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Cyclization of 4-Phenoxy-2-coumarins and 2-Pyrones via a Double C−H Activation

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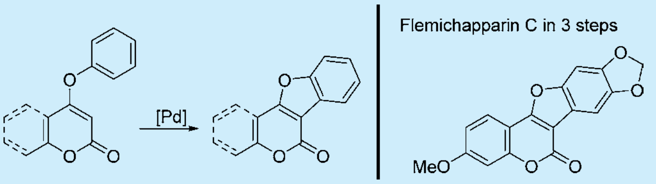
S *Supporting Information*

ABSTRACT: Aryl−heteroaryl coupling via double C−H activation is a powerful transformation that avoids the installation of activating groups. A double C−H activation of privileged biological scaffolds, 2-coumarins and 2-pyrones, is reported. Despite the rich chemistry of these molecular frameworks, the yields are very good. Excellent regioselectivity was achieved on the pyrones. This methodology was applied to the synthesis of flemichapparin C in three steps. Isotope effect experiments were carried out, and a mechanism is proposed.



The formation of aryl−heteroaryl (Ar−HetAr) bonds is an important transformation in organic synthesis[1] due to the abundance of Ar−HetAr moieties in natural products and pharmaceuticals.[2] Direct arylation involving the coupling of a C−H and C−X bond that avoids one of the preactivating groups is certainly progressive;[3] however, the ideal approach would involve the coupling of two C−H bonds.[4] As a green route to biaryls and heteroaryls, this reaction is on the "wanted list" of top pharmaceutical companies.[5] This is challenging for two main reasons: (1) aromatic C−H bonds are highly stable and (2) most molecules possess a number of potential C−H coupling sites, which often poses prohibitive regioselectivity problems.

The 2-pyrone substrate, specifically, 4-hydroxy- and 4-alkoxy-based 2-pyrones (Figure 1),[6] represents a privileged biological scaffold with broad spectrum biological activity spanning cytotoxic, antibiotic, and antifungal activity.[6,7]

Additionally, 2-pyrones are a promising class of biorenewable platform chemicals that provide access to an array of chemical products and intermediates.[8] Finally, the 2-pyrone moiety displays similar reactivity to aromatics, dienes, and enones and is thus bestowed with both challenging and rewarding properties. The related 2-coumarins display a similarly remarkable biological profile.[9] The coumestan subgroup (Figure 1) exhibits impressive biological activities,[10] and thus a number of novel synthetic methods have been developed for constructing the coumestan and related ring systems,[10a,c,11] including the oxygen-containing six-membered variant.[12]

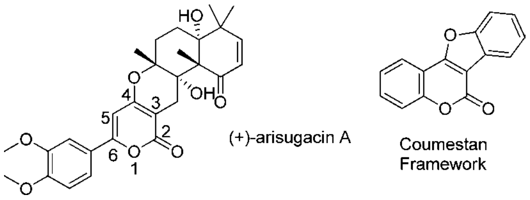


Figure 1. Biologically active 4-alkoxy-2-pyrone and 2-coumarin.

The cyclization of such substrates currently requires the installation of a halogen on one coupling partner.[11c,13] Instead, we sought to gain access to tricyclic pyrones and coumarins by the coupling of phenoxy-substituted substrates via two C−H activation events. This is a far more challenging approach as outlined (vide supra). We initially prepared the 4-phenoxy-2-coumarin by reacting 4-bromocoumarin and phenol (not shown; see Supporting Information (SI)).

Our optimization studies started with two seminal reports by Fagnou[14] and Shi.[15] In summary, $Pd(OAc)_2$ was the best palladium source, PivOH the preferred solvent, and NaO^tBu the preferred base. The reaction failed to progress satisfactorily without added oxidant (Table 1, entry 1). Using Ag_2O as oxidant, the coupling proceeded with excellent yield (Table 1, entry 2). The reaction also worked well in TFA, this time with K_2CO_3 as base (Table 1, entry 3). Only 5 mol % of palladium was required here, and the cyclized product was isolated in an impressive 86% yield. Other solvents, such as DME, gave no reaction (Table 1, entry 4), and other oxidants, such as $K_2S_2O_8$, were ineffective (Table 1, entry 5). A substrate scope was then investigated (Scheme 1). Electron-donating groups at the *para*-position of the phenoxy group provided the corresponding products **15** and **16** in good yields (72−77%). Electron-withdrawing groups gave the highest yields, affording **17−19** in 80−99%. The *meta*-substituted starting materials gave excellent regioselectivity in some cases (92:8 for **8**)[16] but was lower when fluorine was present at the *meta*-position (67:33 for **9**). Interestingly, when a methyl group was located at the *meta*-position, only one regioisomer, **22**, was observed in the ^1H NMR of the crude product mixture, and this was isolated in moderate yield. An

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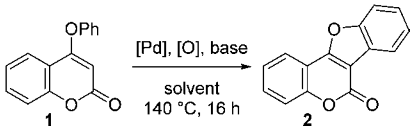
Table 1. Optimization for 2-Coumarin



entry	[Pd] (mol %)	[O] (1.5 equiv)	base (equiv)	solvent	yield[a] (%)
1	$Pd(OAc)_2$ (10)		NaO^{t}Bu (0.2)	PivOH	0
2	**$Pd(OAc)_2$ (10)**	**Ag_2O**	**NaO^{t}Bu (0.2)**	**PivOH**	**92**
3	**$Pd(OAc)_2$ (5)**	**Ag_2O**	**K_2CO_3 (2.5)**	**TFA**	**86**
4	$Pd(TFA)_2$ (5)	Ag_2O	K_2CO_3 (2.5)	DME	0
5	$Pd(OAc)_2$ (5)	$K_2S_2O_8$		TFA	0

[a] Isolated yields.

Scheme 1. 2-Coumarin Scaffold Scope

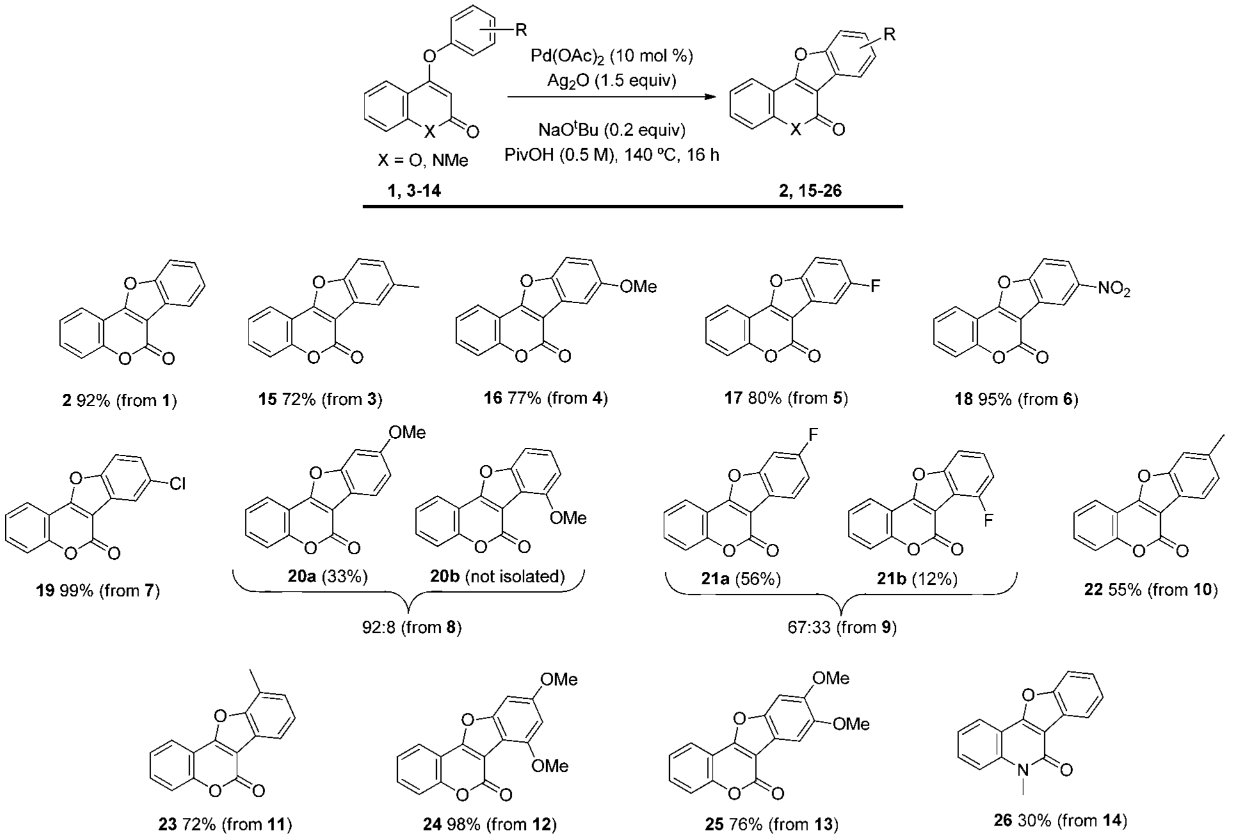
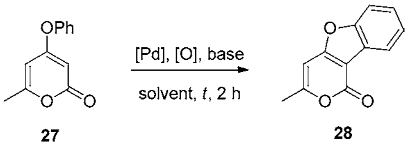


Table 2. Optimization for 2-Pyrone[a]

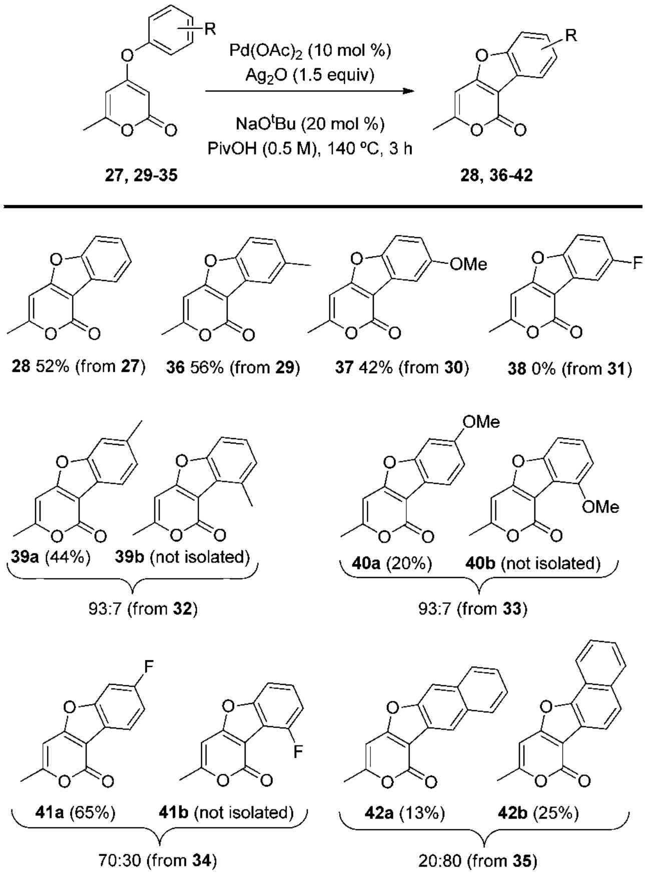


entry	[Pd] (mol %)	[O] (1.5 equiv)	base (equiv)	solvent	t (°C)	yield[b] (%)
1	$Pd(OAc)_2$ (10)	Ag_2O	NaO^{t}Bu (0.2)	THF	70	3
2	**$Pd(OAc)_2$ (10)**	**Ag_2O**	**NaO^{t}Bu (0.2)**	**PivOH**	**140**	**52**
3	**$Pd(OAc)_2$ (5)**	**Ag_2O**	**K_2CO_3 (2.5)**	**TFA**	**140**	**56**
4	$Pd(TFA)_2$ (5)	Ag_2O	K_2CO_3 (2.5)	DMF	100	0

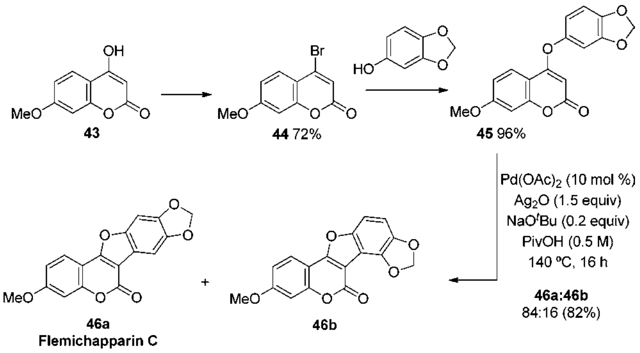
[a] For full optimization studies, see the SI. [b] Isolated yields.

ortho-substituent did not overly affect the reaction progress, and corresponding product **23** was isolated in 72% yield. When the phenoxy group was substituted with two methoxy groups (common in many natural products), the reaction worked well (98% of **24** and 76% of **25**). Finally, 2-quinolone did not work as well; however, product **26** could be isolated in 30% yield. We

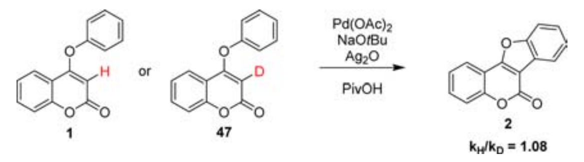
Scheme 2. 2-Pyrone Scaffold Scope



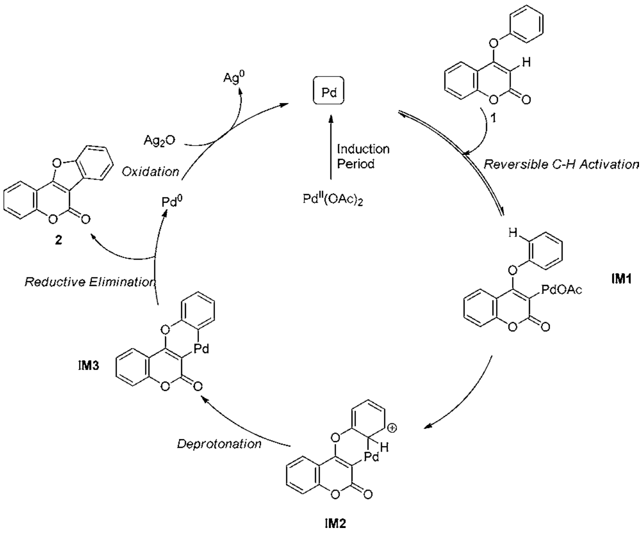
Scheme 3. Synthesis of Flemichapparin C in Three Steps



Scheme 4. Kinetic Isotope Effects



Scheme 5. Plausible Reaction Mechanism



next targeted the 2-pyrone moiety. Here, we expected some added problems given that two sites were now available on the pyrone for C−H activation, and the pyrone unit itself is susceptible to ring opening.[17]

A direct transfer of the optimized conditions which worked for the coumarins, using PivOH as solvent (Table 2, entry 2), gave product **28** in 52% isolated yield, while using TFA as solvent (Table 2, entry 3) gave **28** in 56% yield. Use of Pd(TFA)$_2$/DMF in place of Pd(OAc)$_2$/TFA gave no conversion to product (Table 2, entry 4).

A substrate scope for the 2-pyrone was investigated (Scheme 2). Electron-donating groups at the *para*-position of 4-phenoxy-2-pyrones (**29** and **30**) gave the cyclized products in moderate to good yields. However, an electron-withdrawing group at the *para*-position did not work well, with the presence of a fluoro group (**31**) completely inhibiting the reaction. The *meta*-substituted phenoxy groups (**32**−**34**) gave the products again in moderate yield.[16] Some good regioselectivity toward the least sterically hindered position was observed. For example, the reaction of **32** gave **39a**/**39b** in a 93:7 ratio.

Good yields and regioselectivity observed with coumarin **13** prompted us to attempt to access the coumestan group of natural products.[10] Commercially available 4-hydroxy-2-coumarin **43** (Scheme 3) was brominated at the 4-position in good yield (**44**, 72%) and coupled with sesamol (**45**, 96%). Application of our reactions conditions gave flemichapparin C **46a** and a minor regioisomer, **46b**, in 82% combined yield. Under certain conditions, complete regioselectivity could be observed.[18]

The focus of our study then turned toward mechanistic investigations. Incorporating the deuterium on the coumarin (**47**) allowed us to measure the involvement of the C-3−H bond in the mechanism. The kinetic isotope effect (KIE) was determined to be 1.08 using the initial rates method[19] (Scheme 4; see SI for further details), indicating that C-3−H cleavage is not rate-limiting. In the reaction of **47**, the abstraction of deuterium at C-3 was observed to be reversible, with the ^{1}H NMR integral of the C-3 proton increasing with reaction time.[20] Efforts to elucidate the corresponding KIE values for C−H/D cleavage on the phenoxy group were hampered by scrambling effects (see SI).

Based on these preliminary mechanistic studies, an initial palladation−protodepalladation of the C-3−H bond to give **IM1** as the first step is proposed,[21] accounting for the nonsignificant KIE (Scheme 4). An S$_E$Ar-type step[22] is envisaged next to give **IM2**.[23] Irreversible deprotonation (to give **IM3**) and reductive elimination give the product. Finally, the appearance of an induction period (see Scheme 5 and SI) suggests a key precatalyst → catalyst event. Further mechanistic studies are underway and will be reported in due course.

In conclusion, a double C−H activation protocol applied to 2-coumarins and 2-pyrones gives quick access to the cyclized products. This is certainly one of the most delicate molecular frameworks to have been reported for this type of transformation. Substitution patterns (on the phenoxy), which would be difficult to access via other routes, are available with this methodology. This approach facilitated a short, three-step synthesis to flemichapparin C. Deuterium isotope effects were examined, and a preliminary mechanism has been suggested based on these studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00751.

> General experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all key compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Difficulties with the purification prevented complete isolation of the minor regioisomer in the reactions of **8**, **33**, and **34**. The structure is assigned based on the data available for the minor regioisomer contaminated with some of the major isomer.

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(18) We were able to achieve complete regioselectivity in favor of flemichapparin C with 77% isolated yield when the conditions described in Table 1, entry 3, at 120 °C were employed. However, we found this result was highly dependent upon the quality of the TFA employed in the reaction.

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(23) Based on the mechanistic studies carried out to date, we cannot be certain which C−H bond is activated first. An initial, irreversible C−H activation of the phenoxy group followed by reversible C−H activation of the coumarin C-3−H could give similar results. We thank one reviewer for this point.