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Formal Carbene Insertion into C-O or C-N Bond: An Efficient Strategy for the Synthesis of 2-Substituted 2*H*-Chromene Derivatives from Chromene Acetals or Hemiaminal Ethers

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Abstract: We report the palladium/Brønsted acid co-catalyzed formal insertion of carbene into the C-O or C-N bond of 2*H*-chromene acetals or hemiaminal ethers. This transformation was initiated by the Brønsted acid-promoted cleavage of the C-O or C-N bond, followed by modification of the leaving alcohol or amino fragments with palladium carbenes, and reassembly of the modified fragments. A variety of C-2 functionalized 2*H*-chromene derivatives were obtained in moderate yield (43~73%) with good to excellent diastereoselectivities (up to >95:5 dr) under mild conditions.

Keywords: Metal carbenes; Formal insertions; Multicomponent reactions; Synergistic catalysis; 2*H*-Chromenes

2-Substituted 2*H*-chromenes (2*H*-1-benzopyran derivatives) are among the most prevalent structural moieties present in a vast number of natural products, pharmaceuticals, and materials.[1] For example, natural products gaudichaudianic acid[2] and (+)-myristinin **A**[3] indicated antifungal activities and inhibition of DNA polymerase **B**, respectively; while drug candidate acolbifene[4] is a nonsteroidal selective estrogen receptor modulator (SERM) for the treatment of breast cancer, and iclaprim[5] is an investigational broad-spectrum antibiotic for the treatment of acute bacterial skin and skin structure infections, both in phase III clinical trials. Additionally, 2*H*-chromene analogs are also employed as photochromic materials and precursors to flavylium dyes for solar cells and optical memories.[6] Therefore, a facile synthetic method to access these privileged structures would be attractive.

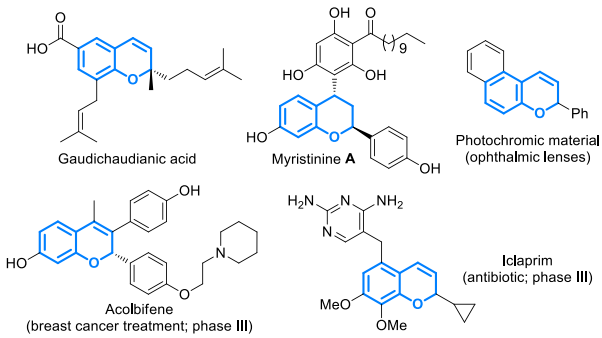

Figure 1. Selected examples of naturally occurring, biologically active, and photochromic 2*H*-chromene derivatives.

Considerable efforts have been made to provide 2-substituted 2*H*-chromenes over the past decades (Scheme 1). The traditional protocols involve construction of benzopyran structure from phenol or salicylaldehyde derivatives by annulations (Scheme 1, a).[7] These synthetic methods typically require multistep manipulations of complicated prefunctionalized substrates, and thus lack the flexibility for the synthesis of C-2 derivatives. As an alternative strategy towards late-stage C-2 modification, nucleophilic substitution of chromene acetals, prepared from readily available coumarins, allows for the facile synthesis of C-2 functionalized 2*H*-chromenes (Scheme 1, b).[8-10] These transformations generally proceed through in situ generation of oxocarbenium ion by elimination of an alkoxyl fragment under the promotion of Lewis acids[8] or Brønsted acids,[9] or through a transition-metal catalyzed process.[10] The nucleophilic species include enamines,[7a] organoboron reagents,[8b-c] organoindium reagents,[8e] alkynyl copper intermediates,[8f-h] and Grignard reagents.[11] However, many of reported examples need harsh conditions, and for all of these methods, the leaving alkoxyl fragment is abandoned as waste. Therefore, the development of more efficient and green solution to offer structurally diverse C-2 functionalized 2*H*-chromenes would be certainly in demand.

Recently, we reported a novel co-catalyzed process[12] that proceeded through the C-N bond cleavage of β-arylamino iminium promoted by Brønsted acid, subsequent modification of the leaving amino fragment with metal carbene[13] to form a transient ammonium ylide intermediate, and selective reunion of two reactive intermediates to give trapping products (Scheme 1, c).[14-15] Huang *et al* also developed a similarly efficient process involving

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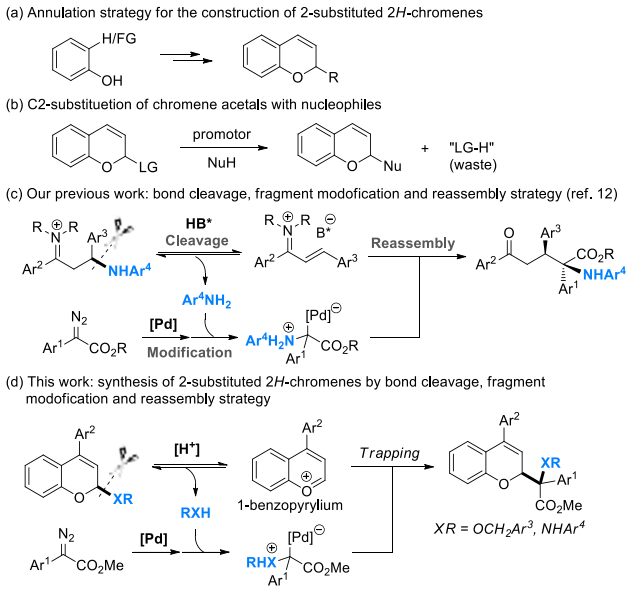
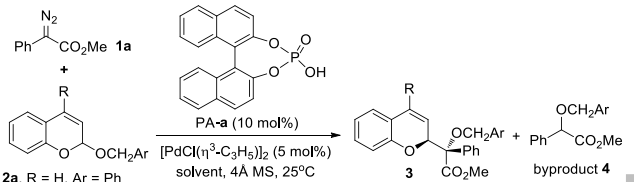


Scheme 1. Synthetic strategy for the synthesis of 2*H*-chromene

the palladium-catalyzed formal C-N insertion of carbenes into aminals.[16] In this unique process, metal carbenes were successfully incorporated into C-N bond via a sequence of bond cleavage/fragment modifications/reassembly. Encouraged by this success, we expected to apply this strategy to the reaction of diazo esters and chromene acetals/hemiaminal ethers for the synthesis of 2-substituted 2*H*-chromenes (Scheme 1, d). It was envisioned that Brønsted acid-induced reversible cleavage of C-O or C-N bond of chromene acetals/hemiaminal ethers could lead to electrophilic 1-benzopyrylium ions as well as free alcohols/ amines. Subsequent modification of the alcohols/ amines with diazo compounds would form nucleophilic oxonium or ammonium ylide intermediates, which were trapped by the pre-formed 1-benzopyrylium intermediates to afford 2-substituted 2*H*-chromenes. Herein, we report the couplings of diazo compounds and 2*H*-chromene acetals/hemiaminal ethers under palladium/Brønsted acid co-catalysis for the synthesis of valuable 2-substituted 2*H*-chromene derivatives. Notably, compared with traditional nucleophilic substitution of chromene acetals,[8-10] in this transformation, alcohol or amine fragments serve not only as a leaving group but also a serviceable component to generate ylide nucleophiles, greatly improving the atom economy.

In initial efforts to implement this proposed C-X bond cleavage/fragment modification/reassembly sequence in the reaction of chromene derivatives and diazo compounds, 2-benzyl-2*H*-coumarin (**2a**) was treated with methyl α-diazo phenylacetate (**1a**) in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and Brønsted acid **PA-a**.[12,14f] Unfortunately, the acetal **2a** was not able to be activated under this condition and therefore no desired product was detected (table 1, entry 1). Similar results were observed even with trifluoromethanesulfonic acid (TfOH), a stronger Brønsted acid (entry 2). The failure of reaction may result from the low stability of the resulting 1-benzopyrylium ion. To facilitate the formation of 1-benzopyrylium ion, an electron-donating *p*-methoxyphenyl (PMP) was introduced at C-4 position of the chromene acetal (**2b**) to stabilize the cation. As a result, the reaction provided desired **3b** in a yield of 49% with 55:45 dr (entry 3). To enhance the diastereoselectivity, a bulky 9-anthryl was set to the chromene acetal (**2c**), and a remarkably improved dr (>95:5) was obtained along with moderate yield of 58% (entry 4). In this reaction, a competing O-H insertion of alcohol and **1a** is the major side reaction, leading to the O-H insertion side product **4** and the decrease in the yield. Screening of solvents (entries 5-9) found that $CHCl_3$ increased the yield to 66% and kept dr value excellent. Another Brønsted acid, *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O), was also effective, but resulted in a decreased yield of 55% (entry 10). Additionally, in the absence of Brønsted acid, **2c** was recovered, indicating the key role of Brønsted acid in the cleavage of C-O bond (entry 11).

Table 1. Optimization of reaction conditions for the reaction of chromene acetal and diazo compounds.[a]



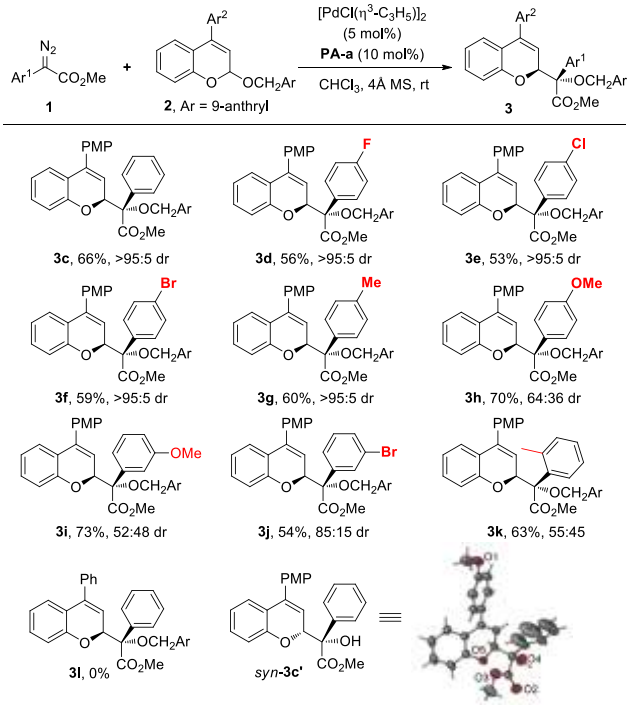
entry	**2**	solvent	Yield of **3**/% [b]	dr[c] of **3**
1	**2a**	DCM	0[d]	/
2[e]	**2a**	DCM	0[d]	/
3	**2b**	DCM	49	55:45
4	**2c**	DCM	58	>95:5
5	**2c**	$(CH_2Cl)_2$	52	>95:5
6	**2c**	$CHCl_3$	66	>95:5
7	**2c**	toluene	43	>95:5
8	**2c**	THF	36	>95:5
9	**2c**	Et_2O	31	>95:5
10[f]	**2c**	$CHCl_3$	55	>95:5
11[g]	**2c**	$CHCl_3$	0[d]	/
12[h]	**2c**	$CHCl_3$	0[i]	/

[a] $[PdCl(\eta^3\text{-}C_3H_5)]_2$/**PA-a**/**1**/**2** = 0.05:0.1:1.5:1.0. [b] Isolated yield. [c] Determined by ^{1}H MMR. [d] Acetal **2a** recovered. [e] TfOH was used instead of **PA-a**. [f] *p*-TsOH·H_2O was used instead of PA-**a**. [g] In the absence of PA-**a**. [h] In the absence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$. [i] **2a** didn't decompose.

Having established the optimal reaction conditions for the formal C-O insertion, we then evaluated the substrate scope of this transformation (Table 2). Diazo compounds with less bulky substituents, such as H, F, Cl, Br and Me, at *para*-position of phenyl ring, provided desired products **3c**–**3g** in moderate yields with excellent diastereoselectivies (> 95:5 dr), while those with a MeO at *para* or *meta*-position of phenyl ring were also tolerated and provided **3g** and **3i** in the yield of 69% and 73%, respectively, but

resulted in dramatically decreased dr. Replacing the *meta*-MeO with a less bulky Br improved the dr to 85:15 (**3j**), while an ortho-Me would again result in significant decrease of dr value (**3k**). The decrease of dr value may result from the steric hindrance between bulky substituent on aryl groups of diazo compounds and extremely bulky 9-anthryl, although the bulky 9-anthryl was the key to improving dr in condition optimizations. In the case of Ph on C-4 of chromene ring, no desired **3l** was obtained, with the corresponding acetal recovered. The structures of products were confirmed and the relative configuration was determined to be *anti* on the basis of X-ray single-crystal analysis of *syn*-**3c**',[17] the diastereoisomer of free hydroxyl derivative of **3c**.[18]

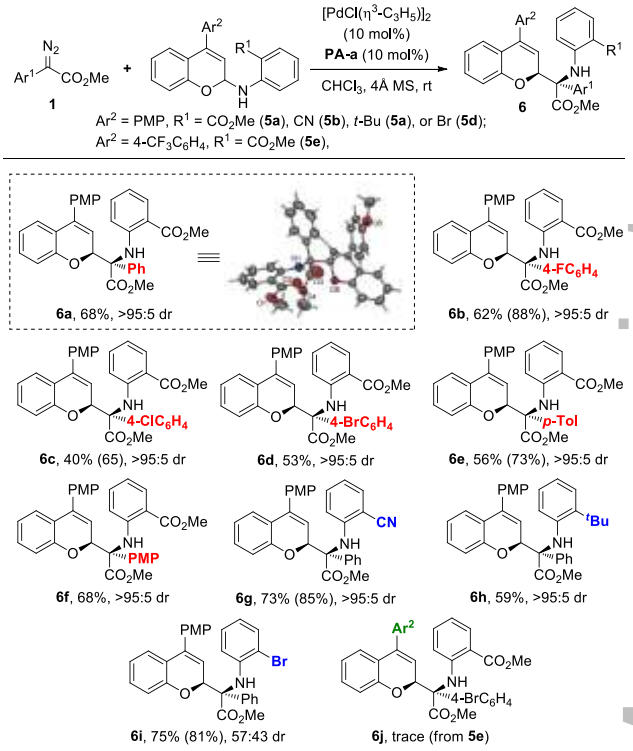
Table 2. Substrate Scope for the reaction of chromene acetals and diazo compounds [a,b,c]



[a] [PdCl(η^3-C_3H_5)]$_2$/**PA-a**/**1**/**2** = 0.05:0.1:1.5:1.0. [b] Isolated yields. [c] Dr was determined by ^{1}H MMR.

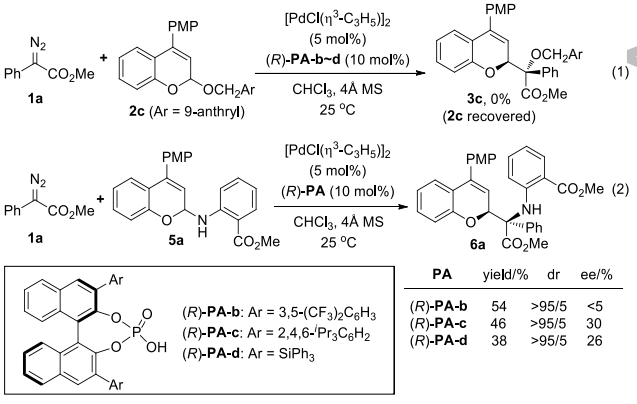
We then extended the substrates to include chromene hemiaminal ethers under the conditions used for chromene acetals (Table 3). With respect to diazo compounds, a halogen atom, Me, or MeO on *para*-position of phenyl ring are tolerated and the desired products **6a-6f** were obtained in yield of 40-68% with excellent diastereoselectivities (>95:5 dr). As for the arylamino moieties in hemiaminal ethers, for, a CO_2Me, CN, or *t*-Bu on *ortho*- position of phenyl rings is essential for high diastereoselectivities, while an *ortho*-Br led to a dramatic drop in dr value. For the chromene ring, substrate with a *p*-$CF_3C_6H_4$ rather than PMP on C-4 position only gave trace of product. Similarly, the major side reaction was [1,2]-H shift of ammonium ylides, which would diminish the yield of desired process. In view of this, the yields of products (**6b**, **6c**, **6e**, **6g**, and **6i**) could be enhanced by the use of corresponding aniline (1.0 equivalent) as an extra reaction component. Finally, X-ray single-crystal analysis of **6a** confirmed the structure and revealed the relative configuration as *syn*,[17] which was opposite to that of alkoxy counterparts **3**.[19]

Table 3. Substrate Scope for the reaction of chromene hemiaminal ethers with diazo compounds.[a,b,c]



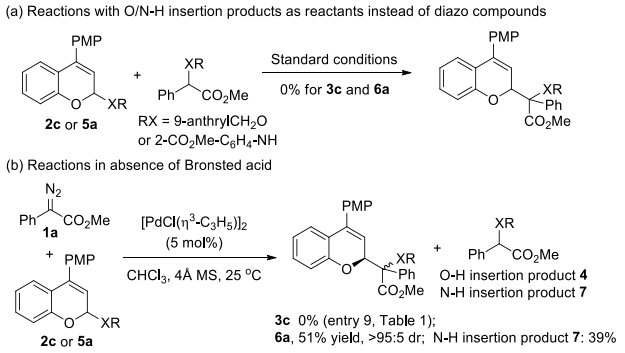
[a] [PdCl(η^3-C_3H_5)]$_2$/**PA-a**/**1**/**5** = 0.05:0.1:1.5:1.0. [b] Isolated yields. [c] dr was determined by ^{1}H MMR.

We also investigated the asymmetric fashion of this reaction by chiral phosphoric acids (*R*)-**PA-b~d**. For the reaction of **1a** and acetal **2c**, the bulky chiral catalysts were not effective to promote the cleavage of C-O (Scheme 3, eq 1). On the other hand, when using **5a** as substrate, the desired product **6a** was obtained in 38-54% yield, with a highest ee of 30% (Scheme 3, eq 2). Asymmetric addition to oxocarbenium ion by chiral anionic catalysis remains a great challenge to explore.

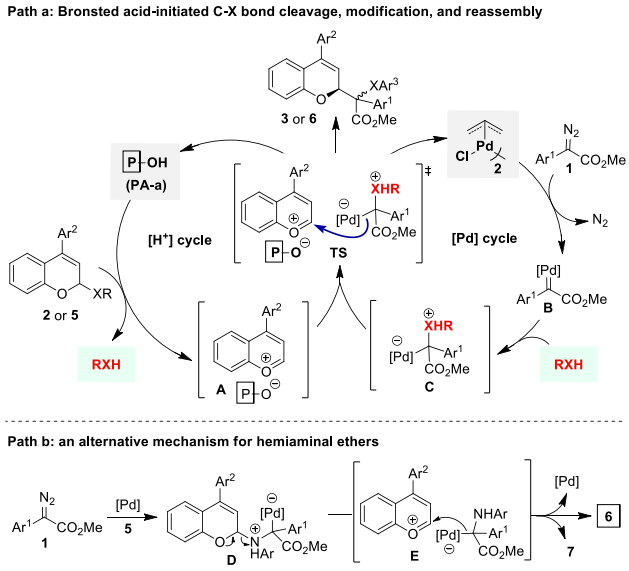


Scheme 2. Preliminary studies of asymmetric reactions.

To get insight into the reaction pathways, we designed the following control reactions (Scheme 4). First, treating **2c** or **5a** with corresponding X-H insertion product under the standard conditions gave no detectable desired products **3c** or **6a**, ruling out the pathway via O-H or N-H insertion products (Scheme 3a). Subsequently, to understand the role of Brønsted acid in the progress of reaction, we carried out control reactions in absence of Brønsted acid (Scheme 3b). For the chromene acetal, **2c** was not activated (Table 1, entry 11), demonstrating the decisive role of **PA-a** in the cleavage of C-O bond. This observation as well as the formation of O-H insertion side product **4** under standard conditions ruled out the Stevens [1,2]-carbon shift[20] process. On the other hand, chromene hemiaminal ether **5a** offered **6a** in 51% yield, along with N-H insertion product **7** in yield of 39% in the absence of **PA-a**, suggesting that hemiaminal ether substrates could directly react with carbenes to give the formal C-N insertion product and a stepwise C-N bond cleavage before the C-C bond formation. Considering the fact that chromene hemiaminal ether could rapid decompose in minutes under the standard conditions, the designed C-N bond cleavage/arylamino fragment modification/ reassembly sequence is still reasonable.



Scheme 3. Control reactions.



Scheme 4. Proposed mechanisms of the title reactions.

According to the experimental results, we proposed a C-X bond cleavage/fragment modification/ reassembly mechanism (Scheme 4). For chromene acetals and hemiaminal ethers, the C-X bond cleavage/fragment modification/reassembly sequence (path a), the C-O was cleaved under the activation of phosphoric acid to form a 1-benzopyrylium ion **A** and a leaving alcohol species, which reacted with palladium carbene **B** generated from palladium-catalyzed decomposition of diazo compound **1** to give an active oxonium ylide **C**. The coupling of the two reactive intermediates, 1-benzopyrylium ion **A** and ylide **C**, provided the assembled products **3**. On the other hand, chromene hemiaminal ethers **5** could undergo a reaction pathway similar to that of 2 (path a). However, an alternative process was also possible based on the phenomenon that 5 could also directly react with carbene B without Brønsted acid. This pathway proceeded through the formation of ammonium ylide **D** from palladium **B** and substrate **5**, followed by cleavage of C-N bond of ylide **D**, and reunion of the two fragments (path b).

In conclusion, we have developed an efficient strategy involving C-X (X = O, N) bond cleavage/fragment modification/reassembly sequence for the reaction of diazo compounds with chromene acetals/hemiaminal ethers to achieve selective formal C-X insertions. This reaction delivers valuable chromene derivatives in moderate yields with moderate to excellent diastereoselectivities in a single step under mind reaction conditions. This cleavage-modification-reassembly process also provides a new strategy for highly selective C-X (X = O, N) insertions.

Experimental Section

Experimental Details: to an oven-dried test tube with a stirring bar were added chromene acetal or hemiaminal ethers (0.2 mmol, 1.0 equiv.), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.01 mol, 3.7 mg, 5.0 mol%), racemic Brønsted acid **PA-a** (0.02 mmol, 7.0 mg, 10 mol%) and 4Å molecular sieve (300 mg), and then the vessel was capped by a septum for injection. Anhydrous $CHCl_3$ (1.5 mL) was added, and the mixture was stirred at 25 °C. Subsequently, diazoester **1** (0.3 mmol, 53 mg, 1.5 equiv) in 1 mL $CHCl_3$ was added during 1 h *via* a syringe pump. Upon completion of the addition, the mixture was stirred in another 5 min. The reaction mixture was filtered and the filtrate was concentrated to give a residue which was subjected to ^1H NMR spectroscopy analysis for the determination of dr value. Purification of the crude products by flash chromatography on silica gel (eluent: EtOAc/petroleum ether/DCM = 1:50:1~1:10:1) afforded pure products *anti*-**3** or *syn*-**6**, in the yields shown in Table 2 and Table 3.

Acknowledgements

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[17] CCDC-1479361 and CCDC-1469821 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] For details, see the Supporting Information.

[19] For a comment on the possible reason for the opposite diastereoselectivity observed between the acetal case and the aminal case, see the Supporting Information.

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COMMUNICATION

Formal Carbene Insertion into C-O or C-N Bond: an Efficient Strategy for Synthesis of 2-Substituted 2*H*-Chromene Derivatives from Chromene Acetals or Hemiaminal Ethers

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