure of Ar, was placed the
propargylic alcohol (50 mmol), anhydrous ether (70 ml, dried over 4 Å molecular sieves), and Cul (10 mol %, 5 mmol, 0.952 g, purified using a literature procedure\(^1\)). To the cooled, stirred mixture at 0 °C (-10 °C for propargyl alcohol itself) was added a 3.0 M ethereal solution of the corresponding Grignard reagent (2.5 equiv, 125 mmol, 42 ml). The first equivalent was added carefully to avoid a build-up of methane (or PhH) gas pressure. Upon complete addition of the Grignard reagent, the mixture was allowed to warm up to room temperature and vigorously stirred for the desired period of time. The dark green mixture was then cooled to -78 °C and a THF solution of I\(_2\) (1.1 equiv, 13.0 g in 40 ml of THF) was added via syringe. After warming up to room temperature and stirring at room temperature for 1 h, the resulting reaction mixture was kept in the refrigerator at about 0-3 °C overnight. The reaction mixture was cooled to 0 °C and quenched with satd aq NH\(_4\)Cl (150 ml). The two phase mixture was warmed to room temperature, poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with ether (3 × 50 ml) and the combined organic layers were then washed with satd aq Na\(_2\)S\(_2\)O\(_3\) (2 × 60 ml) and satd aq NaCl (100 ml), and then dried over Na\(_2\)SO\(_4\). The solvent was removed under vacuum and the concentrate was purified by column chromatography.

**General Procedure to Convert (Z)-β-Iodo-substituted 2-Propanols to (Z)-β-Iodo-substituted 2-Propanals.** A dried 250 ml round bottom flask was flushed with Ar, then the corresponding alcohol (3-12 mmol) and CH\(_2\)Cl\(_2\) (15 ml/mm mol) were added, while the round bottom flask was maintained under an Ar atmosphere. MnO\(_2\) (20 equiv) was added. The resulting reaction mixture was stirred at room temperature for the desired period of time. The black precipitate was filtered off and the filtrate was concentrated under vacuum. The resulting aldehyde was pure enough for the next oxidation reaction, or it could be
purified further by column chromatography using 1:9 EtOAc/hexanes or straight CH₂Cl₂ as the eluent.

**General Procedure to Convert (Z)-β-iodo-substituted 2-Propenals to (Z)-Methyl β-iodo-substituted 2-Propenoates.** The aldehyde (2-6 mmol), MeOH (12 ml/mmol), NaCN (5.2 equiv), AcOH (1.5 equiv), and MnO₂ (20 equiv) were added to a round bottom flask. The mixture was stirred at room temperature for the desired period of time under a positive Ar pressure. The black precipitate was filtered off and the filtrate was concentrated under vacuum. The resulting residue was partitioned between 50 ml of H₂O and 50 ml of Et₂O. The organic layer was separated and the aqueous layer was extracted with ether (2 × 30 ml). The combined ether layers were dried over Na₂SO₄. The ether was removed and the residue was subjected to column chromatography.

**(Z)-3-ido-2-methyl-2-propenol (1).** Stirred at room temperature for 20 h. 1:2 EtOAc/hexanes as eluent afforded a light yellow liquid: ¹H NMR (CDCl₃) δ 1.98 (d, J = 0.75 Hz, 3H); 2.41 (s, 1H), 4.24 (s, 2H), 5.97 (q, J = 0.75 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.5, 67.9, 74.7, 146.0.

**(Z)-3-ido-2-methyl-2-propenal (7).** Stirred at room temperature for 2 h. A light yellow liquid: ¹H NMR (CDCl₃) δ 1.90 (d, J = 1.5 Hz, 3H), 7.46 (q, J = 1.5 Hz, 1H), 9.78 (s, 1H).

**Methyl (Z)-3-ido-2-methyl-2-propenoate (13).** Stirred at room temperature for 18 h. 1:9 EtOAc/hexanes as eluent afforded a light yellow liquid: ¹H NMR (CDCl₃) δ 2.07 (d, J = 1.5 Hz, 3H), 3.81 (s, 3H), 6.86 (q, J = 1.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 22.3, 51.7, 82.9, 138.6, 166.9; IR (neat) 1720 (C=O) cm⁻¹.

**(Z)-3-ido-2-phenyl-2-propenol (2).** Stirred at room temperature for 16 h. 1:7 EtOAc/hexanes and 1:2 EtOAc/hexanes as the eluent afforded a light yellow liquid: ¹H NMR (CDCl₃) δ 1.94 (t, J = 6.3 Hz, 1H), 4.66 (d, J = 6.3 Hz, 2H),
6.61 (s, 1H), 7.28-7.42 (m, 5 H); $^1$H NMR (CDCl$_3$) $\delta$ 66.8, 81.2, 126.5, 128.2, 128.6, 138.9, 149.7.

(Z)-3-iido-2-phenyl-2-propenal (8). Stirred at room temperature for 15 h. A light yellow liquid: $^1$H NMR (CDCl$_3$) $\delta$ 7.25-7.28 (m, 2H), 7.36-7.42 (m, 3H), 7.87 (s, 1H), 10.01 (s, 1H).

Methyl (Z)-3-iido-2-phenyl-2-propenoate (14). Stirred at room temperature for 21 h. 1:9 EtOAc/hexanes as the eluent afforded a light yellow liquid: $^1$H NMR (CDCl$_3$) $\delta$ 3.87 (s, 3H), 7.05 (s, 1H), 7.31-7.35 (m, 5H); $^1$C NMR (CDCl$_3$) $\delta$ 3.87 (s, 3H), 7.05 (s, 1H), 7.31-7.35 (m, 5H); $^1$C NMR (CDCl$_3$) $\delta$ 52.4, 81.8, 126.5, 128.6, 136.4, 146.5, 167.8; IR (neat) 1735 (C=O) cm$^{-1}$.

(Z)-3-iido-2,3 diphenyl-2-propenal (9). Stirred at room temperature for 12 h. 1:12 EtOAc/hexanes as the eluent afforded yellow crystals: mp 102-104 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 6.89-6.92 (m, 2H), 7.12-7.19 (m, 8H), 10.01 (s, 1H); $^1$C NMR (CDCl$_3$) $\delta$ 123.1, 127.7, 127.9, 128.0, 129.1, 130.1, 134.2, 143.1, 143.3, 145.0, 197.9.

Methyl (Z)-3-iido-2,3 diphenyl-2-propenoate (15). Stirred at room temperature for 10 h. 1:30 EtOAc/hexanes as the eluent afforded an off-white solid: mp 93-95 °C (hexanes/EtOAc); $^1$H NMR (CDCl$_3$) $\delta$ 3.87 (s, 3H), 7.05-7.21 (m, 10H); $^1$C NMR (CDCl$_3$) $\delta$ 52.7, 100.7, 127.98, 128.0, 128.2, 128.3, 128.8, 129.3, 135.1, 141.9, 143.6, 169.2; IR (neat) 1725 (C=O) cm$^{-1}$.

(Z)-3-iido-2-methyl-3-phenyl-2-propenal (4). Stirred at room temperature for 24 h. 1:7 EtOAc/hexanes and 1:2 EtOAc/hexanes as the eluent
afforded a light yellow liquid: \( ^1H \text{ NMR (CDCl}_3 \delta 1.82 \text{ (s, 3H), 2.07 (t, } J = 6.3 \text{ Hz, 1H), 4.42 (d, } J = 6.3 \text{ Hz, 2H), 7.20-7.25 \text{ (m, 3H), 7.29-7.36 \text{ (m, 2H); } ^13C \text{ NMR (CDCl}_3 \delta 17.7, 72.7, 95.8, 127.7, 128.2, 128.5, 141.7, 143.9.}

(Z)-3-Iodo-2-methyl-3-phenyl-2-propenal (10). Stirred at room temperature for 11 h. A light yellow liquid: \( ^1H \text{ NMR (CDCl}_3 \delta 1.77 \text{ (s, 3H), 7.25-7.29 \text{ (m, 2H), 7.32-7.35 \text{ (m, 1H), 7.38-7.44 \text{ (m, 2H), 9.81 \text{ (s, 1H); } ^13C \text{ NMR (CDCl}_3 \delta 15.0, 118.3, 127.6, 128.4, 129.1, 138.4, 143.3, 198.9.}

Methyl (Z)-3-iodo-2-methyl-3-phenyl-2-propenoate (16). Stirred at room temperature for 11 h. 1:7 EtOAc/hexanes as the eluent afforded a light yellow solid: mp 60-62 °C (hexanes/EtOAc); \( ^1H \text{ NMR (CDCl}_3 \delta 1.87 \text{ (s, 3H), 3.86 \text{ (s, 3H), 7.23-7.28 \text{ (m, 3H), 7.31-7.38 \text{ (m, 2H); } ^13C \text{ NMR (CDCl}_3 \delta 18.5, 52.2, 97.7, 127.9, 128.2 (2C), 137.7, 142.7, 169.4; IR (neat) 1724 (C=O) cm}^{-1}.}

(Z)-3-Iodo-2-ethyl-2-butenol (5). Stirred at room temperature for 74 h. 1:5 EtOAc/hexanes as the eluent afforded a colorless liquid: \( ^1H \text{ NMR (CDCl}_3 \delta 1.04 \text{ (t, } J = 7.5 \text{ Hz, 3H), 1.62 \text{ (t, } J = 6.3 \text{ Hz, 1H), 2.35 \text{ (q, } J = 7.5 \text{ Hz, 2H), 2.56 \text{ (s, 3H), 4.25 (d, } J = 6.3 \text{ Hz, 2H); } ^13C \text{ NMR (CDCl}_3 \delta 12.2, 22.7, 28.4, 66.0, 80.2, 142.1.}

(Z)-3-Iodo-2-ethyl-2-butenal (11). Stirred at room temperature for 3 h. A colorless liquid: \( ^1H \text{ NMR (CDCl}_3 \delta 1.02 \text{ (t, } J = 7.5 \text{ Hz, 3H), 2.26 \text{ (q, } J = 7.5 \text{ Hz, 2H), 2.70 \text{ (s, 3H), 9.85 \text{ (s, 1H).}

Methyl (Z)-3-iodo-2-ethyl-2-butenoate (17). Stirred at room temperature for 22 h. 1:9 EtOAc/hexanes as the eluent afforded a colorless liquid: \( ^1H \text{ NMR (CDCl}_3 \delta 1.05 \text{ (t, } J = 7.5 \text{ Hz, 3H), 2.35 \text{ (q, } J = 7.5 \text{ Hz, 2H), 2.58 \text{ (s, 3H), 3.80 \text{ (s, 3H); } ^13C \text{ NMR (CDCl}_3 \delta 12.7, 24.6, 29.9, 52.0, 96.2, 142.3, 169.7; IR (neat) 1722 (C=O) cm}^{-1}.}

(Z)-3-Iodo-3-phenyl-2-propenol (6). The title compound was prepared in 87% yield by reacting 3-phenyl-2-propynol with Red-Al and then quenching with
I₂ according to a literature procedure.¹¹ ¹H NMR (CDCl₃) δ 1.76 (t, J = 5.7 Hz, 1H), 4.39 (t, J = 5.7 Hz, 2H), 6.25 (t, J = 5.7 Hz, 1H), 7.25-7.32 (m, 3H), 7.45-7.49 (m, 2H); ¹³C NMR (CDCl₃) δ 68.2, 104.2, 128.1, 128.3, 128.5, 137.4, 142.1.

(Z)-3-Iodo-3-phenyl-2-propenal (12). Stirred at room temperature for 3 h. A light yellow liquid: ¹H NMR (CDCl₃) δ 6.59 (d, J = 6.3 Hz, 1H), 7.37-7.46 (m, 3H), 7.59-7.64 (m, 2H), 9.72 (s, 1H).

Methyl (Z)-3-iodo-3-phenyl-2-propenoate (18). Stirred at room temperature for 16 h. 1:30 EtOAc/hexanes as the eluent afforded a light yellow liquid: ¹H NMR (CDCl₃) δ 3.82 (s, 3H), 7.32-7.46 (m, 4H), 7.54-7.58 (m, 2H); ¹³C NMR (CDCl₃) δ 52.6, 80.2, 86.2, 119.3, 128.4, 130.5, 132.8, 154.2; IR (neat) 1711 (C=O) cm⁻¹.

Ethyl (Z)-3,3-diiodo-2-phenyl-2-propenoate (21). n-BuLi (5.28 ml, 2.5 M in hexane, 13.2 mmol) was added at 0 °C to a solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (2.78 ml, 13.2 mmol) in THF (36 ml). The solution was stirred 30 min at 0 °C and then cooled to -70 °C. A solution of I₂ (1.523 g, 6.0 mmol) in THF (12 ml) was added and then after 5 min, a solution of diethyl iodomethylphosphonate (1.67 g, 6.0 mmol) in THF (12 ml) was added. After 90 min at -70 °C, ethyl benzoyleformate (1.07 g, 6.0 mmol) in THF (6 ml) was added. The mixture was stirred 5 min at -70 °C, then 1 h at 0 °C, and finally 2 h at room temperature. After addition of water (26.4 ml), the aqueous solution was extracted with ether (5 × 60 ml). The combined organic layers were dried over Na₂SO₄ and evaporated. The residue was subjected to column chromatography using 1:7 ether/hexanes as the eluent to afford 2.25 g (88%) of the title compound as an orange liquid: Rₛ = 0.52 (1:9 EtOAc/hexanes); ¹H NMR (CDCl₃) δ 1.31 (t, J = 7.2 Hz, 3H), 4.24 (q, J = 7.2 Hz, 2H), 7.32-7.40 (m, 5H); ¹³C NMR (CDCl₃) δ 13.97, 19.74, 62.20, 127.70, 128.61, 128.91, 139.76, 152.84, 166.55; IR (neat) 1731 (C=O) cm⁻¹.
Methyl \( (Z) \)-3-bromo-3-iodo-2-phenyl-2-propenoate (22). This ester was prepared from \( (Z) \)-3-bromo-3-iodo-2-phenylpropenal\(^6\) (see Scheme 2) using the general procedure for converting \( (Z) \)-\( \beta \)-iodo-substituted-2-propenals to \( (Z) \)-methyl-\( \beta \)-iodo-substituted 2-propenoates mentioned above. The mixture was stirred at room temperature for 16 h. 1:7 EtOAc/hexanes as the eluent afforded an orange liquid: \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 3.79 (s, 3H), 7.36-7.40 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 53.1, 58.7, 128.2, 128.7, 129.1, 136.6, 147.2, 167.5; IR (neat) 1729 (C=O) cm\(^{-1}\).

**General Procedure for the Synthesis of \( \alpha \)-Pyrones.** Pd(OAc)\(_2\) (3 mg, 0.013 mmol), Na\(_2\)CO\(_3\) (26.5 mg, 0.25 mmol), DMF (5 ml), LiCl (10.6 mg, 0.25 mmol), the alkyne (0.5 mmol), and the ester (0.25 mmol) were placed in a 2 dram vial. The vial was heated in an oil bath at 100 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with satd NH\(_4\)Cl, dried over anhydrous Na\(_2\)SO\(_4\), and decanted. The solvent was evaporated under reduced pressure and the product was isolated by chromatography (EtOAc/hexanes) on a silica gel column. The following compounds were prepared by the above procedure.

6-tert.-Butyl-3,5-dimethyl-2H-pyran-2-one (1a) and 5-tert.-butyl-3,6-dimethyl-2H-pyran-2-one (1b) (entry 1, Table 1). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow inseparable liquid (1a : 1b = 69 : 31). Compound 1a (major isomer): \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.30 (s, 9H), 2.39 (s, 3H), 2.70 (d, \( J = 1.0 \) Hz, 3H), 7.25 (d, \( J = 1.2 \) Hz, 1H). Compound 1b (minor isomer): \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.35 (s, 9H), 2.13 (s, 3H), 2.50 (d, \( J = 1.0 \) Hz, 3H), 6.91 (d, \( J = 1.2 \) Hz, 1H). Additional spectral data for the product mixture: \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 15.9, 16.4, 17.2, 20.4, 28.9, 30.8, 32.3, 37.4, 104.1, 109.7, 121.4, 121.9, 123.3, 141.5, 147.0, 156.3, 163.8, 164.2; IR (CHCl\(_3\)) 1699 (C=O) cm\(^{-1}\); HRMS 180.1147 (calcd for C\(_{11}\)H\(_{16}\)O\(_2\) 180.1150).
3-Methyl-5,6-diphenyl-2H-pyran-2-one (entry 2, Table 1). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow liquid: $^1$H NMR (CDCl$_3$) $\delta$ 2.00 (d, $J = 1.2$ Hz, 3H), 7.20 - 7.36 (m, 11H); $^{13}$C NMR (CDCl$_3$) $\delta$ 16.5, 118.0, 123.7, 127.7, 128.1, 128.9, 129.1, 129.2, 129.5, 132.2, 136.5, 144.0, 155.4, 163.2; IR (CHCl$_3$) 1710 (C=O) cm$^{-1}$; HRMS 262.0944 (calcd for C$_{18}$H$_{14}$O$_2$ 262.0994).

6-(1-Hydroxy-1-methylethyl)-3-methyl-5-phenyl-2H-pyran-2-one (3a) and 5-(1-hydroxy-1-methylethyl)-3-methyl-6-phenyl-2H-pyran-2-one (3b) (entry 3, Table 1). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes. Compound 3a: a light yellow liquid; $^1$H NMR (CDCl$_3$) $\delta$ 1.46 (s, 6H), 1.89 (s, 1H), 2.10 (d, $J = 1.2$ Hz, 3H), 6.98 (q, $J = 1.2$ Hz, 1H), 7.23 - 7.27 (m, 2H), 7.36 - 7.44 (m, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 16.2, 29.8, 73.2, 116.1, 122.6, 128.0, 128.6, 129.1, 136.9, 161.8, 162.6; IR (CHCl$_3$) 3447 (OH), 1711 (C=O) cm$^{-1}$; HRMS 244.1101 (calcd for C$_{15}$H$_{16}$O$_2$ 244.1099). Compound 3b: an off-white solid, mp 96-98 °C (EtOAc/hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 1.36 (s, 6H), 2.16 (d, $J = 1.2$ Hz, 3H), 7.37 - 7.45 (m, 5H), 7.53 (q, $J = 1.1$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 16.6, 31.7, 70.9, 123.9, 124.1, 128.2, 129.4, 129.7, 134.4, 140.7, 155.2, 163.1; IR (CHCl$_3$) 3450 (OH), 1699 (C=O) cm$^{-1}$; HRMS 244.1095 (calcd for C$_{15}$H$_{16}$O$_2$ 244.1099).

6-tert.-Butyl-5-methyl-3-phenyl-2H-pyran-2-one (4a) and 5-tert.-butyl-6-methyl-3-phenyl-2H-pyran-2-one (4b) (entry 4, Table 1). The reaction mixture was chromatographed using 1:12 EtOAc/hexanes. Compound 4a: an off-white solid, mp 85-87°C (hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 1.41 (s, 9H), 2.22 (s, 3H), 7.25 (s, 1H), 7.28 - 7.43 (m, 3H) 7.65 - 7.68 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 17.5, 28.8, 37.7, 110.5, 124.2, 128.0, 128.1, 128.3, 134.7, 147.4, 161.7, 166.4; IR (CHCl$_3$) 1699 (C=O) cm$^{-1}$; HRMS 242.1306 (calcd for C$_{16}$H$_{18}$O$_2$ 242.1307).

Compound 4b: an off-white solid, mp 80-82°C (from hexanes); $^1$H NMR (CDCl$_3$) $\delta$
1.35 (s, 9H), 2.47 (s, 3H), 7.31-7.44 (m, 3H), 7.60 (s, 1H), 7.64-7.67 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 20.7, 30.8, 32.6, 1234.9, 128.0, 128.1, 128.4, 135.2, 142.1, 145.0, 158.4, 161.9; IR (CHCl$_3$) 1705 (C=O) cm$^{-1}$; HRMS 242.1309 (calcd for C$_{16}$H$_{18}$O$_2$ 242.1307).

6-(1-Hydroxy-1-methylethyl)-3,5-diphenyl-2H-pyran-2-one (5a) and 5-(1-hydroxy-1-methylethyl)-3,6-diphenyl-2H-pyran-2-one (5b) (entry 5, Table 1). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield an off-white solid (5a, mp 147-148 °C, from EtOAc/hexanes) and a light yellow liquid consisting of a 37:63 mixture of 5a:5b. Compound 5a: $^1$H NMR (CDCl$_3$) δ 1.52 (s, 6H), 1.92 (s, 1H), 7.28-7.32 (m, 3H), 7.34-7.46 (m, 6H), 7.65-7.70 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 29.7, 73.4, 116.8, 124.7, 128.1, 128.2, 128.4, 128.6, 128.7, 129.2, 134.0, 136.7, 145.1, 160.7, 163.5; IR (CHCl$_3$) 3450 (OH), 1718 (C=O) cm$^{-1}$; HRMS 306.1258 (calcd for C$_{20}$H$_{18}$O$_3$ 306.1256). Compound 5b: $^1$H NMR (CDCl$_3$) δ 1.42 (s, 6H), 1.63 (s, 1H), 7.29-7.47 (m, 8H), 7.66-7.75 (m, 2H), 7.90 (s, 1H). Additional spectral data for the mixture of 5a:5b: $^{13}$C NMR (CDCl$_3$) δ 29.8, 31.8, 71.0, 73.4, 116.8, 124.5, 124.8, 126.2, 128.1, 128.2, 128.3, 128.4, 128.57, 128.64, 128.7, 128.8, 129.2, 129.3, 129.9, 134.0, 134.3, 134.6, 136.7, 141.4, 145.1, 156.8, 160.7, 161.2, 163.5, 172.4; IR (CHCl$_3$) 3452 (OH), 1718, 1705 (C=O) cm$^{-1}$; HRMS 306.1254 (calcd for C$_{20}$H$_{18}$O$_3$ 306.1256).

5,6-Bis-(1-hydroxy-1-methylethyl)-3-phenyl-2H-pyran-2-one (entry 6, Table 1). The reaction mixture was chromatographed using 1.5 : 1 EtOAc/hexanes to afford a light yellow liquid: $^1$H NMR (CDCl$_3$) δ 1.64 (s, 6H), 1.66 (s, 6H), 7.42 (s, 1H), 7.36 - 7.45 (m, 3H), 7.60-7.63 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 30.0, 31.9, 72.1, 73.9, 123.0, 124.7, 128.0, 128.5, 128.6, 134.3, 142.3, 160.6, 164.9;
IR (CHCl$_3$) 3293 (OH), 1712 (C=O) cm$^{-1}$; HRMS 288.1363 (calcd for C$_{17}$H$_{20}$O$_4$ 288.1362).

**3,5,6-Triphenyl-2H-pyran-2-one (entry 7, Table 1).** The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield an off-white solid: mp 140-142 °C (hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 7.22-7.47 (m, 13H), 7.62 (s, 1H), 7.74-7.78 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 118.6, 125.6, 127.9, 128.1, 128.2, 128.5, 128.6, 129.0, 129.17, 129.23, 129.9, 131.9, 134.4, 136.4, 144.3, 156.8, 161.2; IR (CHCl$_3$) 1718 (C=O) cm$^{-1}$; HRMS 324.1152 (calcd for C$_{23}$H$_{16}$O$_2$ 324.1150).

**3,5-Diphenyl-6-triethylsilyl-2H-pyran-2-one (entry 8, Table 1).** The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a light yellow liquid: $^1$H NMR (CDCl$_3$) $\delta$ 0.54 (q, $J$ = 7.8 Hz, 6H), 0.87 (t, $J$ = 7.8 Hz, 9H), 7.35-7.55 (m, 8H), 7.68-7.71 (m, 2H), 7.53 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 3.9, 7.3, 108.9, 125.4, 128.1, 128.3, 128.35, 128.44, 129.0, 130.4, 134.8, 135.0, 145.9, 161.6, 166.8; IR (CHCl$_3$) 1719 (C=O) cm$^{-1}$; HRMS 362.1706 (calcd for C$_{23}$H$_{26}$O$_2$Si 362.1702).

**3,4,5,6-Tetraphenyl-2H-pyran-2-one (entry 9, Table 1).** The reaction mixture was chromatographed using 1:12 EtOAc/hexanes to yield a light yellow solid: mp 165-167 °C (lit$^{th}$ 163.5-165.5 °C), whose $^1$H NMR and IR spectral properties were identical with those previously reported.$^{5g-5h}$ $^{13}$C NMR (CDCl$_3$) $\delta$ 119.6, 125.1, 127.2, 127.25, 127.28, 127.34 (2C), 127.7, 127.9, 128.1, 129.37, 129.42, 130.6, 131.4, 132.7, 134.2, 135.0, 136.2, 155.3, 156.6, 162.2; HRMS 400.1458 (calcd for C$_{29}$H$_{20}$O$_2$ 400.1463).

**6-tert.-Butyl-5-methyl-3,4-diphenyl-2H-pyran-2-one (entry 10, Table 1).** The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield an off-white solid: mp 158-159 °C (hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 1.46 (s, 9H), 1.85 (s, 3H), 6.92-6.95 (m, 2H), 7.00-7.25 (m, 8H); $^{13}$C NMR (CDCl$_3$) $\delta$ 15.8,
29.0, 37.8, 110.6, 124.0, 126.9, 127.4 (2C), 127.9, 128.4, 130.3, 134.3, 137.0, 157.8, 162.3, 165.5; IR (CHCl₃) 1697 (C=O) cm⁻¹; HRMS 318.1622 (calcd for C₂₂H₂₂O₂ 318.1620).

**6-(1-Hydroxy-1-methylethyl)-3,4,5-triphenyl-2H-pyran-2-one (entry 11, Table 1).** The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield an off-white solid: mp 161-163 °C (EtOAc/hexanes); ¹H NMR (CDCl₃) δ 1.52 (s, 6H), 1.96 (s, 1H), 6.65-6.68 (m, 2H), 6.86-6.89 (m, 3H), 7.00-7.03 (m, 2H), 7.07-7.16 (m, 8H); ¹³C NMR (CDCl₃) δ 29.8, 73.7, 117.4, 124.6, 127.0, 127.1, 127.3, 127.6 (2C), 127.9, 129.1, 130.4, 130.9, 133.9, 134.5, 135.8, 156.0, 161.5, 162.8; IR (CHCl₃) 3585, 3450 (OH), 1705 (C=O) cm⁻¹; HRMS 382.1565 (calcd for C₂₆H₂₂O₃ 383.1569).

**5-Methyl-3,4-diphenyl-6-trimethylsilyl-2H-pyran-2-one (entry 12, Table 1).** The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield an off-white solid: mp 155-157 °C (hexanes); ¹H NMR (CDCl₃) δ 0.41 (s, 9H), 1.80 (s, 3H), 6.95 - 6.98 (m, 2H), 7.03-7.06 (m, 2H), 7.08-7.13 (m, 3H), 7.15-7.24 (m, 3H); ¹³C NMR (CDCl₃) δ -1.2, 16.0, 123.3, 126.7, 127.1, 127.5, 127.6, 128.0, 128.4, 130.3, 134.2, 136.5, 153.9, 163.7, 165.9; IR (CHCl₃) 1699 (C=O) cm⁻¹; HRMS 334.1392 (calcd for C₂₁H₂₂O₂Si 334.1389).

**3,4,5-Triphenyl-6-triethylsilyl-2H-pyran-2-one (entry 13, Table 1).** The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a light yellow liquid: ¹H NMR (CDCl₃) δ 0.49 (q, J = 7.8 Hz, 6H), 0.90 (t, J = 7.8 Hz, 9H), 6.67-6.71 (m, 2H), 6.90-6.97 (m, 5H), 7.09-7.17 (m, 8H); ¹³C NMR (CDCl₃) δ 3.0, 7.4, 125.9, 127.0, 127.20, 127.22, 127.51, 127.55, 127.7, 129.4, 130.6, 131.2, 132.1, 134.3, 135.1, 136.0, 152.5, 163.6, 166.8; IR (CHCl₃) 1703 (C=O) cm⁻¹; HRMS 438.2023 (calcd for C₂₉H₃₀O₂Si 438.2015).
6-tert.-Butyl-5-methyl-2H-pyran-2-one (14a) and 5-tert.-butyl-6-methyl-2H-pyran-2-one (14b) (entry 14, Table 1). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow liquid consisting of an inseparable 69:31 mixture of 14a:14b. Compound 14a (major isomer): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.31 (s, 9H), 2.42 (s, 3H), 6.134 (dd, \(J = 9.6, 0.6\), 1H), 7.47 (d, \(J = 9.6\) Hz, 1H). Compound 14b (minor isomer): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.37 (s, 9H), 2.16 (s, 3H), 6.130 (d, \(J = 9.3\) Hz, 1H), 7.10 (d, \(J = 9.3\) Hz, 1H). Additional spectral data for the product mixture: \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 17.3, 20.9, 28.7, 30.7, 32.4, 37.8, 109.9, 112.5, 112.8, 123.3, 145.1, 150.7, 159.5, 162.5, 162.6, 167.3; IR (CHCl\(_3\)) 1716 (C=O) cm\(^{-1}\); HRMS 166.0992 (calcd for C\(_{10}\)H\(_{14}\)O\(_2\) 166.0994).

6-(1-Hydroxy-1-methylethyl)-5-phenyl-2H-pyran-2-one (entry 15, Table 1). The reaction mixture was chromatographed using 1:1.5 EtOAc/hexanes to yield a light yellow liquid: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.37 (s, 6H), 1.52 (s, 1H), 6.35 (d, \(J = 9.6\) Hz, 1H), 7.41-7.46 (m, 5H), 7.76 (d, \(J = 9.6\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 31.7, 70.9, 114.7, 123.8, 128.2, 129.2, 129.9, 134.4, 144.8, 145.1, 161.7; IR (CHCl\(_3\)) 3460 (OH), 1722 (C=O) cm\(^{-1}\); HRMS 230.0944 (calcd for C\(_{14}\)H\(_{14}\)O\(_3\) 230.0943).

5,6-Bis-(1-hydroxy-1-methylethyl)-2H-pyran-2-one (entry 16, Table 1). The reaction mixture was chromatographed using 1.5:1 EtOAc/hexanes to yield a light yellow liquid: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.61 (s, 6H), 1.63 (s, 6H), 6.18 (d, \(J = 9.9\) Hz, 1H), 7.33 (d, \(J = 9.9\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 30.0, 31.9, 72.2, 74.0, 113.2, 122.2, 145.6, 161.1, 166.3; IR (CHCl\(_3\)) 3305 (OH), 1716 (C=O) cm\(^{-1}\); HRMS 212.1055 (calcd for C\(_{11}\)H\(_{16}\)O\(_4\) 212.1049).

6-tert.-Butyl-3,5-dimethyl-4-phenyl-2H-pyran-2-one (17a) and 5-tert.-Butyl-3,6-dimethyl-4-phenyl-2H-pyran-2-one (17b) (entry 17, Table 1). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow liquid consisting of an inseparable 75:25 mixture of 17a:17b.
Compound \textbf{17a} (major isomer): \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 1.41 (s, 9H), 1.52 (s, 3H), 1.78 (s, 3H), 7.04-7.07 (m, 2H), 7.38-7.47 (m, 3H). Compound \textbf{17b} (minor isomer): \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 1.76 (s, 9H), 2.18 (s, 3H), 2.33 (s, 3H), 7.04-7.07 (m, 2H), 7.38-7.47 (m, 3H). Additional spectral data for the product mixture: \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 14.2, 15.6, 17.8, 20.1, 29.1, 31.5, 37.5, 38.9, 110.4, 112.4, 119.7, 122.9, 127.3, 127.8, 128.1, 128.7, 129.4, 129.6, 133.6, 137.7, 153.2, 157.0, 162.9, 163.3, 163.7, 164.8; IR (CHCl\textsubscript{3}) 1710 (C=O) cm\textsuperscript{-1}; HRMS 256.1458 (calcd for C\textsubscript{17}H\textsubscript{20}O\textsubscript{2} 256.1463).

\textbf{6-(1-Hydroxy-1-methylethyl)-3-methyl-4,5-diphenyl-2H-pyran-2-one} (entry 18, Table 1). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield an off-white solid: mp 110-112 °C (EtOAc/hexanes); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 1.46 (s, 6H), 1.82 (s, 1H), 1.87 (s, 3H), 6.80-6.84 (m, 2H), 6.94-6.97 (m, 3H), 7.09-7.14 (m, 6H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 14.4, 29.9, 73.5, 117.1, 120.5, 127.4, 127.6, 127.8, 127.86, 127.92, 130.8, 134.7, 136.3, 155.2, 160.9, 162.8; IR (CHCl\textsubscript{3}) 3350 (OH), 1715 (C=O) cm\textsuperscript{-1}; HRMS 320.1415 (calcd for C\textsubscript{21}H\textsubscript{20}O\textsubscript{3} 320.1412).

\textbf{3-Ethyl-4-methyl-5,6-diphenyl-2H-pyran-2-one} (entry 19, Table 1). The reaction mixture was flash chromatographed using 1:15 EtOAc/hexanes as the eluent to yield an off-white solid: mp 178-179 (hexanes); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 1.18 (t, J = 7.5 Hz, 3H), 2.65 (q, J = 7.5 Hz, 2H), 1.93 (s, 3H), 7.11-7.24 (m, 7H), 7.32-7.37 (m, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 12.52, 17.86, 20.86, 120.24, 125.88, 127.68, 127.74, 127.83, 128.81, 128.96, 130.74, 132.72, 135.67, 150.25, 154.05, 162.63; IR (CHCl\textsubscript{3}) 1704 (C=O) cm\textsuperscript{-1}; HRMS 290.1311 (calcd for C\textsubscript{20}H\textsubscript{18}O\textsubscript{2} 290.1307).

\textbf{6-tert.-Butyl-3-ethyl-4,5-dimethyl-2H-pyran-2-one} (entry 20, Table 1). The reaction mixture was flash chromatographed using 1:15 EtOAc/hexanes as an eluent to yield a light yellow liquid: \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 1.08 (t, J = 7.5 Hz, 3H), 1.37 (s, 9H), 2.08 (s, 3H), 2.09 (s, 3H), 2.55 (q, J = 7.5 Hz, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \textsuperscript{\textdelta} 12.66, 14.21, 16.28, 20.42, 29.18, 37.12, 111.47, 124.38, 152.08,
3,4-Dimethyl-5,6-diphenyl-2H-Pyran-2-one (entry 21, Table 1). The reaction mixture was flash chromatographed using 1:9 EtOAc/hexanes as the eluent to yield a white solid: mp 184-185 °C (hexanes); 1H NMR (CDCl₃) δ 1.92 (s, 3H), 2.19 (s, 3H), 7.11-7.35 (m, 10H); 13C NMR (CDCl₃) δ 13.18, 18.15, 120.18, 123.54, 127.78, 127.87, 128.85, 128.98, 129.56, 130.73, 132.68, 135.64, 150.91, 153.95, 163.20; IR (CHCl₃) 1700 (C=O) cm⁻¹; HRMS 276.1152 (calcd for C₁₉H₁₅O₂ 276.1150).

General Procedure for the Palladium-Catalyzed Double Annulation Reactions. Pd(OAc)₂ (6 mg, 0.026 mmol), Et₃N (53 mg, 0.50 mmol), DMF (5 ml), LiCl (21.2 mg, 0.50 mmol), the alkyne (1 mmol for diphenylacetylene and 2.5 mmol for 4,4-dimethyl-2-pentyne), and the dihaloalkene (0.25 mmol) were placed in a 2 dram vial. The vial was heated in an oil bath at 75 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with satd NH₄Cl, dried over anhydrous Na₂SO₄, and decanted. The solvent was evaporated under reduced pressure and the product was isolated by chromatography (EtOAc/hexanes) on a silica gel column. The following compounds were prepared by the above procedure.

7-Ethoxycarbonyl-5,6,12-triphenylbenz[a]anthracene (23, eq 6). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a brown solid: mp 193-195 °C (hexanes); 1H NMR (CDCl₃) δ 1.00 (t, J = 7.2 Hz, 3H), 3.31 (q, J = 7.2 Hz, 2H), 6.66-7.27 (m, 23H); 13C NMR (CDCl₃) δ 13.58, 61.31, 125.06, 126.36, 126.40, 126.46, 126.54, 126.85, 126.96, 127.06, 127.14, 127.22 (2C), 127.35, 127.48, 128.30, 130.09, 130.33, 130.48 (2C), 130.86, 131.46, 133.62,
134.84, 134.90, 135.46, 135.63, 136.27, 143.54, 144.15, 145.63, 146.70, 168.43; IR (CHCl₃) 1720 (C=O) cm⁻¹; HRMS 528.2084 (calcd for C₃₉H₂₈O₂ 528.2089).

**3,6-Di-tert.-butyl-4,5-dimethyl-1H-naphtho[1,2-c]pyran-1-one (24, eq 7).**

The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a light yellow solid: mp 140-142 °C (hexanes); ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.77 (s, 9H), 2.36 (s, 3H), 2.48 (s, 3H), 7.48 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 8.42 (d, J = 8.4 Hz, 1H), 9.74 (d, J = 8.7 Hz, 1H); ¹³C NMR (CDCl₃) δ 19.23, 26.81, 29.12, 33.64, 37.58, 39.57, 107.63, 113.14, 124.46, 126.28, 126.37, 126.78, 128.52, 130.16, 131.95, 147.03, 155.03, 161.59, 162.05; IR (CHCl₃) 1706 (C=O) cm⁻¹; HRMS 336.2094 (calcd for C₂₃H₂₈O₂ 336.2089).

**7-Methoxycarbonyl-5,6,12-triphenylbenz[a]anthracene (25, eq 8).** The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a brown solid: mp 217-219 °C (hexanes); ¹H NMR (CDCl₃) δ 3.02 (s, 3H), 6.66-6.75 (m, 8H), 6.84-7.03 (m, 11H), 7.22-7.25 (m, 4H); ¹³C NMR (CDCl₃) δ 52.01, 125.10, 126.40, 126.46, 126.48, 126.88, 126.97 (2C), 127.09, 127.22, 127.38, 128.23, 128.32, 128.42, 130.09, 130.32, 130.56, 130.85, 131.31, 131.58, 133.50, 133.62, 134.76, 134.84, 135.34, 135.59, 136.19, 143.09, 144.78, 145.78, 146.88, 168.78; IR (CHCl₃) 1715 (C=O) cm⁻¹; HRMS 514.1936 (calcd for C₃₈H₂₆O₂ 514.1933).

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References


(9) Doty, M. J. Ph. D. Dissertation, Iowa State University, **1995**.


(17) The following dihalides failed to give any double annulation products: Br$_2$C=CPhCO$_2$Et, Br$_2$C=C(CO$_2$Et)$_2$ and I$_2$C=C(CO$_2$Et)$_2$.


CHAPTER 3. PALLADIUM-CATALYZED CROSS-COUPLING OF 2,5-CYCLOHEXADIENYL-SUBSTITUTED ARYL AND VINYLIC IODIDES AND CARBON OR HETEROATOM NUCLEOPHILES

A paper to be submitted to the Journal of Organic Chemistry
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Abstract

2,5-Cyclohexadienyl-substituted aryl and vinylic iodides have been reacted with carbon nucleophiles (diethyl malonate, 2-methyl-1,3-cyclohexanedione), nitrogen nucleophiles (morpholine, potassium phthalimide, N-Benzyl tosylamide, di-tert.-butyl iminodicarboxylate, lithium azide and anilines), a sulfur nucleophile (sodium benzenesulfinate), and oxygen nucleophiles (lithium acetate and phenols) to afford products of cyclization and subsequent cross-coupling in good to excellent yields. In most cases, this process is highly diastereoselective and the products are formed as single diastereoisomers. The structures of the representative compounds have been determined by $^1$H NMR, $^{13}$C NMR, COSY, HMQC, and NOESY. The reaction is believed to proceed via (1) oxidative addition of the aryl or vinylic iodide to Pd(0), (2) organopalladium addition to one of the carbon-carbon double bonds, (3) palladium migration along the carbon chain on the same face of the ring to form a $\pi$-allylpalladium intermediate, and (4) nucleophilic displacement of the palladium either through backside nucleophilic attack, or nucleophilic attack on the palladium, followed by reductive elimination.
Introduction

The intramolecular Heck reaction has been extensively used in the construction of polycyclic compounds and in the synthesis of natural products. Shibasaki et al.² have reported asymmetric Heck reactions of conjugated dienyl-substituted vinylic triflates (eq 1) and 2,5-cyclohexadienyl-substituted vinylic triflates and iodides (eq 2). The radical ring-closure reactions of 2,5-cyclohexadienyl-substituted aryl iodides or vinylic bromides have been reported by Beckwith et al. (eq 3).³ This methodology has proven to be a powerful tool for the rapid construction of polycyclic compounds.

\[
\text{ArI} + \text{C}_{\text{n}}\text{CH} = \text{C} + \text{Nu-H} \xrightarrow{\text{cat. Pd(0)}} \text{ArC}_{\text{n}}\text{CH} = \text{C-Nu}
\]

We have previously discovered that aryl halides, non-conjugated dienes, and carbon nucleophiles,⁴ amines,⁵ or heteroatom nucleophiles⁶,⁷ can be coupled in high yields using Pd(dba)₂ as a catalyst (eq 4). We envisioned that if aryl or vinylic iodides and dienyl moieties were put together in the same molecule, the
reactions of the resulting dienyl-substituted aryl or vinylic iodides with external nucleophiles in the presence of a Pd(0) catalyst might afford polycyclic compounds, which contain allylic functional groups, by this novel palladium migration chemistry (eqs 5 and 6). It should be pointed out that under the Shibasaki conditions, bicyclic compounds containing a 1,3-diene moiety were formed from 2,5-cyclohexadienyl-substituted vinylic triflates and iodides (eq 2). In their process, beta hydride elimination, rather than palladium migration, is observed. The possibilities for the formation of highly functionalized carbon- and heteroatom-containing polycyclic compounds in a highly diastereoselective manner, and potential applications of these compounds in natural product syntheses, prompted us to examine further applications of this novel chemistry.

Results and Discussion

The starting materials were efficiently prepared by standard methodology. For example, aryl iodides 1-7 were prepared by the reactions shown in Scheme 1.
Thus, aryl iodide 1 was synthesized by the Mitsunobu reaction\textsuperscript{9} of 2-iodophenol with 2,5-cyclohexadienyl methanol.\textsuperscript{10} Aryl iodide 2 was prepared by the reaction of 2,5-cyclohexadienyl methanol and 2-iodobenzyl bromide in the presence of NaH.\textsuperscript{11} Aryl iodide 3 was synthesized by the reaction of methyl 2,5-cyclohexadienyl carboxylate\textsuperscript{12} with LDA, followed by the addition of 2-iodobenzyl bromide.\textsuperscript{13} Aryl iodide 4 was synthesized by the DIBAL reduction\textsuperscript{14} of aryl iodide 3. Aryl iodide 6 was synthesized by the DIBAL reduction\textsuperscript{14} of amide 5, which was formed by the reaction of 2,4-cyclohexadienyl carboxylic acid with 2-iodoaniline in the presence of DCC.\textsuperscript{15} Aryl iodide 7 was prepared by the reaction of aryl iodide 6 with BnBr in the presence of NaH.\textsuperscript{16}

Vinyllic iodides 14-16, 19, 22 and 25 were synthesized by the reactions
Scheme 2

$$R^1 \text{OH} \xrightarrow{\text{CBr}_4, \text{PPh}_3} R^1 \text{Br} \xrightarrow{\text{CBr}_4, \text{PPh}_3} R^1 \text{CO}_2\text{Me}$$

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>% Yield</th>
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<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>89</td>
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<tr>
<td>Ph</td>
<td>Ph</td>
<td>81</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>60</td>
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</tbody>
</table>

$$\text{CO}_2\text{Et} \xrightarrow{\text{DIBAL}} \text{CO}_2\text{Me}$$

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$$\text{Br} \xrightarrow{\text{NaBH}_4} \text{OH} \xrightarrow{\text{CBr}_4, \text{PPh}_3} \text{Br}$$

<table>
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<tr>
<td>81%</td>
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$$\text{OH} \xrightarrow{1. \text{NaH}} \text{O-H} \xrightarrow{2. 21} \text{N-Ts}$$

<table>
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$$\text{TsNHBOC} \xrightarrow{\text{CBr}_4, \text{PPh}_3} \text{TsNHBOC}$$

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$$\text{TsNHBOC} \xrightarrow{\text{CF}_3\text{CO}_2\text{H}} \text{TsNHBOC}$$

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$$\text{TsNHBOC} \xrightarrow{1. \text{NaH}} \text{TsNHBOC}$$

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<th>% Yield</th>
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shown in Scheme 2. Iodides 14-16 and 19 were prepared by alkylation of the enolate derived from methyl 2,5-cyclohexadienyl carboxylate using allylic bromides 11, 12, 13 or 18 respectively.\textsuperscript{13} Bromides 11-13 and 18 were synthesized by the reaction of the corresponding allylic alcohols 8-10 and 17 with CBr\textsubscript{4} and PPh\textsubscript{3}.\textsuperscript{17} Alcohols 8 and 9 were prepared by Cul-catalyzed Grignard addition to the appropriate propargylic alcohol and subsequent quenching by I\textsubscript{2}.\textsuperscript{18} Alcohol 10 was prepared by the DIBAL reduction of ethyl (Z)-3-iodo-2-propenoate.\textsuperscript{19} Allylic alcohol 17 was prepared by the DIBAL reduction of ethyl 2-iodo-3-methyl-2-butenoate.\textsuperscript{20} Vinylic iodide 22 was prepared by the reaction of 2,5- cyclohexadienyl methanol with allylic bromide 21 in the presence of NaH.\textsuperscript{11} Bromide 21 was produced by the reaction of alcohol 20, which was made by the NaBH\textsubscript{4} reduction\textsuperscript{21} of 2-iodo-cyclohexenone,\textsuperscript{22} with CBr\textsubscript{4} and PPh\textsubscript{3}.\textsuperscript{17} Vinylic iodide 25 was prepared by the reaction of tosylamide 24 with bromide 18 in the presence of NaH.\textsuperscript{23} Tosylamide 24 was prepared by employing trifluoroacetic acid in CH\textsubscript{2}Cl\textsubscript{2} to remove the BOC group from amide 23, which was made from 2,5- cyclohexadienyl methanol and TsNHBOC by the Mitsunobu reaction.\textsuperscript{24}

Using the reaction conditions developed for intermolecular versions of this chemistry,\textsuperscript{4} aryl iodide 1 (0.25 mmol) was reacted with 2 equiv of diethyl malonate in the presence of 10 mol\% Pd(dba)\textsubscript{2}, 1.1 equiv of TBAC, and 2.5 equiv of NaHCO\textsubscript{3} in 5 ml of DMSO at 120 °C for 22 h to afford the desired product 26 as a single diastereoisomer in 45% isolated yield (eq 7).

\[
\begin{align*}
\text{O} & \quad + \quad 2 \quad \text{CH}_2(\text{CO}_2\text{Et})_2 \quad \text{cat. Pd(0)} \\
\text{I} & \quad \rightarrow \quad \text{O} \\
\text{H} & \quad \text{CH}_2(\text{CO}_2\text{Et})_2
\end{align*}
\]
To optimize the yield, the reaction of aryl iodide 1 and diethyl malonate was examined in the presence of a variety of Pd catalysts \([\text{Pd(OAc)}_2, \text{Pd(OAc)}_2/\text{PPh}_3, \text{or Pd(dba)}_2]\), bases (\(\text{NaHCO}_3, \text{KHCO}_3, \text{Na}_2\text{CO}_3, \text{K}_2\text{CO}_3, \text{NaOAc} \text{or KOAc}\)) and chloride sources \([\text{LiCl or } n\text{-Bu}_4\text{NCl (TBAC)}]\) in different solvents (DMSO, DMF or DMA) at different temperatures (120, 100, 80 °C). The results are summarized in Table 1.

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd(0) catalyst</th>
<th>base (equiv), temp, time (^a)</th>
<th>(%^1\text{H} \text{NMR other} )</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% \text{Pd(OAc)}_2</td>
<td>\text{NaHCO}_3 (2.5) 120 °C, 22 h</td>
<td>messy (^1\text{H} \text{NMR} )</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10% \text{Pd(OAc)}_2</td>
<td>\text{NaHCO}_3 (2.5) 120 °C, 22 h</td>
<td>messy (^1\text{H} \text{NMR} )</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10% \text{Pd(OAc)}_2</td>
<td>\text{NaHCO}_3 (2.5) 120 °C, 22 h</td>
<td>messy (^1\text{H} \text{NMR} )</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10% \text{Pd(OAc)}_2</td>
<td>\text{NaHCO}_3 (2.5) 120 °C, 22 h</td>
<td>messy (^1\text{H} \text{NMR} )</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10% \text{Pd(dba)}_2</td>
<td>\text{KHCO}_3 (2.5) 100 °C, 6.5 h</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10% \text{Pd(dba)}_2</td>
<td>\text{K}_2\text{CO}_3 (2.5) 100 °C, 6.5 h</td>
<td>84 (72)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>10% \text{Pd(dba)}_2</td>
<td>\text{KOAc} (2.5) 100 °C, 6.5 h</td>
<td>24(^c)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>10% \text{Pd(dba)}_2</td>
<td>\text{Na}_2\text{CO}_3 (2.5) 100 °C, 6.5 h</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10% \text{Pd(dba)}_2</td>
<td>\text{NaOAc} (2.5) 100 °C, 6.5 h</td>
<td>28(^c)</td>
<td></td>
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</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(0) Source</th>
<th>Base (equiv)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>10</td>
<td>10% Pd(dba)$_2$</td>
<td>NaHCO$_3$ (2.5)</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>10% Pd(dba)$_2$</td>
<td>K$_2$CO$_3$ (2.5)</td>
<td>84 (72)</td>
</tr>
<tr>
<td>12</td>
<td>10% Pd(dba)$_2$</td>
<td>K$_2$CO$_3$ (2.5)</td>
<td>36 (61)$^9$</td>
</tr>
</tbody>
</table>

$^a$All reactions were run in 5 ml of DMSO, except entries 1 and 2, which employed 5 ml of DMF and entry 11 which utilized 2 ml of DMSO. $^b$n-Bu$_4$NCl (1.1 equiv) was used for all of the reactions. $^b$The $^1$H NMR yield was determined using 1,4-dimethoxynbenzene as the internal standard with a 10 second relaxation time (d1 = 10) on a Varian VXR 300 MHz spectrometer. Yields in parenthesis are isolated yields. $^c$Not compound 26, but an unknown compound containing an acetate group. $^d$Based on the recovery of aryl iodide 1.

It was found that the best Pd(0) source is Pd(dba)$_2$; the best base is K$_2$CO$_3$; the best solvent is DMSO and that the temperature could be lowered to 80 °C in 2 ml of DMSO (entry 11). Thus, the isolated yield of compound 26 could be improved to 72% by using 10 mol% Pd(dba)$_2$, 1.1 equiv of TBAC, and 2.5 equiv of K$_2$CO$_3$ in 2 ml of DMSO at 80 °C for 4 h. It is worth mentioning that when an acetate base (NaOAc or KOAc) was used, a product containing an acetate group other than compound 26, was formed in low yield (entries 7 and 9).

The reaction of nucleophiles$^{25}$ (carbon, nitrogen, oxygen and sulfur) with aryl iodide 1 was carried out under conditions similar to our previous intermolecular versions of this chemistry.$^{4-7}$ The results are summarized in Table 2 (entries 2-14).
Table 2. Palladium-catalyzed Cross-coupling of 2,5-Cyclohexadienyl-substituted Aryl and Vinylic Iodides with Various Nucleophiles. *

<table>
<thead>
<tr>
<th>entry</th>
<th>iodide</th>
<th>nucleophile</th>
<th>Cl− (equiv)</th>
<th>product(s) b</th>
<th>% (isomer ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(equiv)</td>
<td>base (equiv)</td>
<td>Nu =</td>
<td>isolated yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>CH₂(CO₂Et)₂ (2)</td>
<td>TBAC (1.1), K₂CO₃ (2.5)</td>
<td>CH(CO₂Et)₂ 26</td>
<td>72 (58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>TBAC (1.1)</td>
<td>NaHCO₃ (2.5)</td>
<td>27</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>TBAC (2)</td>
<td></td>
<td>28</td>
<td>31 (58)</td>
</tr>
</tbody>
</table>

\[\text{Table 2. Palladium-catalyzed Cross-coupling of 2,5-Cyclohexadienyl-substituted Aryl and Vinylic Iodides with Various Nucleophiles.}^* \]

\[\text{entry iodide nucleophile } \text{Cl}^- \text{ (equiv) product(s) }^b \text{ base (equiv) time Nu = isolated yield (isomer ratio)}^c \]

\[\text{1, } \text{CH}_2\text{(CO}_2\text{Et)}_2 \text{ (2) TBAC (1.1), } \text{K}_2\text{CO}_3 \text{ (2.5) CH(CO}_2\text{Et)}_2 \text{ 26 72 (58)} \]

\[\text{2, } \text{TBAC(1.1)} \text{ NaHCO}_3 \text{ (2.5) 27 55} \]

\[\text{3, } \text{TBAC (2) 28 31 (58)} \]

\[\text{* represents the treatment conditions and product yields.} \]
<p>| | | | | |</p>
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<tr>
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<td>4</td>
<td><img src="media/image1.png" alt="Chemical Structure" /> (5)</td>
<td>TBAC (2)</td>
<td>28</td>
<td>91</td>
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</tr>
<tr>
<td>5</td>
<td>NaN₃ (1.5)</td>
<td>LiCl (1)</td>
<td>N₃</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 h</td>
<td>36</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>LiN₃ (2)</td>
<td>LiCl (1), 15 h</td>
<td>29</td>
<td>51°</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="media/image2.png" alt="Chemical Structure" /> (2.5)</td>
<td>LiCl (2)</td>
<td>30</td>
<td>31</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>18 h</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>TsNHCH₂Ph (2)</td>
<td>TBAC (2)</td>
<td>N(Ts)CH₂Ph</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>9</td>
<td>HN(CO₂Bu)₂ (5)</td>
<td>TBAC (2)</td>
<td>N(CO₂Bu)₂</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52°</td>
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</table>
Table 2. (continued)

<table>
<thead>
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<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
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<tr>
<td>10</td>
<td>PhNH₂ (5) TBAC (2) NHPh</td>
<td>16 h</td>
<td>33</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Na₂CO₃ (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>PhSO₂Na (3) TBAC (1)</td>
<td>24 h</td>
<td>34</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>LiCl (1.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>LiOAc•2H₂O (3) TBAC (1)</td>
<td>15 h</td>
<td>35a</td>
<td>80°</td>
</tr>
<tr>
<td></td>
<td>LiCl (1.5)</td>
<td></td>
<td>(10:1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35b</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>PhOH (3) TBAC (1.1)</td>
<td>15 h</td>
<td>36</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>NaHCO₃ (2.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Reagents</td>
<td>Conditions</td>
<td>Yield</td>
<td></td>
</tr>
<tr>
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<td>----------</td>
<td>------------</td>
<td>-------</td>
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</tr>
<tr>
<td>14</td>
<td>$o$-BrC₆H₄OH (3), TBAC (1.1), NaHCO₃ (2.5)</td>
<td>16 h</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>CH₂(CO₂Et)₂ (2), TBAC (1.1), K₂CO₃ (2.5)</td>
<td>28 h</td>
<td>60 (66:13:14:7)</td>
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<tr>
<td>16</td>
<td>HN[O] (5), TBAC (2), Na₂CO₃ (2)</td>
<td>24 h</td>
<td>52</td>
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</tr>
<tr>
<td>17</td>
<td>CH₂(CO₂Et)₂ (2), TBAC (1.1), K₂CO₃ (2.5)</td>
<td>27 h</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>LiOAc·2H₂O (3), TBAC (1), LiCl (1.5)</td>
<td>26 h</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Reaction Conditions</td>
<td>Product Structure</td>
<td>Yield (%)</td>
</tr>
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<tr>
<td>19</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>$\text{CH}_2(\text{CO}_2\text{Et})_2$ (2) TBAC (1.1) $\text{K}_2\text{CO}_3$ (2.5) 24 h</td>
<td><img src="image2" alt="Product Structure" /></td>
<td>69</td>
</tr>
<tr>
<td>20</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>$\text{PhNH}_2$ (5) TBAC (2) $\text{Na}_2\text{CO}_3$ (2) 24 h</td>
<td><img src="image4" alt="Product Structure" /></td>
<td>100</td>
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<tr>
<td>21</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>$\text{CH}_2(\text{CO}_2\text{Et})_2$ (3) TBAC (1.1) $\text{K}_2\text{CO}_3$ (2.5) 24 h</td>
<td><img src="image6" alt="Product Structure" /></td>
<td>(26)$^a$</td>
</tr>
<tr>
<td>22</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>$\text{TsNHCH}_2\text{Ph}$ (2) TBAC (2) $\text{Na}_2\text{CO}_3$ (2) 24 h</td>
<td><img src="image8" alt="Product Structure" /></td>
<td>39</td>
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<td></td>
<td>Reaction</td>
<td>Products</td>
<td>Conditions</td>
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</tr>
</tbody>
</table>
| 23 | PhN. | CH$_2$(CO$_2$Et)$_2$ (2) | TBAC (1.1)  
K$_2$CO$_3$ (2.5)  
24 h | 46a  
(75:25) |
|   |   |   | + | 46b |
| 24 | PhNH$_2$ (5) | TBAC (2)  
Na$_2$CO$_3$ (2)  
24 h |   | 47 |
| 25 | Me-CO$_2$Me | CH$_2$(CO$_2$Et)$_2$ (2) | TBAC (1.1)  
K$_2$CO$_3$ (2.5)  
22 h | 48 |
| 26 | PhNH$_2$ (5) | TBAC (2)  
Na$_2$CO$_3$ (2)  
18 h |   | 49 |
Table 2. (continued)

<p>| | | | | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>27</td>
<td>$p$-C$_6$H$_4$OH (3)</td>
<td>TBAC (1.1)</td>
<td>Me</td>
<td>CO$_2$Me</td>
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<td>NaHCO$_3$ (2.5)</td>
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<td></td>
<td>23 h</td>
<td></td>
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</tr>
<tr>
<td>28</td>
<td>CH$_2$(CO$_2$Et)$_2$ (2)</td>
<td>TBAC (1.1)</td>
<td>Ph</td>
<td>CO$_2$Me</td>
</tr>
<tr>
<td></td>
<td>K$_2$CO$_3$ (2.5)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>23 h</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>29</td>
<td>NH</td>
<td>TBAC (2)</td>
<td>Ph</td>
<td>CO$_2$Me</td>
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<td></td>
<td>Na$_2$CO$_3$ (2)</td>
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<tr>
<td></td>
<td>23 h</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>30</td>
<td>LiOAc•2H$_2$O (3)</td>
<td>TBAC (1)</td>
<td>Ph</td>
<td>OAc</td>
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<td>LiCl (1.5)</td>
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<tr>
<td></td>
<td>26 h</td>
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</table>
Table 2. (continued)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Products</th>
<th>Conditions</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>31</td>
<td><img src="image1" alt="Structure" /></td>
<td>CH$_2$(CO$_2$Et)$_2$ (2) + TBAC (1.1) + K$_2$CO$_3$ (2.5)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 h</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td><img src="image2" alt="Structure" /></td>
<td>PhNH$_2$ (5) + TBAC (2) + Na$_2$CO$_3$ (2)</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 h</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td><img src="image3" alt="Structure" /></td>
<td>PhNH$_2$ (5) + TBAC (2) + Na$_2$CO$_3$ (2)</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 h</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td><img src="image4" alt="Structure" /></td>
<td>CH$_2$(CO$_2$Et)$_2$ (2) + TBAC (1.1) + K$_2$CO$_3$ (2.5)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Reagents</td>
<td>Conditions</td>
</tr>
<tr>
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<tr>
<td>35</td>
<td><img src="image1" alt="Structure" /></td>
<td>TBAC (2) Na$_2$CO$_3$ (2)</td>
<td>16 h</td>
</tr>
<tr>
<td>36</td>
<td><img src="image3" alt="Structure" /></td>
<td>CH$_2$(CO$_2$Et)$_2$ (2) TBAC (1.1) K$_2$CO$_3$ (2.5)</td>
<td>22 h</td>
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(a: 60:40)
Table 2. (continued)

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<thead>
<tr>
<th>Reaction</th>
<th>PhNH₂ (5)</th>
<th>TBAC (2)</th>
<th>Na₂CO₃ (2)</th>
<th>Product</th>
<th>Yield</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td>60a +</td>
<td>60b</td>
</tr>
<tr>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td>(62:38)</td>
<td></td>
</tr>
<tr>
<td>22 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All of the reactions were run in the presence of 10 mol % of Pd(dba)₂, 2 ml of DMSO (except entry 2, 5 ml of DMSO; entry 3, 5 ml of DMF; entries 8 and 22, 2 ml of DMF) at 100 °C (except entries 1, 17, 19, and 21, 80 °C).

*For the assignment of the structures of these compounds, see text. In entries 5, 6, and 15, only the major isomer is shown. *Isomer ratios were determined by ¹H NMR or GC-MS. *The yields are based on the recovery of starting materials. *The product has the same or a very similar ¹H NMR spectrum to that of entry 5. *After flash chromatography, an inseparable mixture of the product and 1,5-diphenyl-1,4-pentadien-3-one (dba) was obtained. The pure product was obtained after chromatography on a basic alumina column. *The reaction afforded an inseparable mixture of two isomers in the ratio of 10:1. Both isomers were obtained in pure form after hydrolysis of the acetates to the corresponding alcohols.
In a manner similar to the synthesis of diester 26, dione 27 was prepared in 55% yield under slightly modified reaction conditions.

Nitrogen nucleophiles have also proven quite successful. The yield of the reaction of iodide 1 with morpholine could be increased from 31% to 91% by switching to DMSO as the solvent in the presence of 2 equiv of Na$_2$CO$_3$ (entries 3 and 4). The yield of the reaction of 1 with azide could also be improved from 36% using 1.5 equiv of NaN$_3$ to 51% using 2 equiv of LiN$_3$ (entries 5 and 6). The formation of a mixture of regioisomers (29 vs 61 and 62 vs 63) in this reaction might be due to azide anion undergoing backside attack on the π-allylpalladium intermediate at both ends of the allylic system and/or [3,3]-sigmatropic rearrangement of the allyl azide.$^{26,27}$ The formation of a mixture of stereoisomers (29 vs 62 and 61 vs 63) might be resulting from the palladium-mediated isomerization of the intermediate π-allylpalladium species or a combination of frontside and backside displacement of palladium by azide.$^{27}$ Although allylic azides can be readily reduced to allylic amines, which are versatile intermediates in organic synthesis, the poor selectivity of this reaction prompted us to search for other protected primary amine derivatives to employ as nucleophiles. When potassium phthalimide (entry 7), N-benzyl tosylamide (entry 8), or di-tert.-butyl iminodicarboxylate (entry 9) was used as the nucleophile, the desired products 30-32 were formed each as a single diastereoisomer in 31, 60 or 52% yields,
respectively. Compounds 31\textsuperscript{28} and 32\textsuperscript{25e} should be readily converted to the corresponding allylic amines under mild conditions. Aniline was chosen as a nucleophile, because allylic anilines can be employed in the 3-aza-Cope rearrangement,\textsuperscript{29} and more importantly the potential tandem Heck reaction of the products obtained when 2-haloanilines are used as the nucleophile. Thus, the reaction of aryl iodide 1 and aniline afforded compound 33 as a single diastereoisomer in 90\% yield (entry 10).

Allylic sulfones are versatile intermediates in organic synthesis, since sulfones can convert the adjacent carbon into either a nucleophilic or an electrophilic center.\textsuperscript{25k} Allylic sulfones can also be prepared by \pi-\text{allylpalladium} displacement processes.\textsuperscript{25k} Thus, allylic sulfone 34 was produced in 62\% yield as a single diastereoisomer when sodium benzenesulfinate was used as the nucleophile (entry 11).

Allylic alcohols and acetates are also versatile intermediates in organic synthesis. The reaction of aryl iodide 1 with 3 equiv of lithium acetate afforded an inseparable 10:1 mixture of two regioisomers in 80\% yield in the presence of 1 equiv of TBAC and 1.5 equiv of LiCl in 2 ml of DMSO at 100 °C for 15 h (entry 12). When the above reaction was run for 5 h or 32 h under otherwise the same conditions, compound 35 was produced in 74 or 76\% isolated yields as an inseparable mixture of the same two regioisomers in the same 10:1 ratio. This suggests that the distribution of products is controlled by thermodynamics and this whole process is finished in less than 5 h. Saponification (K\textsubscript{2}CO\textsubscript{3}/MeOH) of the inseparable mixture (35a and 35b) afforded two readily separable alcohols 64 (84\% yield) and 65 (5\% yield) (eq 8).

Due to the usefulness of allylic phenyl ethers in the Claisen rearrangement,\textsuperscript{29} and more importantly the potential tandem Heck reaction of the
products obtained when 2-halophenols are used as the nucleophiles, phenol and 2-bromophenol were reacted with aryl iodide 1 to afford the desired products 36 and 37 as single diastereoisomers in 62 and 59% yields, respectively. Many synthetically useful transformations might be envisioned by the intramolecular Heck reaction of compound 37, followed by subsequent trapping of the σ-palladium intermediate 66, which lacks a beta hydrogen syn to the C-Pd bond (entry 14, eq 9).

All of the nucleophiles so far discussed, except lithium azide and acetate, which are well known for their poor selectivities in π-allylpalladium chemistry, react with aryl iodide 1 to form the desired products as single diastereoisomers. However, when aryl iodide 2 was reacted with diethylmalonate, an inseparable mixture of four isomers (38:67:68:69) in the ratio of 66:13:14:7 was obtained in
60% yield (entry 15). Compounds 38 and 67 (with cis ring fusion between rings B and C) were probably formed by cis addition of the arylpalladium intermediate to one of the carbon-carbon double bonds from the top face, followed by migration and subsequent backside nucleophilic attack on both ends of the π-allylpalladium intermediate. Similarly, compounds 68 and 69 (with trans ring fusion between rings B and C) were probably formed by cis addition of the arylpalladium to one of the carbon-carbon double bonds from the bottom face, then followed the same reaction pathways as those for the formation of 38 and 67. This poor selectivity can be attributed to the greater flexibility present in the 6,7,6-tricyclic ring of the π-allylpalladium intermediate, and the possibility of the addition of the arylpalladium species to one of the carbon-carbon double bonds from either the top face or the bottom face. However, when morpholine was used as the nucleophile, the desired product was formed as a single diastereoisomer (entry 16). From the results of entries 15 and 16, and 23 and 24, we can see that amine nucleophiles (morpholine in entry 16 and aniline in entry 24) are more diastereoselective than diethylmalonate. It appears that these nitrogen nucleophiles are more sensitive to the steric hindrance present in the π-allylpalladium intermediate, but the reason for this is not clear.
Ester and alcohol functionalities can also be tolerated in the starting aryl iodides employed in this reaction. For example, aryl iodides 3 and 4 were successfully reacted with carbon and heteroatom nucleophiles to give the desired products as single diastereoisomers in good to excellent yields (entries 17-20). The reaction of ester 3 with LiOAc•2H₂O afforded compound 41 as a single diastereoisomer in 67% yield (compare entry 12). The improved selectivity is presumably due to the increased steric hindrance towards backside nucleophilic attack present at the other end of the π-allylpalladium intermediate (see Scheme 3, intermediate 74).

Since nitrogen-containing moieties are often present in naturally-occurring compounds, it was desirable to establish if this process would work for substrates with a free NH group. Reactions of amide-containing aryl iodide 5 with diethyl malonate or morpholine gave none of the desired products, probably due to the presence of a relatively acidic amide hydrogen. The reaction of the secondary amine-containing aryl iodide 6 with diethyl malonate (entry 21) and N-benzyl tosylamide (entry 22) gave the desired products as single diastereoisomers in low yields, while aniline gave only a trace amount of the desired product. However, after protection of the problematic amine hydrogen in aryl iodide 6 by a benzyl group, the desired product was formed in 64% yield as a 75:25 inseparable mixture of two regioisomers (entry 23) when diethyl malonate was reacted with aryl iodide 7, and in 59% yield as a single diastereoisomer (entry 24), when aryl iodide 7 was reacted with aniline. The poor selectivity of the reaction in entry 23 might be attributed to the conformational mobility present in the π-allylpalladium intermediate brought about by the benzyl side chain.

Although vinylic halides have not previously been employed in intermolecular versions of our migration chemistry due to the concern that the initial
homoallylic palladium intermediate might migrate palladium back towards the carbon-carbon double bond originating in the vinylic moiety,\textsuperscript{31} it appeared that the cyclic dienes employed here might circumvent this difficulty and afford unsaturated polycyclic products of considerable utility in natural product synthesis. To test this hypothesis, vinylic iodides 14-16, 19, 22 and 25 were allowed to react with various nucleophiles. Indeed, vinylic iodides can be employed in this process and the results are summarized in Table 2, entries 25-37.

The following observations can be made regarding these results. Vinylic iodide 14 afforded the desired products in good yields as single diastereoisomers (entries 25-27). Compound 50, which was formed in 51% yield as a single diastereoisomer by the reaction of vinylic iodide 14 with 2-iodophenol, might also offer many synthetically useful transformations similar to those shown in eq. 9 for compound 37. Vinylic iodide 15, with a phenyl group adjacent to the iodide, also afforded the desired products in good yields as single diastereoisomers (entries 28-30). When vinylic iodide 15 was reacted with lithium acetate, compound 53 was formed in 50% yield as a single diastereoisomer (compare entries 12 and 18). Most interestingly, vinylic iodide 16 with a hydrogen beta to the iodide also afforded the desired products in good yields as single diastereoisomers (entries 31 and 32). Vinylic iodide 22 afforded the anticipated product 56 in 62% yield as a single diastereoisomer when aniline was used as the nucleophile (entry 33).

Compounds 57 and 58 were produced in 70% and 54% yields as single diastereoisomers when vinylic iodide 19 was reacted with diethyl malonate or morpholine, respectively (entries 34 and 35). It is indeed interesting that the 4-membered ring can be formed here, since we have shown previously that cyclobutylcarbinyl palladium compounds readily ring open and rearrange to \( \pi \)-allylpalladium intermediates.\textsuperscript{32} Compounds 59 and 60 are formed in 61 or 71%
yields as inseparable mixtures of two isomers in the ratios 60:40 and 62:38 respectively, when vinylic iodide 25 was reacted with diethyl malonate or aniline (entries 36 and 37). The poor selectivity in these reactions could possibly be due to conformational effects present in the π-allyl palladium intermediate introduced by the presence of a tosyl group.

The structures of our cyclization products have been elucidated by careful examination of their COSY, HMQC, and NOESY spectra. For example, consider compounds 27, 42, and 59a as products of carbon nucleophiles, compound 53 derived from an acetate nucleophile, compound 36 bearing a phenoxide nucleophile, compound 34 possessing a sulfur moiety, compound 43 derived from a nitrogen nucleophile, compounds 59a and 59b as structural isomers, and compound 38 containing a seven-membered ring (Figure 2). Extensive 1D and 2D NMR studies allow us to assign all of the significant 1H signals for these compounds. Selected NMR data for these compounds can be found in Table 3. The COSY, HMQC, and NOESY spectra of these compounds clearly indicated a cis-junction of rings B and C in compounds 27, 34, 36, 38, 42, and 43 and a cis-junction of rings A and B in compounds 53 and 59a. The structure of compound 27 was assigned as that drawn, in which the cyclohexanedione moiety is trans to ring B, since there was an NOE interaction between H⁹ and H¹⁰ and no NOE interaction between H⁶ and H⁹. The NOESY spectrum of compound 42 indicated that the stereochemistry at C* is that drawn, in which the malonate moiety is trans to ring B, since there is no NOE interaction between H¹₂ and H² or H⁶. Unfortunately, it cannot be determined if there is an NOE interaction between H⁹ and H¹₂, because these two protons' signals overlap. The NOESY spectrum of compound 59a clearly indicates that the stereochemistry at C* is that shown, in which the malonate moiety is trans to ring A, because of the presence of a strong NOE interaction
Figure 2. The structures of compounds 27, 34, 36, 38, 42, 43, 53, 59a, and 59b based on their $^1$H NMR, $^{13}$C NMR, COSY, HMQC and NOESY spectral data.
Table 3. Selected NMR Data for Compounds 27, 34, 36, 38, 42, 43, 53, 59a, and 59b.

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**Compound 42**

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**Compound 43**

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* H-ArN represents the aniline aromatic protons appearing at 6.58 ppm
** H-Ar represents the aromatic protons.

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between H\textsuperscript{11} and H\textsuperscript{12}. The structure of the rest of the compounds derived from carbon nucleophiles were assigned as drawn based on analogy with these three compounds and the fact that stabilized carbanion nucleophiles generally undergo backside nucleophilic attack on π-allylpalladium species.\textsuperscript{7}

The NOESY spectrum of compound 53 indicates that the stereochemistry at C\textsuperscript{*} is that drawn, in which the acetate moiety is \textit{trans} to ring A, because of the absence of an NOE interaction between H\textsuperscript{6} and H\textsuperscript{10} and the presence of an NOE interaction between H\textsuperscript{6} and the aromatic protons. The structure of the rest of the compounds containing an acetate moiety was assigned as drawn based on analogy with compound 53.

The NOESY spectrum of compound 36 indicates that the stereochemistry at C\textsuperscript{*} is that drawn, in which the phenoxide moiety is \textit{cis} to ring B, since there is an NOE interaction between H\textsuperscript{6} and H\textsuperscript{9}, and no NOE interaction between H\textsuperscript{1} and H\textsuperscript{6}. The structure of the rest of the compounds containing a phenoxide moiety was assigned as drawn based on the analogy with compound 36.

The NOESY spectrum of compound 34 indicates that the stereochemistry at C\textsuperscript{*} is that drawn, in which the benzenesulfonyl moiety is \textit{cis} to ring B, because of the presence of an NOE interaction between H\textsuperscript{6} and H\textsuperscript{9}.

The NOESY spectrum of compound 43 indicates that the stereochemistry at C\textsuperscript{*} is that drawn, in which the aniline moiety is \textit{trans} to ring B, because of the absence of an NOE interaction between H\textsuperscript{7} and H\textsuperscript{10} and the presence of an NOE interaction between H\textsuperscript{10} and the aromatic protons from the aniline moiety. The structure of the rest of the compounds containing a nitrogen moiety was assigned as drawn based on the analogy with compound 43 and from the assumption that nitrogen nucleophiles, such as morpholine, potassium phthalimide, N-benzyl
tosylamide, di-tert.-butyl iminodicarboxylate, and lithium azide are soft nucleophiles, just like anilines.

After careful comparison of the $^1$H NMR and COSY spectra of pure compound 59a and the 60:40 mixture of 59a and 59b, it was determined that H$^5$ in compound 59b appears at 1.69 ppm. This indicates that the malonate moiety is attached to the carbon with an asterisk in compound 59b. The stereochemistry at C$^*$ in 59b is that drawn based on the fact that stabilized carbanion nucleophiles generally undergo backside nucleophilic attack on $\pi$-allylpalladium species. Thus, the formation of a mixture of isomers 59a and 59b is due to the malonate anion undergoing backside attack on the $\pi$-allylpalladium intermediate at both ends of the allylic system. The structures of the isomers in entries 12, 23, and 37 of Table 2 were assigned by analogy with compounds 59a and 59b. The formation of two regioisomers in these entries is probably due to backside nucleophilic attack on both ends of the $\pi$-allylpalladium intermediates. After recrystallization of the mixture of 38, 67, 68 and 69, compound 38 was obtained in an almost pure form. For compound 38, which is the major isomer, the presence of a strong NOE interaction between H$^5$ and H$^{11}$ indicates a cis fusion between rings B and C; the presence of NOE interactions between H$^{12}$ and H$^{11}$, and H$^{12}$ and H$^5$ strongly indicates the stereochemistry at C$^*$ is that drawn, in which the malonate moiety is trans to ring A.

The above NOESY spectral studies indicate that carbon nucleophiles (diethyl malonate, 2-methyl-1,3-cyclohexanedicarboxylate), anilines, and lithium acetate give backside attack on the $\pi$-allylpalladium intermediate, while sodium benzenesulfinate and phenols afford products of frontside attack. The stereochemistry of the rest of the compounds were assigned based on the assumption that soft nucleophiles give backside nucleophilic substitution, while
hard nucleophiles attack at palladium in the \( \pi \text{-allylpalladium} \) intermediates and undergo reductive elimination. The above assignment of hardness or softness to a specific nucleophile is in agreement with literature data. 25

This overall coupling process likely proceeds according to the pathway illustrated in Scheme 3 (exemplified using iodide 3). Generation and addition of an aryl- or vinylpalladium intermediate to the internal carbon-carbon double bond, followed by migration of palladium along the carbon chain on the same face of the

**Scheme 3**

\( \text{cat. Pd(0)} \)

\( \text{POAME} \)

\( \text{POGME} \)

\( \text{70} \)

\( \text{71} \)

\( \text{72} \)

\( \text{73} \)

\( \text{74} \)

\( \text{75} \)

\( \text{76} \)

\( \text{77} \)

\( \text{HNu}^1 = \text{diethyl malonate, 2-methyl-1,3-cyclohexanedione, morpholine, potassium phthalimide, } N\text{-benzyl tosylamide, di-tert.-butyl iminodicarboxylate, lithium azide, anilines, } \) and lithium acetate.

\( \text{HNu}^2 = \text{phenols and sodium benzenesulfinate} \)

ring, results in the formation of a \( \pi \text{-allylpalladium} \) species (74). Intermediate 74 undergoes backside intermolecular nucleophilic attack to afford products when soft
nucleophiles, such as diethyl malonate, 2-methyl-1,3-cyclohexanedione, morpholine, potassium phthalimide, N-benzyl tosylamide, di-tert.-butyl iminodicarboxylate, lithium azide, anilines, and lithium acetate are used. However, hard nucleophiles, such as phenols and sodium benzenesulfinate first attack on the palladium to form intermediate 76, which subsequently undergoes reductive elimination to afford products of the type 77. The observed regioselectivities of this process are in agreement with the literature observations that the regioselectivity of nucleophilic attack on the \( \pi \)-allylpalladium intermediates depends greatly on very small steric differences that exist at the two termini of the allylic system, and that nucleophiles other than organometallics attack at the less hindered terminus.\(^7\)\(^3\) For some nucleophiles, such as lithium acetate and diethylmalonate, larger steric differences at the two termini of the allylic system are needed to afford the desired products as single diastereoisomers.

From the above results, we can conclude that not only aryl iodides, but also vinylic iodides (even those which contain a hydrogen beta to palladium), afford the desired products in good yields, usually as single diastereoisomers. In addition, nucleophiles as diverse as morpholine, potassium phthalimide, N-benzyl tosylamide, di-tert.-butyliminodicarboxylate, anilines, and phenols give the desired products as single diastereoisomers in most cases. Nucleophiles, such as diethyl malonate, usually give the desired products as single diastereoisomers, unless certain substrates were used (entries 15, 23 and 36). Nucleophiles, such as lithium azide and acetate, usually give the desired products as inseparable mixtures of at least two isomers (entries 5, 6 and 12). However, some substrates in which one end of the \( \pi \)-allylpalladium intermediate is much more sterically hindered than the other end afford the desired products as single diastereoisomers (entries 18 and 30).
This work presents a novel method for the highly diastereoselective synthesis of polycyclic compounds containing allylic functional groups, and nicely complements the recent intramolecular asymmetric Heck chemistry of Shibasaki, where beta hydride elimination, rather than palladium migration, is observed. The easily-prepared starting materials, good to excellent chemical yields, tandem nature, and more significantly, high diastereoselectivities of this process should find applications in the total synthesis of naturally-occurring compounds.

**EXPERIMENTAL SECTION**

**General.** All $^1$H and $^{13}$C NMR spectra were recorded at 300 or 400 and 75.5 or 100 MHz respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualized with short wavelength UV light (254 nm), and basic KMnO$_4$ solution [3g KMnO$_4$ + 20g K$_2$CO$_3$ + 5 ml NaOH (5%) + 300 ml H$_2$O].

**Reagents.** All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous TBAC was purchased from Lancaster. Palladium chloride was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. Pd(dba)$_2$, methyl 2,5-cyclohexadienyl methanol, methyl 2,5-cyclohexadienyl-1-carboxylate, (Z)-3-iodo-2-methyl-2-propenol, (Z)-3-iodo-2,3-diphenyl-2-propenol, ethyl (Z)-3-iodo-2-propenoate, ethyl 2-iodo-3-methyl-2-butenoate, and 2-iodo-2-cyclohexenone were synthesized by the literature procedures. Aryl iodides 1-7 and vinylic iodides 14-16, 19, 22 and 25 were prepared as follows.

**Cyclohexa-2,5-dienylmethyl 2'-iodophenyl ether (1).** To a solution of 2-iodophenol (4.95 g, 22.5 mmol), 2,5-cyclohexadienyl methanol (1.62 g, 15
mmol), and triphenylphosphine (4.71 g, 18 mmol) in THF (30 ml), cooled in an ice bath under an Ar atmosphere, was added diethyl azodicarboxylate (2.85 ml, 18 mmol) dropwise. The resulting reaction mixture was stirred at 0 °C for 15 min, then room temperature for 8 h. The solvent was removed in vacuo, followed by the addition of 70 ml of ether. The precipitate was filtered and washed with 8 ml of ether. The combined filtrates were concentrated in vacuo and the residue was subjected to flash chromatography using 1:15 EtOAc/hexanes as the eluent to afford 1.63 g of a colorless liquid (35% yield): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.71 (d, \(J = 9.0\) Hz, 2H), 3.29 (t, \(J = 6.9\) Hz, 1H), 3.89 (d, \(J = 6.9\) Hz, 2H), 5.85 (s, 4H), 6.68 (td, \(J = 7.5, 1.2\) Hz, 1H), 6.76 (dd, \(J = 8.1, 1.2\) Hz, 1H), 7.25 (td, \(J = 7.8, 1.5\) Hz, 1H), 7.75 (dd, \(J = 7.8, 1.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 26.5, 35.7, 73.1, 86.6, 112.0, 122.4, 125.3, 126.1, 129.3, 139.3, 157.3; IR (neat) 3058, 3020, 2865, 1120, 1049, 1018 cm\(^{-1}\); HRMS for C\(_{13}\)H\(_{13}\)IO calcd 312.0011, found 312.0015.

Compounds 2 and 22 were prepared according to the following procedure.

(a) Cyclohexa-2,5-dienylmethyl 2'-iodobenzyl ether (2).

**Representative Procedure.** 2,5-Cyclohexadienyl methanol (0.78 g, 7.2 mmol) in THF (7.2 ml) was added to a suspension of NaH (0.36 g, 60% purity, 9.0 mmol) in THF (7.2 ml) at room temperature. The mixture was stirred at room temperature for 15 min, then 2-iodobenzyl bromide (2.46 g, 8.28 mmol) was added to the above mixture. After stirring at room temperature for 17 h, the reaction was quenched with H\(_2\)O (20 ml), extracted with ether (60 ml, 20 ml \(\times\) 2), and dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo and the residue was subjected to flash chromatography using straight hexanes as the eluent to afford 1.90 g of a colorless liquid (82% yield): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.65-2.71 (m, 2H), 3.04-3.12 (m, 1H), 3.50 (d, \(J = 9.6\) Hz, 2H), 4.51 (s, 2H), 5.73-5.84 (m, 4H), 6.98 (td, \(J = 7.5, 1.8\) Hz, 1H), 7.35 (td, \(J = 7.5, 1.2\) Hz, 1H), 7.46 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.81 (dd, \(J = 7.8, 1.2\) Hz, 1H);
(b) Cyclohexa-2,5-dienylmethyl 2'-iodo-2'-cyclohexenyl ether (22): 3-Bromo-2-iodo-1-cyclohexene was used instead of 2-iodobenzyl bromide (32% yield): $^1$H NMR (CDCl$_3$) $\delta$ 1.57-2.18 (m, 6H), 2.65-2.69 (m, 2H), 2.98-3.09 (m, 1H), 3.39 (dd, $J = 8.7$, 6.9 Hz, 1H), 3.50 (dd, $J = 8.4$, 6.9 Hz, 1H), 3.82 (t, $J = 3.9$ Hz, 1H), 5.73-5.87 (m, 4H), 6.53 (t, $J = 4.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 17.1, 26.5, 28.9, 29.4, 36.4, 74.5, 79.5, 99.4, 125.15, 125.21, 126.3, 126.4, 141.6; IR (neat) 3019, 2938, 2859, 1096, 1062 cm$^{-1}$; HRMS for C$_{13}$H$_{11}$IO calcd 316.0324, found 316.0319.

Allylic bromides. Allylic bromides 11-13, 18, and 21 were prepared according to the following procedure.

(a) (Z)-3-Bromo-1-iodo-2-methyl-1-propene (11). Representative procedure. To a mixture of (Z)-3-iodo-2-methyl-2-propen-1-ol (8, 1.19 g, 6 mmol), and carbon tetrabromide (2.59 g, 7.8 mmol) in CH$_2$Cl$_2$ (10 ml), cooled to 0 °C under an Ar atmosphere, was added triphenylphosphine (2.36 g, 9.0 mmol) portionwise. The resulting mixture was stirred at 0 °C for 15 min, then room temperature for 2 h. The solvent was removed in vacuo and the residue was subjected to flash chromatography using straight hexanes as the eluent to afford 1.40 g of a colorless liquid (89% yield): $^1$H NMR (CDCl$_3$) $\delta$ 2.05 (d, $J = 1.5$ Hz, 3H), 4.09 (s, 2H), 6.21 (q, $J = 1.5$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 22.0, 37.4, 79.8, 143.2.

(b) (Z)-3-Bromo-1-iodo-1,2-diphenyl-1-propene (12). (Z)-3-Iodo-2,3-diphenyl-2-propen-1-ol (9) was used instead of (Z)-3-iodo-2-methyl-2-propen-1-ol (8). EtOAc/hexanes (1:20) as the eluent afforded a light yellow liquid (81% yield): $^1$H NMR (CDCl$_3$) $\delta$ 4.62 (s, 2H), 7.05-7.15 (m, 10H); $^{13}$C NMR (CDCl$_3$) $\delta$ 44.0, 106.5, 127.5, 127.7, 127.8, 128.1, 129.1, 129.5, 137.7, 143.7, 144.0.
(c) (Z)-3-Bromo-1-iodo-1-propene (13). (Z)-3-iodo-2-propen-1-ol (10) was used instead of (Z)-3-iodo-2-methyl-2-propen-1-ol (8). EtOAc/hexanes (1:99) as the eluent afforded a colorless liquid (60% yield): $^1$H NMR (CDCl$_3$) $\delta$ 4.01 (dd, $J$ = 6.6, 0.6 Hz, 2H), 6.49 (d, $J$ = 7.5 Hz, 1H), 6.54 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 32.5, 88.1, 136.4.

(d) 1-Bromo-2-iodo-3-methyl-2-butene (18). 2-iodo-3-methyl-2-buten-1-ol (17) was used instead of (Z)-3-iodo-2-methyl-2-propen-1-ol (8). Straight hexanes as the eluent afforded a colorless liquid (78% yield): $^1$H NMR (CDCl$_3$) $\delta$ 1.92 (s, 3H), 1.99 (s, 3H), 4.49 (s, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 19.4, 31.8, 41.7, 94.1, 144.7.

(e) 3-Bromo-2-iodo-1-cyclohexene (21). 2-iodo-2-cyclohexen-1-ol (20) was used instead of (Z)-3-iodo-2-methyl-2-propen-1-ol (8). The reaction mixture was stirred at room temperature for 16 h. EtOAc/hexanes (1:99) as the eluent afforded a colorless liquid (83% yield): $^1$H NMR (CDCl$_3$) $\delta$ 1.79-1.84 (m, 1H), 2.02-2.10 (m, 1H), 2.14-2.23 (m, 1H), 2.26-2.34 (m, 3H), 4.81-4.82 (m, 1H), 6.44 (t, $J$ = 4.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 16.0, 29.0, 33.4, 58.2, 97.4, 142.1.

Allylic alcohols 10 and 17 were prepared according to the following procedure.

(a) (Z)-3-iodo-2-propen-1-ol (10). Representative procedure. DIBAL-H (40 ml, 1M in hexanes, 40 mmol) was added dropwise to a mixture of ethyl (Z)-3-iodo-propenoate (3.0 g, 13.3 mmol) in THF (25 ml) and PhCH$_3$ (25 ml) at -78 °C under a positive Ar atmosphere. The resulting mixture was stirred at -78 °C for 4 h and quenched with aq NH$_4$Cl (100 ml) at -78 °C. The mixture was warmed to room temperature and a sufficient amount of 2N HCl was added to just dissolve the precipitates, followed by extraction with ether (100 ml, 70 ml × 2). The combined ether layers were washed with satd aq NaHCO$_3$ and brine, and then
dried over Na$_2$SO$_4$. The solvents were removed in vacuo and the residue was subjected to flash chromatography using EtOAc/hexanes (1:1) as the eluent to afford 2.20 g of a colorless liquid (90% yield): $^1$H NMR (CDCl$_3$) $\delta$ 2.58 (s, 1H), 4.23 (dd, $J = 5.7, 1.5$ Hz, 2H), 6.36 (dt, $J = 7.8, 1.5$ Hz, 1H), 6.48 (dt, $J = 7.8, 5.7$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 65.5, 82.5, 139.9.

(b) 2-ido-3-methyl-2-buten-1-ol (17). Ethyl 2-ido-3-methyl-2-butenoate was used instead of ethyl (Z)-3-iodo-propenoate (87% yield): $^1$H NMR $\delta$ 1.83-1.86 (m, 1H); 1.94 (s, 3H), 1.98 (s, 3H), 4.36 (s, 2H); $^{13}$C NMR $\delta$ 19.8, 31.5, 67.7, 102.2, 140.3.

2-ido-2-cyclohexen-1-ol (20). To a mixture of 2-iodo-2-cyclohexenone (2.50 g, 11.3 mmol) and CeCl$_3$$\cdot$7H$_2$O (4.29 g, 11.5 mmol) in MeOH (30 ml), was added NaBH$_4$ (0.445 g, 11.8 mmol) in 1 min. The resulting mixture was stirred at room temperature for 3.5 h and quenched with satd aq NH$_4$Cl (10 ml). The solvent was removed in vacuo and the residue was partitioned between ether (120 ml) and satd aq NH$_4$Cl (40 ml). A sufficient amount of 2N HCl was added just to dissolve the precipitate. The ether layer was washed with satd aq NaHCO$_3$ and brine, and dried over Na$_2$SO$_4$. The solvents were removed in vacuo to afford a colorless liquid pure enough for the next reaction (2.40 g, 95% yield): $^1$H NMR (CDCl$_3$) $\delta$ 1.66-2.12 (m, 6H), 2.28 (s, 1H), 4.19 (t, $J = 5.1$ Hz, 1H), 6.50 (t, $J = 4.2$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 17.6, 29.3, 31.9, 72.0, 103.5, 140.9.

Esters. Esters 3, 14-16, and 19 were prepared according to the following procedure.

(a) Methyl 1-(2-iodobenzyl)-2,5-cyclohexadienecarboxylate (3). 

Representative Procedure. Methyl 2,5-cyclohexadienyl carboxylate (1.38 g, 10 mmol) was added dropwise to a mixture of LDA (12 mmol) and HMPA (2.15 g, 12 mmol) in THF (30 ml) at -78 °C. The mixture was stirred at -78 °C for 1 h, followed
by the addition of 2-iodobenzyl bromide in THF (5 ml). The reaction mixture was allowed to warm to room temperature over 2 h and stirred at room temperature for 4 h. The reaction was quenched with 5 ml of H₂O and the resulting mixture was concentrated in vacuo. The residue was extracted with ether (100 ml x 2) and dried over Na₂SO₄. The solvent was removed in vacuo and the residue was subjected to flash chromatography using EtOAc/hexanes (1:20) as the eluent to afford a light yellow liquid (3.20 g, 90 % yield): ¹H NMR (CDCl₃) δ 2.26 (dm, J = 23.1 Hz, 1H), 2.51 (dm, J = 23.1 Hz, 1H), 3.26 (s, 2H), 3.74 (s, 3H), 5.77-5.84 (m, 2H), 5.90-5.95 (m, 2H), 6.26 (ddd, J = 8.1, 6.6, 2.7 Hz, 1H), 7.15-7.22 (m, 2H), 7.79 (dd, J = 7.8, 1.2 Hz, 1H); ¹³C NMR (CDCl₃) δ 25.8, 48.6, 49.5, 52.3, 103.4, 126.3, 126.4, 127.4, 128.1, 130.8, 139.4, 139.8, 174.5; IR (neat) 3024, 2950, 1728, 1176 cm⁻¹; HRMS for C₁₅H₁₅IO₃ calcd 354.0117, found 354.0117.

(b) Methyl 1-[(Z)-3-iodo-2-methyl-2-propenyl]-2,5-cyclohexadienecarboxylate (14). (Z)-3-Bromo-1-iodo-2-methyl-1-propene (11) was used instead of 2-iodobenzyl bromide (88% yield): ¹H NMR (CDCl₃) δ 1.84 (d, J = 1.5 Hz, 3H), 2.65-2.70 (m, 2H), 2.75 (s, 2H), 3.72 (s, 3H), 5.82-5.92 (m, 4H), 6.04 (q, J = 1.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 24.5, 25.9, 47.4, 47.7, 52.4, 78.9, 125.7, 127.0, 143.8, 174.6; IR (neat) 3032, 2950, 1729, 1065, 1012 cm⁻¹; HRMS for C₁₀H₁₄I (M⁺-C₂H₃O₂) calcd 258.9984, found 258.9979.

(c) Methyl 1-[(Z)-3-iodo-2,3-diphenyl-2-propenyl]-2,5-cyclohexadienecarboxylate (15). (Z)-3-Bromo-1-iodo-1,2-diphenyl-1-propene (12) was used instead of 2-iodobenzyl bromide (60% yield): ¹H NMR (CDCl₃) δ 2.54-2.58 (m, 2H), 3.31 (s, 3H), 3.44 (s, 2H), 5.69-5.75 (m, 2H), 5.81 (dt, J = 10.5, 1.8 Hz, 2H), 6.88-6.93 (m, 2H), 6.97-7.07 (m, 8H); ¹³C NMR (CDCl₃) δ 25.9, 47.5, 51.9, 53.6, 104.2, 125.3, 126.7, 126.8, 126.9, 127.3, 127.5, 129.6, 129.7,
138.6, 144.7, 144.9, 174.1; IR (CHCl₃) 1725 cm⁻¹; HRMS for C₂₃H₂,I₂O₂ calcd 456.0586, found 456.0590.

(d) Methyl 1-[(Z)-3-iodo-2-propenyl]-2,5-cyclohexadiene-carboxylate (16). (Z)-3-Bromo-1-iodo-1-propene (13) was used instead of 2-iodobenzyl bromide (75% yield): ¹H NMR (CDCl₃) δ 2.56 (dd, J = 6.9, 1.8 Hz, 2H), 2.65-2.69 (m, 2H), 3.72 (s, 3H), 5.76 (dt, J = 12.6, 2.1 Hz, 2H), 5.88-5.95 (m, 2H), 6.08 (dt, J = 7.5, 6.8 Hz, 1H), 6.32 (dt, J = 7.5, 1.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 26.0, 44.3, 47.2, 52.3, 84.9, 126.3, 126.5, 136.5, 174.2; IR (neat) 3031, 2950, 1723, 1111, 1070 cm⁻¹; HRMS for C₁₃H₁₅O₂ (M⁺-I) calcd 177.0916, found 177.0918.

(e) Methyl 1-[2-iodo-3-methyl-2-butanyl]-2,5-cyclohexadienecarboxylate (19). 1-Bromo-2-iodo-3-methyl-2-butene (18) was used instead of 2-iodobenzyl bromide (69% yield): ¹H NMR (CDCl₃) δ 1.80 (s, 3H), 1.95 (s, 3H), 2.63-2.66 (m, 2H), 3.13 (s, 2H), 3.73 (s, 3H), 5.82-5.92 (m, 4H); ¹³C NMR (CDCl₃) δ 20.7, 26.0, 32.2, 47.5, 50.8, 52.3, 92.5, 125.3, 127.0, 140.8, 174.3; IR (neat) 3034, 2947, 1735, 1124, 1065 cm⁻¹; HRMS for C₁₃H₁₅O₂ (M⁺-I) calcd 205.1228, found 205.1230.

1-(2-Iodobenzyl)-2,5-cyclohexadienylmethyl alcohol (4). Methyl 1-(2-iodobenzyl)-2,5-cyclohexadienecarboxylate (3, 1.06 g, 3 mmol) in PhCH₃ (6 ml) was added dropwise to a solution of DIBAL in hexanes (6.3 ml, 6.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h and was quenched with PhCH₃ (5 ml), MeOH (5 ml), and 2 N HCl (3.3 ml). The resulting mixture was stirred at 0 °C for 30 min, then ether (60 ml) and satd aq NH₄Cl (20 ml) were added. The aqueous layer was extracted with ether (30 ml x 2) and the combined ether layers were dried over Na₂SO₄. The solvent was removed in vacuo to afford a colorless liquid pure enough for the next reaction (100% yield): ¹H NMR (CDCl₃) δ 1.61 (br s, 1H), 2.30 (dd, J = 23.2, 2.0 Hz, 1H), 2.52 (dd, J = 22.8, 1.6 Hz, 1H), 2.88 (s, 2H), 3.54 (d, J =
4.4 Hz, 2H), 5.63 (d, J = 10.4 Hz, 2H), 5.88 (dt, J = 10.2, 2.8 Hz, 2H), 6.84 (td, J = 7.4, 1.2 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 26.2, 45.2, 46.8, 67.0, 103.2, 127.3, 127.7, 127.8, 128.9, 131.0, 139.3, 140.6; IR (CHCl$_3$) 3429 cm$^{-1}$; HRMS for C$_{13}$H$_{12}$I (M$^+$-CH$_3$O) calcd 294.9984, found 294.9974.

**N-2-Iodophenyl-2,5-cyclohexadienecarboxamide (5).** DCC (2.48 g, 12 mmol) in CH$_2$Cl$_2$ (5 ml) was added to the mixture of 2,5-cyclohexadienecarboxylic acid (1.24 g, 10 mmol) and 2-iodoaniline (1.75 g, 8 mmol) in CH$_2$Cl$_2$ (10 ml) at 0 °C under a positive Ar atmosphere. The mixture was stirred at 0 °C for 30 min, then room temperature for 60 h. The solvents were removed in vacuo and the residue was subjected to flash chromatography using EtOAc/hexanes (1:9) to afford white needle crystals (2.3 g, 88% yield): mp 91-93 °C; $^1$H NMR (CDCl$_3$) δ 2.83-2.92 (m, 2H), 3.76-3.82 (m, 1H), 5.92-5.97 (m, 2H), 6.05-6.11 (m, 2H), 6.82 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.75 (dd, J = 8.1, 1.5 Hz, 1H), 7.94 (br s, 1H), 8.29 (d, J = 8.4 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 26.1, 46.4, 89.2, 121.1, 123.1, 125.7, 127.9, 129.2, 138.1, 138.7, 170.6; IR (CHCl$_3$) 3341, 1688 cm$^{-1}$.

**N-2,5-Cyclohexadienylmethyl 2-iodoaniline (6).** N-2-Iodophenyl-2,5-cyclohexadienecarboxamide (5, 0.975 g, 3 mmol) in PhCH$_3$ (12 ml) was added to a solution of DIBAL in hexanes (12 ml, 12 mmol) at 0 °C under a positive Ar atmosphere. The mixture was stirred at 0 °C for 20 min, then room temperature for 8 h, followed by quenching with MeOH (50 ml) and H$_2$O (5 ml). The solution obtained by filtration was concentrated in vacuo and the residue was extracted with ether (30 ml x 2) and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the residue was subjected to flash chromatography using EtOAc/hexanes (1:30) to afford a light yellow liquid (0.53 g, 57% yield): $^1$H NMR (CDCl$_3$) δ 2.65-2.88 (m, 2H), 3.16 (br s, 3H), 4.32 (br s, 1H), 5.64-5.69 (m, 2H), 5.90-5.95 (m, 2H), 6.40 (td, J =
7.5, 1.5 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 7.17 (td, J = 8.1, 1.2 Hz, 1H), 7.61 (dd, J =
7.8, 1.2 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 26.4, 34.9, 48.4, 85.2, 110.5, 118.2, 126.4,
126.9, 129.3, 138.8, 147.3; IR (neat) 3377, 3060, 3018, 2854, 1317, 1285 cm\(^{-1}\); HRMS for C\(_{13}\)H\(_{14}\)I calcd 311.0171, found 311.0170.

**N-Benzyl-N-2,5-cyclohexadienylmethyl 2-iodoaniline (7).** To a mixture of NaH (83.4 mg, 95% purity, 3.3 mmol) in DMF (10 ml) at 0 °C was added N-2',5'-cyclohexadienylmethyl 2-iodoaniline (6, 0.93 g, 3.0 mmol). The mixture was stirred at 0 °C for 75 min, followed by the addition of benzyl bromide (0.564 g, 3.3 mmol). The resulting mixture was stirred at 0 °C for 3 h, then room temperature for 9 h, followed by quenching with satd aq NH\(_4\)Cl (7 ml) and brine (60 ml). The above mixture was extracted with ether (35 ml \(\times\) 2) and the combined ether layers were dried over K\(_2\)CO\(_3\). The solvent was removed and the residue was subjected to flash chromatography using straight hexanes to afford a colorless, viscous liquid (0.42 g, 35% yield): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.55-2.59 (m, 2H), 2.71-2.75 (m, 1H), 2.94 (d, J = 7.2 Hz, 2H), 4.11 (s, 2H), 5.63-5.69 (m, 2H), 5.71-5.77 (m, 2H), 6.80 (ddd, J =
8.0, 7.2, 1.5 Hz, 1H), 7.01 (dd, J = 8.1, 1.5 Hz, 1H), 7.21-7.33 (m, 6H), 7.90 (dd, J =
8.1, 1.5 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 26.4, 33.5, 57.4, 60.6, 100.4, 124.4, 124.5,
126.0, 127.1, 127.6, 128.0, 128.6, 129.1, 137.5, 140.2, 151.6; IR (neat) 3059, 3024,
2817, 1370, 1240 cm\(^{-1}\); HRMS for C\(_{20}\)H\(_{18}\)I (M\(^+\)-H\(_2\)) calcd 399.0484, found:
399.0482.

**N-BOC-N-2,5-cyclohexadienylmethyl-p-toluenesulfonamide (23) and N-2,5-Cyclohexadienylmethyl-p-toluenesulfonamide (24).** To a mixture of 2,5-cyclohexadienyl methanol (2.16 g, 20 mmol), triphenylphosphine (15.7 g, 60 mmol), and N-BOC sulfonamide (8.19 g, 30 mmol) in THF (120 ml) was added diethyl azodicarboxylate (7.88 ml, 50 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min, then room temperature for 12 h. The filtrate was
concentrated in vacuo and the residue was subjected to flash chromatography using 1:9 EtOAc/hexanes to afford 6.17 g of a colorless viscous liquid 23 (85% yield): $^1$H NMR (CDCl$_3$) $\delta$ 1.22 (s, 9H), 2.42 (s, 3H), 2.67-2.72 (m, 2H), 2.90-3.00 (m, 1H), 3.62 (d, $J = 4.5$ Hz, 2H), 5.64-5.70 (m, 2H), 5.88-5.93 (m, 2H), 7.28 (d, $J = 7.2$ Hz, 2H), 7.77 (d, $J = 8.4$ Hz, 2H). Trifluoroacetic acid (3.36 ml, 43.6 mmol) was added to a mixture of N-BOC-N-2,5-cyclohexadienylmethyl-p-toluenesulfonamide 23 (3.95 g, 10.9 mmol) in CH$_2$Cl$_2$ (100 ml) at room temperature. The mixture was stirred at room temperature for 46 h, then washed with satd aq NaHCO$_3$, H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the residue was subjected to flash chromatography using EtOAc/hexanes (1:5) to afford a white solid (2.23 g, 78% yield): $^1$H NMR (CDCl$_3$) $\delta$ 2.42 (s, 3H), 2.60-2.64 (m, 2H), 2.91 (br s, 1H), 2.96 (t, $J = 5.4$ Hz, 2H), 4.87 (t, $J = 5.4$ Hz, 1H), 5.45-5.50 (m, 2H), 5.76-5.81 (m, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.3, 26.0, 34.9, 47.3, 125.2, 126.98, 127.04, 129.5, 136.8, 143.1.

**N-2,5-Cyclohexadienylmethyl-N-(2-iodo-3-methyl-2-butenyl)-p-toluenesulfonamide (25).** To a mixture of NaH (77.8 mg, 95% purity, 3.08 mmol) in DMF (4 ml) was added N-2,5-cyclohexadienylmethyl-p-toluenesulfonamide (24, 0.74 g, 2.8 mmol) in DMF (3 ml) at 0 °C. The mixture was stirred at 0°C for 15 min, then room temperature for 1 h, followed by the addition of 2-iodo-3-methyl-2-butenyl bromide (0.77 g, 2.8 mmol) in DMF (6 ml). After stirring at room temperature for 21 h, the mixture was treated with ether (150 ml), and then washed with brine (35 ml x 2), and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the residue was subjected to flash chromatography using 1:15 EtOAc/hexanes to afford 0.90 g of a colorless, viscous liquid (70% yield): $^1$H NMR (CDCl$_3$) $\delta$ 1.90 (s, 3H), 1.94 (s, 3H), 2.42 (s, 3H), 2.63-2.67 (m, 2H), 3.08-3.19 (m, 3H), 4.23 (s, 2H), 5.66-5.78 (m, 4H), 7.28 (d, $J = 7.5$ Hz, 2H), 7.67 (d, $J = 8.1$ Hz,
$^{13}$C NMR (CDCl$_3$) $\delta$ 20.3, 21.4, 26.3, 31.9, 35.4, 54.7, 57.2, 96.1, 125.2, 126.3, 127.4, 129.3, 136.8, 142.6, 143.1; IR (neat) 3023, 2918, 2861, 1340, 1157 cm$^{-1}$; HRMS for C$_{19}$H$_{17}$NO$_2$Si (M$^+$/C$_6$H$_4$) calcd 378.0025, found 378.0018.

**General Procedure for the Palladium-Catalyzed Reactions:**

Pd(dba)$_2$ (14.4 mg, 0.025 mmol), TBAC (or LiCl), base, nucleophile, organic iodide (0.25 mmol), and solvent (DMSO or DMF) were added accordingly to an Ar flushed 2 dram vial. The vial was flushed with Ar for 2 minutes and heated in an oil bath at the indicated temperature for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with brine solution, dried over anhydrous Na$_2$SO$_4$, and decanted. The solvent was evaporated *in vacuo* and the product was isolated by flash chromatography (EtOAc/hexanes) on a silica gel column. The following compounds were prepared by the above procedure and the results are summarized in Table 2.

**Compound 26** (entry 1). The reaction mixture was chromatographed using 1:12 EtOAc/hexanes to yield a colorless liquid: $^1$H NMR (CDCl$_3$) $\delta$ 1.28 (t, $J$ = 7.2 Hz, 3H), 1.32 (t, $J$ = 7.2 Hz, 3H), 1.83 (dt, $J$ = 14.0, 4.0 Hz, 1H), 2.06 (m, 1H), 2.69 (m, 1H), 2.88 (m, 1H), 3.10 (m, 1H), 3.45 (d, $J$ = 10.0 Hz, 1H), 3.87 (dd, $J$ = 10.8, 8.4, 1H), 4.12 (dd, $J$ = 11.2, 3.6 Hz, 1H), 4.22 (q, $J$ = 6.8 Hz, 2H), 4.27 (q, $J$ = 7.2 Hz, 2H), 5.74 (dq, $J$ = 10.0, 1.6 Hz, 1H), 5.85 (dq, $J$ = 10.0, 2.0 Hz, 1H), 6.80 (d, $J$ = 7.6 Hz, 1H), 6.91 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.10 (td, $J$ = 8.0, 1.2 Hz, 1H), 7.13 (d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.1, 14.2, 30.0, 31.0, 33.0, 33.7, 56.5, 61.4, 61.5, 66.5, 116.8, 120.8, 124.8, 127.4, 128.0, 129.0, 130.8, 154.7, 168.1, 168.2; IR (CHCl$_3$) 1748, 1727 cm$^{-1}$; HRMS for C$_{20}$H$_{24}$O$_5$ calcd 344.1624, found 344.1628.
**Compound 27** (entry 2). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a white solid: mp 152-153 °C (EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.11 (s, 3H, H\(^{10}\)), 1.59-1.73 (m, 1H), 1.77 (td, \(J = 10.0, 3.6\) Hz, 1H, H\(^7\)), 1.93 (dt, \(J = 14.1, 5.7\) Hz, 1H, H\(^6\)), 1.98-2.07 (m, 1H), 2.48 (dt, \(J = 15.3, 3.9\) Hz, 1H, H\(^6\)), 2.58-2.69 (m, 5H, 4H + H\(^3\)), 3.31 (dd, \(J = 9.3, 5.1\) Hz, 1H, H\(^6\)), 4.06 (dd, \(J = 10.8, 2.2\) Hz, 1H, H\(^2\)), 4.15 (dd, \(J = 10.8, 3.4\) Hz, 1H, H\(^1\)), 5.38 (dd, \(J = 3.6, 1.2\) Hz, 1H, H\(^5\)), 5.80 (dt, \(J = 10.2, 2.1\) Hz, 1H, H\(^3\)), 6.80 (dd, \(J = 8.1, 1.2\) Hz, 1H), 6.93 (td, \(J = 7.5, 1.2\) Hz, 1H), 7.11 (t, \(J = 7.8\) Hz, 1H), 7.16 (d, \(J = 7.8\) Hz, 1H); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 11.2, 18.1, 27.7, 31.3, 33.9, 37.3, 37.5, 37.8, 68.3, 70.0, 117.1, 121.1, 123.5, 123.8, 127.1, 127.7, 130.5, 155.2, 208.78, 208.86; IR (CHCl\(_3\)) 1726, 1692 cm\(^{-1}\); HRMS for C\(_{20}\)H\(_{22}\)O\(_3\) calcd 310.1569, found 310.1578. Anal. Calcd for C\(_{20}\)H\(_{22}\)O\(_3\): C, 77.39; H, 7.14. Found: C, 77.03; H, 7.39.

**Compound 28** (entries 3 and 4). The reaction mixture was chromatographed using straight EtOAc to yield a white solid: mp 115-116.5 °C (EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.94-2.13 (m, 2H), 2.55-2.73 (m, 5H), 2.87-2.91 (m, 1H), 3.30 (quintet, \(J = 4.5\) Hz, 1H), 3.73 (t, \(J = 4.5\) Hz, 4H), 3.95 (dd, \(J = 10.8, 7.2\) Hz, 1H), 4.10 (dd, \(J = 10.8, 3.0\) Hz, 1H), 5.80-5.90 (m, 2H), 6.80 (dd, \(J = 8.1, 1.2\) Hz, 1H), 6.90 (td, \(J = 7.5, 1.2\) Hz, 1H), 7.10 (tdd, \(J = 7.2, 1.5, 0.6\) Hz, 1H), 7.20 (d, \(J = 7.5\) Hz, 1H); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 28.8, 30.8, 34.1, 50.1, 56.9, 66.8, 67.4, 116.8, 120.8, 125.0, 127.3, 128.6, 129.5, 130.7, 154.7; IR (CHCl\(_3\)) 1115 cm\(^{-1}\);
HRMS for $\text{C}_7\text{H}_7\text{NO}_2$ calcd 271.1572, found 271.1568. Anal. Calcd for $\text{C}_7\text{H}_7\text{NO}_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.21; H, 8.02; N, 5.07.

**Compound 29** (entries 5 and 6). The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a white solid consisting of an inseparable mixture of four isomers (80:10:5:5): mp 62-64 °C (hexanes); $^1\text{H NMR}$ (CDCl$_3$) $\delta$ 1.64-1.76 (m, 0.05H), 1.97-2.14 (m, 1.80H), 2.2-2.6 (m, 0.25H), 2.74-2.81 (m, 0.95H), 2.95-3.05 (m, 0.10H), 3.16-3.24 (m, 0.90H), 3.67-3.82 (m, 0.95H), 3.88-3.93 (m, 0.75H), 4.02-4.22 (m, 1.25H), 5.84-6.04 (m, 2.0H), 6.78-6.96 (m, 2.0H), 7.09-7.21 (m, 2.0H); $^{13}\text{C NMR}$ (CDCl$_3$) $\delta$ major isomer: 29.2, 33.5, 33.9, 54.2, 65.2, 116.9, 120.9, 124.5, 126.9, 127.7, 129.2, 131.2, 154.5; IR (CHCl$_3$) 2096 cm$^{-1}$; HRMS for $\text{C}_7\text{H}_7\text{NO}_2$ calcd 227.1059, found 227.1060. Anal. Calcd for $\text{C}_7\text{H}_7\text{NO}_2$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.78; H, 6.05; N, 18.26.

**Compound 30** (entry 7). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a white solid: mp 150-152 °C (EtOAc/hexanes); $^1\text{H NMR}$ (CDCl$_3$) $\delta$ 2.36 (dt, $J$ = 13.5, 6.3 Hz, 1H), 2.52 (ddd, $J$ = 13.5, 8.4, 0.75 Hz, 1H), 2.91-2.96 (m, 1H), 3.54 (dd, $J$ = 10.2, 6.3 Hz, 1H), 4.14 (s, 1H), 4.16 (s, 1H), 4.67-4.73 (m, 1H), 5.71 (dt, $J$ = 9.9, 2.4 Hz, 1H), 5.97 (dt, $J$ = 9.9, 2.7 Hz, 1H), 6.82 (dd, $J$ = 8.4, 1.2 Hz, 1H), 6.96 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.13 (td, $J$ = 7.2, 0.9 Hz, 1H), 7.27 (d, $J$ = 6.9 Hz, 1H), 7.71 (dd, $J$ = 5.4, 3.0 Hz, 2H), 7.83 (dd, $J$ = 5.7, 3.0 Hz, 2H); $^{13}\text{C NMR}$ (CDCl$_3$) $\delta$ 31.3, 31.5, 33.7, 44.0, 67.7, 116.9, 121.2, 123.1, 123.3, 127.6, 128.1, 128.4, 130.0, 131.9, 134.0, 154.9, 168.1; IR (CHCl$_3$) 1711 cm$^{-1}$; HRMS for $\text{C}_{12}\text{H}_{17}\text{NO}_3$ calcd 331.1208; found: 331.1202. Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.09; H, 5.43; N, 4.12.

**Compound 31** (entry 8). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a light yellow, very viscous liquid: $^1\text{H NMR}$ (CDCl$_3$) $\delta$ 1.88 (ddd, $J$ = 14.0, 7.6, 3.6 Hz, 1H), 2.13 (dt, $J$ = 14.0, 6.4 Hz, 1H), 2.42
(s, 3H), 2.49-2.54 (m, 1H), 2.85-2.90 (m, 1H), 3.92 (dd, J = 10.8, 5.6 Hz, 1H), 3.98 (dd, J = 11.0, 3.0 Hz, 1H), 4.20 (d, J = 16.4 Hz, 1H), 4.28-4.32 (m, 1H), 4.68 (d, J = 16.4 Hz, 1H), 5.22 (dt, J = 10.0, 2.6 Hz, 1H), 5.78 (dt, J = 10.0, 2.6 Hz, 1H), 6.74 (td, J = 8.0, 0.8 Hz, 2H), 6.84 (td, J = 7.6, 0.8 Hz, 1H), 7.06 (td, J = 7.6, 1.2 Hz, 1H), 7.25-7.30 (m, 3H), 7.35 (t, J = 7.6 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); 13C NMR (CDCl3) δ 21.5, 30.9, 32.9, 33.3, 48.2, 51.7, 67.1, 116.6, 121.1, 123.2, 127.0, 127.3, 127.5, 127.6, 128.1, 128.5, 129.0, 129.7, 131.9, 137.8, 138.9, 143.2, 154.4; IR (CHC13) 1360, 1150 cm⁻¹; HRMS for C27H27NO3S calcd 445.1712, found 445.1712.

**Compound 32** (entry 9). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a yellow liquid (a mixture of the desired product and 1,5-diphenyl-1,4-pentadien-3-one). The above mixture was chromatographed further using basic Alumina (Brockman activity III) with 1:15 EtOAc/hexanes as an eluent to afford an off-white solid: mp 85-86 °C (EtOAc/hexanes); 1H NMR (CDCl3) δ 1.48 (s, 18H), 2.41 (dd, J = 8.4, 4.5 Hz, 2H), 2.75-2.77 (m, 1H), 3.43 (dd, J = 9.3, 4.5 Hz, 1H), 4.08 (dd, J = 8.1, 1.8 Hz, 1H), 4.17 (dd, J = 8.1, 2.7 Hz, 1H), 4.45-4.47 (m, 1H), 5.69 (ddt, J = 19.2, 10.5, 1.8 Hz, 2H), 6.78 (dd, J = 8.1, 0.9 Hz, 1H), 6.92 (td, J = 7.5, 1.2 Hz, 1H), 7.10 (td, J = 7.5, 0.9 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H); 13C NMR (CDCl3) δ 28.0, 30.8, 32.1, 33.8, 50.4, 68.5, 82.3, 116.7, 121.1, 123.3, 127.4, 127.68, 127.70, 131.4, 152.5, 154.9; IR (CHCl3) 1776, 1736 cm⁻¹; HRMS for C23H31NO5 calcd.: 401.2202; found: 401.2192. Anal. Calcd for C23H31NO5: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.78; H, 8.03; N, 3.36.

**Compound 33** (entry 10). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a yellow liquid (74 mg, the desired product was inseparable from 1,5-diphenyl-1,4-pentadien-3-one). The mixture was added to LiAlH₄ (37 mg, 0.9 mmol) in ether (4 ml) at 0 °C. The resulting mixture was stirred
at 0 °C for 10 min and then at room temperature for 4h. After a standard work-up,
the reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield 62.3
mg of a white solid (90% yield): mp 96-98 °C (EtOAc/hexanes); 1H NMR (CDCl₃) δ
1.98 (td, J = 13.8, 4.2 Hz, 1H), 2.11 (dt, J = 13.5, 3.6 Hz, 1H), 2.70-2.75 (m, 1H),
3.14 (dt, J = 11.1, 4.8 Hz, 1H), 3.73 (brs, 1H), 3.84 (dd, J = 10.8, 9.3 Hz, 1H), 3.95
(dd, J = 8.1, 3.9 Hz, 1H), 4.14 (ddd, J = 10.8, 3.6, 0.6 Hz, 1H), 5.82 (ddd, J = 9.9, 4.2,
1.2 Hz, 1H), 5.99 (ddd, J = 9.9, 4.5, 1.2 Hz, 1H), 6.62 (dd, J = 8.4, 0.9 Hz, 2H), 6.72
(tt, J = 7.4, 0.9 Hz, 1H), 6.85 (ddd, J = 14.4, 7.5, 1.2 Hz, 2H), 7.07-7.12 (m, 2H), 7.19
(ddt, J = 8.1, 6.9, 1.8 Hz, 2H); 13C NMR (CDCl₃) δ 29.4, 33.6, 33.7, 46.4, 65.6,
113.0, 116.7, 117.5, 120.8, 125.3, 127.4, 128.5, 129.3, 129.4, 130.7, 146.8, 154.6;
IR (CHCl₃) 3408, 1051 cm⁻¹; HRMS for C₁₉H₁₉NO calcd: 277.1467; found: 277.1461.
Anal. Calcd for C₁₉H₁₉NO: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.14; H, 7.13; N,
4.96.

**Compound 34** (entry 11). The reaction mixture was chromatographed
using 1:4 EtOAc/hexanes to yield white needle crystals: mp 155-156 °C
(EtOAc/hexanes); 1H NMR (CDCl₃) δ 2.18 (ddd, J = 14.7, 10.2, 6.0 Hz, 1H, H³), 2.36
(dt, J = 14.7, 4.2 Hz, 1H, H¹), 2.64-2.70 (m, 1H, H⁴), 3.21 (dt, J = 10.2, 5.1 Hz, 1H,
H³), 3.65-3.70 (m, 1H, H⁵), 3.80 (dd, J = 11.1, 8.4 Hz, 1H, H²), 4.11 (dd, J = 11.1, 3.3
Hz, 1H, H¹), 5.88 (ddd, J = 10.2, 3.6, 2.1 Hz, 1H, H³), 6.08 (ddd, J = 10.2, 3.9, 2.0 Hz,
1H, H³), 6.78 (d, J = 7.8 Hz, 1H), 6.90 (td, J = 7.4, 1.2 Hz, 1H), 7.10 (t, J = 7.2 Hz,
Compounds 35a and 35b (entry 12). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a light yellow liquid consisting of a 10:1 mixture of 35a:35b and 1,5-diphenyl-1,4-pentadien-3-one (dba): 

$^1$H NMR (CDCl$_3$) $\delta$ 1.93-2.14 (m, 2H), 2.10 (s, 3H), 2.42-2.55 (m, 0.2H), 2.72-2.80 (m, 1H), 3.14 (dt, $J = 9.9$, 4.8 Hz, 0.1H), 3.20 (dt, $J = 12.0$, 4.5 Hz, 1H), 3.76 (t, $J = 10.8$ Hz, 1H), 3.93 (t, $J = 11.1$ Hz, 0.1H), 4.14 (ddd, $J = 10.8$, 3.6, 0.9 Hz, 1H), 4.21 (ddd, $J = 10.5$, 3.9, 1.5 Hz, 0.1H), 5.07 (dd, $J = 4.0$, 2.0 Hz, 0.1H), 5.21 (dd, $J = 7.8$, 4.2 Hz, 1H), 5.80-5.83 (m, 0.1H), 5.93 (dd, $J = 10.2$, 4.2 Hz, 1H), 6.02 (ddd, $J = 10.2$, 4.5, 1.5, 0.9 Hz, 1H), 6.83 (dd, $J = 8.1$, 1.0 Hz, 1H), 6.91 (td, $J = 7.2$, 1.2 Hz, 1H), 7.11 (td, $J = 7.8$, 1.8 Hz, 1H), 7.18 (dd, $J = 7.8$, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.2, 21.3, 28.9, 29.2, 30.0, 33.4, 33.6, 35.5, 63.7, 64.8, 66.0, 66.6, 116.7, 116.8, 120.1, 120.8, 123.4, 124.9, 127.56, 127.64, 127.9, 128.3, 128.5, 128.8, 129.4, 130.8, 131.1, 154.4, 170.5 (missing the carbonyl peak of the minor isomer).

Compounds 64 and 65 (eq 8). The mixture of the corresponding acetate and 1,5-diphenyl-1,4-pentadien-3-one (49 mg) was added to a mixture of MeOH (2.5 ml) and K$_2$CO$_3$ (84.6 mg, 0.6 mmol) at r.t. The resulting mixture was stirred at r.t for 2.5 h, then MeOH was removed in vacuo. Water (30 ml) was added to the residue, and the mixture was extracted with ether three times (30 ml, 10 ml, 10 ml). The combined ether layers were dried over Na$_2$SO$_4$ and chromatographed using 1:3 EtOAc/hexanes to afford the major isomer as a colorless liquid and the minor isomer as a colorless liquid. Alcohol 64 (major isomer): $^1$H NMR (CDCl$_3$) $\delta$ 1.83
(br s, 1H), 1.93-2.11 (m, 2H), 2.71-2.77 (m, 1H), 3.24 (dt, J = 11.4, 5.1 Hz, 1H), 3.79 (dd, J = 11.1, 9.9 Hz, 1H), 4.12 (ddd, J = 11.1, 3.6, 0.9 Hz, 1H), 4.18 (dd, J = 7.8, 3.9 Hz, 1H), 5.84 (dd, J = 9.9, 4.5 Hz, 1H), 6.03 (dddd, J = 9.9, 4.5, 1.8, 0.9 Hz, 1H),
6.83 (dd, J = 8.1, 1.2 Hz, 1H), 6.91 (td, J = 7.2, 1.2 Hz, 1H), 7.11 (td, J = 7.6, 1.5 Hz, 1H), 7.21 (dd, J = 7.8, 1.5 Hz, 1H); 13C NMR (CDCl3) δ 28.6, 33.6, 36.9, 63.4, 65.1, 116.8, 120.8, 125.4, 127.4, 129.2, 129.3, 131.4, 154.5; IR (CHCl3) 3368 cm⁻¹;

Alcohol 65 (minor isomer):
1H NMR (CDCl3) δ 1.59 (br s, 1H), 2.21 (dd, J = 17.6, 8.8 Hz, 1H), 2.37-2.43 (m, 1H), 2.44-2.52 (m, 1H), 3.14-3.19 (m, 1H), 4.03 (t, J = 10.6 Hz, 1H), 4.04-4.06 (m, 1H), 4.16 (ddd, J = 10.8, 4.0, 1.2 Hz, 1H), 5.82-5.88 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.86 (td, J = 7.2, 1.2 Hz, 1H), 7.07-7.15 (m, 2H); 13C NMR (CDCl3) δ 29.2, 29.8, 38.4, 64.4, 64.7, 116.6, 120.2, 126.0, 127.4, 127.8, 128.4, 128.7, 153.6; IR (CHCl3) 3359 cm⁻¹; HRMS for C₁₃H₁₄O₂ calcd 202.0994, found 202.0999.

Compound 36 (entry 13). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield an off-white solid: mp 63-65 °C
(EtOAc/hexanes); 1H NMR (CDCl3) δ 2.05 (ddd, J = 14.2, 11.7, 4.2 Hz, 1H, H⁶), 2.28 (dd, J = 14.1, 3.6, 0.9 Hz, 1H, H⁷), 2.79-2.84 (m, 1H, H³), 3.36 (dt, J = 11.7, 4.5 Hz, 1H, H⁶), 3.84 (dd, J = 11.1, 9.9 Hz, 1H, H¹), 4.16 (ddd, J = 11.1, 3.6, 0.9 Hz, 1H, H⁶), 4.73 (dd, J = 8.1, 4.2 Hz, 1H, H⁵), 5.96 (ddd, J = 10.2, 4.5, 0.6 Hz, 1H, H⁴), 6.13 (dd, J = 8.1, 0.9 Hz, 1H, H⁵), 6.83 (dd, J = 8.1, 0.9 Hz, 1H, H⁵), 6.89 (td, J =
7.4, 1.2 Hz, 1H), 6.95 (dd, J = 7.8, 0.9 Hz, 2H), 6.98 (dt, J = 7.2, 0.9 Hz, 1H), 7.10 (dd, J = 7.8, 1.5 Hz, 1H), 7.15 (dd, J = 7.5, 1.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H); 13C NMR (CDCl₃) δ 29.0, 33.5, 33.7, 65.2, 68.8, 116.0, 116.8, 120.8, 121.1, 125.2, 127.5, 128.4, 129.3, 129.6, 130.7, 154.5, 157.6; IR (CHCl₃) 1238, 1065, 1049 cm⁻¹; HRMS for C₁₉H₁₈O₂ calcd 278.1307, found 278.1304. Anal. Calcd for C₁₉H₁₈O₂: C, 81.99; H, 6.52. Found: C, 81.61; H, 6.81.

**Compound 37** (entry 14). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless liquid: ¹H NMR (CDCl₃) δ 2.00 (ddd, J = 14.4, 11.7, 3.9 Hz, 1H), 2.29 (dt, J = 14.1, 3.3 Hz, 1H), 2.81-2.89 (m, 1H), 3.52 (dt, J = 11.7, 4.5 Hz, 1H), 3.82 (t, J = 10.2 Hz, 1H), 4.17 (ddd, J = 10.8, 3.6, 0.6 Hz, 1H), 4.73 (dd, J = 8.1, 3.9 Hz, 1H), 5.98 (dd, J = 9.9, 4.2 Hz, 1H), 6.16 (dddd, J = 9.9, 4.5, 1.5, 0.9 Hz, 1H), 6.58 (td, J = 8.4, 0.9 Hz, 2H), 6.91 (td, J = 9.9, 1.5 Hz, 1H), 6.99 (dd, J = 8.1, 1.5 Hz, 1H), 7.12 (td, J = 7.8, 1.5 Hz, 1H), 7.20-7.28 (m, 2H), 7.57 (dd, J = 7.8, 1.5 Hz, 1H); 13C NMR (CDCl₃) δ 28.9, 33.7, 65.0, 71.4 (2C), 114.2, 116.6, 116.8, 120.8, 122.7, 125.2, 127.5, 127.9, 128.4, 129.4, 131.4, 133.6, 154.4, 154.5; IR (CHCl₃) 1242, 1070, 1045 cm⁻¹; HRMS for C₁₉H₁₉BrO₂ calcd: 356.0412; found: 356.0417.

**Compounds 38 and 67-69** (entry 15). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a white solid consisting of an inseparable 66:13:14:7 mixture of 38, 67, 68 and 69: ¹H NMR (CDCl₃) δ 1.19 (t,
$J = 7.2 \text{ Hz, } 2.89\text{H}, 1.23-1.31 \text{ (m, } 5.0\text{H}), 2.18-2.29 \text{ (m, } 1.99\text{H}), 2.43-2.57 \text{ (m, } 1.26\text{H}), 2.60 \text{ (d, } J = 3.6 \text{ Hz, } 0.07\text{H}), 2.63-2.69 \text{ (m, } 0.93\text{H}), 2.70-2.76 \text{ (m, } 0.16\text{H}), 2.89 \text{ (dd, } J = 16.0, 4.4 \text{ Hz, } 0.30\text{H}), 3.06 \text{ (dd, } J = 16.0, 11.2 \text{ Hz, } 0.30\text{H}), 3.12-3.22 \text{ (m, } 1.20\text{H}), 3.48 \text{ (d, } J = 10.4 \text{ Hz, } 1.0\text{H}), 3.51-3.56 \text{ (m, } 0.50\text{H}), 3.60-3.78 \text{ (m, } 0.62\text{H}), 3.89-4.05 \text{ (m, } 2.16\text{H}), 4.09-4.26 \text{ (m, } 4.91\text{H}), 4.34 \text{ (dd, } J = 11.2, 4.0 \text{ Hz, } 0.30 \text{H}), 4.67-4.76 \text{ (m, } 2.48\text{H}), 5.55-5.59 \text{ (m, } 1.01\text{H}), 5.72-5.79 \text{ (m, } 0.40\text{H}), 5.85-5.89 \text{ (m, } 1.0\text{H}), 7.08 \text{ (d, } J = 7.2 \text{ Hz, } 1.16\text{H}), 7.13-7.26 \text{ (m, } 4.48\text{H}); ^{13}\text{C NMR (CDCl}_3\text{) } \delta 13.3, 13.9, 13.98, 14.05, 27.9, 29.3, 34.8, 37.3, 38.8, 39.2, 41.1, 42.3, 43.6, 43.9, 49.9, 56.62, 56.66, 56.72, 61.1, 61.4, 61.5, 63.8, 73.2, 73.8, 74.5, 75.8, 76.6, 125.3, 126.3, 127.3, 127.5, 127.7, 127.9, 128.0, 128.5, 128.6, 128.70, 128.72, 128.79, 128.82, 128.87, 128.93, 130.3, 130.4, 130.8, 139.2, 139.3, 139.6, 139.8, 142.8, 143.4, 167.9, 168.1, 168.3, 169.7; \text{IR (CHCl}_3\text{) 1748, 1729 cm}^{-1}; \text{HRMS for C}_{21}\text{H}_{26}\text{O}_5 \text{ calcd } 358.1780, \text{found } 358.1782. \text{ After recrystallization of the mixture of } 38 \text{ plus } 67-69, \text{ compound } 38 \text{ was obtained in an almost pure form: mp } 100-104^\circ\text{C (EtOAc/hexanes); } ^{1}\text{H NMR (CDCl}_3\text{) } \delta 1.19 \text{ (t, } J = 6.8 \text{ Hz, } 3\text{H}), 1.29 \text{ (t, } J = 5.4 \text{ Hz, } 3\text{H}), 2.23 \text{ (t, } J = 4.6 \text{ Hz, } 1\text{H, H}^{10}), 2.25 \text{ (td, } J = 18.0, 4.8 \text{ Hz, } 1\text{H, H}^{5}), 2.53 \text{ (ddq, } J = 18.4, 11.6, 2.0 \text{ Hz, } 1\text{H, H}^{5}), 2.66 \text{ (dd, } J = 10.4, 2.4 \text{ Hz, H}^{6}), 3.14-3.18 \text{ (m, } 1\text{H, H}^{11}), 3.48 \text{ (d, } J = 10.4 \text{ Hz, } 1\text{H, H}^{12}), 3.89-4.01 \text{ (m, } 2\text{H, H}^{3} \text{ and H}^{4}), 4.09-4.25 \text{ (m, } 4\text{H}), 4.69 \text{ (d, } J = 14.0 \text{ Hz, } 1\text{H, H}^{3}),
4.74 (d, J = 14.0 Hz, 1H, H'), 5.56-5.59 (m, 1H, H'), 5.86-5.90 (m, 1H, H'), 7.09 (d, J = 7.2 Hz, 1H), 7.16 (td, J = 7.2, 2.4 Hz, 1H), 7.19-7.24 (m, 2H); 13C NMR (CDCl₃) δ 14.0, 14.1, 29.4, 37.3, 38.9, 41.2, 56.7, 61.5, 61.6, 73.8, 74.5, 125.4, 126.3, 127.8, 128.7, 129.0, 130.4, 139.6, 142.9, 168.0 (one carbon missing due to overlap).


**Compound 39** (entry 16). The reaction mixture was chromatographed using 1:1 EtOAc/hexanes to yield a light yellow solid: mp 111-113 °C (EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.33-2.38 (m, 2H), 2.51-2.56 (m, 6H), 3.50-3.56 (m, 1H), 3.66 (t, J = 4.2 Hz, 4H), 3.81 (dd, J = 12.0, 3.9 Hz, 1H), 4.08 (br s, 1H), 4.71 (s, 2H), 5.66-5.72 (m, 1H), 5.95-6.02 (m, 1H), 7.10-7.23 (m, 4H); ¹³C NMR (CDCl₃) δ 29.9, 38.8, 40.6, 50.3, 60.8, 67.4, 73.6, 75.0, 125.9, 126.2, 127.5, 128.3, 128.7, 129.4, 129.6, 139.7; IR (CHCl₃) 1118, 1005 cm⁻¹; HRMS for C₁₈H₂₃NO₃ calcd 285.1729; found 285.1733. Anal. Calcd for C₁₈H₂₃NO₃: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.81; H, 8.20; N, 4.88.

**Compound 40** (entry 17). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless liquid: ¹H NMR (CDCl₃) δ 1.24 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.90 (ddd, J = 14.0, 11.0, 4.0 Hz, 1H), 2.36 (dtd, J = 13.6, 4.4, 0.8 Hz, 1H), 2.71-2.74 (m, 1H), 2.98 (d, J = 16.0 Hz, 1H), 3.28 (d, J = 8.8 Hz, 1H), 3.43 (d, J = 16.0 Hz, 1H), 3.74 (s, 3H), 3.89 (t, J = 4.0 Hz, 1H), 4.17 (qd, J = 7.2, 0.8 Hz, 2H), 4.23 (qd, J = 7.2, 2.8 Hz, 2H), 5.62 (dt, J = 10.4, 1.2 Hz, 1H), 5.69 (ddd, J = 10.0, 2.4, 1.2 Hz, 1H), 7.15-7.18 (m, 2H), 7.20-7.21 (m, 2H); ¹³C NMR (CDCl₃) δ 14.0, 14.1, 26.0, 31.0, 43.1, 44.6, 52.2, 53.6, 56.2, 61.3 (2C), 123.0, 124.8, 126.7, 126.9, 130.1, 130.2, 140.3, 142.7, 168.07, 168.14, 175.0; IR (CHCl₃) 1730 cm⁻¹; HRMS for C₂₁H₂₆O₅ calcd 386.1729, found 386.1728.

**Compound 41** (entry 18). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a light yellow liquid: ¹H NMR (CDCl₃) δ 2.05 (s,
3H), 2.08 (ddd, J = 13.4, 10.0, 4.2 Hz, 1H), 2.62 (dtd, J = 13.2, 6.8, 1.0 Hz, 1H), 3.00 (d, J = 15.9 Hz, 1H), 3.45 (d, J = 15.9 Hz, 1H), 3.76 (s, 3H), 3.96 (t, J = 3.9 Hz, 1H), 5.10 (ddt, J = 9.9, 5.7, 1.5 Hz, 1H), 5.69 (ddd, J = 10.2, 1.8, 1.2 Hz, 1H), 5.78 (ddd, J = 10.2, 1.5, 1.5 Hz, 1H), 7.16-7.29 (m, 4H); 13C NMR (CDCl3) δ 21.2, 27.8, 43.0, 44.3, 52.4, 53.7, 66.7, 123.0, 124.8, 127.0, 127.1, 129.2, 131.5, 139.8, 142.2, 170.6, 174.6; IR (CHCl₃) 1735 cm⁻¹; HRMS for C₁₅H₂₀O₂ (M⁺-C₂H₅O₂) calcd 226.0994, found 226.0996.

**Compound 42** (entry 19). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a light yellow liquid: ¹H NMR (CDCl₃) δ 1.26 (t, J = 7.2 Hz, 3H, CH₃), 1.29 (t, J = 6.8 Hz, 3H, CH₃), 1.88-1.95 (m, 2H, H⁴ and H⁵), 2.17 (dt, J = 13.2, 5.6 Hz, 1H, H¹¹), 2.72 (d, J = 15.6 Hz, 1H, H⁶), 2.73-2.79 (m, 1H, H⁷), 2.94 (d, J = 15.6 Hz, 1H, H¹), 3.39 (d, J = 8.0 Hz, 1H, H¹²), 3.41 (br s, 1H, H⁶), 3.62 (d, J = 10.8 Hz, 1H, H³), 3.68 (d, J = 10.8 Hz, 1H, H⁴), 4.16-4.25 (m, 4H, 2 CH₂), 5.56 (dd, J = 10.0, 2.4 Hz, 1H, H⁵), 5.75 (dd, J = 10.0, 2.4 Hz, 1H, H⁷), 7.14-7.18 (m, 4H); ¹³C NMR (CDCl₃) δ 14.02, 14.07, 27.1, 31.7, 41.1, 44.0, 49.6, 56.0, 61.32, 61.34, 68.6, 123.2, 124.9, 126.4, 126.0, 130.8, 132.9, 141.4, 144.6, 168.37, 168.38; IR (CHCl₃) 3510, 1728 cm⁻¹; HRMS for C₂₁H₂₆O₅ calcd 358.1780, found 358.1789.
Compound 43 (entry 20). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a white solid: mp 114-116 °C (EtOAc/hexanes); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.92 (ddd, \(J = 13.0, 8.0, 4.4\) Hz, 1H, \(H^9\)), 2.27 (dtd, \(J = 13.2, 5.6, 1.6\) Hz, 1H, \(H^9\)), 2.77 (d, \(J = 16\) Hz, 1H, \(H^7\)), 2.92 (d, \(J = 16\) Hz, 1H, \(H^5\)), 3.42 (dd, \(J = 13.0, 5.6, 1.6\) Hz, 1H, \(H^9\)), 3.59 (d, \(J = 10.8\) Hz, 1H, \(H^5\)), 3.65 (d, \(J = 10.8\) Hz, 1H, \(H^6\)), 3.85-3.89 (m, 1H, \(H^7\)), 5.61 (dd, \(J = 10.0, 1.2\) Hz, 1H, \(H^6\)), 5.91 (dd, \(J = 10.0, 2.8\) Hz, 1H, \(H^6\)), 6.58 (dd, \(J = 8.8, 0.8\) Hz, 2H), 6.69 (tt, \(J = 7.6, 0.8\) Hz, 1H), 7.13-7.21 (m, 6H), missing OH and NH; \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 30.7, 40.9, 43.1, 45.6, 49.3, 68.6, 113.4, 117.5, 123.4, 125.0, 126.6, 126.7, 129.3, 131.4, 133.2, 141.3, 144.8, 147.0; IR (CHCl\(_3\)) 3530, 3407 cm\(^{-1}\); HRMS for C\(_{30}\)H\(_{27}\)NO calcld 291.1623, found 291.1624. Anal. Calcd for C\(_{30}\)H\(_{27}\)NO: C, 82.44; H, 7.26; N, 4.81. Found: C, 83.08; H, 7.54; N, 4.75.

Compound 44 (entry 21). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a colorless liquid: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.28 (t, \(J = 7.2\) Hz, 3H), 1.32 (t, \(J = 7.2\) Hz, 3H), 1.76 (dt, \(J = 14.4, 3.6\) Hz, 1H), 2.04 (ddd, \(J = 14.2, 11.2, 5.2\) Hz, 1H), 2.58-2.62 (m, 1H), 2.90-2.95 (m, 1H), 3.02-3.06 (m, 1H), 3.04 (dd, \(J = 11.2, 9.2\) Hz, 1H), 3.25 (dd, \(J = 11.2, 3.6\) Hz, 1H), 3.48 (d, \(J = 10.0\) Hz, 1H), 4.22 (q, \(J = 7.2\) Hz, 2H), 4.27 (q, \(J = 7.2\) Hz, 2H), 5.75-5.82 (m, 2H), 6.52 (dd, \(J = 8.0, 0.8\) Hz, 1H), 6.69 (td, \(J = 7.4, 0.8\) Hz, 1H), 6.98 (td, \(J = 7.6, 1.2\) Hz, 1H), 7.05 (d, \(J = 7.6\) Hz, 1H), missing NH; \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 14.1, 14.2, 31.5, 31.9, 33.6, 33.8, 43.5, 56.7, 61.4, 61.5, 114.6, 117.9, 124.2, 126.9, 129.1, 129.4, 130.6, 144.5,
168.2, 168.4; IR (CHCl₃) 3412, 1729 cm⁻¹; HRMS for C₇H₁₃NO₄ calcd 343.1784, found 343.1782.

**Compound 45** (entry 22). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a light yellow, viscous liquid: ¹H NMR (CDCl₃) δ 1.84 (ddd, J = 14.0, 6.8, 4.0 Hz, 1H), 2.13 (ddd, J = 14.2, 8.0, 6.0 Hz, 1H), 2.41 (s, 3H), 2.45-2.50 (m, 1H), 2.81 (dt, J = 8.4, 4.0 Hz, 1H), 2.99 (dd, J = 11.2, 6.4 Hz, 1H), 3.17 (dd, J = 11.2, 3.2 Hz, 1H), 3.72 (br s, 1H), 4.22 (d, J = 16.4 Hz, 1H), 4.39-4.44 (m, 1H), 4.70 (d, J = 16.4 Hz, 1H), 5.17 (dt, J = 10.0, 2.6 Hz, 1H), 5.79 (dt, J = 10.0, 2.6 Hz, 1H), 6.42 (d, J = 8.4 Hz, 1H), 6.56-6.62 (m, 2H), 6.93 (td, J = 7.4, 1.6 Hz, 1H), 7.24-7.29 (m, 3H), 7.34 (t, J = 7.4 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.5, 32.3, 33.2, 33.4, 44.1, 48.1, 51.9, 114.6, 118.1, 122.4, 126.9, 127.0, 127.2, 127.5, 127.6, 128.1, 128.4, 129.7, 134.4, 137.9, 139.1, 143.1, 144.1; IR (CHCl₃) 3408, 1335, 1158 cm⁻¹; HRMS for C₇H₁₃N₂O₂S calcd 444.1872, found 444.1868.

**Compounds 46a and 46b** (entry 23). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow liquid as an inseparable mixture of two isomers (65 : 35): ¹H NMR (CDCl₃) δ 1.18-1.35 (m, 6H), 1.77 (dt, J = 14.1, 3.3 Hz, 0.65H), 2.00-2.13 (m, 1H), 2.19-2.34 (m, 0.35H), 2.66-2.76 (m, 1H), 2.92-3.27 (m, 3.65H), 3.36-3.53 (m, 1.35H), 4.09-4.31 (m, 4H), 4.41-4.58 (m, 1H), 4.47 (s, 1H), 5.54-5.58 (m, 0.35H), 5.71-5.84 (m, 1.65H), 6.50-6.60 (m, 1.35H), 6.66 (td, J = 7.5, 0.9 Hz, 0.65H), 6.96-7.02 (m, 1.35H), 7.08 (dd, J = 6.6, 0.9 Hz, 0.65H), 7.20-7.34 (m, 5H); ¹³C NMR (CDCl₃) δ 14.0, 14.1, 14.2, 30.0, 32.1, 32.4, 33.1, 33.4, 33.7, 36.9, 50.0, 51.1, 54.5, 55.4, 56.8, 57.2, 61.36, 61.44, 61.49, 61.54, 110.6, 111.6, 115.5, 116.6, 124.7, 124.8, 125.9, 126.4, 126.6, 126.8, 127.1, 127.2, 127.7, 128.4, 128.54, 128.57, 129.1, 129.5, 130.4, 138.4, 138.7, 143.7,
118

145.2, 168.0, 168.2, 168.4 (four carbons missing due to overlap); IR (CHCl₃) 1747, 1728 cm⁻¹; HRMS for C₂₇H₃₁NO₄ calcd 433.2253, found 433.2259.

**Compound 47** (entry 24). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow oil: ¹H NMR (CDCl₃) δ 1.93-2.04 (m, 1H), 2.10 (dt, J = 13.5, 3.0 Hz, 1H), 2.69-2.77 (m, 1H), 3.10-3.27 (m, 3H), 3.83 (br s, 1H), 4.00-4.02 (m, 1H), 4.49 (s, 2H), 5.86 (dd, J = 9.9, 1.2 Hz, 1H), 5.94 (dd, J = 9.9, 1.2 Hz, 1H), 6.55-6.74 (m, 5H), 6.95-7.04 (m, 2H), 7.16-7.34 (m, 7H); °C NMR (CDCl₃) δ 31.7, 33.4, 34.8, 46.9, 50.4, 55.4, 111.5, 113.1, 116.6, 117.4, 125.2, 126.6, 126.8, 127.2, 128.6, 129.3, 129.4 (2C), 131.1, 138.7, 145.1, 146.9; IR (CHCl₃) 3402 cm⁻¹; HRMS for C₂₇H₃₁NO₄ calcd 366.2096, found 366.2099.

**Compound 48** (entry 25). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless liquid consisting of a 2.3:1 mixture of compound 48 and diethyl malonate: ¹H NMR (CDCl₃) δ 1.24-1.31 (m, 6H), 1.58 (ddd, J = 13.0, 11.1, 4.2 Hz, 1H), 1.67 (d, J = 1.2 Hz, 3H), 1.84 (dt, J = 13.2, 0.9 Hz, 1H), 2.26 (d, J = 15.9 Hz, 1H), 2.85-2.95 (m, 2H), 3.24 (d, J = 9.3 Hz, 1H), 3.43 (br s, 1H), 3.69 (s, 3H), 4.16-4.25 (m, 4H), 5.12 (d, J = 0.9 Hz, 1H), 5.60 (dd, J = 10.2, 2.4 Hz, 1H), 5.70 (dt, J = 10.2, 1.5 Hz, 1H); °C NMR (CDCl₃) δ 13.98, 14.0, 16.5, 28.0, 31.6, 45.8, 47.9, 52.0, 52.4, 56.3, 61.2, 61.4, 126.4, 129.0, 131.1, 138.3, 168.2, 168.3, 175.8; IR (CHCl₃) 1753, 1730 cm⁻¹; HRMS for C₁₉H₂₆O₆ calcd 350.1729, found 350.1729.

**Compound 49** (entry 26). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a light yellow liquid: ¹H NMR (CDCl₃) δ 1.65 (ddd, J = 13.0, 10.2, 4.2 Hz, 1H), 1.71 (d, J = 0.9 Hz, 3H), 2.16 (dt, J = 12.9, 4.2 Hz, 1H), 2.29 (d, J = 16.2 Hz, 1H), 2.93 (dd, J = 16.2, 1.2 Hz, 1H), 3.45-3.50 (m, 1H), 3.59 (br s, 1H), 3.72 (s, 3H), 3.99-4.04 (m, 1H), 5.18 (s, 1H), 5.63 (dd, J = 10.2, 1.5 Hz, 1H), 5.87 (d, J = 10.2 Hz, 1H), 6.61 (d, J = 7.5 Hz, 2H), 6.69 (t, J = 7.5 Hz, 1H),
7.16 (dd, J = 8.4, 7.2 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 16.6, 31.2, 45.6, 46.0, 47.9, 52.2, 52.6, 113.5, 117.4, 126.3, 129.3, 130.9, 131.0, 138.6, 147.0, 175.9; IR (CHCl$_3$) 3395, 1728 cm$^{-1}$; HRMS for C$_{11}$H$_2$NO$_2$ calcld 283.1572, found 283.1572.

Compound 50 (entry 27). The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a colorless liquid: $^1$H NMR (CDCl$_3$) δ 1.70 (d, J = 0.9 Hz, 3H), 2.04 (ddd, J = 13.2, 10.2, 4.5 Hz, 1H), 2.25-2.35 (m, 2H), 2.92 (d, J = 16.2 Hz, 1H), 3.59 (br s, 1H), 3.74 (s, 3H), 4.79-4.85 (m, 1H), 5.17 (s, 1H), 5.73 (d, J = 10.2 Hz, 1H), 5.99 (d, J = 10.2 Hz, 1H), 6.70 (td, J = 7.5, 0.9 Hz, 1H), 6.83 (dd, J = 8.1, 0.9 Hz, 1H), 7.26 (td, J = 7.8, 1.5 Hz, 1H), 7.77 (dd, J = 7.8, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) δ 16.6, 30.3, 45.5, 48.2, 52.3, 52.5, 71.8, 88.1, 114.1, 122.7, 126.1, 128.6, 129.2, 132.3, 138.6, 139.7, 156.6, 175.4; IR (CHCl$_3$) 1727, 1241, 1063 cm$^{-1}$; HRMS for C$_{11}$H$_2$IO$_3$ calcld 410.0379, found 410.0378.

Compound 51 (entry 28). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a very viscous, light yellow liquid: $^1$H NMR (CDCl$_3$) δ 1.04 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 1.60-1.70 (m, 1 H), 1.73-1.81 (m, 1H), 2.66-2.74 (m, 1H), 3.04 (dd, J = 16.2, 2.1 Hz, 1H), 3.17 (d, J = 9.3 Hz, 1H), 3.32 (dd, J = 16.2, 2.4 Hz, 1H), 3.75 (s, 3H), 3.87-4.17 (m, 5H), 5.82 (dd, J = 10.2, 1.8 Hz, 1H), 5.88 (dd, J = 10.2, 1.8 Hz, 1H), 7.04-7.26 (m, 10H); $^{13}$C NMR (CDCl$_3$) δ 13.8, 13.9, 26.2, 31.4, 47.8, 49.0, 50.6, 52.3, 56.2, 61.1, 126.8, 127.8, 128.2, 128.5, 129.8, 130.3, 134.7, 136.47, 136.53, 138.7, 167.9, 168.0, 175.6 (three carbons missing due to overlap); IR (CHCl$_3$) 1729 cm$^{-1}$; HRMS for C$_{39}$H$_{32}$O$_6$ calcld 488.2199, found 488.2205.

Compound 52 (entry 29). The reaction mixture was chromatographed using 1:1 EtOAc/hexanes to yield a light yellow oil: $^1$H NMR (CDCl$_3$) δ 1.72 (ddd, J = 13.1, 11.1, 4.2 Hz, 1H), 1.88 (dtd, J = 13.2, 4.2, 1.2 Hz, 1H), 2.22-2.40 (m, 4 H), 2.89-2.95 (m, 1H), 3.02 (dd, J = 16.5, 2.1 Hz, 1H), 3.27 (dd, J = 16.5, 3.0 Hz, 1H),
3.54-3.67 (m, 4H), 3.76 (s, 3H), 4.11 (br s, 1H), 5.83 (dd, J = 10.2, 2.1 Hz, 1H), 5.91 (d, J = 10.2 Hz, 1H), 7.04-7.27 (m, 10H); 13C NMR (CDCl3) δ 21.7, 47.9, 48.7, 49.3, 50.7, 52.2, 56.0, 67.2, 126.8, 127.8, 128.26, 128.35 (2C), 128.4, 131.2, 131.5, 134.6, 136.4, 136.6, 138.6, 175.5; IR (CHCl₃) 1730, 1116 cm⁻¹; HRMS for C₂₇H₂₉NO₃ calcd 415.2147, found 415.2146.

**Compound 53** (entry 30). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield white crystals: mp 108-110 °C (EtOAc/hexanes); ¹H NMR (CDCl₃) δ 1.87 (ddd, J = 13.5, 9.3, 1.5 Hz, 1H, H⁶), 1.96 (s, 3H, H⁷), 2.00-2.08 (m, 1H, H⁸), 3.04 (dd, J = 16.5, 2.1 Hz, 1H, H¹), 3.34 (dd, J = 16.5, 2.4 Hz, 1H, H²), 3.77 (s, 3H, H⁹), 4.05 (br s, 1H, H¹⁰), 5.08 (dd, J = 9.0, 5.4 Hz, 1H, H⁶), 5.91 (br s, 2H, H⁴ and H⁵), 7.03 - 7.31 (m, 10H); ¹³C NMR (CDCl₃) δ 21.1, 27.8, 47.6, 48.7, 50.7, 52.5, 66.4, 127.0, 127.1, 127.9, 128.2, 128.45, 128.47, 128.5, 131.9, 134.6, 136.3, 136.4, 138.7, 170.4, 175.2; IR (CHCl₃) 1729 cm⁻¹; HRMS for C₂₅H₂₄O₄ calcd 388.1675, found 388.1670. Anal. Calcd for C₂₅H₂₄O₄: C, 77.30; H, 6.23. Found: C, 77.11; H, 6.34.

**Compound 54** (entry 31). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless liquid: ¹H NMR (CDCl₃) δ 1.26 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.65 (ddd, J = 13.2, 11.1, 4.2 Hz, 1H), 1.92 (dt, J = 13.2, 4.5 Hz, 1H), 2.44 (d, J = 16.2 Hz, 1H), 2.85-2.95 (m, 2H), 3.25 (d, J = 9.0 Hz, 1H), 3.46 (br s, 1H), 3.71 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H),
5.53-5.78 (m, 4H); $^{13}$C NMR (CDCl$_3$) δ 14.0, 27.7, 31.7, 44.1, 45.7, 52.0, 52.1, 56.3, 61.3, 128.8, 129.2, 130.9, 133.1, 168.17, 168.26, 175.7 (two carbons missing due to overlap); IR (CHCl$_3$) 1735 cm$^{-1}$; HRMS for C$_{18}$H$_{24}$O$_6$ calcd 336.1573, found 336.1570.

**Compound 55** (entry 32). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a light yellow liquid: $^1$H NMR (CDCl$_3$) δ 1.72 (ddd, $J = 13.0, 10.2, 4.5$ Hz, 1H), 2.21 (dt, $J = 12.9, 4.2$ Hz, 1H), 2.46 (ddd, $J = 16.2, 3.6, 2.4$ Hz, 1H), 2.97 (ddd, $J = 16.2, 5.1, 2.7$ Hz, 1H), 3.47-3.52 (m, 1H), 3.58 (br s, 1H), 3.73 (s, 3H), 3.97-4.03 (m, 1H), 5.58-5.73 (m, 3H), 5.88 (dt, $J = 10.2, 1.2$ Hz, 1H), 6.60 (dd, $J = 8.4, 0.9$ Hz, 2H), 6.70 (tt, $J = 7.2, 1.2$ Hz, 1H), 7.16 (dd, $J = 8.4, 7.2$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 30.8, 44.0, 45.6, 45.8, 52.2, 52.3, 113.4, 117.5, 129.0, 129.3, 130.8, 131.0, 133.1, 146.9, 175.8; IR (CHCl$_3$) 3395, 1726 cm$^{-1}$; HRMS for C$_{17}$H$_{19}$NO$_2$ calcd 269.1416, found 269.1412.

**Compound 56** (entry 33). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield an off-white solid: mp 160-162 °C (EtOAc/hexanes); $^1$H NMR (CDCl$_3$) δ 1.40-1.56 (m, 2H), 1.70 (d, $J = 12.6$ Hz, 2H), 1.84-1.94 (m, 1H), 1.98-2.12 (m, 3H), 2.47-2.61 (m, 2H), 3.38 (t, $J = 11.1$ Hz, 1H), 3.77 (br s, 1H), 3.83 (dd, $J = 11.4, 4.8$ Hz, 1H), 3.96-4.05 (m, 2H), 5.49 (t, $J = 3.3$ Hz, 1H), 5.74 (dd, $J = 9.9, 4.5$ Hz, 1H), 5.91 (dd, $J = 9.9, 5.1$ Hz, 1H), 6.62 (d, $J = 7.8$ Hz, 2H), 6.89 (t, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 20.6, 25.3, 29.6, 29.7, 34.8, 37.4, 47.0, 66.9, 71.6, 112.9, 117.2, 124.2, 128.9, 129.3, 129.9, 138.5, 146.8; IR (CHCl$_3$) 3335 cm$^{-1}$; HRMS for C$_{19}$H$_{23}$NO calcd 281.1780, found 281.1780. Anal. Calcd for C$_{19}$H$_{23}$NO: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.23; H, 8.38; N, 5.00.

**Compound 57** (entry 34). The reaction mixture was chromatographed using 1:12 EtOAc/hexanes to yield a colorless liquid consisting of a 2.9:1 mixture of
compound 57 and diethyl malonate: $^1$H NMR (CDCl$_3$) $\delta$ 1.24 (t, $J = 7.2$ Hz, 6H), 1.34 (ddd, $J = 13.6$, 11.2, 4.4 Hz, 1H), 1.46 (d, $J = 1.2$ Hz, 3H), 1.59 (d, $J = 1.6$ Hz, 3H), 2.08 (dt, $J = 13.6$, 4.0, 0.8 Hz, 1H), 2.42 (dt, $J = 14.8$, 1.2 Hz, 1H), 2.87-2.95 (m, 1H), 2.99 (d, $J = 15.6$ Hz, 1H), 3.26 (d, $J = 9.2$ Hz, 1H), 3.64-3.68 (m, 1H), 3.67 (s, 3H), 4.15-4.21 (m, 4H), 5.73 (dt, $J = 10.2$, 1.6 Hz, 1H), 5.95 (ddd, $J = 10.2$, 2.8, 0.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.0, 19.1, 19.3, 27.2, 31.9, 40.6, 41.3, 43.0, 52.0, 56.4, 61.28, 61.30, 125.8, 126.4, 129.48, 129.55, 168.2, 168.3, 175.4 (one carbon missing due to overlap); IR (CHCl$_3$) 1730 cm$^{-1}$; HRMS for C$_{29}$H$_{28}$O$_6$ calcd 364.1886, found 364.1890.

**Compound 58** (entry 35). The reaction mixture was chromatographed using 2:1 EtOAc/hexanes to yield a colorless liquid: $^1$H NMR (CDCl$_3$) $\delta$ 1.43-1.50 (m, 1H), 1.45 (d, $J = 0.8$ Hz, 3H), 1.59 (d, $J = 1.6$ Hz, 3H), 2.14 (dtd, $J = 13.2$, 4.0, 1.2 Hz, 1H), 2.39 (dt, $J = 14.8$, 1.2 Hz, 1H), 2.52-2.61 (m, 4H), 2.99 (ddd, $J = 14.8$, 1.2 Hz, 1H), 3.19-3.23 (m, 1H), 3.69 (s, 3H), 3.70 (t, $J = 4.8$ Hz, 4H), 3.73 (br s, 1H), 5.89 (d, $J = 10.4$ Hz, 1H), 5.98 (ddd, $J = 10.4$, 2.4, 0.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 19.3, 19.4, 23.0, 41.1, 41.8, 42.7, 49.0, 52.1, 57.0, 67.5, 125.4, 126.9, 130.2, 131.3, 175.5; IR (CHCl$_3$) 1729 cm$^{-1}$; HRMS for C$_{17}$H$_{25}$NO$_3$ calcd 291.1834, found 291.1839.

**Compounds 59a and 59b** (entry 36). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a white solid consisting of an inseparable mixture of two isomers (60:40): $^1$H NMR (CDCl$_3$) $\delta$ 1.07 (d, $J = 14.2$ Hz, 0.6H), 1.16-1.24 (m, 6H), 1.64 (s, 3H), 1.69 (s, 1.2H), 1.71 (s, 1.8H), 1.65-1.71 (m, 1H), 1.74-1.78 (m, 1H), 2.13 (t, $J = 12$ Hz, 0.6H), 2.29-2.46 (m, 0.4H), 2.38 (s, 1.2H), 2.39 (s, 1.8H), 2.43 (t, $J = 11.6$ Hz, 0.4H), 2.58-2.64 (m, 1H), 2.76-2.97 (m 2H), 3.30 (d, $J = 10.4$ Hz, 0.4H), 3.35 (d, $J = 11.2$ Hz, 0.6H), 3.48 (dd, $J = 11.2$, 4.4 Hz, 0.4H), 3.63 (ddd, $J = 12.0$, 4.4, 1.6 Hz, 0.6H), 4.09-4.18 (m, 4H), 4.36 (d, $J = 13.6$ Hz, 0.4H), 4.48 (d, $J = 13.2$ Hz, 0.6H), 5.45-5.49 (m, 0.4H), 5.58-5.69 (m, 1.6H),...
7.23-7.28 (m, 2H), 7.59-7.62 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.08, 14.11, 19.7, 19.8, 20.5, 20.6, 21.6, 24.2, 25.0, 29.7, 30.0, 34.4, 35.2, 36.1, 37.2, 43.1, 44.4, 45.8, 46.6, 56.7, 57.4, 61.6, 61.7, 124.6, 126.4, 127.4, 127.6, 127.7, 127.9, 128.1, 129.1, 129.66, 129.70, 130.1, 133.6, 133.9, 143.3, 143.5, 167.86, 167.92, 167.97, 168.2 (six carbons missing due to overlap); IR (CHCl$_3$) 1747, 1728, 1337, 1163 cm$^{-1}$; HRMS for C$_{26}$H$_{35}$NO$_5$S calcd 489.2185, found 489.2185. The mixture was recrystallized from EtOAc/hexanes to afford pure 59a as white crystals: mp 172-174 °C; $^1$H NMR (CDCl$_3$) $\delta$ 1.08 (d, $J$ = 14.4 Hz, 1H, H$^8$), 1.23 (t, $J$ = 6.8 Hz, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H), 1.68 (s, 3H, H$^{13}$), 1.69-1.77 (m, 1H, H$^{10}$), 1.75 (s, 3H, H$^{14}$), 2.17 (t, $J$ = 12.0 Hz, 1H, H$^9$), 2.33-2.40 (m, 1H, H$^5$), 2.44 (s, 3H), 2.68 (d, $J$ = 13.2 Hz, 1H, H$^1$), 2.83 (dt, $J$ = 13.6, 3.8 Hz, 1H, H$^{11}$), 2.91 (dt, $J$ = 10.4, 5.2 Hz, 1H, H$^5$), 3.40 (d, $J$ = 11.2 Hz, 1H, H$^{12}$), 3.68 (ddd, $J$ = 11.6, 4.0, 1.6 Hz, 1H, H$^4$), 4.13-4.23 (m, 4H), 4.53 (d, $J$ = 13.6 Hz, 1H, H$^6$), 5.66-5.74 (m, 2H, H$^6$ and H$^7$), 7.32 (d, $J$ = 8.2 Hz, 2H), 7.65 (d, $J$ = 8.2 Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 14.1, 19.6, 20.5, 21.5, 24.9, 30.0, 34.3, 35.2, 44.3, 46.5, 56.6, 61.5, 126.4, 127.7, 127.8, 129.0, 129.6, 130.1, 133.6, 143.4, 167.9, 168.1 (two carbons missing due to overlap). Anal. Calcd for C$_{26}$H$_{35}$NO$_5$S: C, 63.78; H, 7.20; N, 2.86. Found: C, 63.80; H, 7.29; N, 2.84.
Compounds 60a and 60b (entry 37). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield an off-white solid consisting of an inseparable mixture of two isomers (62 : 38): mp 178-188 °C (EtOAc/hexanes); $^1$H NMR (CDCl$_3$) δ 1.51 (s, 1.86H), 1.62 (s, 1.14H), 1.68 (s, 3H), 1.48-1.74 (m, 1.38H), 1.81-1.85 (m, 0.62H), 2.10-2.21 (m, 1H), 2.40 (s, 1.14H), 2.42 (s, 1.86H), 2.37-2.50 (m, 1H), 2.69 (d, $J = 13.2$ Hz, 0.62H), 2.94-2.98 (m, 1H), 3.10 (d, $J = 13.6$ Hz, 0.38H), 3.55-3.62 (m, 0.76H), 3.69-3.73 (m, 1.62H), 3.91 (s, 0.62H), 4.37 (d, $J = 14.0$ Hz, 0.38H), 4.52 (d, $J = 13.6$ Hz, 0.62H), 5.67-5.88 (m, 2H), 6.51 (d, $J = 8.0$ Hz, 0.76H), 6.54 (d, $J = 8.0$ Hz, 1.24H), 6.65 (t, $J = 7.2$ Hz, 0.62H), 6.70 (t, $J = 7.2$ Hz, 0.38H), 7.11 (t, $J = 8.0$ Hz, 1.24H), 7.16 (t, $J = 8.0$ Hz, 0.76H), 7.27 (d, $J = 8.0$ Hz, 0.76H), 7.31 (d, $J = 8.0$ Hz, 1.24H), 7.66 (d, $J = 8.0$ Hz, 1.24H), 7.67 (d, $J = 8.0$ Hz, 0.76H); $^{13}$C NMR (CDCl$_3$) δ 19.6, 20.0, 20.47, 20.49, 21.6, 24.3, 27.0, 29.1, 29.6, 35.4, 36.9, 43.3, 44.3, 44.5, 46.1, 47.2, 49.9, 112.9, 113.2, 117.50, 117.55, 124.8, 126.3, 126.4, 127.4, 127.67, 127.72, 127.75, 129.28, 129.36, 129.45, 129.54, 129.7, 131.0, 133.6, 134.0, 143.4, 143.5, 146.5, 146.8 (two carbons missing due to overlap); IR (CHCl$_3$) 3390, 1335, 1159 cm$^{-1}$; HRMS for C$_{25}$H$_{30}$N$_2$O$_2$S calcd 422.2028, found 422.2030. Anal. Calcd for C$_{25}$H$_{30}$N$_2$O$_2$S: C, 71.06; H, 7.16; N, 6.63. Found: C, 69.89; H, 7.24; N, 6.40.

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References


Azides


GENERAL CONCLUSION

In this dissertation, the scope and limitations of some palladium(0)-catalyzed reactions of allenes, dienes and alkynes with aryl iodides, vinylic iodides and triflates are presented.

Chapter 1 described the synthesis of five- and six-membered ring heterocycles containing a 1,3-diene moiety by the palladium-catalyzed annulation of allenes and internal alkynes using functionally-substituted vinylic iodides. The palladium-catalyzed annulation of allenes has been extended to vinylic iodides which contain a tertiary hydroxyl group or sulfonamide functionality. The results obtained from this study further support the proposed mechanism. The reaction of some of these vinylic iodides with diphenylacetylene afforded the anticipated pyrrolidine derivatives, as previously reported for cyclic sulfonamides. On the other hand, the reaction of some of these vinylic iodides with 4,4-dimethyl-2-pentyne afforded unexpected α,β-unsaturated aldehydes.

Chapter 2 showed that a variety of 3,4,6-tri and 3,4,5,6-tetrasubstituted α-pyrones can be prepared in modest to good yields by the reaction of vinylic iodides or triflates bearing ester functionality with internal alkynes in the presence of a palladium catalyst. This chemistry has also been extended to a double annulation process by employing geminal dihalo-substituted esters. Thus, polycyclic aromatics with ester functionality or an isocoumarin moiety can be readily synthesized.

Chapter 3 described the synthesis of highly-functionalized polycyclics by the palladium-catalyzed cross-coupling of 2,5-cyclohexadienyl-substituted aryl and vinylic iodides and carbon or heteroatom nucleophiles. This work presents a novel method for the highly diastereoselective synthesis of polycyclic compounds containing allylic functional groups, and nicely complements the recent
intramolecular asymmetric Heck chemistry of Shibasaki, where beta hydride elimination, rather than palladium migration, is observed. The easily-prepared starting materials, good to excellent chemical yields, tandem nature of the reaction, and more significantly, high diastereoselectivities of this process should find applications in the total synthesis of naturally-occurring compounds.
APPENDIX A. CHAPTER 1 $^1$H AND $^{13}$C NMR SPECTRA
\[ \text{H}_3\text{C} = \text{CH} - \text{NTs} + \text{H}_3\text{C} = \text{CH} - \text{NTs} \]
\[ n\text{-C}_9\text{H}_{17} + \text{H}_7\text{C}_8\text{-n} \]
\[ (86:14) \]
H₃C
\[\text{NTs}\]
\[n-C₈H₁₇\]
H₃C
\[\text{NTs}\]
\[H₁₇C₈-n\]

(6:1)
in Acetone-d$_6$
Me\_2\_C=CH\_2
\begin{align*}
\text{Me} & \text{Me} \\
\text{Ph} & \\
\text{CMe}_3
\end{align*}

(57:18:17:8)
Me

Me

Ph

Me

CMe₃

(57:18:17:8)
APPENDIX B. CHAPTER 2 $^1$H AND $^{13}$C NMR SPECTRA
Ph

O

C(CH₃)₃

CH₃
\[ \text{Ph}O\text{C(CH}_3\text{)}_2\text{OH} + \text{Ph}O\text{C(CH}_3\text{)}_2\text{OH} \]

(37.63)
(75:25)
H₃C

O

O

Ph

C(CH₃)₂OH

Ph

Ph
APPENDIX C. CHAPTER 3 \( ^1H, ^{13}C \) NMR, COSY, HMQC, and NOESY SPECTRA
\[ \text{CH(CO}_2\text{Et)}_2 \]
$\text{CH(CO}_2\text{Et)}_2$
\[
\text{OAc} + \text{OAc} + \text{Ph} = \text{Ph}
\]
\[ \text{CO}_2 \text{Me} \]

\[ \text{CH(CO}_2\text{Et)}_2 \]
NHPh

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

/dat2/data/xhan/nmr/han.582b.fid/1/pdata/1  xhan  Sat Oct 25 18:00:03 1997
Me\(\text{CO}_2\text{Me}\) + CH\(_2\)(CO\(_2\)Et\(_2\))\(_2\) (2.3:1)
Me

\[
\text{CO}_2\text{Me} + \text{CH}_2(\text{CO}_2\text{Et})_2
\]

Me

\[
\text{CH}(\text{CO}_2\text{Et})_2
\]

(2.3:1)
L. COgMe + CH₂(CO₂Et)₂
CH(CO₂Et)₂ (2.9:1)
\[ \text{Me} \quad \text{CO}_2\text{Me} \quad + \quad \text{CH}_2(\text{CO}_2\text{Et})_2 \]

(2.9:1)
HMQC

\[ CH(\text{CO}_2\text{Et})_2 \]
NOESY

\( \text{CH(CO}_2\text{Et)}_2 \)
HMBC
COSY
NOESY

Chart showing a 2D NMR spectrum with ppm values on the x-axis and y-axis.
COSY mixture

han.596y 2 1

(47: 53)
Han.596 3 1
HMOC

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{Ts}
\end{align*}
\]

\[
(\text{EtO}_2\text{C})_2\text{HC}^\omega
\]

ppm

6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
`han.596h 21
NOESY`

Chemical shift diagram with peaks at various ppm values.
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