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Palladium-Catalyzed Synthesis of Benzothiophenes via Cross-Dehydrogenative Coupling of 4-Arylthiocoumarins and Pyrones

Jin Zhang,[a,*] Yuyu Zhuang,[a] Yangmin Ma,[a] Xiufang Yang [a,*] and Michal Szostak[a,b,*]

[a] College of Chemistry and Chemical Engineering, Shaanxi Key Laboratory of Chemical Additives for Industry, Shaanxi University of Science and Technology, Xi'an 710021, China
Fax: (+86)- 029-8161-8312; phone: (+86)- 029-8161-8312; e-mail: zhangjin@sust.edu.cn; yangxf@sust.edu.cn

[b] Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, United States
Fax: (+1)-973-353-1264; phone: (+1)-973-353-5329; e-mail: michal.szostak@rutgers.edu

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Abstract. Benzothiophenes represent a pivotal class of sulfur heterocycles and their synthesis has attracted significant attention to generate bioactive scaffolds. Herein, we report a convergent, atom- and step-economic method for the synthesis benzothiophenes by cross-dehydrogenative coupling (CDC) of 4-arylthiocoumarins in good to excellent yields. We further demonstrate cross-dehydrogenative coupling of 4-arylthio-2-pyrones to afford alternative substitution of benzothiophenes. The presence of a labile ester carbonyl moiety provides functional handle for further functionalization by coumarin deconstruction. Most crucially, the manuscript demonstrates that the use of readily accessible templated synthesis has a significant potential for the rapid assembly of sulfur heterocycles by dehydrogenative coupling mechanism.

Keywords: benzothiophenes; sulfur heterocycles; sulfur; cross-dehydrogenative coupling; C–H functionalization

Benzothiophenes are privileged sulfur-containing scaffolds widely present in natural products, biologically active molecules and pharmaceuticals and serve as key building blocks for organic optoelectronic materials.[1-2] The main driving force in the emerging strategies for the synthesis of benzothiophenes is the extraordinary impact of sulfur on the properties of drugs in medicinal chemistry (Figure 1).[3,4] It is estimated that more than 25% of top-selling drugs contain this heteroatom and the number is rapidly increasing.[5] Because of the importance of benzothiophenes in diverse fields of chemistry, it is not surprising that novel methods for their convergent, atom- and step-economic synthesis are in high demand.[6]

We proposed that widely available coumarin would act as a template for the direct synthesis of benzothiophenes by cross-dehydrogenative coupling (CDC) (Scheme 1).[7–9] In particular, accessing benzothieno[2,3]coumarins has proven challenging;[10,11] the classic methods involve directed ortho-metallation reported by Snieckus[10a] and carbonylative cross-coupling using an acetoxy group as the nucleophile reported by Larock[10b] (Scheme 1 A-B). However, both methods build-up on an existing benzothiopene ring, and are limited in terms of atom- and step-economy. The direct templated *de novo* synthesis[12,13] of benzothieno[2,3]coumarins by a C–H functionalization mechanism would enable access to these important heterocycles avoiding any pre-functionalization and provide an avenue for the synthesis of densely functionalized 2-aryl-benzothiophenes by well-established deconstruction of the coumarine ring (Scheme 1C).[12]

We were attracted by the recent progress made in cross-dehydrogenative coupling reaction.[8a,b] Intramolecular cross-dehydrogenative couplings have been widely used in the synthesis of heterocycles beacuse of their advantageous green and sustainable profile as well as operational-simplicity, step- and atom-economic nature.[8a-h] However, the synthesis of benzothiophenes via cross-dehydrogenative coupling is unknown.[11e,f] The synthesis of benzothiophenes by cross-dehydrogentive coupling presents major challenges, such as: (1) catalyst poisoning due to strong coordination of sulfur atom;[14a] (2) high stability of aromatic C–H bonds;[14b] (3) the presence of C-3 and C-5 active sites on the coumarine ring, which affects regioselectivity of the reaction.[9a,b] As a result, although syntheses of N- and O-benzofused heterocycles by CDC have been reported,[11e-g] the synthesis of benzothiophenes by a CDC pathway is unknown due to the poisoning effect of the sulfur atom.

In order to expand the scope of application of sulfur heterocycles, we envisioned templated synthesis enabling efficient double C–H activation. Herein, we report the successful execution of this strategy and describe efficient dehydrogenative coupling of 4-arylthiocoumarins to furnish benzothiophenes in good to excellent yields.

Notable features of our study include: (1) robust palladium-catalyzed oxidative cyclization in the presence of silver as the terminal oxidant, furnishing

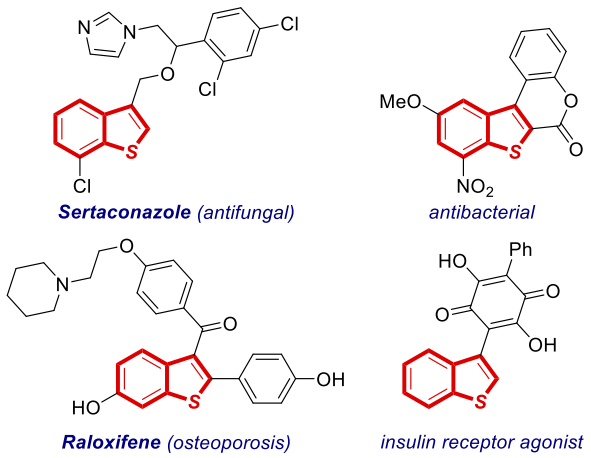
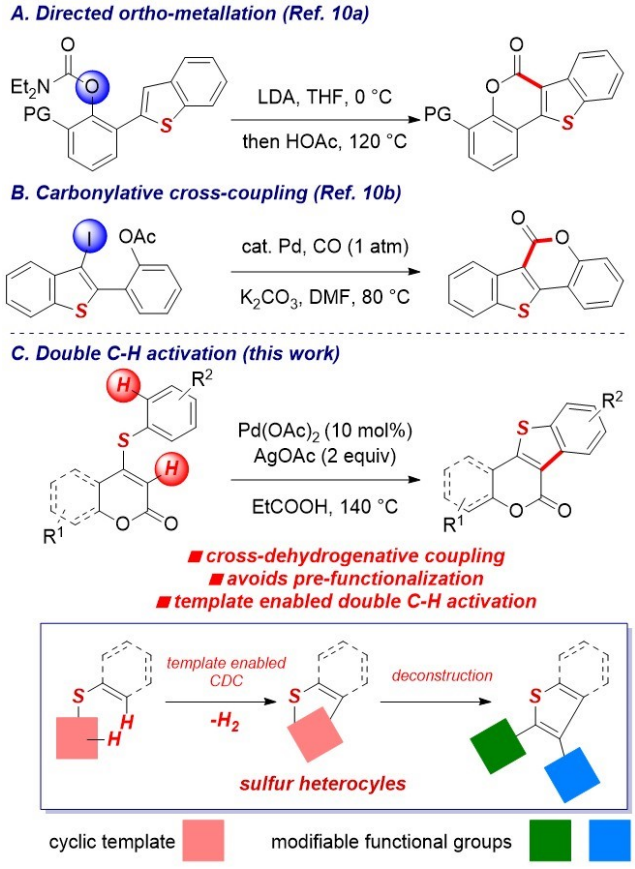


Figure 1 Selected examples of benzothiophenes with pharmacological activity.



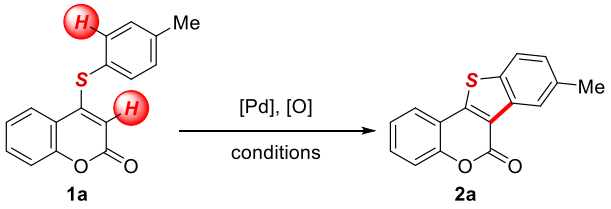
Scheme 1 Previous studies and this work: templated approach to sulfur-containing heterocycles by dehydrogenative coupling.

the corresponding benzothiophenes with broad substrate generality; (2) facile dehydrogenative coupling of 4-arylthiopyrones, affording the alternative substitution of the benzothiophene ring; (3) the presence of labile ester carbonyl moiety, which provides functional handle for further functionalization of the fused benzothiophene ring by coumarin ring deconstruction.

More broadly, the template-directed dehydrogenative strategy provides an attractive entryway to the synthesis of sulfur heterocycles in atom-economic fashion.

We commenced our studies by using 4-(*p*-tolylthio)-2*H*-chromen-2-one (**1a**) as the model substrate to evaluate the optimal reaction conditions (Table 1). Initially, treatment of (**1a**) with 5 mol% of $Pd(OAc)_2$ catalyst in the presence of 2.0 equiv of Ag_2O in AcOH at 100 °C for 24 h did not produce any desired product (entries 1-2). We were pleased to observe the formation of the benzothiophene product (**2a**) using AgOAc as the oxidant (entry 3). Next, various oxidants, including $Cu(OTf)_2$, $Cu(OAc)_2$, $K_2S_2O_8$, BQ (1,4-benzoquinone), DTBP (di-*tert*-butyl peroxide) were screened to optimize the reaction conditions (entries 4-8). AgOAc was found to be the most effective (entry 3). Other palladium catalysts, including $PdCl_2$, $Pd(dppf)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$, were ineffective in the reaction (entries 9-11).

Table 1. Optimization of Reaction Conditions.[a]

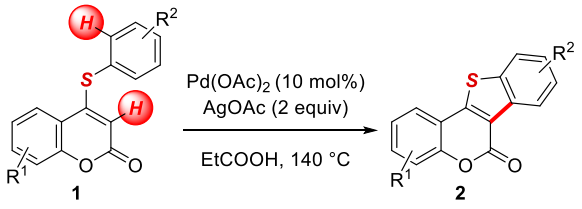


Entry	[Pd]	[O]	Solvent	Yield (%)
1	$Pd(OAc)_2$	Ag_2O	AcOH	<5
2[b]	$Pd(OAc)_2$	Ag_2O	AcOH	<5
3	$Pd(OAc)_2$	AgOAc	AcOH	35
4	$Pd(OAc)_2$	$Cu(OTf)_2$	AcOH	<5
5	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	14
6	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	<5
7	$Pd(OAc)_2$	BQ	AcOH	<5
8	$Pd(OAc)_2$	DTBP	AcOH	<5
9	$PdCl_2$	AgOAc	AcOH	10
10	$Pd(dppf)Cl_2$	AgOAc	AcOH	16
11	$Pd(PPh_3)_2Cl_2$	AgOAc	AcOH	13
12	$Pd(OAc)_2$	AgOAc	TFA	<5
13	$Pd(OAc)_2$	AgOAc	HCO_2H	18
14	$Pd(OAc)_2$	AgOAc	$EtCO_2H$	64
15	$Pd(OAc)_2$	AgOAc	MsOH	<5
16[c]	$Pd(OAc)_2$	AgOAc	$EtCO_2H$	70
17[d]	$Pd(OAc)_2$	AgOAc	$EtCO_2H$	79
18[d,e]	$Pd(OAc)_2$	AgOAc	$EtCO_2H$	82

[a]Conditions: **1a** (0.20 mmol), [Pd] (5 mol%), oxidant (2.0 equiv), solvent (0.20 M), 100 °C, 24 h. [b]K_2CO_3 (2.0 equiv). [c]120 °C. [d]140 °C. [e][Pd] (10 mol%).

Since in CDC studies we found that an acid solvent played an indispensable role in promoting the reaction, we tested the effect of several solvents on the reaction (entries 12-15). Pleasingly, we found that CH_3CH_2COOH was the optimal solvent for the reaction (entry 15). Although its precise role is unclear, propionic acid is believed to promote the reaction by higher solubility and/or lower acidity compared to acetic acid. Further investigations indicated that the yield could be improved by conducting the reaction at

Table 2. Pd-catalyzed CDC in the templated synthesis of benzothiophenes using coumarins.[a,b]



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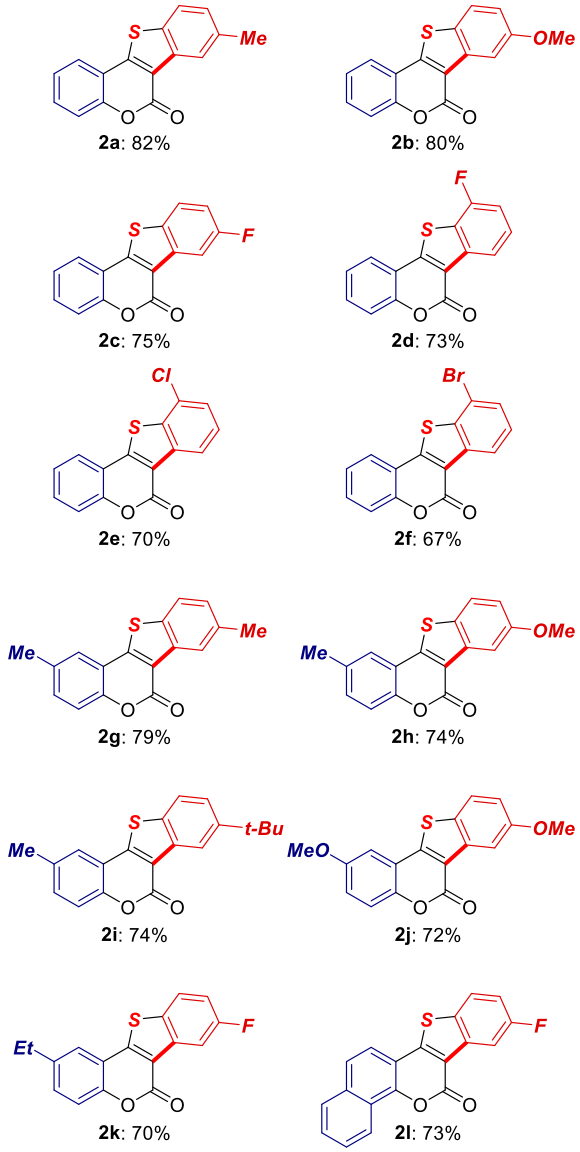
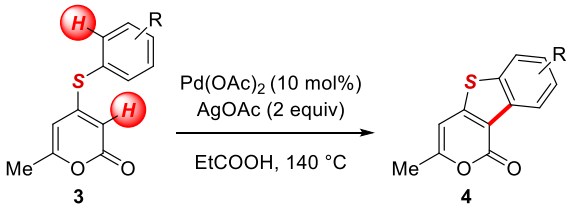


[a]Conditions: **1** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), EtCOOH (0.20 M), 140 °C. [b]Isolated yields.

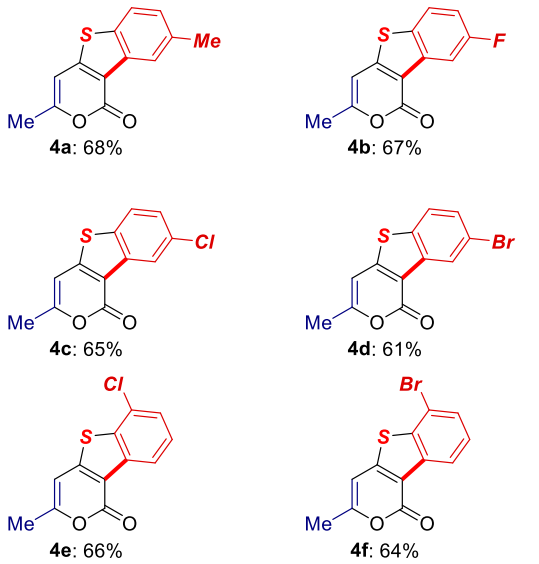
higher temperature (entries 16-17). A further improvement in the reaction efficiency was observed upon increasing $Pd(OAc)_2$ loading from 5 mol% to 10 mol% (entry 18). Under the optimized conditions, the benzothiophene product (**2a**) was isolated in 82% yield. The conditions are as follows: 4-(*p*-tolylthio)-2*H*-chromen-2-one (1.0 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), CH_3CH_2COOH (0.20 M), 140 °C.

With the optimized reaction conditions in hand, we next investigated the substrate scope of the reaction

Table 3. Pd-catalyzed CDC in the templated synthesis of benzothiophenes using 2-pyrones.[a,b]



3 4



[a]Conditions: **3** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), EtCOOH (0.20 M), 140 °C. [b]Isolated yields.

(Table 2). As shown, a wide range of 4-arylthiocoumarins bearing substituents with diverse electronic properties on either of the aryl rings of the coumarin template provided the desired benzothiophenes in good to excellent yields. Electron-donating groups at the para-position of the *S*-aryl group provided the corresponding products in 80-82% yields (**2a-2b**). Electron-withdrawing groups also afforded good yields (**2c**, 75%). Interestingly, the reaction is well-compatible with sensitive halide functional groups, such as F, Cl, Br, including those located at the ortho-position, furnishing the corresponding benzothiophene products in 67-73% yields, and thus providing valuable handles for further functionalization. Gratifyingly, the reaction is tolerant of various substituents on the coumarin ring (**2g-2l**, 70-79%). These reactions furnish functionalized benzothieno[2,3]coumarins that could be readily deconstructed to 2-arylbenzothiophenes by standard reduction or hydrolysis methods.[12] At this stage, meta-substituted substrates have not been tested. These substrates are well-known to result in mixtures of the regioisomeric products.[8f-h]

Next, to expand the generality of the templated approach to benzothiophenes, we investigated 4-arylthio-2-pyrones (Table 3). Note that in both cases (coumarines and pyrones) the sulfur-containing template is accessed in a single, high yielding step from the commercial materials, making the technology

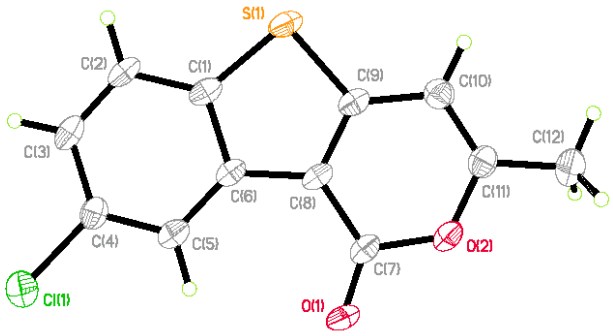
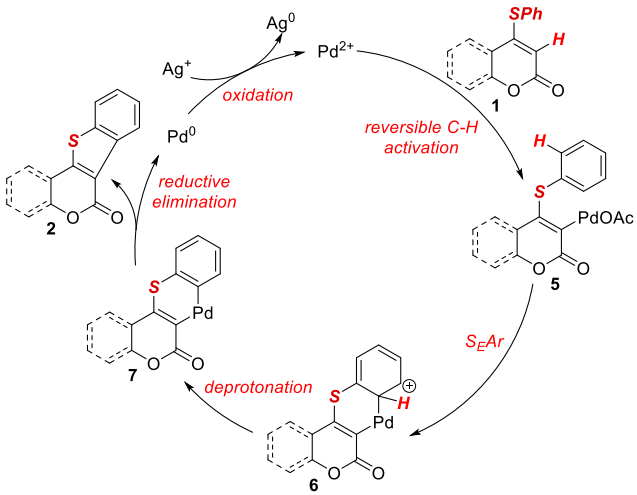


Figure 2. X-ray structure of (**4c**). Selected bond lenghts (Å) and angles (deg): S1–C1, 1736(3); S1–C9, 1.726(3); C9–C8, 1.370(4); O2–C7, 1.399(3). C2–C1–S1–C9, -178.8(3); C11–C10–C9–S1, -176.5(3); C8–C7–O2–C11, 1.6(5).[15]

appealing for benzothiophene synthesis. Furthermore, this approach allows one to rapidly introduce structural diversity by convergent *de novo* benzothiophene assembly. We found that although 4-arylthio-2-pyrones proved more challenging in the dehydrogenative coupling, the developed conditions were amenable to a broad range of benzothiophenes (Table 3). As shown, electron-donating and electron-withdrawing groups at the para-position of the *S*-aryl moiety gave the benzothiophene products in good yields (**4a-4d**, 61-68%). Furthermore, halide functional handles (Cl, Br) located at the ortho-position were well-compatible, and the corresponding products (**4e-4f**) were isolated in 61-64% yields. Note that the reaction is compatible with sensitive halides that would be problematic in previous approaches to thieno[2,3]pyrones using either strong metal bases or low valent metals, showcasing the advantage of the present methodology.

Benzothiophene (**4c**) was crystalline and we were able to confirm its structure by X-ray crystallography (Figure 2). The heterocyclic ring is planar and the S1–C1 bond length (1.736 Å) is comparable to those found in fused benzothiophenes.[1,2]



Scheme 2. Proposed mechanism.

On the basis of our results and previous literature precedents,[8,15,16] we propose a reaction mechanism shown in Scheme 2. An initial activation of the C–H bond at the C3 position of the coumarin template gives intermediate (**5**).[16] An S_EAr-type reaction[17] affords palladacycle (**6**). Irreversible deprotonation and reductive elimination furnish the final product. The Pd(II) catalyst is regenerated after oxidation. The key step involves template directed electrophilic C–H activation to form the benzothiophene ring.

In conclusion, we have developed a general, mild and operationally-convenient method for the synthesis of benzothiophenes by Pd-catalyzed dehydrogenative coupling. The key features involve convergent, atom- and step-economic benzothiophene synthesis and the use of template to facilitate double C–H activation. The reaction demonstrates good functional group tolerance and broad substrate scope, providing rapid access to functionalized benzothiophenes from simple starting materials. Most crucially, the use of readily accessible templated synthesis has a significant potential to facilitate the assembly of sulfur heterocycles by C–H functionalization.

Experimental Section

General procedure for synthesis of thieno[3,2-*c*]coumarins. An oven-dried sealed tube equipped with a stir bar was charged with 4-arylsulfanylcoumarin substrate (neat, typically, 0.20 mmol, 1.0 equiv), $Pd(OAc)_2$ (typically, 10 mol%) and AgOAc (typically, 2.0 equiv). CH_3CH_2COOH (0.20 M) were added with vigorous stirring at room temperature, and the reaction mixture was stirred for 24 h at 140 °C. After the indicated time, the reaction mixture was neutralized with saturated sodium hydrogen carbonate (1.0 *N*, 1.0 mL) and extracted with ethyl acetate, then the organic layer was dried and concentrated. A sample was analyzed by ^1H NMR ($CDCl_3$, 400 MHz) and/or GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

General procedure for synthesis of 4-arylthio-2-pyrones. An oven-dried sealed tube equipped with a stir bar was charged with 4-arylsulfanyl-6-methyl-2-pyrone substrate (neat, typically, 0.20 mmol, 1.0 equiv), $Pd(OAc)_2$ (typically, 10 mol%) and AgOAc (typically, 2.0 equiv). CH_3CH_2COOH (0.20 M) were added with vigorous stirring at room temperature, and the reaction mixture was stirred for 24 h at 140 °C. After the indicated time, the reaction mixture was neutralized with saturated sodium hydrogen carbonate (1.0 *N*, 1.0 mL) and extracted with ethyl acetate, then the organic layer was dried and concentrated. A sample was analyzed by ^1H NMR ($CDCl_3$, 400 MHz) and/or GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

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Palladium-Catalyzed Synthesis of Benzothiophenes via Cross-Dehydrogenative Coupling of 4-Arylthiocoumarins and Pyrones

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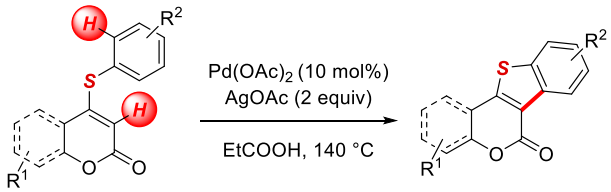
Jin Zhang,* Yuyu Zhuang, Yangmin Ma, Xiufang Yang* and Michal Szostak*



R^1,R^2= Alkyl, halogen

18 examples
61-82 % yields

- ***cross-dehydrogenative coupling***
- ***avoids pre-functionalization***
- ***template enabled double C-H activation***