Palladium-Catalyzed Formal [4+2] Cycloaddition of Benzoic and Acrylic Acids with 1,3-Dienes via C-H Bond Activation: Efficient Access to 3,4-Dihydroisocoumarin and 5,6-Dihydrocoumalins

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We report a palladium-catalyzed formal intermolecular [4+2] cycloaddition of benzoic and acrylic acids with 1,3-dienes including the stock chemicals 1,3-butadiene and isoprene leading to synthetically useful 3,4-dihydroisocoumarins and 5,6-dihydrocoumalins. Stepwise C-H bond cleavage and annulation are likely involved in the reaction pathway. The synthetic potential of the methodology was demonstrated by two short derivatizations and total synthesis of natural product Clausamine B.

Keywords Palladium (II) • C-H bond activation • 1,3-diene • cycloaddition • natural product

Introduction

The 3,4-dihydroisocoumarin and 5,6-dihydrocoumalins structural motifs are common in many pharmaceuticals, natural products, and organic synthetic intermediates (Scheme 1). Many of them have a broad spectrum of biological activities (e.g., antifungal, antiallergenic, anticancer, and antimalarial).[1] Common synthesis methods use annulation of preformed o-alkenylbenzoic acid derivatives or o-halobenzoic acids that often require multistep synthesis.[2] Therefore, the applicable and simpler methods used to access these valuable molecular scaffolds from less expensive and more readily available reagents are highly desired.

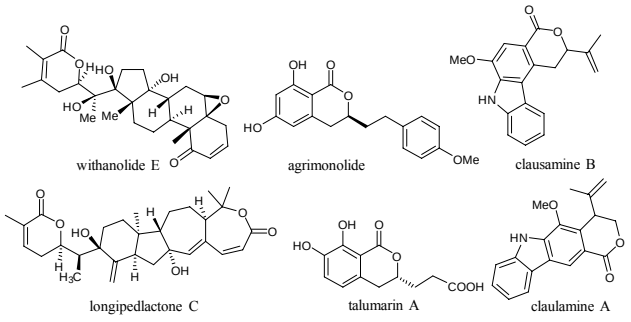

Figure 1 Representative natural products.

Due to their broad availability and versatile reactivity, the use of carboxylic acids as directing groups for C-H functionalization has been increasingly recognized and appreciated by the research community over the past decades.[3] In this context, Fujiwara–Moritani type/ lactonization reactions of benzoic and acrylic acids with alkenes and alkynes have been significantly advanced by Miura,[4] Ackermann,[5] Lee,[6] You,[7] Su,[8] and others. With proper combination of substrates, catalysts and oxidants, isocoumarin, 3-benzylidenephthalide, α-pyrone, butenolide, and phthalide derivatives could be readily accessed in a highly selective manner (Eqs 1-2). While 1,3-diene has been frequently utilized in C-H activation and functionalization,[9] the use of 1,3-diene as a cyclization partner with benzoic acid en route to 3,4-dihydroisocoumarin and 5,6-dihydrocoumalins is rare. One such example was reported by the Daugulis group regarding cobalt-catalyzed 3,4-dihydro- isocoumarin formation from benzoic acid and functionalized 1,3-dienes (Eq. 3).[10]

The 1,3-dienes and derivatives are readily available material. Specifically, 1,3-butadiene is a feedstock with an annual production scale of >10 million tons from petroleum cracking.[11] The development of efficient methods for the conversion of 1,3-butadiene to value-added fine chemicals continues to draw broad research interests due to economic and environmental benefits.[12] In our continuing efforts for selective difunctionalization of 1,3-dienes,[13] we envisioned the feasibility of a Pd-catalyzed C−H activation and cyclization between benzoic or acrylic acid and simple 1,3-dienes. Success of this hypothesis would be an alternative approach to prepare 3,4-dihydro- isocoumarin and 5,6-dihydrocoumalins.

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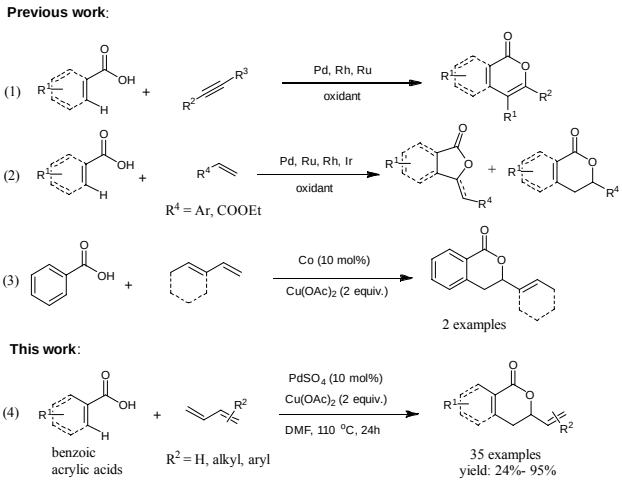
Dedicated to Professor Xiyan Lu on the Occasion of his 90th birthday



Herein, we report a palladium(II)-catalyzed formal [4+2] cycloaddition of benzoic and acrylic acids with 1,3-dienes. Under these optimized conditions, benzoic, or acrylic acids reacted efficiently with a broad range of 1,3-dienes including 1,3-butadiene and isoprene via a tandem *ortho* C-H bond activation and annulation (Eq. 4). The synthetic potential of this method was demonstrated in the total synthesis of natural product Clausamine B in just five steps.

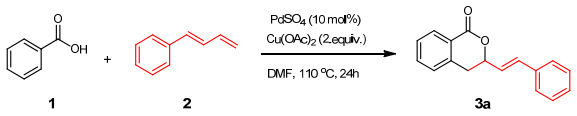
Experimental

In a glovebox, in a 10 mL tube with seal, anhydrous palladium(II) sulfate (4.1 mg, 0.02 mmol), benzoic acid (73.3 mg, 0.6 mmol), (*E*)-buta-1,3-dien-1-ylbenzene (**2b**) (26 mg, 0.2 mmol), copper acetate (72.4 mg, 0.4 mmol) were added in subsequently, then DMF (2 mL) was added. The tightly sealed tube was put in an oil bath and heated at 110 °C with stirring for 24 hours. After the full consumption of diene, the reaction mixture was diluted with ethyl acetate and the resulting suspension was filtered through a pad of silica gel using ethyl acetate as eluent. The filtrate was added to water (100 mL) and then extracted with ethyl acetate (100 mL x 3). The combined organic solution solution were washed with brine and dried with anhydrous sodium sulfate. Then filtered, evaporated in vacuum. The residue was purified by chromatography using petroleum ether/ethyl acetate (5/1) as eluent to give the desired product.

Results and Discussion

We began our studies by exploring the reaction of benzoic acid with (*E*)-buta-1,3-dien-1-ylbenzene; the representative data are summarized in Table 1. When the reaction was performed in the presence of $Pd(OAc)_2$ (5 mol%) and $Cu(OAc)_2$ (2.0 equiv.) in DMF at 110°C for 12 h, the envisioned [4+2] annulation product (*E*)-3-styrylisochroman-1-one **3a** was obtained in 26% yield (Table 1, entry 1). The reactions were catalyzed by many other Pd salts including $Pd(TFA)_2$, $PdCl_2$, $(PPh_3)_2PdCl_2$, etc., and these provided comparable results (Table 1, entries 2-5). To our surprise, an unusual $PdSO_4$ was the best catalyst of those tested,[14] and a 55% yield was observed (Table 1, entry 5). Further attempts with other solvents used for Pd(II)-catalyzed C−H functionalization reactions led to low reactivities (Table 1, entries 6-7). The optimal temperature was 110°C—higher temperatures resulted in a lower yield (Table 1, entry 8). Notably, increasing the ratio of acid over diene improved the yields (Table 1, entries 9-10). Finally, we emphasize that oxidants other than $Cu(OAc)_2$ performed less efficiently (Table 1, entries11-12).

Table 1 Optimization of the reaction conditions for the palladium (II)-catalyzed [4+2] cycloaddition.



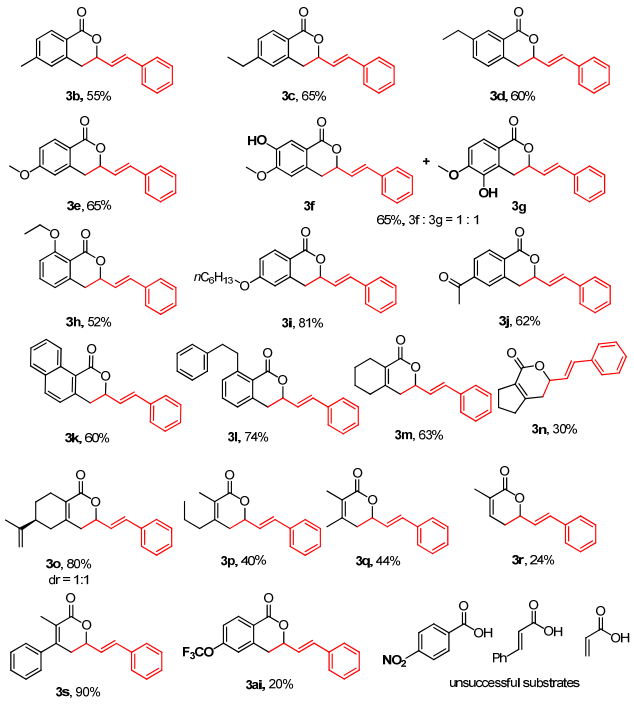
Entry[a]	Catalyst	solvent	Temp (°C)	oxidant	Yield (**3a**) [%][b]
1	$Pd(OAc)_2$	DMF	110	$Cu(OAc)_2$	26
2	$Pd(TFA)_2$	DMF	110	$Cu(OAc)_2$	30
3	$PdCl_2$	DMF	110	$Cu(OAc)_2$	27
4	$(PPh_3)_2PdCl_2$	DMF	110	$Cu(OAc)_2$	35
5	$PdSO_4$	DMF	110	$Cu(OAc)_2$	55
6	$PdSO_4$	Tol	110	$Cu(OAc)_2$	trace
7	$PdSO_4$	CH_3CN	110	$Cu(OAc)_2$	30
8	$PdSO_4$	DMF	140	$Cu(OAc)_2$	34
9[c]	$PdSO_4$	DMF	110	$Cu(OAc)_2$	52
10[d]	$PdSO_4$	DMF	110	$Cu(OAc)_2$	60
11	$PdSO_4$	DMF	110	Ag_2O	N.D.
12	$PdSO_4$	DMF	110	BQ	trace

[a]Unless otherwise noted, reaction conditions were, 1,3-diene (0.2 mmol), **1a** (2 equiv.), palladium salt (5 mol %), oxidant (2 equiv.), heated in solvent (0.2 M) at 110 °C for 24 h; [b]NMR yield using diethyl phthalate as internal standard; [c]**1**/**2** ratio was 1/1; [d]**1**/**2** ratio was 3/1

The substrate scope of the reaction was investigated using the optimized conditions (Table 1, entry 10) (Tables 2, 3). In general, the use of unsubstituted, *para*-, and *ortho*-substituted benzoic acids afforded 3,4-dihydroisocoumarins as single products. Benzoic acids with electron-donating groups (EDGs such as alkoxy, alkyl) and electron-withdrawing group (EWG such as Ac) gave comparable yields. Interestingly, the reaction of 3-ethylbenzoic acid provided mostly **3d** indicating that C−H cleavage on the benzoic acid ring selectively occurred at the less hindered *ortho* site, while **3f** and **3g** were obtained in 1/1 ratio. The reaction can be extended to other aromatic acids. For instance, 1-naphthoic acid reacted to afford **3k** in 60% yield. We were pleased to find that the reaction of 1-cyclohexene-1-carboxylic acid proceeded efficiently under standard conditions to afford a bicyclic product **3m** in 63% yield. The cyclopent-1-enecarboxylic acid

also reacted to provide the desired product **3n** albeit in relatively low yield. We also found that a naturally occurring citronellic acid was compatible under current reaction conditions, giving product **3o** in 80% yield. Besides the cyclic acrylic acid, other α-substituted acrylic acids with various combination of β-substitutions were suitable substrates as well leading to products **3p-3s** from low to excellent yields.

Table 2 Scope studies: different carboxylic acid.[a, b]

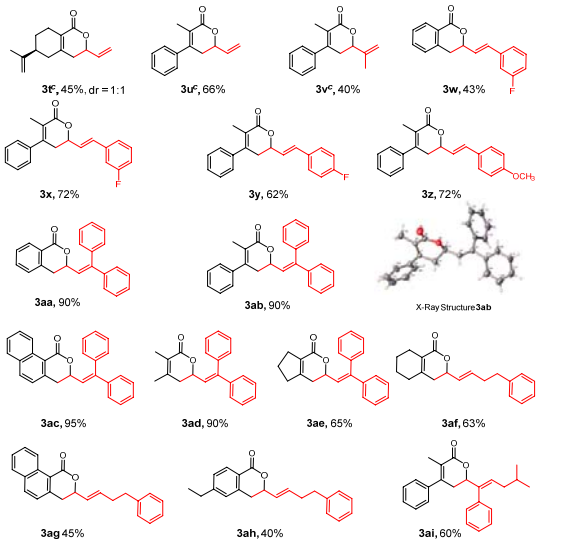


[a]the reactions were carried out under these optimized conditions (Table 1, entry 10). [b]isolated yield.

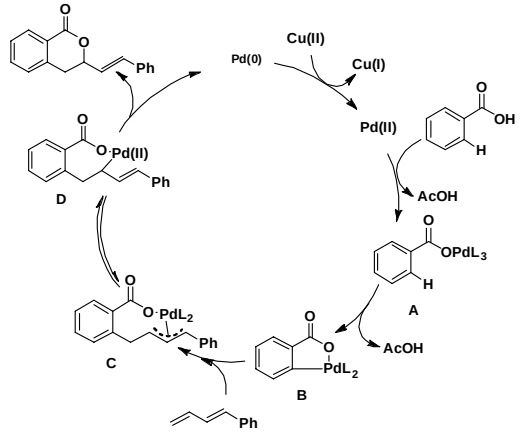
We note that the α-substitution is crucial to the success of this chemistry—neither cinnamic acid nor acrylic acid provides any product at all. In these two cases, the starting material remains intact suggesting that the rigid conformation is maintained by the α-substitution and is essential for the C-H activation. In addition, strongly electron withdrawing groups such as CF_3O and NO_2, either decreased the product yield (**3ai**) or shut down the reaction.

We then turned our attention to the variations on 1,3-diene partners. Feedstock 1,3-butadiene and isoprene were successfully engaged in this 4+2 cycloaddition with citronellic acid and (*E*)-2-methyl-3-phenylacrylic acid to give the desired products in moderate yields (**3t-3v**). Benzene on (*E*)-buta-1,3-dien-1-ylbenzene could be freely functionalized with fluoro and methoxy groups without impacting the efficiency (**3w-3z**). An even better substrate for this chemistry was buta-1,3-diene- 1,1-diyldibenzene because these reactions with four representative acids proceeded cleanly to provide the products in over 90% yields (**3aa-3ad**); moreover, a moderate 65% yield was achieved from the reaction with challenging cyclopent-1-enecarboxylic acid (**3ae**). Dienes with aliphatic substitution were coupling partners as well—the corresponding products were obtained in moderate yields (**3af-3ah**). Finally, 1,2-disubstituted 1,3-diene was applicable to the current reaction conditions indicating this protocol tolerated extra steric congestion (**3ai**).

Table 3 Scope studies: different dienes [a, b]



[a]Unless otherwise noted, the reaction was carried out under these optimized conditions (Table 1, entry 10). [b]isolated yield. [c]ratio of diene and acid is 1:1.

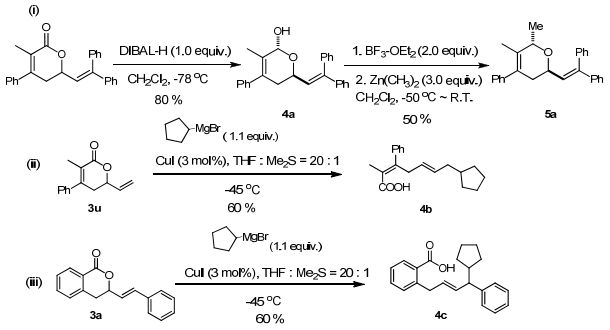


Scheme 1 Proposed catalytic cycle

According to previous studies and our observations, we propose a stepwise reaction mechanism (Scheme 1). First, heating the palladium catalyst with acid is likely to form a palladium acetate complex **A**. This can then undergo the well-known cyclometallation with *ortho* C-H bond to give palladacycle **B** and liberating one equivalent of acid.[6] Migratory insertion of the 1,3-diene **2a** with **B** can then occur to give a new palladacycle **C** containing a π-allylpalladium species in an equilibrium form.[9e] An inner sphere C–C bond-forming reductive elimination of favored **D** provides the lactone **3a** and the palladium(0) species.[9f]

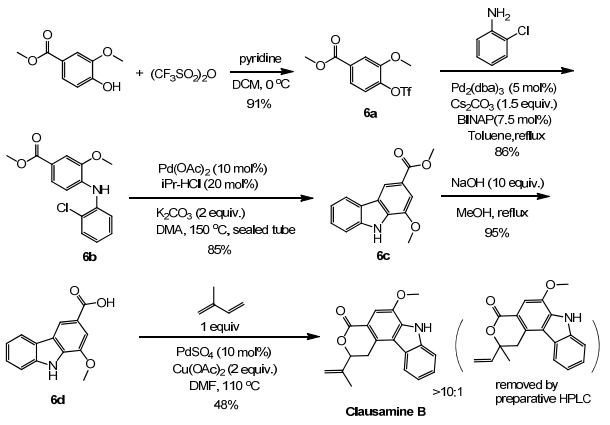
These then undergo oxidation by $Cu(OAc)_2$ to regenerate palladium(II) to initiate a new catalytic cycle.

This series of 6-allyl-5,6-dihydro-2*H*-pyran-2-ones are synthetically versatile building blocks due to the presence of several different functional groups for further elaborations (Scheme 2). For example, reduction of the ketone in **2a** produced the corresponding hemiacetal **4a** in 80% yield as a single diastereomer. Treatment of **4a** with BF_3-Et_2O followed by $Zn(Me)_2$ provided tetrasubstituted dihydropyran **5a**.[15] An S_N2' addition of organo copper(I) reagent with **3a**, **3u** at the terminal carbon of the double bond resulting in the ring opening and formal 1,4 difunctionalization of the original 1,3-butadiene.[16]



Scheme 2 Synthetic utilities of lactone products.

The total synthesis of Clausamine B was pursued to further demonstrate the potential of this methodology. Following a slightly modified known procedure, **6c** was prepared in three steps. [17] Hydrolysis of **6c** lead to the key intermediate **6d** that was applied to the standard conditions with isoprene.[18] The desired 4+2 cycloaddition occurred exclusively at the less hindered C-H site to afford Clausamine B. This synthesis featured not only significantly shortened steps [2c] but also served as an excellent starting point for accessing other natural products in this family.



Scheme 3 Total synthesis of Clausamine B

Conclusions

In conclusion, we developed a palladium(II)-catalyzed cycloaddition reaction of 1,3-dienes with both benzoic and acrylic acids to form 3,4-dihydroisocoumarin and 5,6-dihydrocoumalins in moderate to excellent yields. The synthetic potential of this protocol was demonstrated via several easy derivatizations of the products and was further showcased in the short synthesis of natural product Clausamine B.

Acknowledgement

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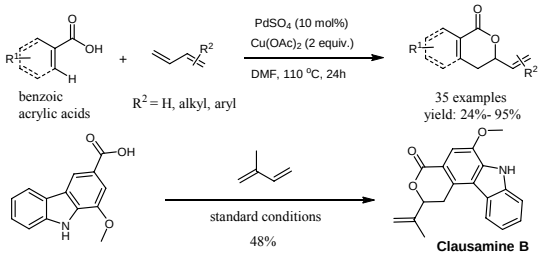

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