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Palladium-catalyzed double C–H functionalization of 2-aryl-1, 3-dicarbonyl compounds: a facile access to alkenylated benzopyrans

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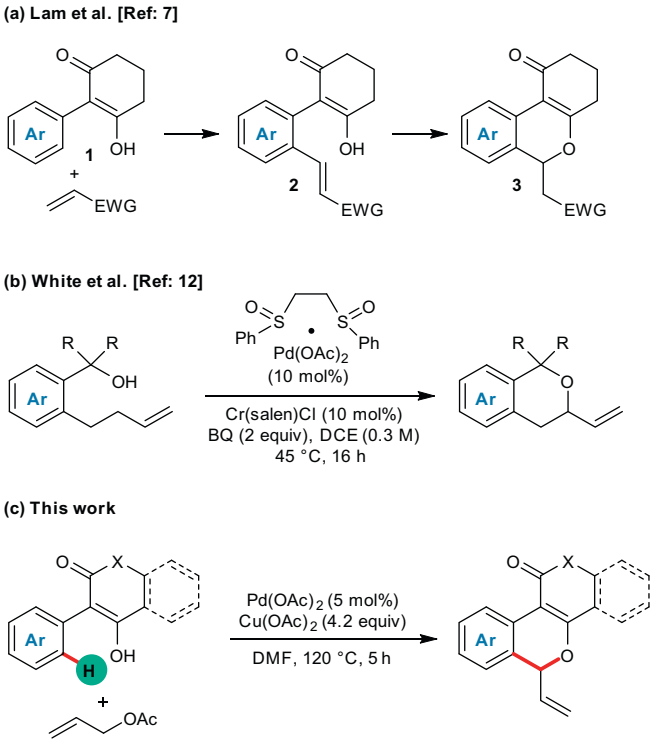
ABSTRACT

The present study reports the development of a palladium-catalyzed oxidative annulation/nucleophilic substitution sequence affording a library of alkenylated benzopyrans using 2-aryl-1,3-dicarbonyl compounds and allylic acetate. The process is compatible to a wide range of substrates with good functional group tolerance producing the desired heterocycles in moderate to good yields.

Transition metal-catalyzed C–H functionalization of unreactive bonds has gained eminence as a powerful and transformative tool in synthetic chemistry,[1] with additional applications to natural product syntheses,[2] drug discovery,[3] and material sciences.[4] The most advantageous use of this strategy is the atom-economic construction of C–C, C–N, and C–O bonds by functionalization of the aromatic C(sp^2)–H bonds, directed by a coordinating functional group delivering a diverse variety of heterocyclic compounds.[5] Recently, Lam and co-workers have developed catalytic oxidative annulations of α-aryl cyclic 1,3-dicarbonyl compounds (or their enol tautomers) with various coupling partners including alkynes,[6] terminal alkenes (Scheme 1a),[7] 1,3-dienes,[8] and 1,3-enynes[9] that provide efficient access to carbo- and heterocycles. On the other hand, allyl functionality is a versatile tool offering a range of opportunities for further functionalizations.[10] Recently, several methods have been developed for the direct allylation of aromatic C–H bonds using transition-metal catalysts.[11] In addition, allylic C–H oxidation is an established and well-studied strategy used to construct complex organic molecules (Scheme 1b).[12] In this regard, Pd (II)/bis-sulfoxide-catalyzed allylic C–H functionalizations of terminal olefins have demonstrated broad applicability in synthetic methodology.[13]



Scheme 1. Pd-catalyzed oxidative annulations and allylic C–H oxidation.

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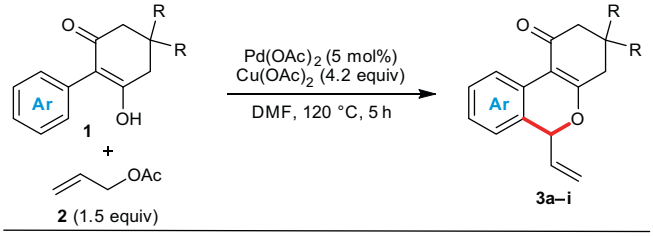
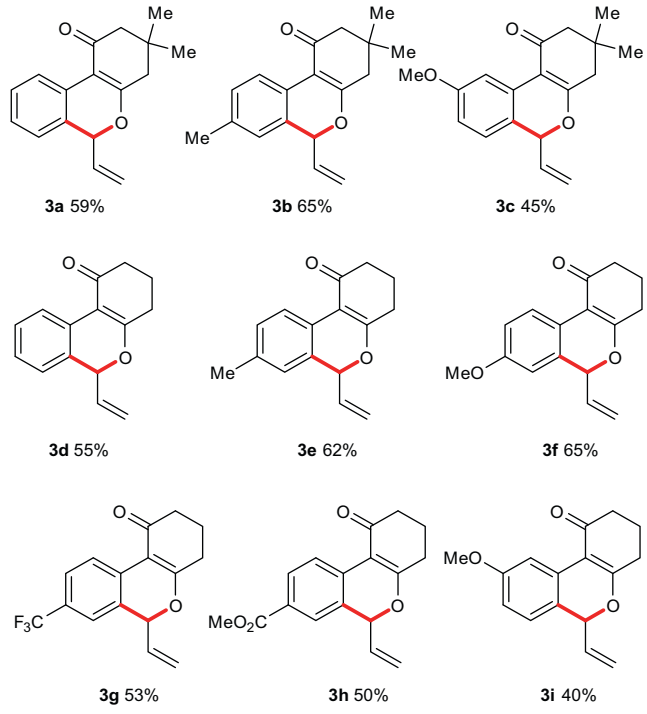
Table 1
Optimization of reaction conditions for the synthesis of **3a**[a]

Entry	[M]	Mol (%)	Solvent	Temp (°C)	Yield[b] (%)
1	$Pd(OAc)_2$	5	DMF	90	40
2	**$Pd(OAc)_2$**	**5**	**DMF**	**120**	**59**
3	$Pd(OAc)_2$	10	DMF	120	62
4	$Pd(OAc)_2$	5	*t*-AmOH	120	20
5	$Pd(OAc)_2$	5	Dioxane	120	35
6	$[RuCl_2(p\text{-cymene})]_2$	2.5	DMF	120	<5
7	$[RuCl_2(p\text{-cymene})]_2$	2.5	*t*-AmOH	120	NR
8	—	—	DMF	120	NR
9[c]	$Pd(OAc)_2$	5	DMF	120	NR
10[d]	$Pd(OAc)_2$	5	DMF	120	37

[a] Reactions were conducted using 0.50 mmol of **1a**.
[b] Isolated yield.
[c] Reaction conducted without $Cu(OAc)_2$.
[d] Reaction conducted in the presence of K_2CO_3 (2.0 equiv). DMF = *N*,*N*′-dimethylformamide, *t*-Am = *tert*-amyl.

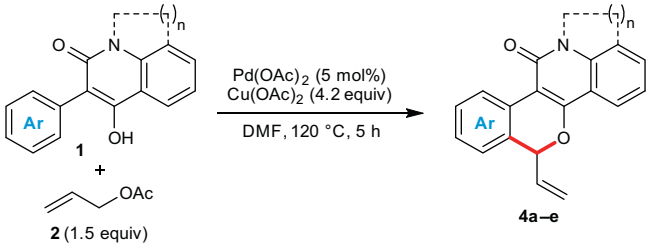
Table 2
Pd(II)-catalyzed synthesis of alkenylated benzopyrans[a]

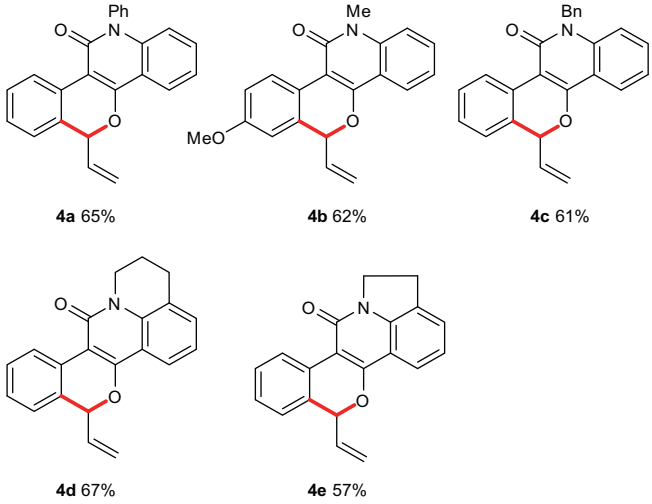




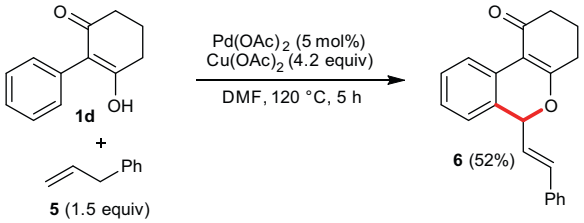
[a] Reactions were conducted with 0.50 mmol scale. Yields are of isolated material.

Table 3
Scope of Pd(II)-catalyzed synthesis of alkenylated benzopyrans[a]





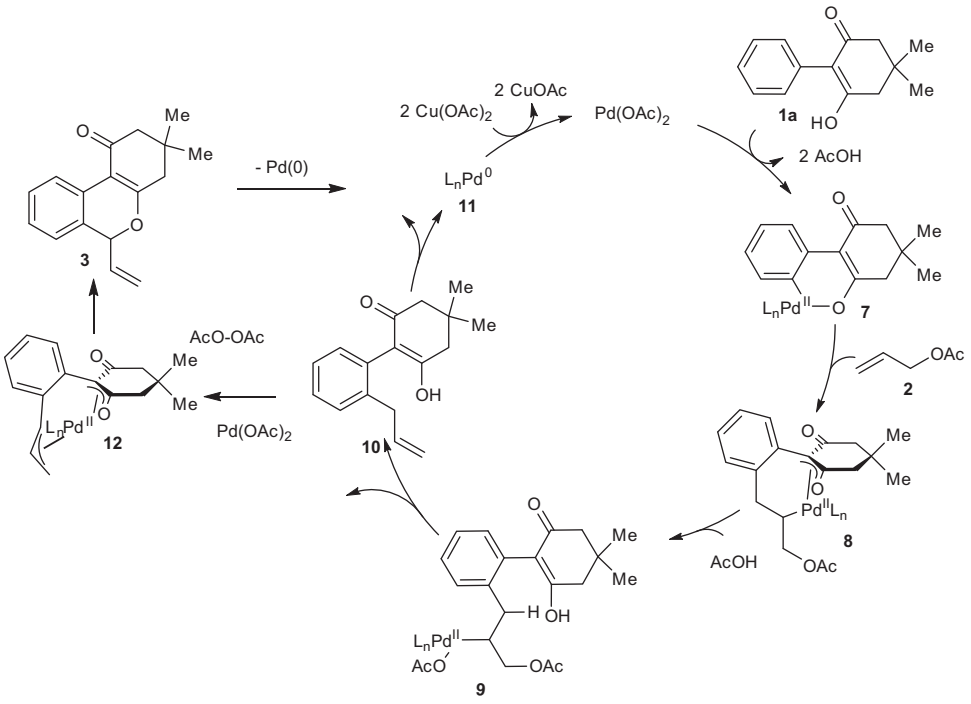
[a] Reactions were conducted with 0.50 mmol scale. Yields are of isolated material.



Scheme 2. Oxidative annulation reaction of allylbenzene with 3-hydroxy-2-phenyl-2-cyclohexenone.

In the present work, we report the efficient construction of alkenylated benzopyrans using a Pd(II)-catalyzed oxidative coupling of 1,3-dicarbonyl compounds with allyl acetate. This process involves C–H activation of a C(sp^2)–H bond to generate an allylated product which on nucleophilic substitution to a π-allyl Pd-species affords the desired heterocycles (Scheme 1c).

We initiated our study by exploring the reaction of 2-phenyldimedone (**1a**) with allyl acetate **2** (1.5 equiv) in the presence of $Pd(OAc)_2$ (5 mol %) in DMF using $Cu(OAc)_2$ (4.2 equiv) as an oxidant. Pleasingly, the alkenylated benzopyran product **3a** was obtained in 40% yield after reacting for 5 h at 90 °C (Table 1, entry 1). By elevating the reaction temperature to 120 °C, the yield of the desired product was increased to 59% (entry 2). A comparable yield of **3a** was achieved using 10 mol % of $Pd(OAc)_2$ in DMF (entry 3). Other solvents such as *t*-AmOH and dioxane provided limited reaction and gave inferior results (entries 4 and 5). $[RuCl_2(p\text{-cymene})]_2$ complex[14] commonly employed in C–H functionalizations was completely unproductive in different solvents (entries 6 and 7). No product formation was observed in the absence of the palladium catalyst or $Cu(OAc)_2$ (entries 8 and 9).



Scheme 3. Proposed mechanism for benzopyran formation.

Lower yield (37%) of **3a** was obtained with the addition of K_2CO_3 (entry 10).

With the optimized reaction conditions in hand (Table 1, entry 2), the scope of palladium-catalyzed oxidative annulation/nucleophilic substitution reaction was then explored, for the synthesis of alkenylated benzopyrans (**3a**–**i**). Several 1,3-dicarbonyl substrates bearing a variety of functional groups (electron-donating and electron-withdrawing) were well tolerated affording the benzopyran products in 40–65% yields (Table 2). Initially, substrates derived from dimedone (**3a**–**c**) were tested in the annulation reaction. Apart from phenyl ring at 2-position of 1,3-dicarbonyl compound, aryl ring incorporating functional groups at the *para*- (**3b**) and *meta*-positions (**3c**) proceeded efficiently with moderate to good yields. In case of **3c**, the C–H functionalization occurred exclusively at the sterically more accessible position, *para*- to the substituent, which is consistent with the literature.[6–8] Next, the scope of the reaction was extended to substrates derived from 1,3-cyclohexanedione. As illustrated in Table 2 and 1,3-dicarbonyl compounds incorporating both electron-rich (**3e**, **3f**, and **3i**) and electron-deficient groups (**3g** and **3h**) proceeded efficiently with moderate to good yields. Again, in case of *meta*-substituted substrate (**3i**), the annulated product was obtained through the formation of C–C bonds at the least sterically hindered position (see Table 3).

Next, the reaction scope was further extended by employing 1,3-dicarbonyl substrates containing various polycyclic ring systems (**4a**–**e**). The annulated products were obtained in 57–67% yields. Several keto-amide substrates protected with different groups led to the successful formation of benzopyran products.

Furthermore, the reaction of 3-hydroxy-2-phenyl-2-cyclohexenone (**1d**) with allylbenzene (**5**) also afforded the annulated benzopyran product (**6**) in 52% yield under the optimized reaction conditions (Scheme 2).

The proposed mechanism for this oxidative annulation reaction, using substrates **1a** and **2**, is depicted in Scheme 3. Initially, the enolate of **1a** forms the six membered palladacycle **7** by reacting with $Pd(OAc)_2$. Coordination of the allyl acetate **2** and migratory insertion then provides a second metallacycle **8** which on protonation by AcOH delivers species **9**. β-OAc elimination of **9** releases palladium (0) **11** and provides the allylated product **10**. Palladium-catalyzed oxidative nucleophilic substitution of **10** affords an intermediate **12** with a π-allyl palladium species which on intramolecular nucleophilic substitution delivers the desired benzopyran product **3**. Meanwhile, $Cu(OAc)_2$-promoted oxidation of the Pd(0) species **11** regenerates the palladium acetate complex.

Conclusion

In summary, we have developed a palladium-catalyzed oxidative annulation/nucleophilic substitution protocol for the synthesis of a variety of alkenylated benzopyrans. This approach provides an atom-economic pathway to access this class of valuable compounds from a diverse range of 2-aryl-1,3-dicarbonyl compounds and allylic acetate. Good functional group tolerance and broad substrate scope are the advantages of this methodology.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.089.

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