



# Intermolecular C–O addition of carboxylic acids to arynes: synthesis of *o*-hydroxyaryl ketones, xanthenes, 4-chromanones, and flavones



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## ARTICLE INFO

### Article history:

Received 9 December 2012  
Received in revised form 23 January 2013  
Accepted 25 January 2013  
Available online 4 February 2013

## ABSTRACT

An efficient and simple route to biologically and pharmaceutically important *o*-hydroxyaryl ketones, xanthenes, 4-chromanones, and flavones has been developed utilizing readily available carboxylic acids and commercially available *o*-(trimethylsilyl)aryl triflates.

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## 1. Introduction

Aryne insertions into C–N,<sup>1,2</sup> C–C,<sup>3</sup> C–Si,<sup>4</sup> C–Sn,<sup>5</sup> and C–Hal<sup>6</sup> bonds and the C=O bond of aldehydes<sup>7</sup> have been well documented in the literature. The formal insertion of a benzyne ring into the C–O bond of a carboxylic acid would provide a powerful synthetic transformation to access a range of biologically important molecules. In our previous work, we have reported that the reaction of arenecarboxylic acids with arynes in MeCN provides the corresponding aryl esters in excellent yields, i.e., the product is formed by formal benzyne insertion into the O–H bond of the starting material (Scheme 1).<sup>8</sup> Following up on this chemistry, we found and reported in an earlier communication reaction conditions, which allow one to obtain good to excellent yields of the

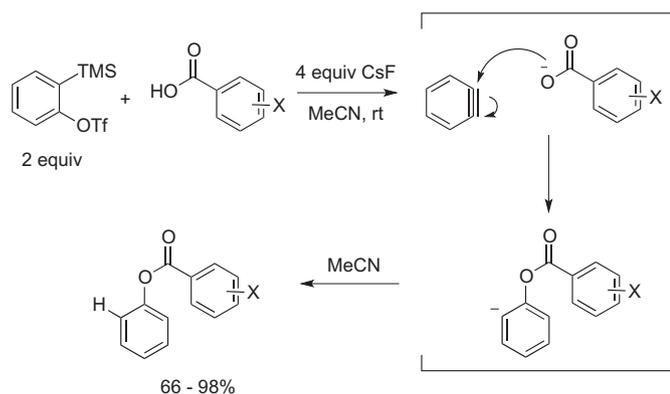
corresponding C–O insertion products.<sup>9</sup> Later, Ma and co-workers reported an interesting cascade sequence that starts from 2,3-allenoic acids and affords chromones in good to excellent yields using KF/18-crown-6 in THF.<sup>10</sup> The present manuscript provides a complete account of the scope and limitations of the synthesis of *o*-hydroxyaryl ketones starting from carboxylic acids, as well as its applications to the synthesis of xanthenes, 4-chromanones, and flavones.

## 2. Results and discussion

### 2.1. Synthesis of *o*-hydroxyaryl ketones

We allowed a simple aliphatic carboxylic acid (butyric acid, **1**) to react with the Kobayashi benzyne precursor *o*-(trimethylsilyl) phenyl triflate<sup>11</sup> (**2**) in the presence of CsF in acetonitrile (Table 1). At both room temperature and at 65 °C, as expected,<sup>8</sup> the *O*-arylation product, ester **4**, was predominately formed (entries 1 and 2). To avoid the formation of the latter product, we switched to a far less acidic solvent, THF. To our delight, together with the monoarylation product **4**, the *o*-hydroxyaryl ketone **3** was formed in a 26% yield (entry 3).

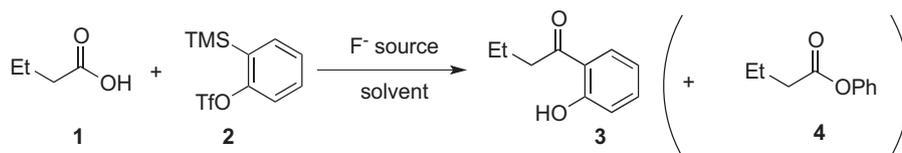
A closer examination of the reaction mixture revealed that additional products inseparable by chromatography, namely tertiary alcohol **5** and xanthene **6**, both bis-aryne insertion products, are produced (Scheme 2). Based on our findings, we propose the following mechanism for the formation of products **3–6**. The aryl anion intermediate **8**, formed after nucleophilic attack of the carboxylate group of the carboxylic acid on the highly electrophilic benzyne (**7**) generated in situ, undergoes a formal anionic Fries rearrangement to the phenoxide **10** by a four-membered ring intermediate **9**.<sup>12</sup> This results in formation of the desired *o*-hydroxyaryl ketone **3** after proton abstraction from the reaction media. The monoarylation product **4** can be formed by protonation of the



Scheme 1. Known reaction of arenecarboxylic acids and arynes in MeCN.

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**Table 1**  
Optimization of benzyne insertion into the C–O bond of an aliphatic carboxylic acid<sup>a</sup>



Entry	Equiv of <b>2</b>	Fluoride source (equiv)	Solvent, mL	Temp (°C)	% Yield of <b>3</b> <sup>b</sup>
1	1.0	CsF (3)	MeCN, 5	rt	0 <sup>c</sup>
2	1.0	CsF (3)	MeCN, 5	65	0 <sup>c</sup>
3	1.0	CsF (3)	THF, 5	65	26
4	1.0	CsF (3)	THF, 5	125	43
5	1.0	CsF (3)	DME, 5	65	20 <sup>c</sup>
6	1.0	CsF (3)	DME, 5	125	27 <sup>c</sup>
7 <sup>d</sup>	1.0	CsF (3)	THF, 5	125	14 <sup>c</sup>
8 <sup>e</sup>	1.0	CsF (3)	THF, 5	125	4 <sup>c</sup>
9	1.2	CsF (3)	THF, 15	125	50
<b>10</b>	<b>1.5</b>	<b>CsF (4)</b>	<b>THF, 15</b>	<b>125</b>	<b>77</b>
11	1.75	CsF (4.7)	THF, 15	125	70
12	2	CsF (6)	THF, 15	125	34
13	1.5	TBAT (2)	Tol, 5	50	34 <sup>c</sup>

Bold values depict the optimized conditions that were used for investigation of the reaction's scope.

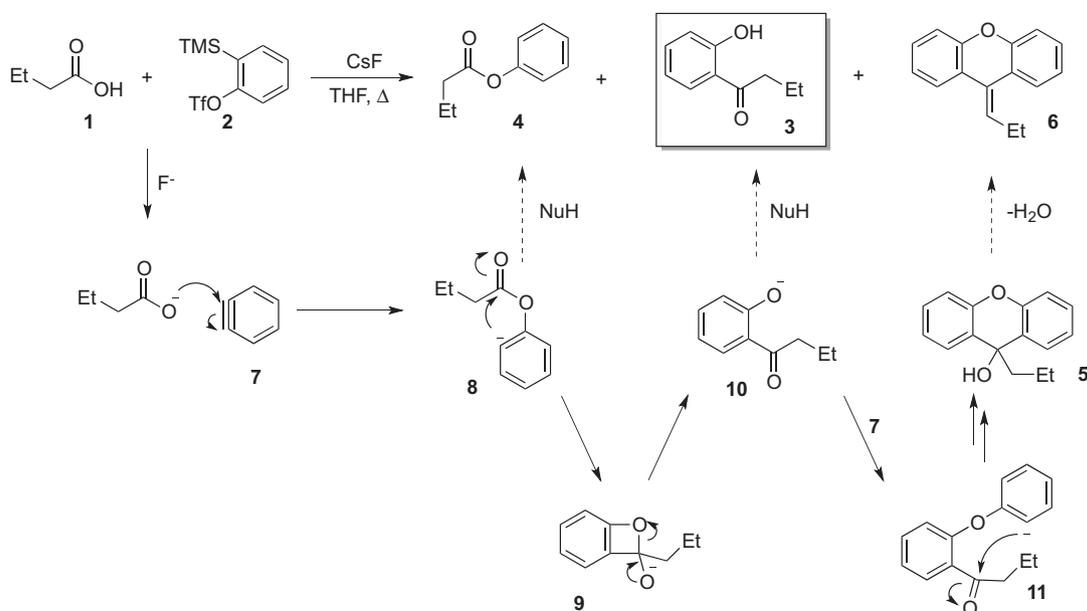
<sup>a</sup> All reactions were carried out on a 0.25 mmol scale in 5 mL of solvent during a 24 h period.

<sup>b</sup> Isolated yields, unless stated otherwise.

<sup>c</sup> <sup>1</sup>H NMR spectroscopic yields using an internal standard.

<sup>d</sup> K<sub>2</sub>CO<sub>3</sub> (1 equiv) was added to the reaction mixture.

<sup>e</sup> Cs<sub>2</sub>CO<sub>3</sub> (1 equiv) was added to the reaction mixture.



**Scheme 2.** Proposed mechanism for the reaction of butyric acid and benzyne.

aryl anion **8**. The by-product **5** is likely formed from reaction of the phenoxide **10** with an additional benzyne intermediate **7**,<sup>13</sup> which followed by dehydration, leads to formation of the xanthene **6**. The proposed four-membered ring intermediate **9** is consistent with similar intermediates reported recently by Greaney's group in a related study of primary aromatic amides.<sup>2</sup>

Isolation of the C–O insertion product **3** prompted us to pursue this project, as it constitutes an expeditious route to *o*-hydroxyaryl ketones, often used as precursors for the synthesis of biologically important flavones and chalcones,<sup>14</sup> starting from cheap and easily accessible carboxylic acids. Most traditional synthetic approaches to *o*-hydroxyaryl ketones ultimately proceed by the Friedel–Crafts acylation of phenols with acyl chlorides in the presence of Lewis

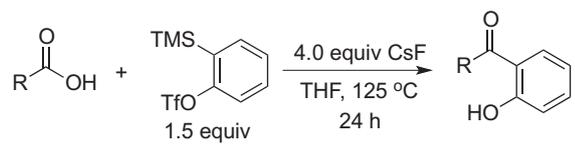
acids,<sup>15</sup> or the Fries rearrangement of suitable phenyl esters.<sup>16</sup> Both of these procedures suffer from regioselectivity issues and proceed in the presence of strong Lewis acids, which limits the potential of this transformation. It is noteworthy that *o*-hydroxyaryl ketones are an important class of biologically interesting structures,<sup>17</sup> and some of them, such as cotoin and hydrocotoin, have been found in nature.<sup>18</sup>

Unexpectedly, running the reaction at higher temperatures allowed us to achieve higher yields of the desired hydroxyaryl ketone, at the same time lowering the relative ratios of the major side-products **4**–**6**. Running the reaction at 125 °C (sealed vial) allowed us to isolate the desired hydroxyaryl ketone **3** in a 43% yield (Table 1, entry 4). Changing the solvent to 1,2-dimethoxyethane (DME) resulted in lower yields of the desired product **3** and

higher ratios of the arylation product **4** at both 65 °C and 125 °C (entries 5 and 6). To test the possibility that the undesired protonation of the intermediate **8** is caused by the proton of the starting acid, we attempted to run the reaction in the presence of a stoichiometric amount of different bases. Unfortunately, the use of K<sub>2</sub>CO<sub>3</sub> as an additive resulted in a lower (14%) yield, which might be caused by the poor solubility of the butyrate formed (entry 7). Running the reaction in the presence of Cs<sub>2</sub>CO<sub>3</sub> resulted in a still lower (4%) yield of the desired product with significant amounts of the ester **4** and the alkene **6** being detected (entry 8). Other bases (e.g., NaH, Na<sub>2</sub>CO<sub>3</sub>, KOPiv, *sym*-collidine) failed to improve the yield of the desired hydroxyaryl ketone. Using the sodium salt of the butyric acid or its TMS-ether resulted in lower yields of the desired product **3** and higher relative ratios of the alkene **6**.

Increasing the amount of the benzyne precursor **1** from 1.0 to 1.2 equiv and diluting the reaction mixture resulted in an increased (50%) yield of the desired product (entry 9). A further increase in the amount of the benzyne precursor (up to 2 equiv) revealed that the highest yield (entry 10, 77%) is achieved with a 1.5-fold excess of the benzyne precursor to the starting butyric acid (entries 9–12). A further increase in the amount of benzyne results in higher ratios of the bis-arylated products **5** and **6**, thus lowering the yield of the desired product **3**. Extending the time of the reaction and using more CsF does not have any significant effect on the yield of the desired ketone **3**. We also attempted to run the reaction under Greaney's conditions, tetrabutylammonium triphenyldifluorosilicate (TBAT) in toluene at 50 °C.<sup>2</sup> However, only a 34% yield of the product **3** was observed in this case, while the undesired ester **4** was detected in a 54% yield (entry 13). We subsequently applied our optimized conditions (Table 1, entry 10) to other carboxylic acids (Table 2).

**Table 2**  
Reaction of carboxylic acids with arynes<sup>a</sup>



Entry	R	Product	Yield <sup>b</sup> (%)
1	Et	<b>3</b>	77
2	Cyclopentyl	<b>12</b>	68
3	Ph	<b>13</b>	62
4	CH <sub>2</sub> =CH-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	<b>14</b>	72
5	MeO-C(=O)-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	<b>15</b>	58
6	Ph-C(=O)-CH <sub>2</sub> -CH <sub>2</sub> -	<b>16</b>	39
7	2-thienyl	<b>17</b>	30
8	1-naphthyl	<b>18</b>	44

<sup>a</sup> Reaction conditions: 0.25 mmol of acid, 1.5 equiv of benzyne precursor and 4.0 equiv of CsF in 15 mL of THF were heated in a closed vial at 125 °C for 24 h.

<sup>b</sup> Isolated yield.

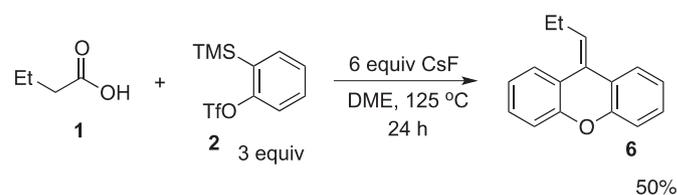
This methodology tolerates cycloalkyl and benzyl groups. The corresponding products **12** and **13** were obtained in 68% and 62% yields, respectively (entries 2 and 3). The alkene-containing

product **14** was successfully isolated in a 72% yield (entry 4). The ester- and ketone-containing carboxylic acids provided the desired products **15** and **16** in lower 58% and 39% yields, respectively (entries 5 and 6).

A number of  $\alpha$ -substituted carboxylic acids, such as *N*-methylindoleacetic acid, *N*-acetylglycine, succinimidoacetic acid, and  $\alpha$ -bromophenylacetic acid were examined under our optimized reaction conditions. Unfortunately, presumably due to either the increased acidity of the protons next to the reacting carboxylic acid functionality and/or the low solubility of some of these substrates in THF, most of these reactions resulted in the formation of inseparable mixtures of by-products with the undesired *O*-arylation products often being formed in considerable amounts. One of the more successful examples of this type of carboxylic acid is 3-thiopheneacetic acid, which resulted in formation of the hydroxyaryl ketone **17** in a 30% yield (entry 7).

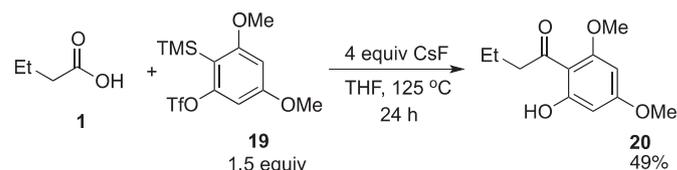
In the case of arenecarboxylic acids, perhaps due to the increased acidity of the resulting hydroxyaryl ketones, over-arylation products were a major concern not only because of decreased yields of the desired insertion products, but also because of complications during their isolation. Thus, in the case of *p*-nitrobenzoic acid, the corresponding tertiary alcohol analogous to intermediate **5** could be isolated in a 54% yield and none of the desired hydroxyaryl ketone was detected. Changing the electronic properties of the substituents on the phenyl ring had little effect on the outcome of the reaction. The desired products of *p*-methoxy- and *p*-methylbenzoic acids were formed in less than 30% yields (as measured by <sup>1</sup>H NMR spectroscopic analysis using an internal standard). Unfortunately, none of these products could be isolated due to a number of side-products with similar polarities. One of the more successful reactions was with  $\beta$ -naphthoic acid, which afforded the corresponding *o*-hydroxyaryl ketone **18** in a 44% yield (entry 8).

Allowing butyric acid to react with an excess (3 equiv) of the benzyne precursor in DME, the bis-aryne insertion xanthene product **6** was obtained in a 50% yield (Scheme 3).<sup>19</sup> Xanthenes are a pharmaceutically important scaffold with many members shown to possess antimalarial,<sup>20</sup> antitrypanosomal,<sup>21</sup> antileishmanial,<sup>21</sup> and antitumor<sup>22</sup> activities.



**Scheme 3.** Synthesis of a xanthene.

We also examined the reaction of butyric acid with the unsymmetrical dimethoxy-substituted benzyne precursor **19**.<sup>23</sup> We were delighted to observe the regioselective formation of the desired isomer **20** in a 49% yield (Scheme 4). The regioselectivity is consistent with that reported by the Stoltz group.<sup>23</sup> The product **20** is a natural product that has been found in an Indian shrub *Dysophylla stellata* Benth.<sup>24</sup>



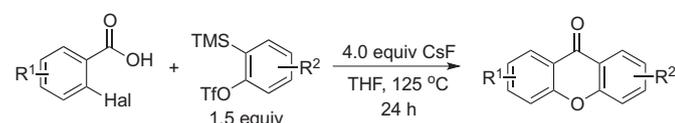
**Scheme 4.** Synthesis of a naturally-occurring hydroxyaryl ketone.

## 2.2. Synthesis of xanthenes

While the low efficiency of the reaction of arenecarboxylic acids with arynes is likely due to the high reactivity of the phenolic OH group of the resulting *o*-hydroxyaryl ketones toward arynes, trapping the phenol by an intramolecular  $S_NAr$  reaction could provide an interesting route to xanthenes and analogues, which are very important ring systems in biology and pharmacy.<sup>25</sup>

Indeed, a close examination of the reaction between *o*-methoxybenzoic acid and benzyne revealed that about 58% of the starting material has been converted to the xanthone **21** and only 12% could be assigned as the expected *o*-hydroxyaryl ketone. When *o*-halobenzoic acids are allowed to react with the benzyne precursor and CsF under our previously optimized conditions, we were delighted to see formation of the xanthone **21** (Table 3). While *o*-chloro and *o*-iodobenzoic acids provided poor yields (30% and 38%, respectively), the *o*-fluorobenzoic acid afforded the desired xanthone in an 80% yield (entry 1).

**Table 3**  
Reaction of *o*-haloarene-carboxylic acids with arynes<sup>a</sup>



Entry	Hal	Product	Yield <sup>b</sup> (%)
1	F		80
2	F		79
3	Cl		22
4	Cl		87 <sup>c</sup>
5	Br		55 <sup>c</sup>
6	Br		59 <sup>c,d</sup>

**Table 3** (continued)

Entry	Hal	Product	Yield <sup>b</sup> (%)
7	Br		49 <sup>c,d,e</sup>
8	F		47 <sup>f</sup>
9	F		71 <sup>g</sup>

<sup>a</sup> Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the benzyne precursor and 4.0 equiv of CsF in 15 mL of THF were heated in a closed vial at 125 °C for 24 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the aryne precursor, and 2.0 equiv of TBAT in 5 mL of toluene were heated at 60 °C for 24 h.

<sup>d</sup> The isolated *o*-hydroxyaryl ketone was heated in MeCN in the presence of 2 equiv of  $K_2CO_3$  at 100 °C for 24 h to provide the desired xanthone.

<sup>e</sup> 3,5-Dimethoxy-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

<sup>f</sup> 4,5-Dimethyl-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

<sup>g</sup> 3-Methoxy-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

Our xanthone process tolerates other halides present in the benzoic acid moiety. Thus, the bromo-substituted xanthone **22** was isolated in a 79% yield (entry 2). The presence of the bromide functionality provides a useful handle for further diversification of the system if a combinatorial library of these compounds is desired.<sup>26</sup>

We could obtain 4-aza-xanthone (**23**), albeit in only a 22% yield (entry 3), starting from 2-chloronicotinic acid. The poor yield in this reaction can be attributed to the high reactivity of the nucleophilic pyridine nitrogen toward benzyne, an often reported process in the literature.<sup>27</sup> The reaction of the electron-poor nitro-substituted carboxylic acid under our optimized reaction conditions provided the desired xanthone **24** in only a 48% yield, with complications during isolation of the desired product. However, running this reaction under reaction conditions reported by the Greaney group for a related insertion into the C–N bond of aromatic amides<sup>2</sup> afforded the xanthone **24** in a high 87% yield (entry 4). Running the reaction of 1-bromo-2-naphthoic acid under analogous conditions afforded the tetracyclic xanthone **25** in a 55% yield (entry 5).

The reaction of electron-rich 2-bromo-4,5-dimethoxybenzoic acid with benzyne afforded only trace amounts of the desired product **26** in both THF and DME. Employing the reaction conditions reported by the Greaney group, in this case provided the uncyclized *o*-hydroxyaryl ketone that upon cyclization in acetonitrile at elevated temperatures in the presence of  $K_2CO_3$  afforded the desired xanthone **26** in a 59% overall yield (entry 6). Interestingly, the bis-demethylated version of xanthone **26** has been shown to significantly inhibit the growth of melanoma cancer cells and the mitogenic response of human lymphocytes to a common mitogen PHA.<sup>28</sup>

Our standard xanthone protocol has also been used for the reaction of 2-bromo-4,5-dimethoxybenzoic acid with the unsymmetrical dimethoxybenzyne precursor **19**. After the benzyne insertion and subsequent induced  $S_NAr$  reaction, the final

tetraoxygenated xanthone **27** was isolated in a 49% overall yield (entry 7). It is noteworthy that the compound **27** is found in nature, as well as partially demethylated analogues.<sup>29</sup> The tetrademethylated version, norathyriol, has been found in at least 19 different natural sources and has been shown to possess hypotensive activity.<sup>30</sup> It is also an effective inhibitor of cutaneous plasma extravasation<sup>31</sup> and a monoamine oxidase inhibitor.<sup>32</sup>

Reacting *o*-fluorobenzoic acid with 4,5-dimethylbenzylidene and unsymmetrical 3-methoxybenzylidene under our CsF/THF optimized conditions afforded the corresponding xanthenes **28** and **29** in 47% and 71% yields, respectively (entries 8 and 9). The low yield in the former case may be attributed to the poor solubility (and hence isolation complications) of the desired product **28**. The unsymmetrical benzylidene precursor provided the product **29** as a single regioisomer.<sup>33</sup>

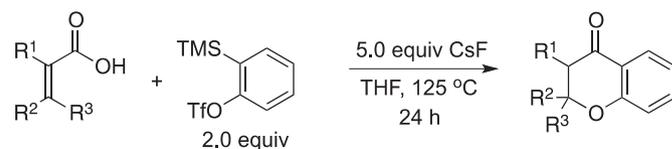
### 2.3. Synthesis of 4-chromanones and flavones

The phenolate anion (see intermediate **10** in Scheme 2) formed in situ could also be potentially trapped with a Michael acceptor in an intramolecular fashion. This would open up a novel route to biologically interesting 4-chromanones, flavones, and chromones from readily available acrylic and propiolic acids.<sup>34</sup>

Indeed, in the reaction of methacrylic acid with benzyne under the optimized reaction conditions used in the synthesis of *o*-hydroxyaryl ketones, the 4-chromanone **30** was formed in a moderate 58% yield. Surprisingly, none of the dihydrocoumarin product that could result from the ring closure of an intermediate like **8** was detected, which suggests that the formation of the four-membered ring intermediate is a more favorable pathway. None of the uncyclized hydroxyaryl ketone product was detected either, suggesting a very fast rate of cyclization for the final Michael addition reaction. Running the methacrylic acid reaction in the presence of various bases (e.g., Cs<sub>2</sub>CO<sub>3</sub>, Et<sub>3</sub>N, <sup>*i*</sup>Pr<sub>2</sub>NEt, *sym*-collidine) failed to improve the yield of the reaction. Substituting the substrate with either the TES- or TBDMS-esters of methacrylic acid both afforded the desired product in lower yields. Running the reaction at decreased temperatures and/or switching the solvent to DME resulted in a lower yield of the desired product. After additional optimization, we have found that diluting the reaction mixture helps to improve the yield of the 4-chromanone **30** by ~10%. Apparently, one of the side reactions involves an intermolecular process. One of the significant challenges observed in this transformation is the poor reactivity of the starting carboxylic acid. As a result, running the reaction with <1.5 equiv of the benzyne precursor does not lead to complete conversion of the starting carboxylic acid.<sup>35</sup> Running the reaction with >2.0 equiv of the precursor **2** allows the carboxylic acid to react completely. However, it also results in increased amounts of over-arylation products (e.g., an alcohol analogous to intermediate **5** in Scheme 2). Running the reaction under dilute conditions with 1.75 equiv of the benzyne precursor provides an 80% yield of the desired product **30**. Finally, adding the benzyne precursor and CsF in two separate portions allowed us to improve the yield up to 84%.<sup>36</sup> The latter reaction conditions were applied to a number of other 2-alkenoic acids (Table 4).

3-Alkyl-substituted acrylic acids successfully provided the corresponding cyclohexyl-substituted and propyl-substituted 4-chromanones **31** and **32** in 85% and 82% yields, respectively (entries 2 and 3). The carboxylic acid with a nitrile substituent at the end of an alkyl chain provided the 4-chromanone **33** in a 71% yield (entry 4). 3,3-Dialkyl-substituted acrylic acids (3-methyl-2-butenoic acid and geranic acid) provided the corresponding chromanones **34** and **35** in good yields (77% and 64%, respectively) (entries 5 and 6).  $\alpha$ -Phenylacrylic acid provided the cyclized product **36** in a 56% yield (entry 7). Interestingly, in the case of cinnamic acid, a 60% yield of the desired product **37** was obtained along with the uncyclized

**Table 4**  
Reaction of acrylic acids with arynes<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Product	Yield <sup>b</sup> (%)
1	Me	H	H	<b>30</b>	84
2	H		H	<b>31</b>	85
3	H	<sup><i>n</i></sup> Pr	H	<b>32</b>	82
4	H	NC(CH <sub>2</sub> ) <sub>3</sub>	H	<b>33</b>	71
5	H	Me	Me	<b>34</b>	77
6	H		Me	<b>35</b>	64
7	Ph	H	H	<b>36</b>	56
8	H	Ph	H	<b>37</b>	74 <sup>c</sup>
9	Me	Me	H	<b>38</b>	76 <sup>d</sup>
10	Me	Ph	H	<b>39</b>	67 <sup>e</sup>
11			H	<b>40</b>	78
12	H	CO <sub>2</sub> Me	H	<b>41</b>	0
13	H	Me	Me		53 <sup>f</sup>
14	H	Ph	H		29 <sup>c,g</sup>

<sup>a</sup> Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of aryne precursor and 4.0 equiv of CsF in 15 mL of THF were heated in a closed vial at 125 °C for 18 h. Then an additional 0.5 equiv of the aryne precursor and 1.0 equiv of CsF were added and the heating continued at 125 °C for 6 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> The yield includes the product obtained after base-induced cyclization of the *o*-hydroxyaryl ketone (see the Supplementary data).

<sup>d</sup> The *E/Z* ratio is ~1.8/1.

<sup>e</sup> The *E/Z* ratio is ~5.1/1.

<sup>f</sup> 4,5-Dimethoxy-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

<sup>g</sup> 3,5-Dimethoxy-2-(trimethylsilyl)phenyl triflate was used as the aryne precursor.

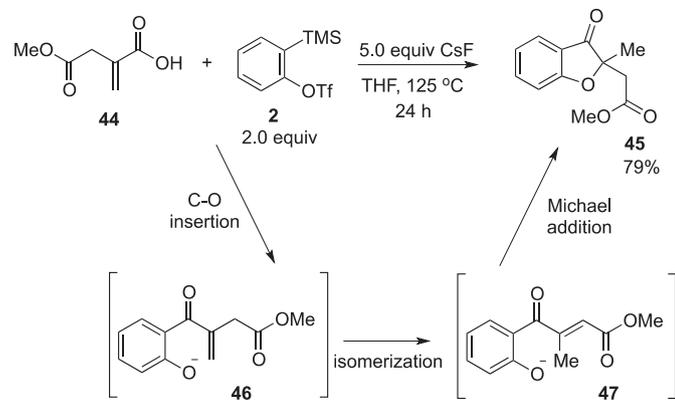
*o*-hydroxyaryl chalcone. Treating the reaction mixture with a base (piperidine/THF/H<sub>2</sub>O)<sup>37</sup> cyclized the hydroxyaryl ketone to the desired flavanone **37** in a 74% overall yield (entry 8). 2,3-Disubstituted acrylic acids provided diastereomeric mixtures of chromanones **38** and **39** in 76% and 67% yields, respectively (entries 9 and 10). Cyclopentene-1-carboxylic acid afforded the tricyclic product **40** in a 78% yield with exclusively a *cis* configuration at the 5,6-ring junction (entry 11). Unfortunately, monomethyl fumarate (as well as monomethyl maleate), bearing an ester group on the carbon-carbon double bond, did not provide any of the expected chromanone product (entry 12). One possible explanation might be the decreased nucleophilicity of the carboxylic group toward the benzyne caused by the presence of the two electron-withdrawing groups. Other carboxylic acids that provided low yields (less than 30%) of the

expected products include 2,4-alkadienoic (2,4-hexadienoic and 5-phenyl-2,4-pentadienoic) acids and 3-heteroaryl-substituted (2-thienyl and 3-indolyl) acrylic acids. These substrates could potentially engage in Diels–Alder reactions with the dienophilic benzyne at such high temperatures.

We have also examined the reaction of alkenoic acids with other benzyne precursors. The symmetrical 4,5-dimethoxybenzyne, when allowed to react with 3,3-dimethylacrylic acid, provided the cyclized product **42** in a 53% yield.<sup>38</sup> It is noteworthy that an analogue of this compound, precocene II, exhibits significant anti-juvenile hormone activity in insects.<sup>39</sup>

When cinnamic acid was allowed to react with the unsymmetrical dimethoxybenzyne precursor **19**, at first the uncyclized *o*-hydroxychalcone was isolated in a 68% yield. Subjecting the latter compound to a piperidine-promoted intramolecular Michael addition reaction resulted in formation of the desired chromanone **43** in a 48% yield, along with 42% of the unreacted starting material. A chiral version of compound **43** is a natural product found in *Caesalpinia pulcherrima*,<sup>40</sup> and the monodemethylated version of the latter, known as pinostrobin, is reported to be an effective aromatase inhibitor.<sup>41</sup>

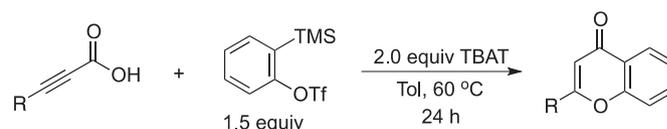
The reaction of itaconic acid methyl ester **44** with benzyne under our optimized conditions did not result in formation of the expected flavanone. Instead, the 3-coumaranone derivative **45** was isolated in a 79% yield (Scheme 5). Since monomethyl fumarate did not provide any isolable product under identical reaction conditions (Table 4, entry 12), this reaction is best explained mechanistically as follows: (a) the carboxylic acid undergoes the expected insertion with benzyne to provide intermediate **46**; (b) the latter isomerizes to a more stable isomer **47** under the reaction conditions; (c) intramolecular Michael addition in the substrate **47** results in formation of the five-membered ring product **45**.



Scheme 5. Mechanism for the formation of coumaranone **45**.

We have also examined the reaction of phenylpropionic acid with benzyne in THF under our optimized reaction conditions. Unfortunately, due to the high temperature of the reaction, the major product observed was the decarboxylated starting material. To minimize the side reaction observed in the reaction of phenylpropionic acid, we attempted to decrease the temperature to 90 °C. Gratifyingly, the yield of the product increased to 48%. If we employed TBAT, the desired product **48** could be isolated in a similar 49% yield, while running the reaction at only 65 °C. We then replaced THF with toluene, essentially employing reaction conditions analogous to those reported by Greaney's group using amides.<sup>2</sup> Running the reaction in toluene at 60 °C allowed us to obtain the flavone **48** in increased yields, with the optimal conditions employing 1.5 equiv of the benzyne precursor (56% yield; Table 5, entry 1).

Table 5  
Reaction of 2-alkynoic acids with arynes<sup>a</sup>



Entry	R	Product	Yield <sup>b</sup> (%)
1	Ph	<b>48</b>	56
2	Me	<b>49</b>	64
3	H	<b>50</b>	71 <sup>c</sup>

<sup>a</sup> Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the aryne precursor and 2.0 equiv of TBAT in 5 mL of toluene were heated at 60 °C for 24 h.

<sup>b</sup> Isolated yield.

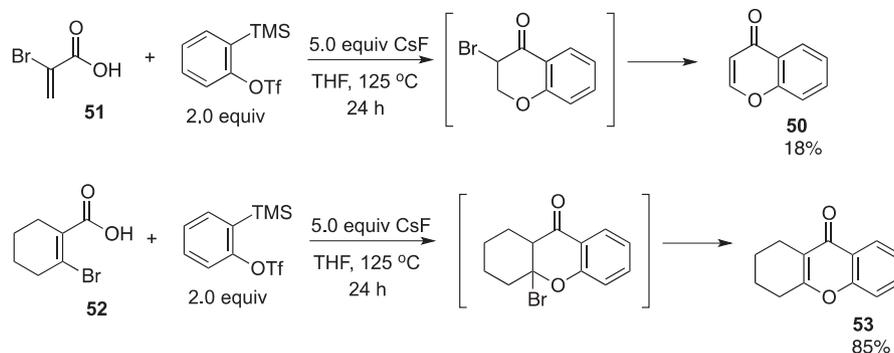
<sup>c</sup> Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the aryne precursor and 2.0 equiv of TBAT in 15 mL of THF were heated at 65 °C for 24 h.

Using these optimized reaction conditions, we have examined the reaction of several 2-alkynoic acids with benzyne. 2-Butynoic acid provided the chromone **49** in a 64% yield (entry 2). The reaction of the unsubstituted propionic acid with CsF in THF did not provide any recognizable products. However, running the reaction in the presence of TBAT provided the desired chromone **50** in a 71% yield (entry 3). Unfortunately, acetylenedicarboxylic acid provided mixtures of unidentified products using either the CsF- or TBAT-mediated protocols.

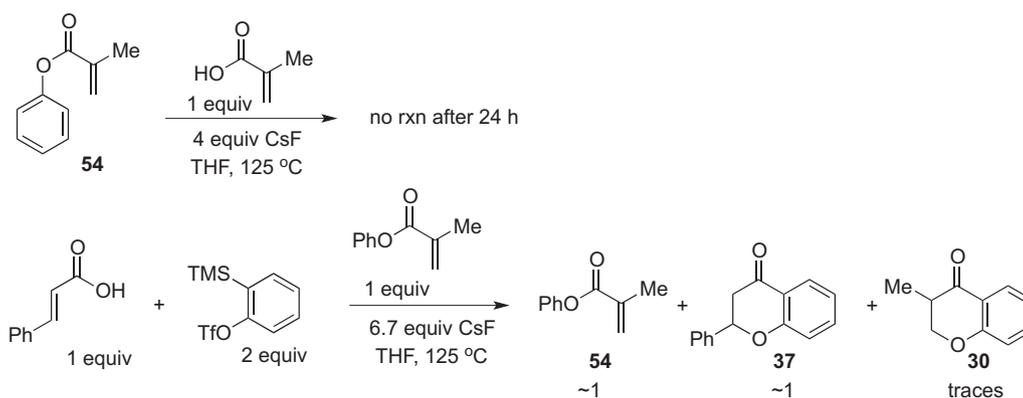
It is noteworthy that we can also obtain chromones in the reaction of 2- and 3-haloalkenoic acids with benzyne. Apparently, the chromanones produced with 2-bromoacrylic and 2-bromocyclohexenoic acids undergo an elimination reaction furnishing the chromones **50** and **53** in 18% and 85% yields, respectively (Scheme 6). The low yield of the former product might be due to a less favorable dehydrohalogenation reaction, as well as the possible low stability of the starting material under the reaction conditions that we have employed.

2.3.1. Further mechanistic considerations. Some further mechanistic considerations follow. An acid-catalyzed Fries rearrangement leading from ester **4** (see Scheme 2) to an *o*-hydroxyaryl ketone (analogous to compound **3**) has been considered as a mechanistic possibility for our overall transformation. Based on literature accounts, however, strong acidic media is absolutely necessary for such a rearrangement to occur.<sup>42</sup> Nevertheless, we allowed phenyl methacrylate (**54**) to react with methacrylic acid in THF in the presence of CsF at 120 °C (Scheme 7). As expected, no 4-chromanone was detected under these reaction conditions after 24 h. Replacing the basic CsF media with 1 equiv of BF<sub>3</sub>•Et<sub>2</sub>O did not result in the formation of the target compound **30** either. However, the benzyne intermediate or molecules that result from its generation might play the role of a Lewis acid in this transformation. In a crossover experiment, we have allowed cinnamic acid to react with 2 equiv of the benzyne precursor in the presence of CsF and phenyl methacrylate at 125 °C. Unexpectedly, the chromanone **30**, that could only be formed from the ester **54**, was detected in the <sup>1</sup>H NMR spectrum of the crude reaction mixture, albeit in only trace amounts. This suggests that the cationic Fries mechanism is, at the most, a very minor pathway for the transformation of acrylic acids into the corresponding chromanones.

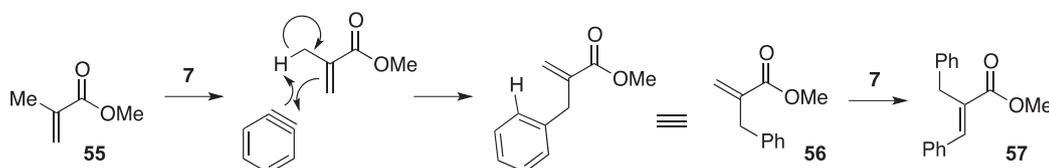
We have also examined the possibility that methyl esters can engage in a similar C–O insertion process with a benzyne. While no traces of any reaction were observed in the case of methyl benzoate, methyl methacrylate unexpectedly resulted in the formation of two stable products in ~10% yields. Once the structures of these products were established, it became evident that no C–O insertion had taken place in the starting ester **55**. Instead, because of the favorable configuration of the methacrylate unit, a set of two ene-reactions apparently occurs to produce the two ester products **56** and **57** (Scheme 8).



Scheme 6. Reaction of haloalkenoic acids with benzyne.



Scheme 7. Mechanistic investigation of the possible cationic Fries rearrangement.



Scheme 8. Mechanism of the double ene reaction.

After optimization studies, it was found that running the methyl methacrylate reaction in acetonitrile at room temperature in the presence of an excess of the benzyne (3 equiv), the diarylated product **57** can be isolated in an 80% yield.

Other methods leading to stereodefined trisubstituted alkenes usually utilize multiple synthetic steps and require the use of expensive rhodium catalysts.<sup>43</sup> We therefore examined the scope of our aryne ene reaction. Unfortunately, allylic systems similar to methyl methacrylate, such as methacrylonitrile, methyl *trans*-2-butenolate, 3-methyl-2-cyclohexenone, allyl, and benzyl cyanides, resulted in only a very low conversion of the starting material or in the formation of mixtures of unidentified products. While a few ene reactions with a benzyne intermediate have been observed before,<sup>43</sup> our reaction of methyl methacrylate proceeds under very mild conditions (MeCN, room temperature) and allows one to obtain the diarylated product **57** in a high yield.

### 3. Conclusions

In conclusion, we have developed an efficient and simple route to *o*-hydroxyaryl ketones, xanthenes, 4-chromanones, flavones and their analogues by aryne incorporation into the C–O bond of easily

accessible carboxylic acids and subsequent reactions. Various functional groups have proven to be compatible with the reaction conditions. The method should prove useful and reliable for accessing these biologically and pharmaceutically important heterocyclic structures.

## 4. Experimental section

### 4.1. General

The <sup>1</sup>H NMR spectra were recorded at 300, 400, and 600 MHz as specified for particular compounds. The <sup>13</sup>C NMR spectra were recorded at 75, 100, and 150 MHz. Chemical shifts are reported in  $\delta$  units (parts per million) by assigning the TMS resonance in the <sup>1</sup>H NMR spectrum as 0.00 ppm and the CDCl<sub>3</sub> resonance in the <sup>13</sup>C NMR spectrum as 77.23 ppm. All coupling constants (*J*) are reported in Hertz (Hz). Thin layer chromatography was performed using 60 mesh silica gel plates, and visualization was effected by short wavelength UV light (254 nm). All melting points are uncorrected. High resolution mass spectra (HRMS) were recorded using EI at 70 eV or using a QTOF mass spectrometer (APCI at a voltage of 70 eV). All reagents were used directly as obtained commercially, unless otherwise noted.

The characterization of compounds **3**, **6**, **12–15**, **18**, **21**, **23**, **29**, **30**, **32**, **34**, **36–40**, **42**, **48**, and **49** can be found in our earlier report.<sup>9</sup>

#### 4.2. General procedure for the reaction of carboxylic acids with arynes

The aryne precursor (1.5 equiv) was added to a mixture of carboxylic acid (0.25 mmol) and CsF (4.0 equiv) in 15 mL of freshly distilled THF, and the reaction mixture was then stirred in a closed vial at 125 °C for 18 h. After the reaction mixture was allowed to cool to room temperature, it was eluted through a plug of silica gel with ethyl acetate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired *o*-hydroxyaryl ketone.

**4.2.1. 1-(2-Hydroxyphenyl)-4-phenylbutane-1,4-dione (16).** This compound was obtained as a white solid in a 39% yield: mp 107–108 °C <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.43–3.54 (m, 4H), 6.94 (t, *J*=7.6 Hz, 1H), 6.99 (d, *J*=8.1 Hz, 1H), 7.46–7.53 (m, 3H), 7.60 (t, *J*=7.3 Hz, 1H), 7.91 (d, *J*=8.0 Hz, 1H), 8.04 (d, *J*=7.5 Hz, 2H), 12.12 (s, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 32.3 (×2), 118.7, 119.2, 119.5, 128.3, 128.9, 130.1, 133.5, 136.6, 136.8, 162.5, 198.4, 204.8; HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>16</sub>H<sub>15</sub>O<sub>3</sub> 255.1016, found 255.1014.

**4.2.2. 1-(2-Hydroxyphenyl)-2-(thiophen-3-yl)ethanone (17).** This compound was obtained as a yellow semisolid in a 30% yield: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.34 (s, 2H), 6.91 (t, *J*=7.6 Hz, 1H), 7.00 (d, *J*=8.8 Hz, 1H), 7.03 (d, *J*=5.7 Hz, 1H), 7.15 (s, 1H), 7.33 (dd, *J*=4.9, 3.0 Hz, 1H), 7.48 (t, *J*=8.4 Hz, 1H), 7.85 (d, *J*=8.0 Hz, 1H), 12.20 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 39.8, 118.7, 118.9, 119.0, 123.1, 126.1, 128.5, 130.3, 133.4, 136.6, 162.9, 203.3; HRMS (EI) calcd for C<sub>12</sub>H<sub>10</sub>O<sub>2</sub>S 218.0396, found 218.0391.

**4.2.3. 1-(2-Hydroxy-4,6-dimethoxyphenyl)butan-1-one (20).** This compound was obtained as a white solid in a 49% yield: mp 69–72 °C (lit.<sup>44</sup> mp 70 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.98 (t, *J*=7.4 Hz, 3H), 1.59–1.65 (m, 2H), 2.96 (t, *J*=7.3 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 5.92 (d, *J*=2.4 Hz, 1H), 6.06 (d, *J*=2.5 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.0, 18.1, 46.1, 55.5 (×2), 90.7, 93.6, 105.8, 162.7, 165.7, 167.6, 205.8; HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>12</sub>H<sub>17</sub>O<sub>4</sub> 225.1121, found 225.1122.

**4.2.4. 2-Bromoxanthone (22).** This compound was obtained as a white solid in a 79% yield: mp 148–150 °C (lit.<sup>45</sup> mp 150 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33–7.42 (m, 2H), 7.47 (d, *J*=8.5 Hz, 1H), 7.69–7.79 (m, 2H), 8.29 (dd, *J*=7.9, 1.7 Hz, 1H), 8.42 (d, *J*=2.5 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 117.3, 118.3, 120.2, 121.7, 123.3, 124.5, 127.0, 129.4, 135.4, 137.9, 155.1, 156.2, 176.2; HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>13</sub>H<sub>8</sub>BrO<sub>2</sub> 274.9702, found 274.9706. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data are in good agreement with the literature data.<sup>13</sup>

**4.2.5. 2,3-Dimethylxanthone (28).** This compound was obtained as a white solid in a 47% yield: mp 156–158 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.35 (s, 3H), 2.38 (s, 3H), 7.24 (s, 1H), 7.34 (t, *J*=7.5 Hz, 1H), 7.44 (d, *J*=8.3 Hz, 1H), 7.68 (t, *J*=7.8 Hz, 1H), 8.04 (s, 1H), 8.32 (d, *J*=8.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.5, 20.8, 118.1, 118.3, 119.9, 122.1, 123.8, 126.5, 126.9, 133.3, 134.6, 145.7, 154.9, 156.3, 177.3. HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>15</sub>H<sub>13</sub>O<sub>2</sub> 225.0910, found 225.0911. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data are in good agreement with the literature data.<sup>13</sup>

**4.2.6. Synthesis of 2-nitroxanthone (24).** *o*-(Trimethylsilyl)phenyl triflate (1.5 equiv) was added to a mixture of 2-chloro-5-nitrobenzoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of toluene, and the reaction mixture was then stirred at 60 °C for

24 h. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL×2) from the brine solution (40 mL), the organic fractions were combined, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired xanthone **24** as a pale brown solid in an 87% yield: mp 203–205 °C (lit. mp<sup>46</sup> 202–203 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47 (t, *J*=7.6 Hz, 1H), 7.55 (d, *J*=8.5 Hz, 1H), 7.64 (d, *J*=9.2 Hz, 1H), 7.81 (ddd, *J*=8.7, 7.1, 1.7 Hz, 1H), 8.33 (dd, *J*=7.9, 1.7 Hz, 1H), 8.54 (dd, *J*=9.2, 2.8 Hz, 1H), 9.19 (d, *J*=2.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 118.2, 119.7, 121.3, 121.6, 123.5, 125.3, 126.9, 129.0, 135.9, 155.8, 159.1, 175.7; HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>13</sub>H<sub>8</sub>NO<sub>4</sub> 242.0448, found 242.0452. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data are in good agreement with the literature data.<sup>47</sup>

**4.2.7. Synthesis of benzo[*c*]xanthone (25).** *o*-(Trimethylsilyl)phenyl triflate (1.5 equiv) was added to a mixture of 1-bromo-2-naphthoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of toluene, and the reaction mixture was then stirred at 60 °C for 24 h. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL×2) from the brine solution (40 mL), the organic fractions were combined, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired xanthone **25** as a white solid in a 55% yield: mp 149–151 °C (lit. mp<sup>48</sup> 147–149 °C); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.43 (s, 1H), 7.61–7.80 (m, 5H), 7.90–7.94 (m, 1H), 8.27 (d, *J*=8.2 Hz, 1H), 8.40 (d, *J*=6.4 Hz, 1H), 8.66 (d, *J*=6.5 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 117.6, 118.1, 121.5, 122.5, 122.9, 124.0, 124.1, 124.4, 126.6, 126.9, 128.1, 129.6, 134.4, 136.6, 153.7, 155.8, 176.9; HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>17</sub>H<sub>11</sub>O<sub>2</sub> 247.0754, found 247.0751. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data are in good agreement with the literature data.<sup>13</sup>

**4.2.8. Synthesis of 2,3-dimethoxyxanthone (26).** *o*-(Trimethylsilyl)phenyl triflate (1.5 equiv) was added to a mixture of 2-bromo-4,5-dimethoxybenzoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of toluene, and the reaction mixture was then stirred at 60 °C for 24 h. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL×2) from the brine solution (40 mL), the organic fractions were combined, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the corresponding hydroxyaryl ketone. The latter was dissolved in 4 mL of MeCN and heated in the presence of K<sub>2</sub>CO<sub>3</sub> (2 equiv) at 100 °C for 24 h. After allowing the reaction mixture to cool to room temperature, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired xanthone **26** as a light brown solid in a 59% yield: mp 161–162 °C (lit.<sup>49</sup> mp 163–164 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.99 (s, 3H), 4.01 (s, 3H), 6.90 (s, 1H), 7.36 (t, *J*=7.6 Hz, 1H), 7.44 (d, *J*=8.3 Hz, 1H), 7.63–7.70 (m, 2H), 8.30–8.35 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 56.3, 56.5, 99.6, 105.3, 114.9, 117.6, 121.5, 123.7, 126.5, 133.9, 146.7, 152.4, 155.4, 156.0, 176.0; HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>15</sub>H<sub>13</sub>O<sub>4</sub> 257.0808, found 257.0809. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data are in good agreement with the literature data.<sup>13</sup>

**4.2.9. Synthesis of 1,3,6,7-tetramethoxyxanthone (27).** The corresponding dimethoxyaryne precursor (1.5 equiv) was added to a mixture of 2-bromo-4,5-dimethoxybenzoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of toluene, and the reaction mixture was then stirred at 60 °C for 24 h. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL×2) from the brine solution (40 mL), the organic fractions

were combined and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the corresponding hydroxyaryl ketone. The latter was dissolved in 4 mL of MeCN and heated in the presence of  $K_2CO_3$  (2 equiv) at 100 °C for 24 h. After allowing the reaction mixture to cool to room temperature, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired xanthone **27** as a light brown solid in a 49% yield: mp 202–203 °C (lit.<sup>50</sup> mp 202 °C);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.86 (s, 3H), 3.92–3.95 (m, 9H), 6.29 (d,  $J=2.1$  Hz, 1H), 6.40 (d,  $J=2.1$  Hz, 1H), 6.74 (s, 1H), 7.60 (s, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  55.6, 56.2, 56.3, 56.3, 92.5, 95.0, 98.9, 105.7, 106.9, 116.0, 146.4, 150.7, 154.3, 159.7, 161.8, 164.2, 174.6; HRMS (APCI) calcd for  $[M+H]^+$   $C_{17}H_{17}O_6$  317.1020, found 317.1023. The  $^1H$  and  $^{13}C$  NMR spectral data are in good agreement with the literature data.<sup>51</sup>

### 4.3. General procedure for the reaction of 2-alkenoic acids with arynes

The aryne precursor (1.5 equiv) was added to a mixture of 2-alkenoic acid (0.25 mmol) and CsF (4.0 equiv) in 15 mL of freshly distilled THF, and the reaction mixture was then stirred in a closed vial at 125 °C for 18 h. After allowing the reaction mixture to cool, additional aryne precursor (0.5 equiv) and CsF (1.0 equiv) were quickly added and heating was continued at 125 °C for 6 h. After the reaction mixture was allowed to cool to room temperature, it was eluted through a plug of silica gel with ethyl acetate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired 4-chromanones.

**4.3.1. 2-Cyclohexylchroman-4-one (31).** This compound was obtained as a pale yellow oil in an 85% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.06–1.34 (m, 5H), 1.64–1.85 (m, 5H), 1.98 (d,  $J=12.3$  Hz, 1H), 2.60–2.77 (m, 2H), 4.14–4.24 (m, 1H), 6.94–7.01 (m, 2H), 7.46 (ddd,  $J=8.7, 7.2, 1.8$  Hz, 1H), 7.86 (dd,  $J=7.8, 1.8$  Hz, 1H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  25.9, 26.0, 26.3, 28.2, 28.3, 40.3, 41.8, 82.0, 117.9, 121.0, 126.9, 135.9, 161.9, 193.2 (doubled signals at 25.9–26.0 and 28.2–28.3 are likely due to different electronic environments of the corresponding carbons); HRMS (APCI) calcd for  $[M+H]^+$   $C_{15}H_{19}O_2$  231.1380, found 231.1382. The  $^1H$  and  $^{13}C$  NMR spectral data are in good agreement with the literature data.<sup>52</sup>

**4.3.2. 4-(4-Oxochroman-2-yl)butanenitrile (33).** This compound was obtained as a pale yellow oil in a 71% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.82–2.08 (m, 4H), 2.48 (t,  $J=6.6$  Hz, 2H), 2.63–2.78 (m, 2H), 4.41–4.51 (m, 1H), 6.96 (d,  $J=8.4$  Hz, 1H), 7.02 (t,  $J=7.5$  Hz, 1H), 7.48 (t,  $J=7.8$  Hz, 1H), 7.87 (d,  $J=7.9$  Hz, 1H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  17.1, 21.3, 33.7, 42.9, 76.9, 117.9, 119.2, 120.9, 121.6, 127.1, 136.2, 161.2, 191.8; HRMS (APCI) calcd for  $[M+H]^+$   $C_{13}H_{14}NO_2$  216.1019, found 216.1021.

**4.3.3. 2-Methyl-2-(4-methylpent-3-en-1-yl)chroman-4-one (35).** This compound was obtained as a colorless oil in a 64% yield:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.41 (s, 3H), 1.57 (s, 3H), 1.63–1.73 (m, 4H), 1.75–1.85 (m, 1H), 2.05–2.17 (m, 2H), 2.66 (d,  $J=16.4$  Hz, 1H), 2.79 (d,  $J=16.4$  Hz, 1H), 5.02–5.10 (m, 1H), 6.89–7.01 (m, 2H), 7.46 (ddd,  $J=8.6, 7.2, 1.8$  Hz, 1H), 7.84 (dd,  $J=7.8, 1.8$  Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  17.8, 22.5, 24.2, 25.9, 39.5, 47.7, 81.3, 118.5, 120.6, 120.8, 123.5, 126.6, 132.5, 136.3, 160.0, 192.9; HRMS (APCI) calcd for  $[M+H]^+$   $C_{16}H_{21}O_2$  245.1536, found 245.1541.

**4.3.4. Synthesis of 5,7-dimethoxy-2-phenylchroman-4-one (43).** After the reaction between cinnamic acid and the

unsymmetrical dimethoxy-substituted benzyne precursor **19**, the uncyclized o-hydroxyaryl ketone was isolated in a 68% yield as a yellow solid: mp 71–74 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.84 (s, 3H), 3.92 (s, 3H), 5.96 (s, 1H), 6.11 (s, 1H), 7.33–7.47 (m, 4H), 7.58–7.65 (m, 3H), 7.78 (d,  $J=15.6$  Hz, 1H), 7.91 (d,  $J=15.6$  Hz, 1H); HRMS (APCI) calcd for  $[M+H]^+$   $C_{17}H_{17}O_4$  285.1121, found 285.1129. The latter was dissolved in 5 mL of THF, then 10 mL of water and 10  $\mu$ L of piperidine were added, and the mixture was stirred for 2 h at 40 °C. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL $\times$ 2), the organic fractions were combined, and the solvent was evaporated under reduced pressure. Flash chromatography on silica gel using hexanes/EtOAc as the eluent afforded 42% of the unreacted starting material and 48% of the desired 4-chromanone **43** as a white solid: mp 144–146 °C (lit.<sup>53</sup> mp 145–146 °C);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.80 (dd,  $J=16.4, 2.7$  Hz, 1H), 2.97–3.07 (m, 1H), 3.82 (s, 3H), 3.90 (s, 3H), 5.41 (d,  $J=14.8$  Hz, 1H), 6.10 (s, 1H), 6.16 (s, 1H), 7.31–7.49 (m, 5H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  45.6, 55.6, 56.2, 79.3, 93.2, 93.6, 106.0, 126.1, 128.7, 128.8, 138.8, 162.3, 165.0, 166.0, 189.2; HRMS (APCI) calcd for  $[M+H]^+$   $C_{17}H_{17}O_4$  285.1121, found 285.1124. The  $^1H$  and  $^{13}C$  NMR spectral data are in good agreement with the literature data.<sup>53</sup>

**4.3.5. Methyl 2-(2-methyl-3-oxo-2,3-dihydrobenzofuran-2-yl)acetate (45).** This compound was obtained as a yellow solid in a 79% yield starting from the monomethyl ester of itaconic acid: mp 127–130 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.46 (s, 3H), 2.93 (d,  $J=16.4$  Hz, 1H), 3.02 (d,  $J=16.4$  Hz, 1H), 3.53 (s, 3H), 7.08 (t,  $J=8.1$  Hz, 2H), 7.59 (t,  $J=7.8$  Hz, 1H), 7.69 (d,  $J=7.6$  Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  22.6, 41.5, 52.1, 86.5, 113.5, 120.6, 122.2, 124.8, 138.0, 169.3, 171.1, 202.8; HRMS (APCI) calcd for  $[M+H]^+$   $C_{12}H_{13}O_4$  221.0808, found 221.0809.

### 4.4. Procedure for the reaction of 2-alkynoic acids with arynes

The aryne precursor (1.5 equiv) was added to a mixture of 2-alkynoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of anhydrous toluene, and the reaction mixture was then stirred in a closed vial at 60 °C for 24 h. After the reaction mixture was allowed to cool to room temperature, the reaction mixture was then poured into brine (15 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 $\times$ 15 mL) and the organic layers were combined and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired chromone derivatives.

**4.4.1. Chromone (50).** This compound was obtained as a yellow semisolid in a 71% yield running the reaction in 15 mL of THF at 65 °C, instead of toluene at 60 °C. The same compound was also obtained in an 18% yield starting from 2-bromoacrylic acid (**51**) using the CsF/THF protocol at 125 °C:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.34 (d,  $J=6.0$  Hz, 1H), 7.40 (t,  $J=7.6$  Hz, 1H), 7.45 (d,  $J=8.4$  Hz, 1H), 7.67 (t,  $J=7.8$  Hz, 1H), 7.85 (d,  $J=6.0$  Hz, 1H), 8.20 (d,  $J=8.0$  Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  113.3, 118.4, 125.1, 125.5, 126.0, 134.0, 155.5, 156.7, 177.8; HRMS (EI) calcd for  $C_9H_6O_2$  146.0368, found 146.0370. The  $^1H$  and  $^{13}C$  NMR spectral data are in good agreement with the literature data.<sup>54</sup>

**4.4.2. 3,4-Dihydro-1H-xanthen-9(2H)-one (53).** This compound was obtained as a white solid in an 85% yield starting from 2-bromocyclohexenoic acid (**52**) using the CsF/THF protocol at 125 °C: mp 87–88 °C (lit.<sup>55</sup> mp 91–92 °C);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.71–1.91 (m, 4H), 2.56–2.68 (m, 4H), 7.29–7.39 (m, 2H), 7.59 (ddd,  $J=8.6, 7.1, 1.7$  Hz, 1H), 8.19 (dd,  $J=8.0, 1.7$  Hz, 1H);  $^{13}C$  NMR

(150 MHz, CDCl<sub>3</sub>)  $\delta$  21.0, 21.7, 21.9, 28.2, 117.6, 118.4, 123.2, 124.4, 125.7, 132.9, 155.9, 163.9, 177.8; HRMS (APCI) calcd for [M+H]<sup>+</sup> C<sub>13</sub>H<sub>13</sub>O<sub>2</sub> 201.0910, found 201.0916. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data are in good agreement with the literature data.<sup>56</sup>

#### 4.5. Procedure for the preparation of methyl (E)-2-benzyl-3-phenylacrylate (57)

o-(Trimethylsilyl)phenyl triflate (3.0 equiv) was added to a mixture of methyl methacrylate (0.25 mmol) and CsF (6.0 equiv) in 5 mL of MeCN, and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then eluted through a plug of silica gel with ethyl acetate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired diarylated product **57** as a colorless oil in an 80% yield: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.76 (s, 3H), 3.97 (s, 2H), 7.17–7.41 (m, 10H), 7.95 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  33.4, 52.3, 126.3, 128.1, 128.7, 128.8, 129.0, 129.4, 130.9, 135.6, 139.6, 141.2, 168.8; HRMS (EI) calcd for C<sub>17</sub>H<sub>16</sub>O<sub>2</sub> 252.1150, found 252.1170. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data are in good agreement with the literature data.<sup>43b</sup>

#### Acknowledgements

We thank the National Science Foundation, the National Institute of General Medical Sciences (GM079593) and the National Institutes of Health Kansas University Center of Excellence in Chemical Methodology and Library Development (P50 GM069663) for their generous financial support. We also thank Dr. Feng Shi, while at Iowa State University, for the preparation of some aryne precursors.

#### Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2013.01.078>.

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