DOI: 10.1002/adsc.201200539

Regioselective Cleavage of Unstrained C–C Bond and C–H Bond: Palladium–Copper Catalyzed Deacetophenonylative Arylation of Coumarin Derivatives

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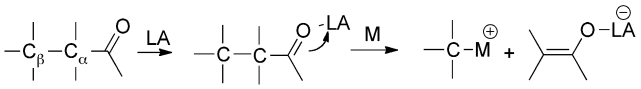
Received: June 19, 2012; Revised: October 10, 2012; Published online: November 28, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200539.

Abstract: A C_α–C_β bond activation of the carbonyl group in unstrained ketones catalyzed cooperatively by palladium and copper(II) with the departure of the acetophenone has been developed, and the subsequent coupling with a variety of aromatics *via* the formal C–H activation similar to the Friedel–Crafts reaction affords the skeleton-reconstructed coumarin derivatives with high regioselectivity.

Keywords: C–C bond cleavage; copper; coumarins; palladium

The selective C–H activation approach, due to its sustainable and environmentally benign features, has received substantial attention and success.[1] Selective catalytic activation of the inert carbon-carbon bond, owing to its fundamental scientific interest and synthetic importance, has also received the increasing attention of chemists, while it remains an ongoing challenge due to the inherent strength of the C–C bond.[2] Of the systems developed thus far, two approaches of C–C single bond cleavage are oxidative addition[3] and β-carbon elimination,[4] and most of them have benefitted from special driving forces, such as the ring strain,[5] the chelation[6] and the departure of small molecules.[7] The heterolysis of the C_α–$C_{C=O}$ bond in strained ketones[8] and unstrained ketones with a chelating group[9] or without[10] is known to be reasonable. On the other hand, the cleavage of the C_α–C_β bond in unstrained ketones is considered to be extraordinarily difficult, and only a handful of similar C_α–C_β bond fractures was achieved by hydrogenolysis.[11] To the best of our knowledge, no example of the fragmentation of the C_α–C_β bond *via* transition metal catalysis to cleave acetophenone has been reported, although photolysis with cleavage of acetophenone was known[12]. The Lewis acids (LA), that are assumed to activate electrophilic centers, may play a key role in the activation of the C–C bond, and the addition of Lewis acids may further induce the potential of transition metal catalysis[2a,5d,13] (Scheme 1).



Scheme 1. Activation of the C_α–C_β bond of the carbonyl group catalyzed by a transition metal and an LA cooperatively.

Coumarin derivatives are of great importance because of their physiological, photodynamic, anticoagulant, spasmolytic, bacteriostatic, antibiotic, antifungal and rodenticidal activities,[14] for example, warfarin **A** and the warfarin derivative **B** used as antithrombotic drugs (Figure 1). Some hydroxycoumarin derivatives have been reported to possess biological activities similar to those of R-glucosidase inhibitors.[15] Additionally, chromenes are very common in nature, and some chromene skeletons have also elicited pharmaceutical interest as structural elements in drug-like

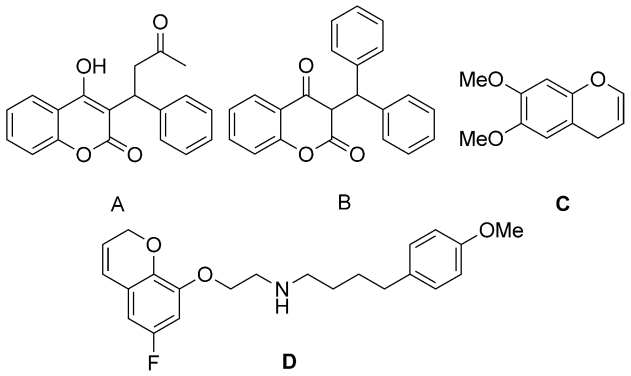
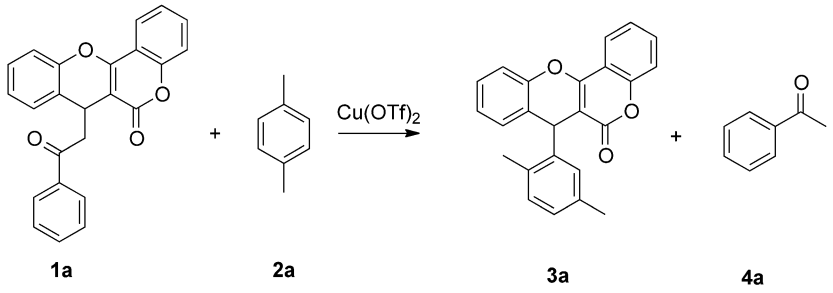


Figure 1. The active coumarin and chromene derivatives.



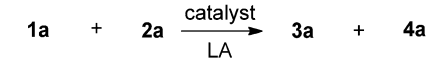
Scheme 2. A new coumarin derivative was obtained.

compounds,[16] such as the 6,7-dimethoxy-4*H*-chromene **C** isolated from the plant *Wisteria sinensis* and the 2*H*-chromene derivative **D** which exhibits the highest 5-HT_{1A} receptor affinity (Figure 1). Therefore, it is interesting to prepare and evolve the chromene-fused coumarin compounds.

In the course of our study on modifying the structures of coumarin derivatives, we accidentally discovered an interesting fragmentation of the C_α–C_β bond near the carbonyl group promoted by a catalytic system comprised of a transition metal and a Lewis acid. After treatment of 7-(2-oxo-2-phenylethyl)chromeno[4,3-*b*]chromen-6(7*H*)-one (**1a**) in *p*-xylene (**2a**) in the presence of $Cu(OTf)_2$ as catalyst at 140 °C for 16 h, to our surprise, a new coumarin derivative (**3a**) was isolated in 27% yield. After the structure had been characterized, it was realized that the C_α–C_β bond near the carbonyl group was cut and a new C–C bond with *p*-xylene was formed as shown in Scheme 2. There have been few reports on new C–C bond formation *via* C–H activation after C–C bond cleavage, but most were limited to C–X bond activation[10,17].

Then various reaction conditions were studied to help to understand the details of the reaction (Table 1). Firstly, different Lewis acids were used to promote the reaction, however, no product was detected, no matter whether a weak salt like $Cu(OAc)_2$ or a strong Lewis acid like $FeCl_3$ was used (Table 1, entries 2 and3). When stoichiometric $Cu(OTf)_2$ was used, the yield changed slightly (Table 1, entry 4). Then several transition metal catalysts such as $Pd(OAc)_2$, $PdCl_2$, $Pd(dppf)Cl_2$ and $Ru(cod)_2Cl_2$ were employed. Excitingly, the yields were greatly improved, ranging from 48% to 63%, and $PdCl_2$ gave the best result (Table 1, entries 5–8). Further screening showed that the optimized reaction conditions were to carry out the reaction at 140 °C using both $PdCl_2$ and $Cu(OTf)_2$ as catalysts, in which the $PdCl_2$ may play a key role. Generally, the C–C bond cleavage by the way of oxidative addition is often promoted by rhodium complexes, whereas catalysis by palladium complexes is rare[5e].

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	LA	T [°C]	Yield [%][b]
1	–	$Cu(OTf)_2$	140	27
2	–	$Cu(OAc)_2$	140	0
3	–	$FeCl_3$	140	0
4[c]	–	$Cu(OTf)_2$	140	25
5	$Pd(OAc)_2$	$Cu(OTf)_2$	140	52
6	**$PdCl_2$**	**$Cu(OTf)_2$**	**140**	**63**
7	$Pd(dppf)Cl_2$	$Cu(OTf)_2$	140	53
8	$Ru(cod)_2Cl_2$	$Cu(OTf)_2$	140	48
9	$PdCl_2$	$Cu(OTf)_2$	120	19
10	$PdCl_2$	$Cu(OTf)_2$	150	59

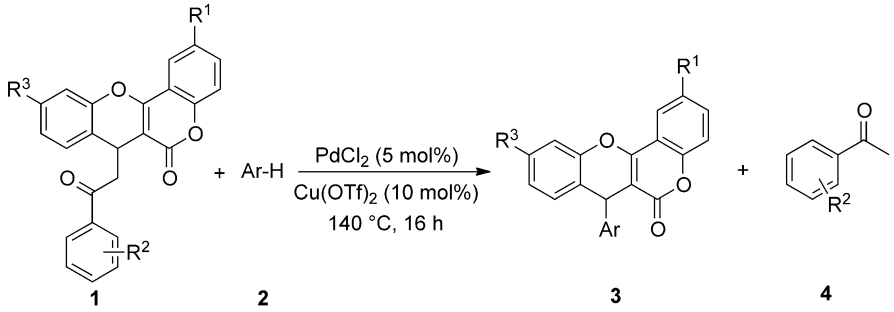
[a] *Reaction conditions:* catalyst (0.01 mmol), LA (0.02 mmol) and substrate **1a** (0.2 mmol) in *p*-xylene (2.0 mL) for 16 h.
[b] Yield of isolated product.
[c] Stoichiometric $Cu(OTf)_2$ was used.

With the optimal conditions in hand, a series of coumarin derivatives and different aromatics were subjected to this C–C cleavage and coupling reaction (Table 2). Firstly, a variety of aromatics was examined. Obviously the reaction depends mainly on the electronic effects, and aromatics with high electron density such as **2a**, **2b**, **2d**, **2f**, **2h** and **2i**, reacted well (Table 2, entries 1, 2, 4, 6, 8–10); with low electron density such as **2c**, **2e** and **2g**, did not work so well (Table 2, entries 3, 5 and 7). However, chlorobenzene and *N*,*N*-dimethylaniline both failed to furnish the corresponding products, maybe the chlorobenzene was not active enough and the *N*,*N*-dimethylaniline reacted with itself[18] (Table 2, entries 11 and 12). The molecular structure of **3i** was unambiguously elucidated by X-ray crystallography (Figure 2). Interestingly, when **1a** reacted with the substrate **2h**, the unexpected single product **3g** or **3h** could be obtained in moderate yield by controlling the amount of $Cu(OTf)_2$ and the temperature (Table 2, entries 8 and 9). Then various coumarin derivatives with functional groups such as CH_3 (R^1), OMe, C_6H_5 (R^2) and CH_3, Cl (R^3) were ex-

amined and moderate yields were obtained (Table 2, entries 13–18).

However, when benzene (**2l**) was heated with **1a** in a sealed tube, the reaction only gave the simple cleaved product **5a** and acetophenone in 34% yield together with the recovered substrates (reaction i, Scheme 3). On the other hand **5a** could couple with diphenyl ether to give corresponding product **3f** in

Table 2. Synthesis of coumarin derivatives by C–C bond and C–H bond activation.[a]



1 2 3 4

Entry	1	2	3	Yield [%][b]
1	**1a**	**2a**	**3a**	63
2		**2b**	**3b**	70
3[c]		**2c**	**3c** (91 : 9)	45
4		**2d**	**3d**	80
5		**2e**	**3e**	30

Table 2. (Continued)

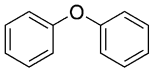
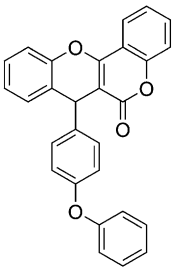
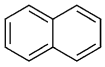
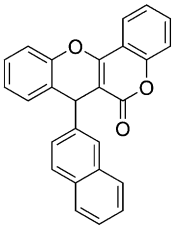
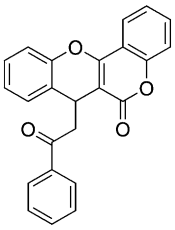
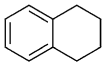
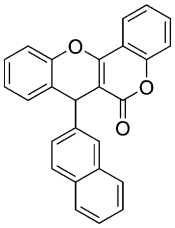
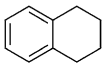
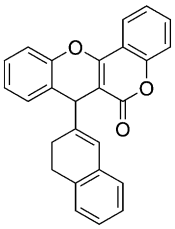
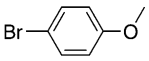
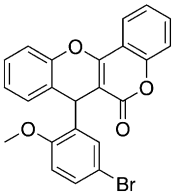
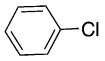
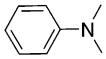
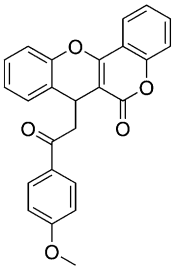
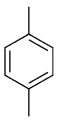
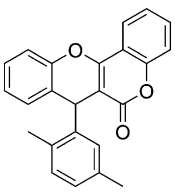
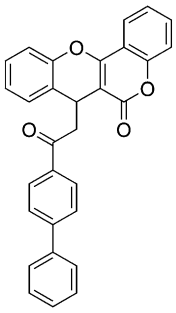
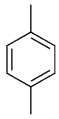
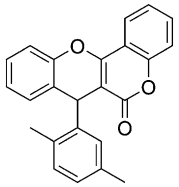
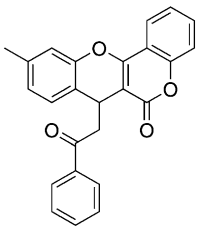
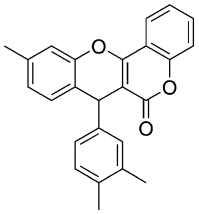
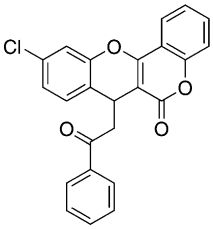
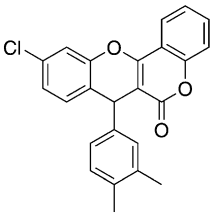
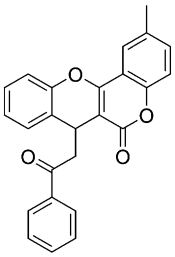
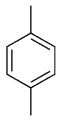
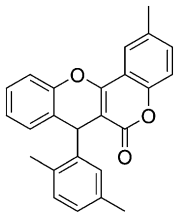
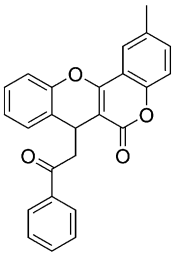
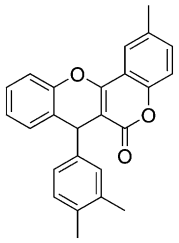
Entry	1	2	3	Yield [%][b]
6		**2f** 	**3f** 	85
7		**2g** 	**3g** 	38
8		**2h** 	**3g** 	65
9[d]		**2h** 	**3h** 	55
10		**2i** 	**3i** 	81
11		**2j** 	–	–
12		**2k** 	–	–
13	**1b** 	**2a** 	**3a** 	51

Table 2. (Continued)

Entry	1	2	3	Yield [%][b]
14	**1c** 	**2a** 	**3a** 	42
15	**1d** 	**2b** 	**3j** 	65
16	**1e** 	**2b** 	**3k** 	76
17	**1f** 	**2a** 	**3l** 	61
18	**1f** 	**2b** 	**3m** 	64

[a] *Reaction conditions:* $PdCl_2$ (0.01 mmol), $Cu(OTf)_2$ (0.02 mmol) and substrate **1** (0.2 mmol) in **2** (2.0 mL or 10 mmol) at 140 °C for 16 h.
[b] Yield of isolated product.
[c] $Cu(OTf)_2$ (0.24 mmol, 1.2 equiv.) was used in a sealed tube.
[d] $Cu(OTf)_2$ (0.01 mmol, 0.05 equiv.) was used in 120 °C.

91% yield (reaction ii, Scheme 3). According to all the above results, a plausible mechanism was proposed as shown in Scheme 4. Firstly, Pd(0) and $Cu(OTf)_2$ were coordinated with the carbonyl groups, respectively.

Then with the assistant of $Cu(OTf)_2$, the oxidative addition of Pd(0) formed the Pd-coordinated cation intermediate **B** based on the five-membered ring structure theory[19] *via* the cleavage of the acetophenone part. Only aromatics with high electron density

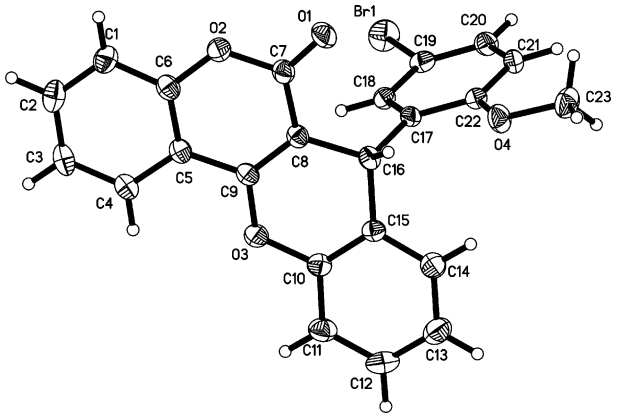
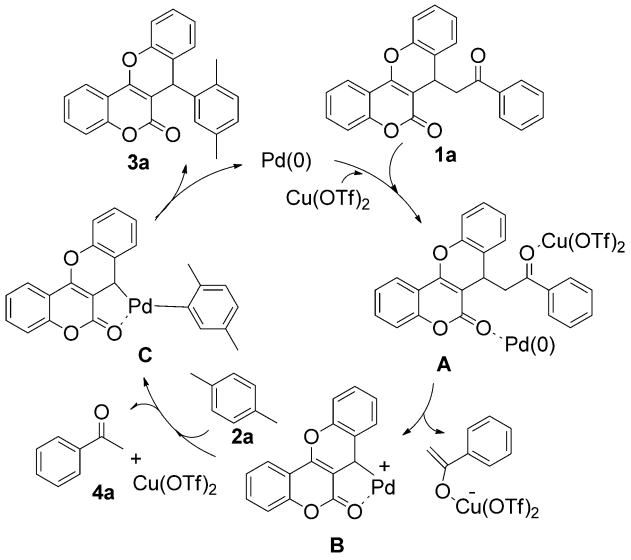
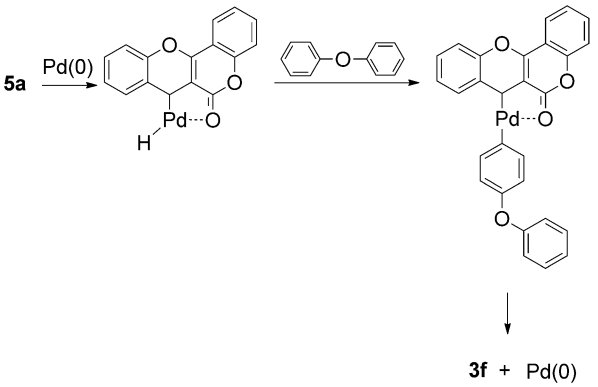


Figure 2. Molecular structure of **3i**.

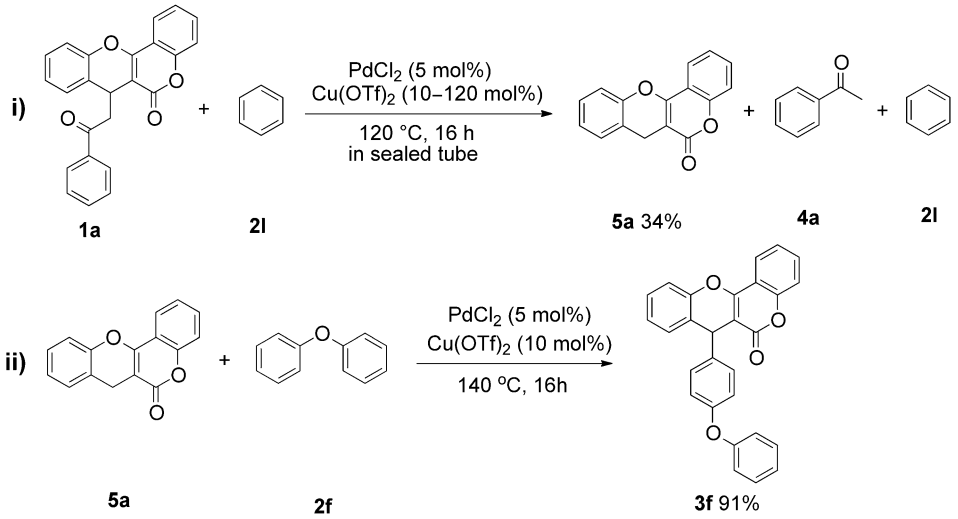




Scheme 4. Plausible mechanisms.

can coordinate to [Pd], and the reductive elimination of the intermediates **C** produced the products **3a** and **4a**, and regenerated the Pd(0) and the $Cu(OTf)_2$. As for the mechanism of **5a** with diphenyl ether (Scheme 4), it is a little bit different from the above, and this may be the reason why the yields were greatly improved when Pd catalysts were used.

In summary, we have developed a C_α–C_β bond activation of the unstrained carbonyl group catalyzed cooperatively by palladium and copper(II) with the departure of acetophenone. The formed Pd-coordinated cation intermediate undergoes the new C–C bond formation with a variety of aromatics *via* the formal C–H activation similar to the Friedel–Crafts reaction to obtain the skeleton-reconstructed coumarin derivatives in moderate to excellent yields with high regioselectivity, which might be potentially applicable in the pharmaceutical and biochemical areas. This sp^3-sp^3 C–C bond cleavage method may be developed to become a general way and may be useful in organic synthesis.



Scheme 3. Simple cleavage of the substrate.

Experimental Section

General Procedure

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, $PdCl_2$ (0.01 mmol), $Cu(OTf)_2$ (0.02 mmol), substrates **1** (0.2 mmol), **2** (2.0 mL or 10 mmol). The reaction vessel was sealed and the mixture stirred at 140 °C for 16 h. The reaction was monitored by TLC. After the starting material had been consumed completely, the resulting suspension was cooled to room temperature and filtered through a pad of filter paper with the help of 50 mL of ethyl acetate. After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel to give the pure product (AcOEt/petroleum ether v/v = 1/10). For more details, see the Supporting Information.

CCDC 905151 contains the supplementary crystallographic data for compound **3i**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

This work is financially supported by the Natural Science Foundation of China (No. 21072168).

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