Direct Sequential C–O and C–C Formation via Double sp^2 C–H Bond Activations to Construct 6*H*-Benzo[*c*]chromen-6-ones

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Abstract: A new method for the direct *ortho* acyloxylation of sp^2 C–H bond with various carboxylic acids was developed. A novel strategy to synthesize 6*H*-benzo[*c*]chromen-6-one derivatives was designed via Pd-catalyzed double activations of adjacent sp^2 C–H bonds.

Key words: C–H bond activation, *ortho* acyloxylation, 6*H*-benzo[*c*]chromen-6-one

6*H*-Benzo[*c*]chromen-6-one is a common core structure existing in various natural products, as well as many pharmaceutical compounds, such as families of graphislactones and chrysomycins (Figure 1).[1] Many methods have been presented to construct such a unit by different research groups in the past.[2] Based on these previous studies and our recent work, we proposed a new strategy to synthesize this unique scaffold through direct sequential C–O and C–C formation via selective Pd(II)-catalyzed double C–H activations (Scheme 1).

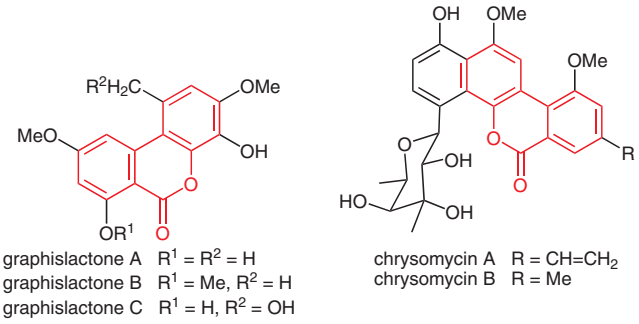
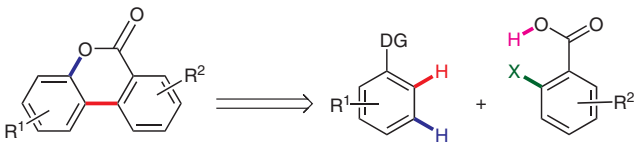


Figure 1 Natural products and pharmaceutical compounds with 6*H*-benzo[*c*]chromen-6-one as a core structure



Scheme 1 A new strategy via Pd-catalyzed double C–H activation

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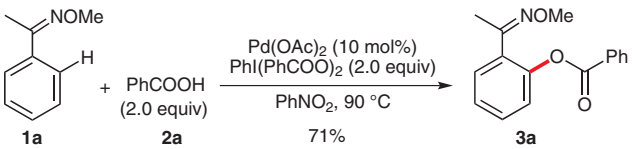
Transition-metal-catalyzed direct C–H functionalization, particularly palladium-catalyzed reactions, have been widely developed and applied in organic synthesis.[3] Among these methods, highly regioselective transformations of C–H bonds into new C–X bonds (X = Cl, O, etc.) have been reported.[4] Sanford and co-workers have reported methods on Pd-catalyzed directed acetoxylation and methoxylation of sp^2 aand sp^3 C–H bonds, as well as mechanistic investigations.[5] Yu and Cheng also reported directed *ortho* Cu-catalyzed acyloxylation of sp^2 C–H bonds.[6] From these studies, the challenge of the formation of aryl C–O from C–H with different carboxylates or carboxylic acids as nucleophiles was also addressed. Herein, we demonstrate the selective C–O formation with various carboxylic acids and subsequent C–H activation to construct 6*H*-benzo[*c*]chromen-6-one scaffolds for the first time, expanding the utility of the recent C–H activation methods in synthetic chemistry.

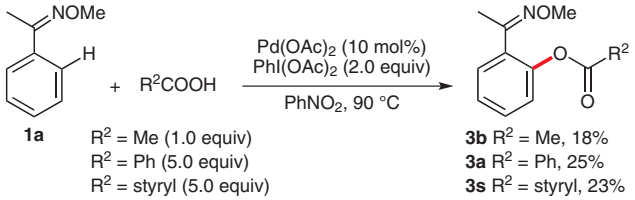
Because *O*-methyl oximyl group has been successfully applied for *ortho* acetoxylation and amination[4a,5d] and also it can be further transformed into other functional groups, we selected *O*-methyl aryloximes as the substrates. We first tested $PhI(RCO_2)_2$ as an oxidant as well as various carboxylates. We found that the reaction occurred well in the presence of two equivalents of PhCOOH (**2a**) with $PhI(PhCO_2)_2$ in $PhNO_2$ and the desired product **3a** was isolated in 71% yield (Scheme 2). We found that the reaction can be complicated and give the corresponding ester products with either the oxidant $PhI(RCO_2)_2$ or carboxylic acid used.



Scheme 2 Conditions A, with $PhI(PhCOO)_2$ as an oxidant

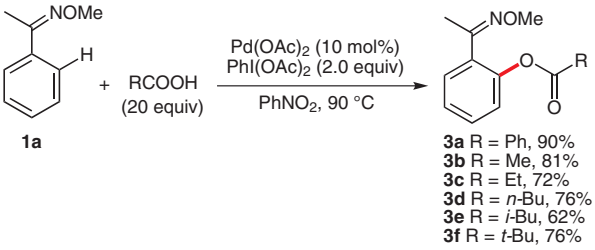
We further searched for a universal oxidant for the reaction. Many organic and inorganic oxidants were tested. Although some of them, such as $K_2S_2O_8$, showed partial activity, it was not sufficient for further application. Due to the differences in their nucleophilicities, various car-

boxylic acids were further tested under the same conditions. Equal amounts of carboxylic acids were submitted to the reaction in the presence of $PhI(OAc)_2$ as an oxidant. To our disappointment, a comparable reactivity of acetic acid, benzoic acid and cinnamic acid was observed, as monitored by GC (Scheme 3). However, the result did imply that the selectivity might be controlled by the simple increase of the ratio of different acids.



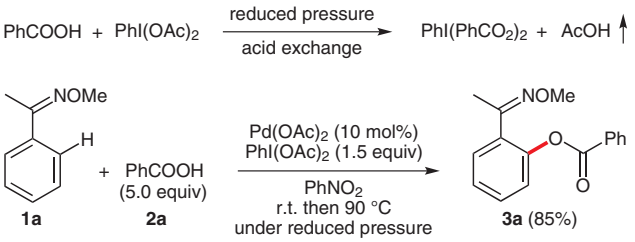
Scheme 3 Comparable reactivity of acetic acid, benzoic acid and cinnamic acid

After the systematical screening, we found that five times of benzoic acid [based on the acetate of $PhI(OAc)_2$] could suppress the *ortho* acetoxylation from acetate present in the oxidant and the designed *o*-benzoyloxylated product **3a** was obtained in 90% yield. Different aliphatic acids were tested and all the reactions showed high selectivity and efficiency, and the activity was not significantly affected by their boiling points and steric hindrance (Scheme 4). It is very important to note that this method offers an efficient approach to form different aryl C–O with simple $PhI(OAc)_2$ as the only oxidant by avoiding the side acetoxylation.



Scheme 4 Conditions B, with an excess amount of aliphatic acids

Mechanistically, an acid exchange might take place at either initiating stage with $PhI(OAc)_2$ or the last stage before reductive elimination to produce **3** with Pd complexes.[5b] We proposed that an acid exchange may occur first. Further exploration offered evidence for this assumption. $PhI(OAc)_2$ was transformed into the corresponding $PhI(RCO_2)_2$ under reduced pressure in the absence of **1a**.[7] The following steps were the same as described in Sanford's research.[5] Supposedly, after the exchange of acids, acetic acid was efficiently removed and the corresponding $PhI(RCO_2)_2$ was generated in situ (Scheme 5). Thus, we further optimized the reaction for this *ortho* acyloxylation. After stirring under reduced pressure at room temperature for one hour, the reaction mixture was heated to 90 °C for another 24 hours and the desired product was obtained in the comparable yield



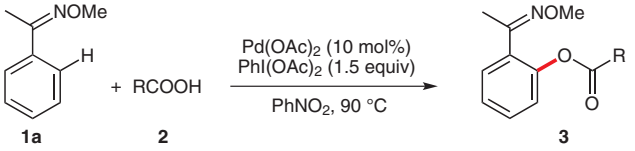
Scheme 5 Conditions C. with a lower amount of carboxylic acids and acid-exchange process under reduced pressure

(85%). Importantly, the amount of acid could be decreased to five equivalents (based on **1a**; Scheme 5).

Various carboxylic acids were further tested under the optimized conditions (Table 1). Benzoic acids bearing electron-donating groups worked well and the corresponding products **3** were obtained in good to excellent isolated yields. C–X bonds were compatible, which could be further transformed into different functionalities. However, benzoic acids bearing electron-withdrawing groups such as NO_2 and benzoyl gave lower yields. 2-Naphthalic acid and 2-furic acid also gave the corresponding products in moderate yields. It is important to note that cinnamic acid and its derivatives worked well. Obviously, this modified conditions was not suitable for short chain aliphatic acids, such as propanoic acid, due to their relatively lower boiling points. Thus, the original protocol condition B is better suited for such substrates.

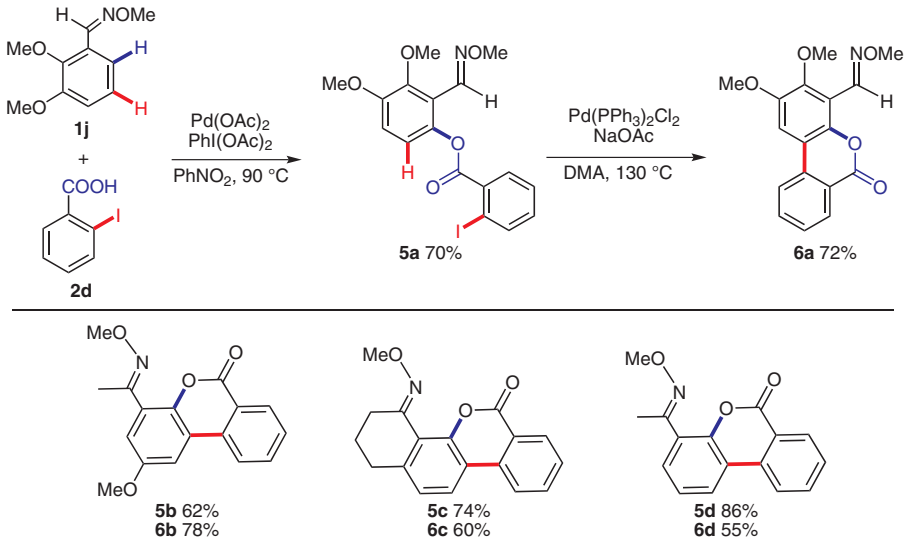
Further exploration to expand this transformation to different *O*-methyl aryl oximes was investigated (Figure 2). All the reactions were carried out in good conversions under the modified conditions. Substituted *O*-methyl ace-

Table 1 Directed *ortho* Acyloxylations of *O*-Methyl Oximes **1a**[a,b]



Entry	R	Yield (%)	Entry	R	Yield (%)
1	*p*-MeC_6H_4	**3g**, 76	9	2-naphthyl	**3o**, 55
2	*p*-$MeOC_6H_4$	**3h**, 76	10	2-furyl	**3p**, 37
3	*o*-IC_6H_4	**3i**, 86	11	Bn	**3q**, 61
4	*o*-BrC_6H_4	**3j**, 78	12	$PhCH_2CH_2$	**3r**, 66
5	*o*-ClC_6H_4	**3k**, 66	13	styryl	**3s**, 86
6	*o*-BzC_6H_4	**3l**, 50	14	4′-MeO-styryl	**3t**, 69
7	*m*-$NO_2C_6H_4$	**3m**, 39	15	3′-MeO-styryl	**3u**, 73
8	*m*-NO_2-*p*-$MeOC_6H_4$	**3n**, 57	16	4′-Me-styryl	**3v**, 74

[a] Reaction conditions: **1a** (0.2 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), and $PhI(OAc)_2$ (0.3 mmol) in $PhNO_2$ (3 mL), r.t., 1 h, then 90 °C, reduced pressure, for an appropriate time.
[b] Isolated yields.



Scheme 6 Double C–H activation towards 6*H*-benzo[*c*]chromen-6-one; DMA = *N*, *N*-dimethylacetamide

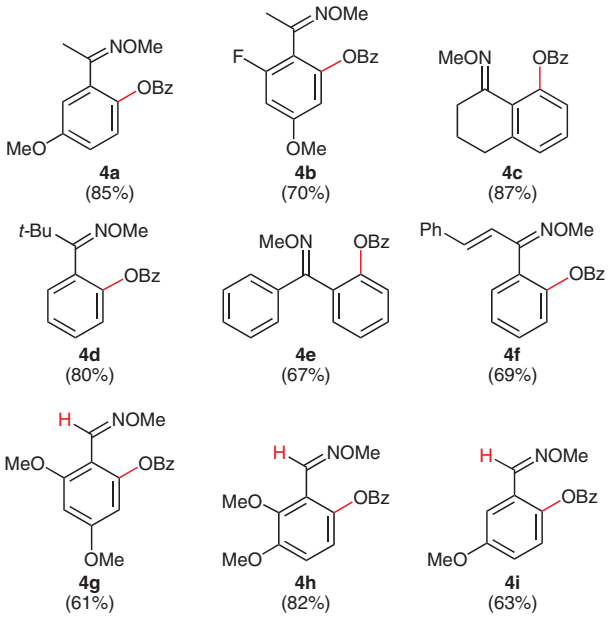


Figure 2 Directed *ortho* benzoyloxylation of various *O*-methyl oximes; all the reactions were carried out on a 0.2 mmol scale under conditions C and isolated yields are reported

tophenone oximes gave *ortho* benzoyloxylation products in good yields. Different groups such as, *tert*-butyl, phenyl and styryl could survive well, as well as cyclic aryl oximes derived from 1-tetralone. Furthermore, the *O*-methyl benzaldoximes bearing electron-donating groups on the aromatic ring also worked well providing good yields.

Our attention was further drawn back to the original design to construct 6*H*-benzo[*c*]chromen-6-one. *o*-Iodobenzoic acid was selected to undergo the acyloxylation reaction in high efficiency. After that, further C–C formation was developed to obtain the designed product in an excellent efficiency via second Pd-catalyzed C–H activation, which is a well-studied Pd-catalyzed cross-coupling of C–H with C–X bond.[8] With this strategy, various 6*H*-benzo[*c*]chromen-6-one derivatives **6a–d** were obtained in moderate to good yields (Scheme 6). Further efforts to apply this method to natural product synthesis are still underway.

In conclusion, we have developed a novel method for the direct *ortho* acyloxylation of sp^2 C–H bond with various carboxylic acids. A new strategy to synthesize 6*H*-benzo[*c*]chromen-6-one derivatives was further developed via highly selective sequential Pd-catalyzed double activations of sp^2 C–H bond.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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