DOI: 10.1002/cjoc.201600527

Synthesis of Substituted Benzoxacycles via a Pd(II)-Catalyzed Intramolecular Arylation Reaction of Allylic Alcohols

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Herein a Pd-catalyzed intramolecular allylation reaction of unprotected allylic alcohols was developed, and the reaction proceeded through a Pd(II)-mediated allylic carbocation species formation, followed by a Friedel-Crafts type annulation to afford functionalized chromanes.

Keywords Pd-catalyzed, Friedel-Crafts reaction, benzoxacycles, arylation, allylic compound

Introduction

Chromanes (2,3-dihydrobenzopyrans) and benzoxepines feature in numerous biologically important natural products. They are also used as versatile intermediates for the preparation of pharmaceuticals and functional materials,[1] and so the development of efficient strategies for the synthesis of structurally diverse chromanes in an atom-economical manner is of great importance.[2] Convenient approaches for the synthesis of such heterocycles involve either cyclization using a C—O bond-forming reaction, or using a C—C bond-forming reaction with the heteroatom as the tether,[3] and significant progress has been achieved with the latter approach.[4]

Pd-catalyzed allylation has emerged as a reliable and powerful method for the formation of C—C, C—N, C—O and C—S bonds in organic synthesis.[5] The use of unprotected allylic alcohols as substrates is important with regard to waste minimization and atom economy.[6] In this context, Pd-catalyzed allylation using unprotected allylic alcohols has been widely used as an efficient method for the synthesis of structurally diverse allylated products.[7] Despite significant advances in Pd-catalyzed allylations using allylic alcohols[8] with a variety of nucleophiles (*e.g.*, amines, alcohols, alkenes, alkynes, aldehydes, ketone, esters, amides, and indoles), a Pd-catalyzed Friedel-Crafts allylation has not been reported.[9] Herein, we report a Pd-catalyzed Friedel- Crafts cyclization of phenyl-tethered allylic alcohols, to give structurally diverse and biologically important 4-substituted chromanes.[10]

We recently reported Pd-catalyzed oxidative rearrangement of tertiary allylic alcohol, in which a 1,3-isomerization of tertiary allylic alcohols catalyzed by palladium was realized via a Pd(II)-catalyzed dehydration of the allylic alcohol to form allylic carbocation species followed by a nucleophilic addition of water to the newly generated allylic carbocation species [Eq. (1)] (Figure 1).[11] We later found that Pd-catalyzed carbonylative cyclizations of aryl alkenes/alkenols were an effective method for the synthesis of structurally diverse chromanes [Eq. (2), Figure 1].[12] Based on these results, we envisioned that the chromane scaffold could be constructed via an integrated approach involving a Pd(II)-catalyzed dehydration of an allylic alcohol via anallylic carbocation formation followed by an intramolecular Friedel-Crafts reaction [Eq. (3), Figure 1].

Experimental

A dry flask with stir bar was charged with $Pd(CH_3CN)_2Cl_2$ (3.1 mg, 12 μmol) or $Pd(CH_3CN)_4(BF_4)_2$ (5.3 mg, 12 μmol) in the glovebox, sealed with a septum, and brought out of the glovebox. DCE (DCE= dichloroethane) (3 mL) was added, and the vigorously stirred mixture (1 mL) was added to a solution of free allylic alcohol (0.2 mmol) in DCE (1 mL) at room temperature. The reaction mixture was warmed to 40 ℃ or 60 ℃. After the reaction was completed, the reaction mixture was cooled to room temperature. The organic

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Received August 22, 2016; accepted October 3, 2016; published online XXXX, 2016.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201600527 or from the author.
Dedicated to the Memory of Professor Enze Min.

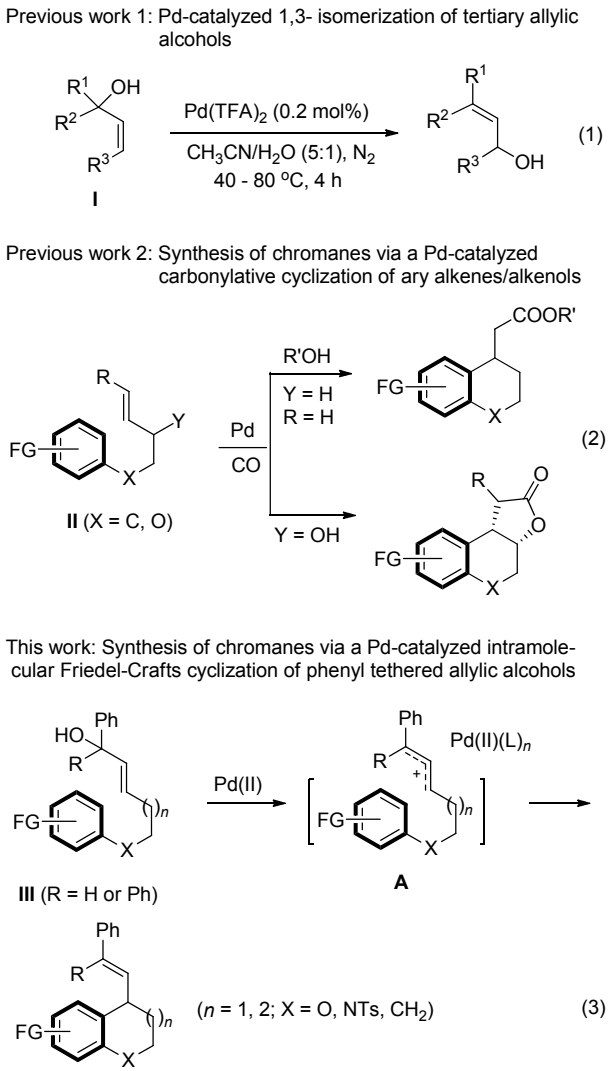


Figure 1 Pd-catalyzed annulations.

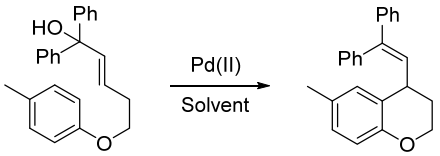
solvent was directly evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc as eluent) to give analytically pure product.

Results and Discussion

Our investigation began by identifying conditions for the proposed Friedel-Crafts reaction. Initial efforts focused on the effect of catalysts and solvents on the outcome of the Friedel-Crafts reaction of allylic alcohol **1a** (Table 1).

A previous report concerning the Pd-catalyzed isomerization of allylic alcohols[11] identified $Pd(TFA)_2$ as an effective catalyst for the isomerization of allylic alcohols. We therefore selected $Pd(TFA)_2$ as a catalyst for the proposed Friedel-Crafts reaction. When allylic alcohol **1a** was treated with $Pd(TFA)_2$ (2 mol%) in acetonitrile at 40 ℃ and 60 ℃ for 48 h and 24 h, product **2a** was obtained in 61% and 74% yield, respectively (Table 1, Entries 1 and 2). We also tested two other Pd-catalysts, $Pd(CH_3CN)_2Cl_2$ and $Pd(CH_3CN)_4(BF_4)_2$, under the same conditions listed above. An 87% yield of product **2a** was obtained when $Pd(CH_3CN)_2Cl_2$ was used as the catalyst at 60 ℃ for 4 h (Table 1, Entries 3—6).

Table 1 Pd-catalyzed Friedel-Crafts annulation of **1a**[a]



Entry	Catalyst (2 mol%)	Solvent	Temp./℃	Time/h	Yield[b]/%
1	$Pd(TFA)_2$	CH_3CN	40	48	61
2	$Pd(TFA)_2$	CH_3CN	60	24	74
3	$Pd(CH_3CN)_2Cl_2$	CH_3CN	40	24	72
4	$Pd(CH_3CN)_2Cl_2$	CH_3CN	60	4	87
5	$Pd(CH_3CN)_4(BF_4)_2$	CH_3CN	40	4	67
6	$Pd(CH_3CN)_4(BF_4)_2$	CH_3CN	60	2	53
7	$Pd(CH_3CN)_2Cl_2$	THF	40	48	17
8	$Pd(CH_3CN)_2Cl_2$	THF	60	48	31
9	$Pd(CH_3CN)_2Cl_2$	Toluene	40	48	13
10	$Pd(CH_3CN)_2Cl_2$	Toluene	60	48	16
11	$Pd(CH_3CN)_2Cl_2$	DCE	40	2	98
12	$Pd(CH_3CN)_2Cl_2$	DCE	60	1	91
13[c]	$Pd(CH_3CN)_2Cl_2$	DCE	40	6	77
14[c]	$Pd(CH_3CN)_2Cl_2$	DCE	60	4	75

[a] Reactions were carried out with **1a** (0.2 mmol) in solvent (2 mL) under N_2. [b] Isolated yield. [c] 1.0 mol% of catalyst.

$Pd(CH_3CN)_2Cl_2$ was therefore selected as the catalyst to investigate the Friedel-Crafts reaction in different solvents. To this end, substrate **1a** was treated with $Pd(CH_3CN)_2Cl_2$ in THF and toluene at either 40 ℃ or 60 ℃, however, product **2** was obtained in low yield (Table 1, Entries 7—10). When the same reaction was carried out in DCE (Table 1, Entries 11—12), the best result was obtained when the reaction was carried out in the presence of 2 mol% of catalyst [$Pd(CH_3CN)_2Cl_2$] at 40 ℃ for 2 h, affording 98% of the annulated product **2** (Table 1, Entry 11). When the catalyst loading was reduced to 1 mol%, lower yields were observed (Table 1, Entries 13 and 14).

With the optimized Friedel-Crafts conditions in hand, we then explored the scope and limitations of this annulation reaction. A series of substrates (**1b**—**1r**) were prepared and annulated under the optimized reaction conditions (Table 2). The results in Table 2 demonstrate that: (i) all the selected substrates afforded the expected annulated products except substrates **1q** and **1r**, and substrates with electron-donating substituents (**1c**—**1j**) gave slightly better results than those with electron-withdrawing substituents (**1k**—**1n**); (ii) notably, when **1h** and **1i** were used as substrates, products **2h** and **2i**

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were obtained as a pair of regio-isomers, with the *para*-substituted product as the major isomer; and substrates **1f**, **1g** and **1j** gave high regio-selectivity; (iii) when the oxygen tether was replaced by N-Ts in substrate **1o**, the Pd-catalyzed annulation also afforded a high yield of annulated product **2o**. However, when the oxygen tether was replaced by CH_2 in substrate **1p**, the yield for annulated product **2p** decreased dramatically; (iv) substrates bearing electron-withdrawing groups such as F, CF_3, and COOMe gave high yields of products when $Pd(CH_3CN)_4(BF_4)_2$ was used as the catalyst; (v) the seven- and five-membered rings (products **2q** and **2r**) could not be formed under these conditions.

To further expand the substrate scope, we then investigated the intramolecular Friedel-Crafts annulation with secondary allylic alcohols for the formation of chromanes. To this end, substrates **3a**—**3q** were prepared and annulated under the optimized conditions (Table 3). We observed that: (i) the isolated yields for the secondary allylic alcohol-based substrates were similar to that of the tertiary ones; (ii) all the newly generated double bonds in the products are the *trans* isomers; (iii) when $n=2$, seven-membered ring 2,3,4,5-tetrahydrobenzo[*b*]oxepine **4p** was generated in good yield, indicating that this methodology can be applied to the synthesis of a broad range of 2,3,4,5-tetrahydrobenzo-[*b*]oxepines.

Figure 2 illustrates the proposed reaction mechanism for this transformation. The annulation reaction is thought to proceed through the coordination of Pd(II) to the hydroxyl group to give complex **B**, which undergoes a dehydration to form allylic carbocation complex **A** by direct cleavage of its C—O bond. The generated allylic carbocation then partakes in an intramolecular Friedel-Crafts reaction to afford product **IV**. The proposed mechanism is consistent with earlier reports[11,13] concerning the Pd-catalyzed dehydration of allylic alcohols to form anallylic carbocation complex as an active species to initiate the downstream reactions.

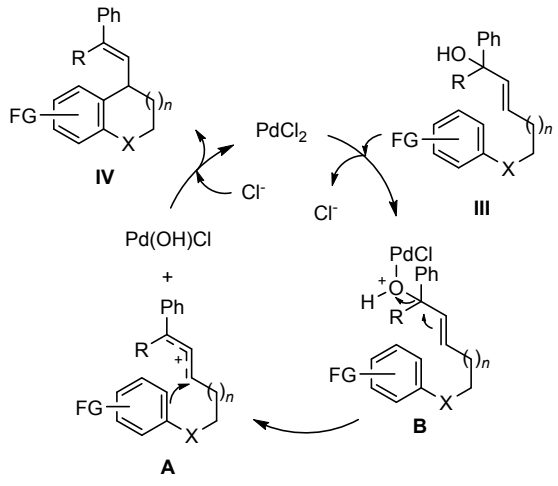
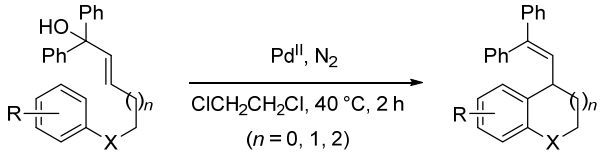
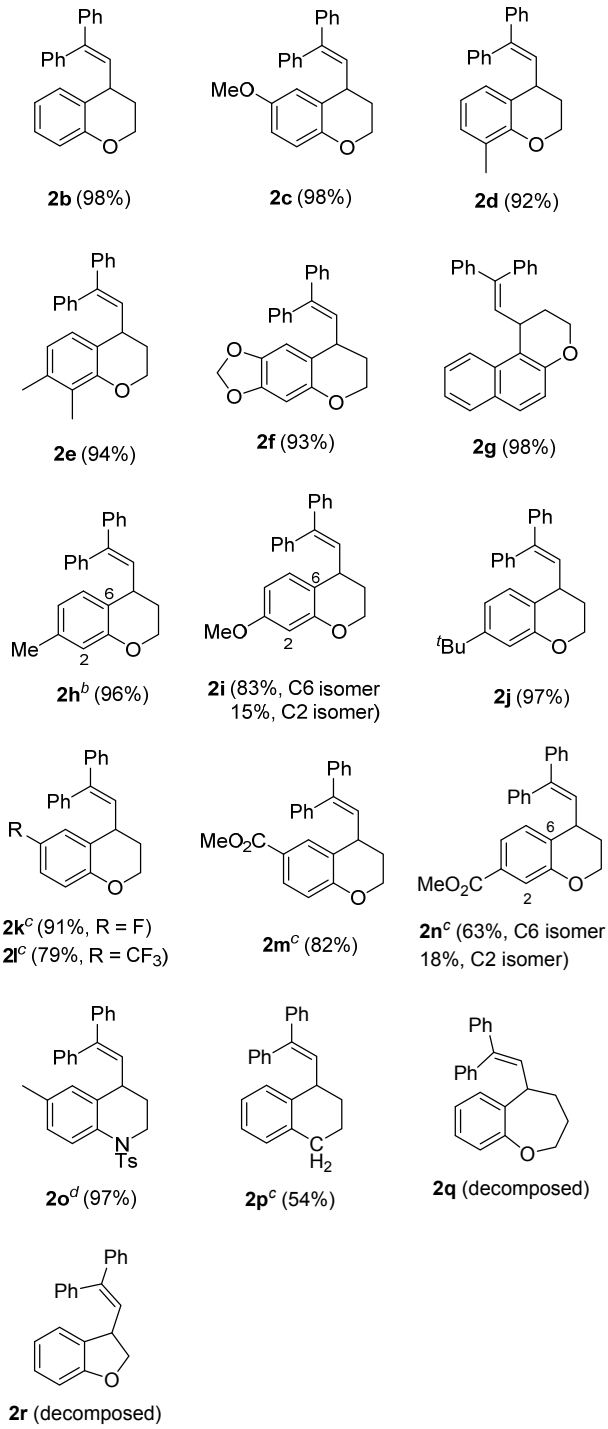


Figure 2 Proposed reaction mechanism.

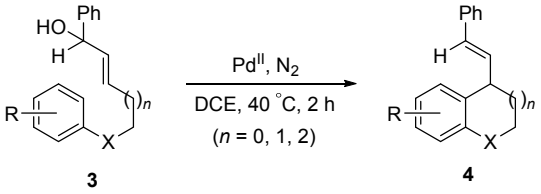
Table 2 Scope and limitation of tertiary allylic alcohols[a]

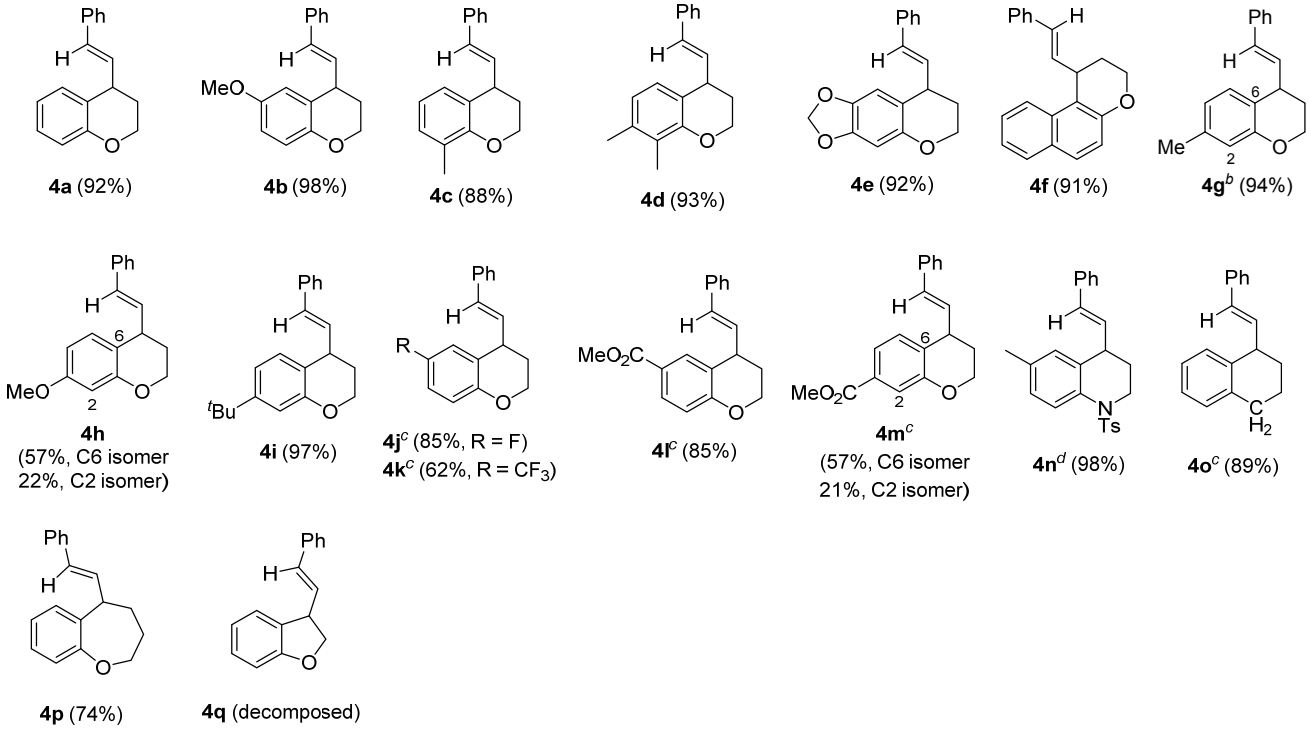




[a] Reaction conditions: substrate (0.2 mmol), $Pd(CH_3CN)_2Cl_2$ (2 mmol%) in DCE (2 mL). [b] C6 isomer∶C2 isomer=4∶1. [c] $Pd(CH_3CN)_4(BF_4)_2$ was utilized as the catalyst. [d] The reaction was carried out at 60 ℃.

Table 3 Scope and limitation of secondary allylic alcohols[a]





[a] Reaction conditions: substrate (0.2 mmol), $Pd(CH_3CN)_2Cl_2$ (2 mmol%) in DCE (2 mL). [b] C6 isomer∶C2 isomer=4∶1. [c] $Pd(CH_3CN)_4(BF_4)_2$ was utilized as the catalyst. [d] The reaction was carried out at 60 ℃.

To support our proposed mechanism, we conducted a reaction where enantiomerically enriched substrate **3o** (92% *ee*) was treated with the Pd-catalyst under the optimized conditions. Product **4o** was obtained in 87% yield with 0% *ee*, indicating that Pd-mediated C—O bond cleavage had occurred, and the resultant allylic carbocation complex had undergone a Friedel-Crafts reaction to give racemic product **4o**.

Conclusions

In summary, we have developed an efficient approach for the synthesis of structurally diverse chromanes by a Pd(II)-catalyzed intramolecular allylation reactions of unprotected allylic alcohols via an allylic carbocation intermediate. Good to excellent yields were obtained with a variety of secondary and tertiary allylic alcohols bearing electron-donating or electron-withdrawing groups. The reaction is atom-economic, environmentally benign (water is the only by-product), and does not need any additives. In view of the readily available substrates, the efficiency and the excellent regioselectivity and high yield, this method is expected to complement the current methods for chromane syntheses.

Acknowledgement

We thank the National Natural Science Foundation of China (Grant Nos. 21372016, 21572009 and 21402002), Guangdong Natural Science Foundation (Grant Nos. 2014A030312004 and 2016A030306011), Shenzhen Basic Research Program (Grant Nos. ZDSYS20140509094114168, JSGG20140717102922014, JCYJ20150629144231017, JCYJ20160226105337556 and JCYJ20160330095629781), and the Shenzhen Municipal Development and Reform Commission (Disciplinary Development Program for Chemical Biology) for financial support.

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