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Palladium-Catalyzed [2+2+1] Oxidative Annulation of 4-Hydroxycoumarins with Unactivated Internal Alkynes: Access to Spiro Cyclopentadiene-Chroman-2,4-dione Complexes

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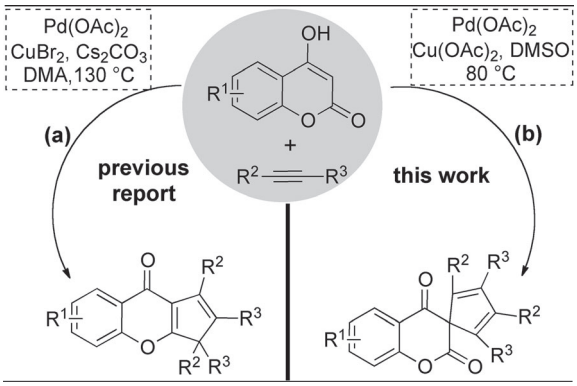
Abstract: Herein, we report our new results regarding a palladium-catalyzed [2+2+1] oxidative annulation of 4-hydroxycoumarins with unactivated internal alkynes, which affords a new class of compounds: the spiro cyclopentadiene-chroman-2,4-diones.

Keywords: C–H activation; palladium-catalyzed oxidative annulations; [2+2+1] reactions; spiro complexes

The realm of transition metal-catalyzed cross-coupling reactions has traditionally depended on prefunctionalized substrates for both reactivity and selectivity.[1] The quest for improved atom economy and efficiency has brought forward revolutionary changes and important advances especially in the palladium-catalyzed direct C–H functionalization, which efficiently leads to the diversity-oriented synthesis of various functional molecules.[2] Although these strategies offer numerous advantages (e.g., mild conditions, readily accessible starting materials and environmentally benign procedures), the development of general and flexible routes to a vast number of heterocycles still remains an important goal.

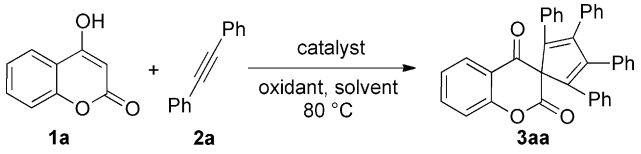
Internal alkynes are important building blocks extensively used in the palladium-catalyzed direct C–H functionalization for the preparation of a wide range of pharmaceuticals, agrochemicals, and heterocycles.[3] In recent reports, the Ellman group described a synthesis of dihydropyridine and pyridine from imines and internal alkynes through a palladium-catalyzed direct C–H functionalization.[4] Jiao and co-workers reported an elegant Pd-catalyzed oxidative annulation *via* a C–H functionalization to construct indoles.[5] The group of Wu used a similar strategy to successfully access substituted naphthalenes using internal alkynes as building blocks.[6] Most recently, Sahoo et al. disclosed an example of benzofuran synthesis through a palladium-catalyzed oxidative annulation of phenols and internal alkynes.[7] Our group recently disclosed the palladium-catalyzed oxidative annulations of 4-hydroxycoumarins and internal alkynes to access highly substituted cyclopentadiene-fused chromones (Scheme 1a).[8b] As part of our continued interest in transition metal-catalyzed oxidative coupling processes,[8] herein, we report our new discovery regarding a palladium-catalyzed [2+2+1] oxidative annulation of 4-hydroxycoumarins with unactivated internal alkynes, which affords a new class of compounds: the spiro cyclopentadiene-chroman-2,4-diones (Scheme 1b).

Initially, we investigated the influence of various catalyst parameters on the catalytic activity for annulation of 4-hydroxycoumarin **1a** with diphenyl acety-



Scheme 1. Palladium-catalyzed cascade reactions of 4-hydroxycoumarins with internal alkynes.

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



1a 2a 3aa

Entry	Catalyst	Oxidant	Solvent	**3aa** [%][b]
1	$PdCl_2$	$Cu(OAc)_2$	DMSO	–[c]
2	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2$	DMSO	58
3	$Pd(TFA)_2$	$Cu(OAc)_2$	DMSO	–[c]
4	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	69
5	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	23
6	$Pd(OAc)_2$	$Cu(OAc)_2$	1,4-dioxane	27
7	$Pd(OAc)_2$	$Cu(OAc)_2$	THF	27
8	$Pd(OAc)_2$	$Cu(OAc)_2$	MeCN	8
9[d]	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**DMSO**	**79**
10[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	66
11[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	57
12	$Pd(OAc)_2$	O_2	DMSO	24
13	$Pd(OAc)_2$	AgOAc	DMSO	64
14	$Pd(OAc)_2$	$PhI(OAc)_2$	DMSO	–[c]
15	$Pd(OAc)_2$	BQ[g]	DMSO	–[c]
16	$Pd(OAc)_2$	Oxones	DMSO	–[c]
17	$Pd(OAc)_2$	DDQ[h]	DMSO	–[c]
18[i]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	52
19[j]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	33

[a] *Reaction conditions:* **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.5 mmol, 2.5 equiv.), catalyst (10 mol%), oxidant (2.0 equiv.), solvent (2 mL), 80 °C, 48 h unless otherwise indicated.
[b] Isolated yield of **3aa**.
[c] No desired product detected.
[d] Using **2a** (0.8 mmol, 4.0 equiv.).
[e] At 60 °C.
[f] At 100 °C.
[g] 1,4-Benzoquinone.
[h] 2,3-Dichloro-5,6-dicyanobenzoquinone.
[i] Using 5 mol% of catalyst for 48 h.
[j] Using 1 mol% of catalyst for 96 h.

lene **2a** in DMSO at 80 °C with 10 mol% of catalysts [e.g., $PdCl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(TFA)_2$, $Pd(OAc)_2$] and 2.0 equivalents of oxidant $Cu(OAc)_2$ for 48 h (Table 1, entries 1–4). It was found that the reaction occurred and yielded the desired product **3aa**[9] only in the presence of $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ catalysts (entries 2 and 4, 58% and 69%, respectively). Next, we examined a series of solvents (entries 4–8). As a result, DMSO supported a high chemical yield (entry 4). To further improve the efficacy of the reaction, we tested the ratio of **1a/2a**. Notably, changing the ratio of **2a** from 2.5 to 4.0 equivalents increased the chemical yield to 79% (entry 9). Variation of the oxidants [e.g., O_2, AgOAc, $PhI(OAc)_2$, BQ, Oxones, DDQ] led to no reaction (entries 14–17) or a decrease in chemical yield (entries 12 and 13). The effects of temperature are summarized in Table 1. However, further lowering (60 °C) or increasing the temperature (100 °C) led to a slow reaction progress (entries 10 and 11, 66% and 57%, respectively). Moreover, the lowering of the catalyst loading decreased the chemical yields dramatically (entries 18 and 19).

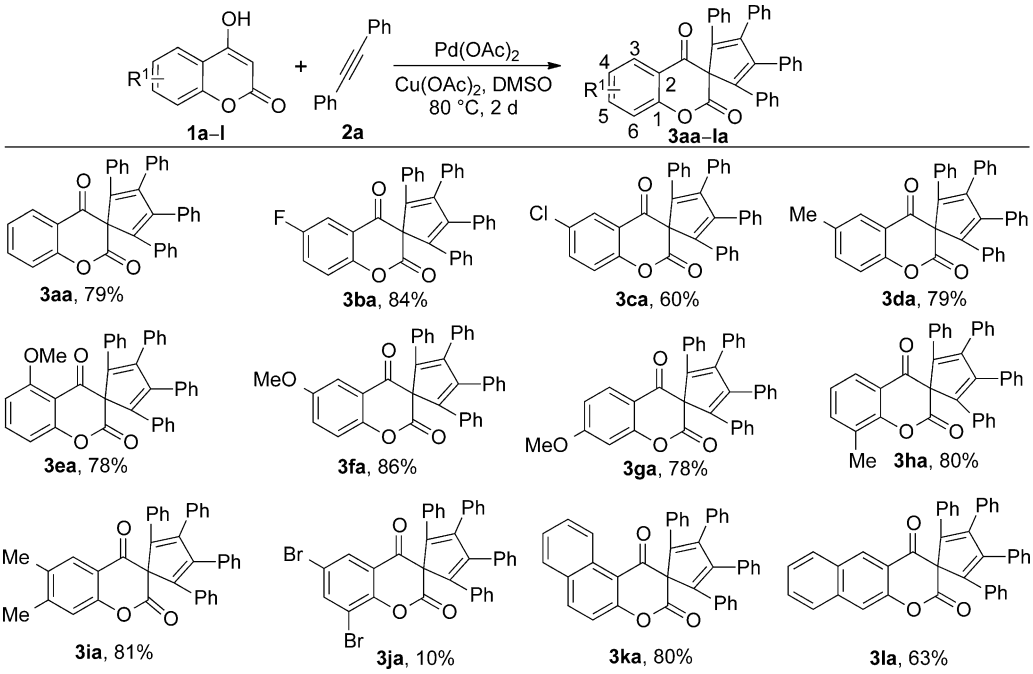
With these optimized conditions in hand, we surveyed the scope of 4-hydroxycoumarins **1**. Table 2 illustrates the substitution pattern on our validated 4-hydroxycoumarins **1a–l**. Electron-withdrawing, neutral and electron-donating substituents on the C-4 position were tolerated and gave high yields (**3aa–da**, **3fa**). Substrates with electron-withdrawing or electron-donating substituents at the C-3, C-5 or C-6 position also showed moderate to high reactivity and afforded the corresponding spiro cyclopentadiene-chroman-2,4-dione products (Table 2, **3ea**, **3ga–ja**). In addition, naphthalene ring-based 4-hydroxycoumarins were also tolerated and gave the corresponding spiro products in good yields (Table 2, **3ka** and **3la**, 80% and 63%, respectively).

Given the great value of alkynes, we then examined various internal alkynes **2** that could potentially react with **1a** to construct a diversity of spiro cyclopentadiene-chroman-2,4-dione complexes. As the results indicated in Table 3 demonstrate, the reaction presented a broad substrate tolerance among internal alkynes. Electron-rich internal alkynes reacted to give good reaction yields (Table 3, **3ab–ad, 3af–ag**) while electron-deficient systems were less facile (Table 3, **3ae**). A heteroaryl-containing alkyne was also tolerated (**3aj**). When asymmetrical internal alkynes were employed, a mixture of regioisomers was usually observed (**3ah**, **3ai**, and **3aj**).

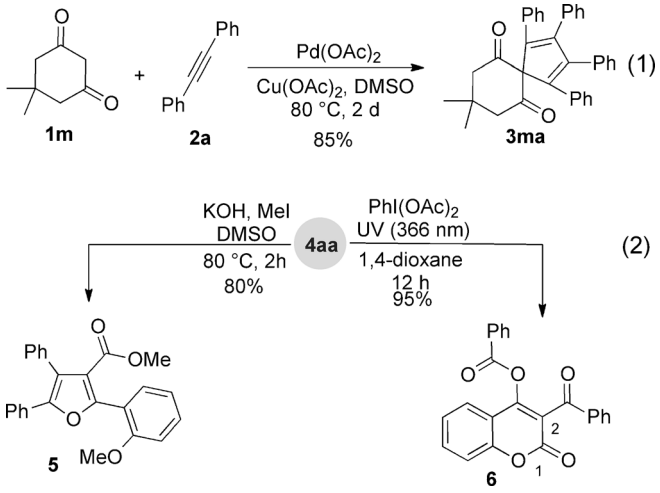
In the survey of oxidants, an exception was observed using oxidant $K_2S_2O_8$. As shown in Table 4, 4-hydroxycoumarins reacted with various alkynes in the presence of $K_2S_2O_8$ oxidant to directly generate a variety of valuable furo[3,2-*c*]coumarins **4** in moderate yields (33–53%).[10] We predicted that the reaction could involve a Pd(II) to Pd(IV) mechanism to afford **4aa**.[11] As indicated in Scheme 2, a plausible key intermediate **7** could be generated in the presence of oxidant $K_2S_2O_8$. Further optimization studies to improve the reaction efficiency are under way in our laboratory.

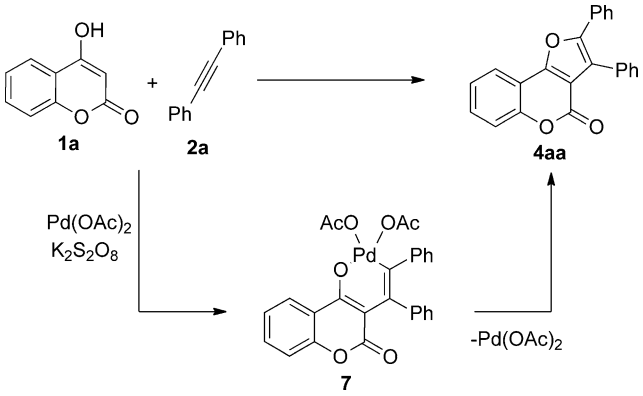
Due to the various bioactivities of heterocycles, we turned our attention to the late-stage diversification of functional molecules. It was found that cyclic ketone **1m** efficiently reacted with diphenylacetylene **2a** to form the corresponding spiro structure **3ma** in 85% yield under the standard conditions [Eq. (1)]. Upon treatment of product **4aa** with KOH and MeI in DMSO at 80 °C for 2 h, the tetrasubstituted furan **5** was obtained in 80% yield [Eq. (2)]. The photolysis of **4aa** was accomplished in the presence of iodobenzene diacetate and UV light, smoothly affording the C-2 functionalized coumarin **6**.

Table 2. Substrate scope of coumarins.[a]



[a] *Reaction conditions:* DMSO (2 mL), **1a–l** (0.2 mmol, 1.0 equiv.), **2a** (0.8 mmol, 4.0 equiv.), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv.), 80 °C, 48 h.



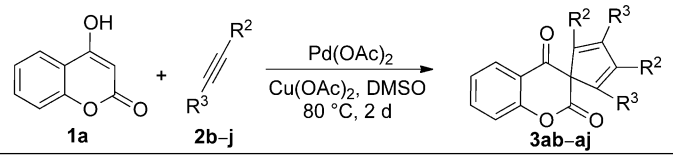


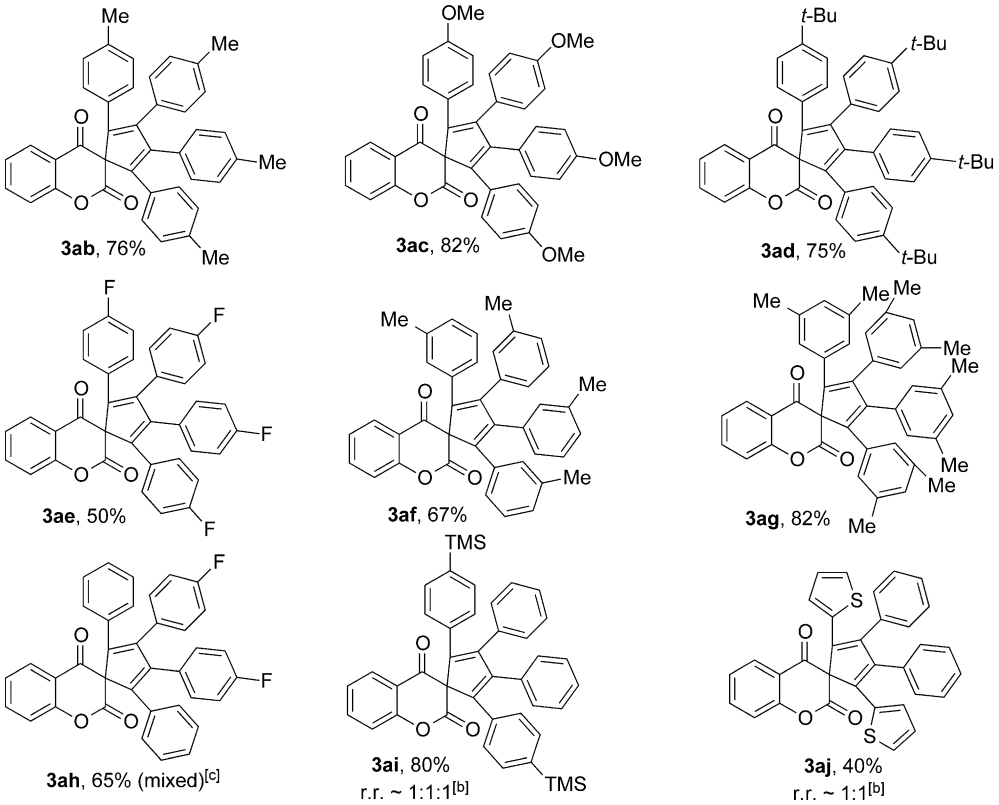
Scheme 2. Plausible mechanism.

A plausible mechanism for the synthesis of spiro cyclopentadiene-chroman-2,4-diones is illustrated in Scheme 2. The catalytic cycle starts from the palladation of 4-hydroxycoumarin **1a** to yield the palladium intermediate **8** (Scheme 3). Then the *syn*-addition of intermediate **8** to diphenylacetylene **2a** generates the vinylpalladium intermediate **9**. The following insertion of the **2a** entity affords the butadienylpalladium intermediate **10**. Finally, the intramolecular palladation of **10** leads to the formation of palladabenzocyclodiene **11**, which subsequently undergoes reductive elimination to yield the spiro cyclopentadiene-chroman-2,4-dione **3aa**.

In summary, we have developed an efficient synthesis of spiro cyclopentadiene-chroman-2,4-dione heterocycles. The method employs a direct Pd(II)-catalyzed oxidative [2+2+1] cycloaddition of readily available 4-hydroxycoumarins and unactivated internal alkynes. Various substituents are well tolerated in the reaction, which leads to a number of unique molecular structures. Further extension of this synthetic

Table 3. Substrate scope of alkynes.[a]





[a] *Reaction conditions:* DMSO (2 mL), **1a** (0.2 mmol, 1.0 equiv.), **2b–j** (0.8 mmol, 4.0 equiv.), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv.), 80 °C, 48 h.
[b] Ratio of regioisomers (r.r.), determined by NMR.
[c] Mixture of regioisomers.

strategy to other types of substrates is under way in our laboratory and will be presented in due course.

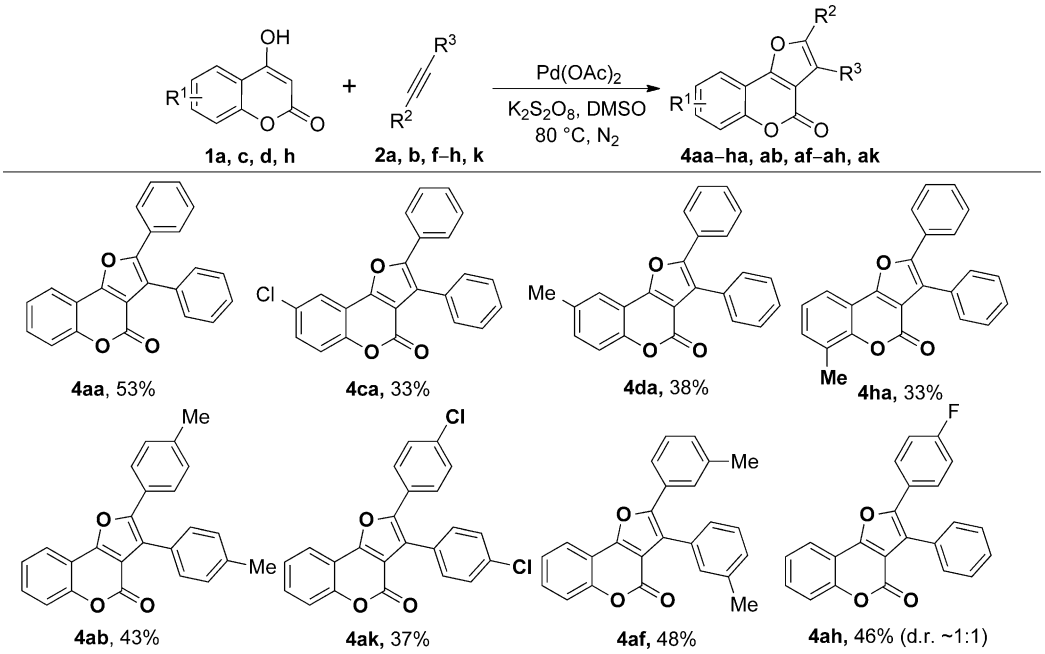
Experimental Section

Typical Procedure

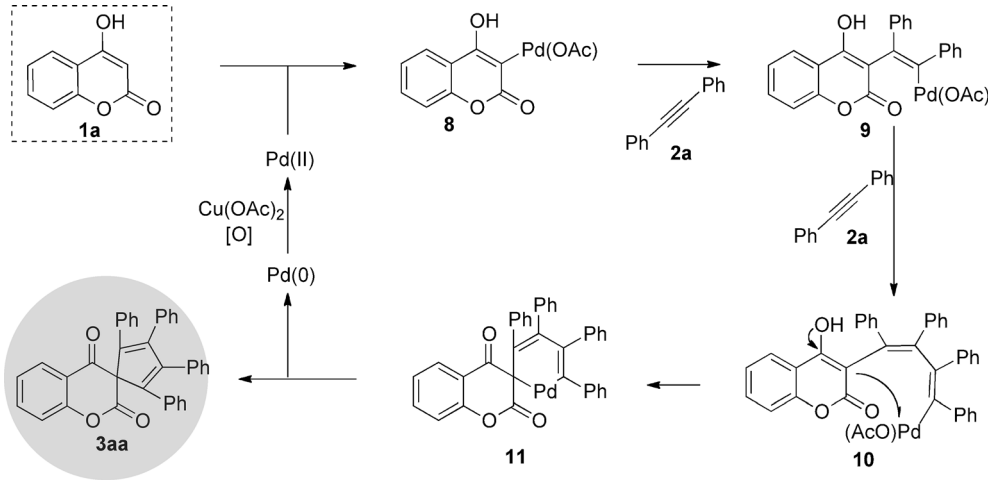
4-Aminocoumarin **1a** (0.2 mmol), diphenylacetylene **2a** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol) and $Cu(OAc)_2$ (0.4 mmol) were added into DMSO (2 mL). The mixture was stirred at 80 °C under an N_2 atmosphere for 48 h. The crude product was purified by column chromatography on silica gel eluted by EtOAc/hexane = 1:30 to afford the desired product **3aa** as a yellow solid; yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.84$ (d, $J = 7.6$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz 1H), 7.16–6.98 (m, 22H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 188.27$, 164.89, 154.83, 149.09, 142.68, 137.40, 134.24, 133.52, 130.09, 129.36, 128.35, 127.93, 127.80, 127.55, 127.37, 125.02, 119.91, 117.62, 80.24, 77.42, 77.16, 76.91; HR-MS (EI): $m/z = 516.1727$, calcd. for $[C_{37}H_{24}O_3]^+$: 516.1725.

4-Hydroxycoumarin **1a** (0.2 mmol), diphenylacetylene **2a** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), and $K_2S_2O_8$ (0.4 mmol) were added into DMSO (2 mL). The mixture was stirred at 80 °C under an N_2 atmosphere for 2 d. For work-up the crude mixture was cooled down to room temperature and then poured into ethyl acetate (20 mL), which was washed with brine (10 mL × 4), dried with $MgSO_4$ and filtered. The solvent was removed to obtain crude product, which was purified by column chromatography on silica gel eluted by ethyl acetate/hexane = 1:30 to afford the desired product **4aa** as a yellow solid; yield: 35.9 mg (53%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.99$ (d, $J = 7.7$ Hz, 1H), 7.59–7.49 (m, 5H), 7.48–7.42 (m, 4H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.35–7.29 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 157.59$, 156.56, 152.82, 151.50, 130.84, 130.36, 130.30, 129.43, 128.94, 128.72,

Table 4. Synthesis of furan-fused chromen-2-one complexes.[a]



[a] *Reaction conditions:* DMSO (2 mL), **1** (0.2 mmol, 1.0 equiv.), **2** (0.4 mmol, 4.0 equiv.), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv.), 80 °C, 48 h, N_2 balloon.



Scheme 3. Plausible mechanism.

128.70, 128.53, 126.82, 124.55, 121.02, 120.99, 117.35, 112.87, 111.43, 77.41, 77.16, 76.91; HR-MS (EI): $m/z = 338.0954$, calcd. for $[C_{23}H_{14}O_3]^+$: 338.0943.

Acknowledgements

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References

[1] a) *Metal-Catalyzed Cross-Coupling Reactions*, Vol. 2, 2nd edn., (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) *Metal-Catalyzed Cross-Coupling Reactions*, Vol. 1, 2nd edn., (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinhein, **1998**.

[2] For selected recent reviews on transition metal-catalyzed C–H functionalization, see: a) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami,

Angew. Chem. **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; c) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; d) C. Zhu, R. Wang, J. R. Falck, *Chem. Asian J.* **2012**, *7*, 1502; e) M. C. White, *Science* **2012**, *335*, 807; f) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; g) T. Newhouse, P. S. Baran, *Angew. Chem.* **2011**, *123*, 3422; *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; h) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; i) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; j) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; k) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; l) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; m) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; n) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; o) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; p) M. Lautens, P. Thansandote, *Chem. Eur. J.* **2009**, *15*, 5874; q) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; r) J. F. Hartwig, *Chem. Soc. Rev.* **2011**, *40*, 1992; s) *C–H Activation,* (Eds.:J.-Q. Yu, Z.-J. Shi), in: *Topics in Current Chemistry*, Springer, Berlin, **2010**; t) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; u) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761.

[3] For selected references on metal-catalyzed C–H activation cross-coupling reactions with internal alkynes, see: a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744; c) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565; d) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585; e) C. Wang, S. Rakshit, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 14006; f) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050; g) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474; h) M. Yamashita, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 2337; i) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068; j) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407; k) J. Chen, G. Song, C.-L. Pan, X. Li, *J. Org. Chem.* **2010**, *75*, 7487; l) Y. Minami, Y. Shiraishi, K. Yamada, T. Hiyama, *J. Am. Chem. Soc.* **2012**, *134*, 6124; m) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908.

[4] D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645.

[5] a) Z.-Z. Shi, C. Zhang, S. Li, D.-L. Pan, S.-T. Ding, Y.-X. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; b) Z. Z. Shi, Y. X. Cui, N. Jiao, *Org. Lett.* **2010**, *12*, 2908; c) S. T. Ding, Z. Z. Shi, N. Jiao, *Org. Lett.* **2010**, *12*, 1504.

[6] J.-L. Wu, X.-L. Cui, X. Mi, Y. Li, Y.-J. Wu, *Chem. Commun.* **2010**, *46*, 6771.

[7] M. R. Kuram, M. Bhanuchandra, A. K. Sahoo, *Angew. Chem. Int. Ed.* **2013**, *52*, 4607.

[8] For examples of our group's recently developed palladium-catalyzed C–H activation in the absence of directing groups, see: a) L. Wang, J. Y. Huang, S. Y. Peng, H. Liu, X.-F. Jiang, J. Wang, *Angew. Chem.* **2013**, *125*, 1812; *Angew. Chem. Int. Ed.* **2013**, *52*, 1768; b) L. Wang, S. Y. Peng, J. Wang, *Chem. Commun.* **2011**, *47*, 5422.

[9] CCDC 875492 (the structure of compound **3aa** was determined by X-ray crystal analysis) contains the supplementary crystallographic data for this paper. These data can be ontained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[10] CCDC 90919 (the structure of compound **4aa** was determined by X-ray crystal analysis) contains 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.

[11] L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141.

