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Synthetic Methods

Direct Carbocyclizations of Benzoic Acids: Catalyst-Controlled Synthesis of Cyclic Ketones and the Development of Tandem aHH (acyl Heck–Heck) Reactions

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Abstract: The formation of *exo*-methylene indanones and indenones from simple *ortho*-allyl benzoic acid derivatives has been developed. Selective formation of the indanone or indenone products in these reactions is controlled by choice of ancillary ligand. This new process has a low environmental footprint as the products are formed in high yields using low catalyst loadings, while the only stoichiometric chemical waste generated from the reactants in the transformation is acetic acid. The conversion of the active cyclization catalyst into the Hermman–Beller palladacycle was exploited in a one-pot tandem acyl Heck–Heck (aHH) reaction, and utilized in the synthesis of donepezil.

The generation and subsequent functionalization of acylmetal species is a useful approach to carbon–carbon bond formation.[1] Common methods to generate acylmetal species include the activation of acyl halides[2] or thioesters,[3] which are typically prepared from the corresponding carboxylic acids. The direct employment of carboxylic acids to generate acylmetal species would eliminate an extra synthetic step and lessen the amount of chemical waste. Acylmetal species are also generated from the insertion of carbon monoxide (CO) into pre-existing metal–carbon bonds.[4] Despite the use of CO in large-scale industrial processes, the development of carbonylation methods that avoid the use of CO is important because of the toxicity and handling issues associated with this gas.[5] In parallel with our group's work on the use of carboxylic acid derivatives in synthetic methodology,[6] we have developed a catalytic strategy to prepare indanones and indenones from benzoic acids.

Among the compounds formed from metal-catalyzed carbocyclization reactions, indanones and indenones are popular targets. These ketones are prevalent in many potent biologically active molecules, such as Aricept,[7] indanorine,[8] indanocine,[9] and the pterosin family of natural products (Figure 1).[10]

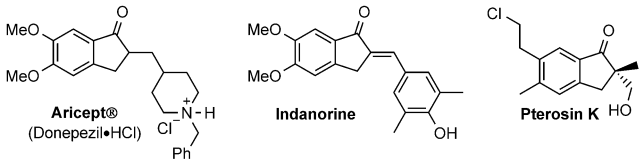

Figure 1. Examples of biologically active molecules that contain indanone cores.

Due to the biological importance of this scaffold, several metal-mediated processes have been developed including classical Friedel–Crafts chemistry, the carbonylation of arynes,[11] carbocyclizations of *ortho*-halobenzaldehydes[12] and thioesters[13] (Scheme 1). In general, all of the current methods to prepare indanones or indenones have one or more of the following unfavorable attributes: i) low atom economy; ii) poor regioselectivity; iii) high pressures of CO. The method reported herein generates acetic acid as the only stoichiometric byproduct, bypasses regioselectivity issues, and does not require the use of CO. Moreover, the products formed from this reaction can shuttle between *exo*-methylene indanones or indenones depending upon the choice of catalyst.

We investigated the activation and subsequent annulation of *ortho*-allyl benzoic acids with acetic anhydride. As shown in Scheme 2, formation of the benzoic acid to the anhydride, followed by subsequent selective insertion of the palladium catalyst would give the acylpalladium complex **3**. Insertion of the alkene into the palladium–acyl bond would give complex **4**, which could undergo β-hydride elimination to expel the carbocyclization product **5**. Elimination of acetic acid from **6** would regenerate the palladium(0) complex and turnover the catalyst. Isomerization of the *exo*-methylene indanone **5** could potentially be isomerized to indenone **7** under controlled reaction conditions. The formal transformation of the *ortho*-allylbenzoic acid to the indanone could be regarded as an acyl-Heck reaction. One of the challenges facing this chemistry is the ability of palladium to selectively insert into the in situ generated anhydride (**2**). Previously, pivalic anhydride has been required in intermolecular insertion reactions of this type, in order to favor the specific C–O bond.[14] However, we hypothesized that the selectivity of the initial oxidative addition reaction could be controlled by the stronger π-bonding interaction between the palladium center and the more proximal alkene (Scheme 2).

The hypothesis proposed in Scheme 2 was tested by treating *ortho*-allylbenzoic acid **1** with acetic anhydride in the presence of 1 mol% $Pd(OAc)_2$ and 1.2 mol% P(*o*-tol)$_3$ in THF at am-

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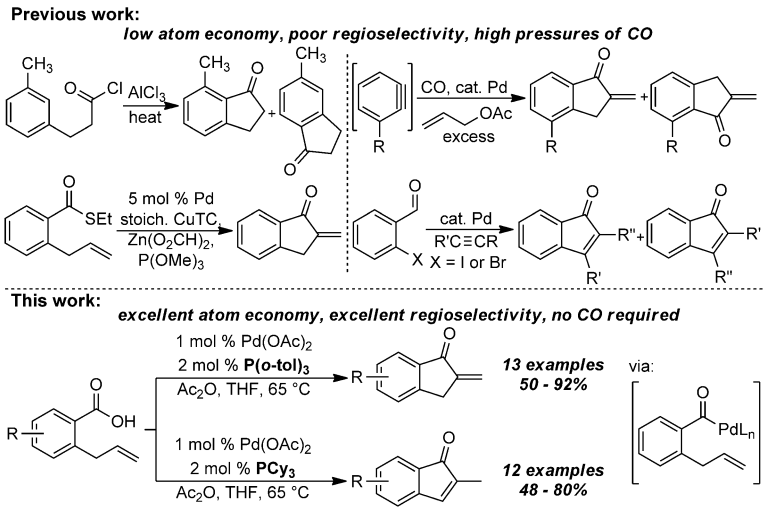
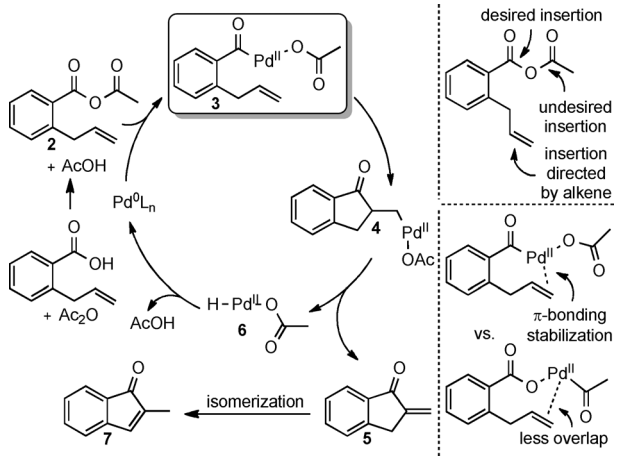


Scheme 1. Common synthetic routes to indanones and indenones.

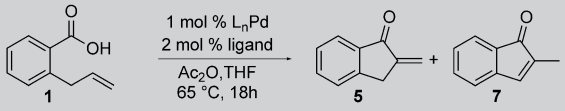


Scheme 2. Proposed reaction mechanism for the carbocyclization reaction.

With the optimized conditions in hand, a variety of *ortho*-allyl benzoic acids were cyclized to the corresponding *exo*-methylene indanones (Table 2). The parent allylbenzoic acid substrate was transformed into the desired indanone in 88% yield. Electron-donating groups did not greatly affect the yield of indanone as methyl or methoxy groups in various positions about the aromatic ring were converted to the corresponding products in 86–92% yield (**8**–**12**). Expectedly 2-allyl-5-hydroxybenzoic acid underwent cyclization to indanone **13**, with concomitant protection of the hydroxy group as an acetate in 82% yield. Submission of 2-allyl-5-bromobenzoic acid under the reaction conditions required the use of the less basic triphenylarsine ligand, in order to avoid insertion of the palladium complex into the carbon–bromine bond (**14**). Stronger carbon–halogen bonds, such as carbon–chlorine (**15**) and carbon–fluorine (**16** and **17**) did not require alternative ligands, providing high yields of indanone products. *o*-Allylnaphthoic acid cyclized to indanone **18** in 75% yield, while the tosyl-protected indole cyclized to the annulated indole product **19** in 50% yield.

The formation of the indenone product with the $Pd(OAc)_2$/PCy_3 catalyst system, as discovered in the initial ligand screen (Table 1, entry 5), was further examined. The reaction scope of this carbocyclization to the corresponding indenones tolerated a variety of functional groups and heterocyclic partners (Table 3). Unsubstituted *ortho*-allylbenzoic acid was converted to the indenone product **7** in 73% yield. The methyl-substituent temperature (Table 1, entry 1). We were pleased to find the cyclization proceeded smoothly to afford the corresponding *exo*-methylene indanone (**5**) in 78% yield (entry 1). Heating the reaction to 65 °C and increasing the P(*o*-tol)$_3$ loading to 2 mol%, increased the yield to 89%. Although switching the ancillary ligand to $AsPh_3$ and PPh_3 did not greatly improve the yield, the use of PCy_3 unexpectedly furnished 2-methyl indenone (**7**) as the major product (entries 3–5). The scope of this process was examined further (vide infra). Omission of acetic anhydride from the reaction conditions shut down the reaction pathway to product (entry 6), while removal of the ligand dropped the yield of indanone to 17% (entry 7). Replacement of $Pd(OAc)_2$ with $[Pd(dba)_2]$ resulted in diminished yields of the indanone (entry 8), while no carbocyclization product was observed with $PdCl_2$ or without palladium (entry 9 and 10). In the absence of palladium, quantitative conversion to the corresponding anhydride **2** was observed. Preformation of the anhydride **2**, and submission to the catalytic reaction conditions produces similar yield and selectivity to the in situ generated anhydride.

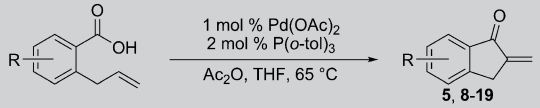
Table 1. Initial reaction screening of the carbocyclization of *ortho*-allyl benzoic acid.

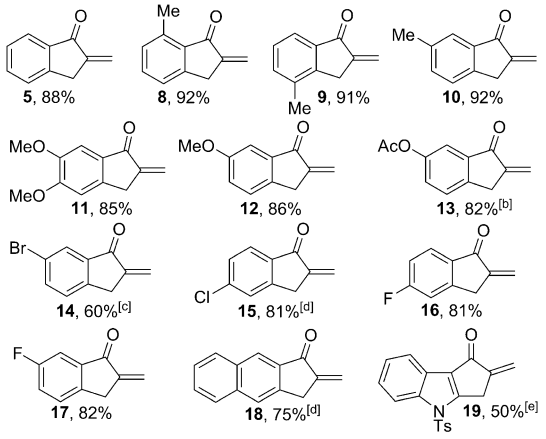


Entry[a]	Pd	Ligand	Yield **5**[b]	Yield **7**[b]
1[c]	$Pd(OAc)_2$	P(*o*-tol)$_3$	78	3
2	**$Pd(OAc)_2$**	**P(*o*-tol)$_3$**	**89**	**3**
3	$Pd(OAc)_2$	$AsPh_3$	82	5
4	$Pd(OAc)_2$	PPh_3	53	8
5	**$Pd(OAc)_2$**	**PCy_3**	**14**	**68**
6[d]	$Pd(OAc)_2$	P(*o*-tol)$_3$	0	0
7	$Pd(OAc)_2$	none	17	0
8	$Pd(dba)_2$	P(*o*-tol)$_3$	63	16
9	$PdCl_2$	P(*o*-tol)$_3$	0	0
10	none	P(*o*-tol)$_3$	0	0

[a] Reaction conditions: 2-allylbenzoic acid (1 equiv), Ac_2O (2 equiv), $Pd(OAc)_2$ (1 mol%), P(*o*-tol)$_3$ (2 mol%), THF (1 M), 65 °C, 18 h. [b] Yields determined by ^{1}H NMR spectroscopy using an internal standard. [c] Reaction performed at 23 °C for 24 h with 1.2 mol% P(*o*-tol)$_3$. [d] No Ac_2O

Table 2. Substrate scope of the carbocyclization of *ortho*-allyl benzoic acids to *exo*-methylene indanones.[a]

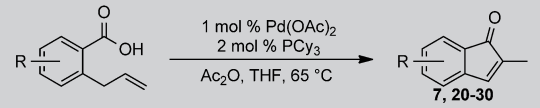


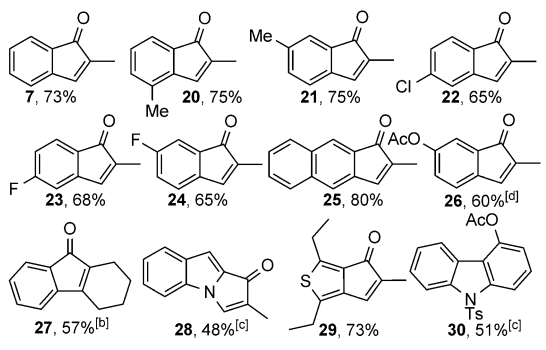


[a] Yields are an average of two, one mmol reactions. [b] 3 equiv of Ac_2O used. [c] 2 mol% $Pd(OAc)_2$ 4 mol% $AsPh_3$. [d] 2 mol% of $Pd(OAc)_2$/4 mol% P(*o*-tol)$_3$ was used. [e] 5 mol% $Pd(OAc)_2$, 10 mol% P(*o*-tol)$_3$ in dioxane at 100 °C.

ed benzoic acids provided indenone **20** and **21** in 75% yield. Electron-deficient aryl chloride and aryl fluorides, as well as a naphthoic derivative smoothly cyclized in 60–80% yields (**22**–**25**). Electron-rich phenol substrate cyclized with concomitant acetylation of the phenol, to provide **26** in 60% yield. A sterically hindered disubstituted olefin also participated in the carbocyclization reaction, giving 57% yield of the dihydrofluorenone derivative **27**. Heterocyclic substrates were also reactive, forming interesting thiophenyl and carbazole products in 48–73% yield (**28**–**30**).[15] The slightly decreased yields of the indenone series with respect to the indanone series is likely caused by the tandem reaction sequence of indenone formation, followed by isomerization. Thus, two reactions are required to form a single indenone product (Scheme 1).

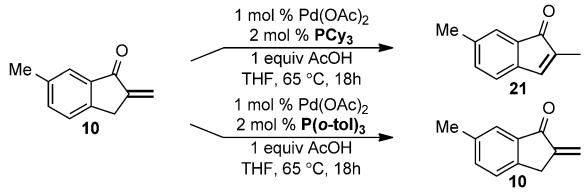
Table 3. Substrate scope of the carbocyclization of *ortho*-allyl benzoic acids to indenones.[a]





[a] Yields are an average of two, one mmol reactions. [b] 3 mol% of $Pd(OAc)_2$/6 mol% $P(Cy)_3$ in dioxane at 100 °C. [c] 5 mol% $Pd(OAc)_2$, 10 mol% $P(Cy)_3$ in dioxane at 100 °C. [d] 3 equiv of Ac_2O used.

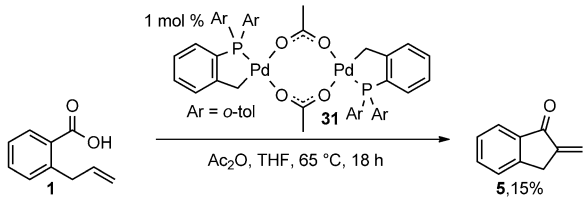
We have demonstrated that *exo*-methylene indanone **10** isomerizes in the presence of PCy_3 as ligand to give **21**, while little to no isomerization is seen in the presence of P(*o*-tol)$_3$ as ligand (Scheme 3). The isomerization required the addition of acetic acid, which is presumably formed in situ under the reaction conditions. Interestingly, these isomerization results are in contrast to palladium-catalyzed isomerizations that employ P(*o*-tol)$_3$ as ligand.[6]



Scheme 3. Conversion of *exo*-methylene indanone **10** to the corresponding indenone **21**.

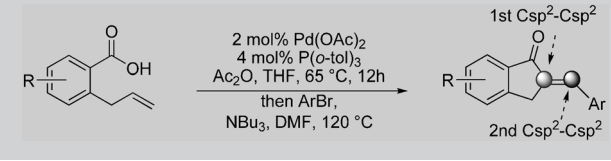
The $Pd(OAc)_2$/P(*o*-tol)$_3$ catalyst system was monitored by ^{31}P NMR spectrum and after several hours, a new resonance appeared near 35 ppm. Independent synthesis of the Hermann–Beller palladacycle **31** confirmed the identity of the complex that evoked this resonance. However, when the palladacycle was subjected to the reaction conditions with acid **1** it was not chemically competent and is likely the product of catalyst decomposition. (Scheme 4).

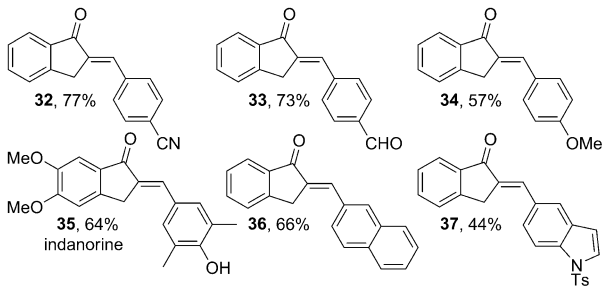
Previously, Hermann and Beller showed that their namesake palladacycle is a robust catalyst that promotes the Heck reaction of aryl halides and olefins with high turnover numbers.[17] We exploited the known catalytic activity of this complex by adding aryl halide and base to the crude indanone reaction mixture post-carbocyclization to promote the formation of a second sp^2–sp^2 carbon–carbon bond via a traditional Heck reaction. The in situ generated Hermann–Beller catalyst eliminated the need to add additional palladium for the second Heck reaction. This one-pot reaction worked well and provided (*E*)-selective acyl-Heck–Heck (aHH) products in 44–77% yields (Table 4, **32**–**37**). Notably, the known antiproliferative agent, indanorine (**35**),[8] was formed in 64% yield from the corresponding *o*-allyl benzoic acid. The higher temperatures for the second Heck reaction is indicative of reactions using this palla-



Scheme 4. Testing the potential catalytic activity of the Hermann–Beller palladacycle **31**.

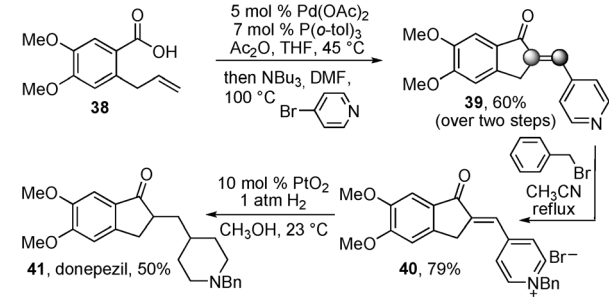
Table 4. One-pot aHH reactions form two sp^2–sp^2 carbon–carbon bonds of trisubstituted olefins.





dacycle, and is also likely required because the formation of trisubstituted olefins in Heck reactions is typically sluggish.

This newly developed one-pot acyl-Heck–Heck (aHH) reaction was applied to the synthesis of donepezil, whose HCl salt is marketed as Aricept by Pfizer for the treatment of Alzheimer's disease.[18] Our aHH reaction allows a complementary synthesis of donepezil that is more atom economical than previously reported.[19] Subjecting 4,5-dimethoxy-2-allylbenzoic acid and 4-bromopyridine to the optimized one-pot reaction conditions yielded the aHH product **39** in 60%. Quaternization of the pyridine with benzyl bromide gave pyridinium **40** in 79% yield. Hydrogenation of the alkene and pyridine ring in **40** furnished donepezil (**41**) in 50% yield (Scheme 5).



Scheme 5. Synthesis of Donepezil via an aHH reaction.

In summary, we present a highly efficient, selective, and functional group tolerant method to form *exo*-methylene indanones and indenones from readily accessible substituted benzoic acids. The reaction avoids the use of toxic carbon monoxide and produces acetic acid as the only stoichiometric byproduct. A simple change in ligand selectively controls the formation of the indanone or indenone likely through an additional isomerization reaction. The conversion of this active catalyst to the Hermann–Beller palladacycle was exploited as the second catalyst in a one-pot acyl Heck–Heck coupling reaction that forms two sp^2–sp^2 carbon–carbon bonds of trisubstituted olefins.

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Keywords: carboxylic acids · catalysis · cyclization · green chemistry · palladium

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