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# Single-Flask Multicomponent Synthesis of Highly Substituted α-Pyrones via a Sequential Enolate Arylation and Alkenylation Strategy

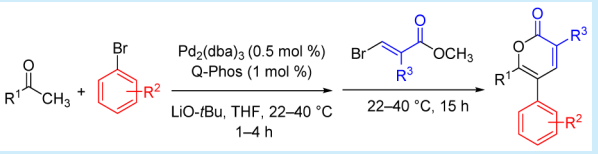
Michael Grigalunas,[†] Olaf Wiest,[†,‡] and Paul Helquist*[,†]

[†]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46566, United States

[‡]Lab of Computational Chemistry and Drug Design, School of Chemical Biology and Biotechnology, Peking University, Shenzhen Graduate School, Shenzhen 518055, China

Supporting Information

**ABSTRACT:** Trisubstituted α-pyrones are obtained by a Pd-catalyzed three-component, single-flask operation via an α-arylation, subsequent α-alkenylation, alkene isomerization, and dienolate lactonization. A variety of coupling components under mild conditions afforded isolated yields of up to 93% of the pyrones with complete control of regioselectivity. Metal dependence was noted for three of the steps of the pathway. Utility of the pyrone products was demonstrated by further transformations providing convenient access to polyaromatic compounds, exhibiting broad molecular diversity.




α-Pyrones are valuable heterocycles found in many biologically active compounds[1] and are versatile synthetic building blocks[2] for further transformations.[3] Because of the importance of α-pyrones, several synthetic procedures have been reported for their synthesis using either conventional organic[4] or organometallic reactions.[5] Typical approaches involve intramolecular or intermolecular ring-forming processes, but often require multistep syntheses to obtain the necessary substrates, resulting in limitations on facile access to molecularly diverse α-pyrones.[3] Furthermore, a number of procedures employ harsh reaction conditions, have a limited substrate scope, and are non-regiospecific, leading to an undesired mixture of regioisomers or to a predominance of an undesired isomer.[5a−d,6] Thus, there is a clear need for improved methods to access more readily a diverse array of these compounds. With the growing need to explore chemical space for medicinal and material science purposes, multicomponent reactions that present an avenue for facile access to molecular diversity while decreasing the number of individual operations and eliminating the need for isolation and purification of intermediates are especially desirable.[7−9]

To provide facile and modular access to molecularly diverse α-pyrones, we set out to design a multicomponent, single-flask approach to α-pyrones employing a sequence of ketone α-arylation, α-alkenylation, and *E*/*Z*-isomerization/lactonization. While each individual reaction is known, incorporating all three reactions into a single-flask operation would streamline access to highly substituted α-pyrones. Our envisioned multicomponent approach (Figure 1) would begin with a Pd-catalyzed coupling of a methyl ketone **1** with an aryl halide **2**.[10] Under the basic reaction conditions, the α-arylated product **3** would be deprotonated and, after the addition of a β-bromoacrylate **4** to the reaction mixture, a further coupling would occur.[11] The α-alkenylated intermediate **5** would undergo deprotonation followed by *E*/*Z*-isomerization and lactonization to afford an α-pyrone **6**. Herein we report the successful implementation of this approach to a diverse range of trisubstituted α-pyrones under mild conditions from simple, readily available starting materials, and we demonstrate the utility of the resulting pyrones in various further transformations.

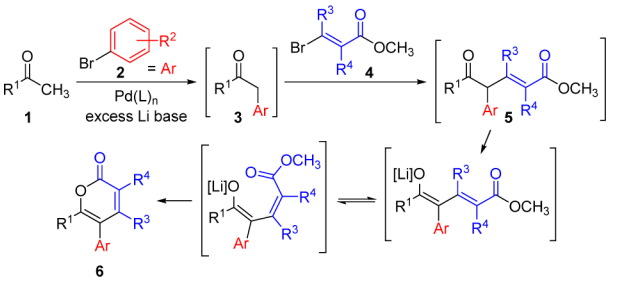



**Figure 1.** Proposed multicomponent pathway to α-pyrones.

To approach the development of the multicomponent sequence systematically, we needed to take into account whether the basic and metal-catalyzed conditions required for the α-arylation and α-alkenylation reactions were suitable for the final steps of *E*/*Z*-isomerization and lactonization. Based on conditions from our previous α-alkenylation studies,[9a,11c] we subjected unsaturated ketone (**5a**) to $Pd_2(dba)_3$ (0.5 mol %), Q-Phos (1 mol %), and LiO*t*-Bu (2 equiv) in THF at 22 °C. The desired α-pyrone **6a** was obtained but only in a moderate yield after 3 h (Table 1, entry 1). We then examined whether the absence of a catalytic amount of $Pd_2(dba)_3$ and Q-Phos has positive or negative consequences for the isomerization and

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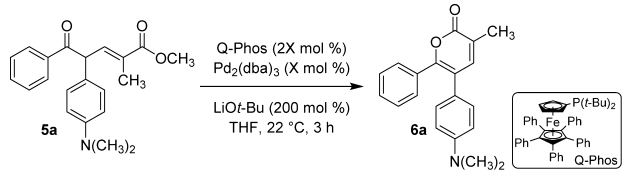
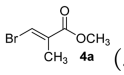
**Table 1. Optimization and Identification of the Active Catalyst for Isomerization/Lactonization of 5a**




| entry | X[a] | additive | yield (%)[b] |
|---|---|---|---|
| 1 | 0.5 | ---- | 50 |
| 2 | 0 | ---- | 52 |
| 3 | 0 | $Pd(OAc)_2$ (1 mol %) | 99 |
| 4 | 0.5 |  (5 mol %) | 99 |

[a]Reported in mol %. [b]Yield based on NMR internal standard.

cyclization. α-Alkenyl ketone **5a** was subjected to LiO-*t*Bu in THF, affording again only a moderate yield (entry 2). When $Pd(OAc)_2$ (1 mol %) was used as a Pd(II) rather than a Pd(0) source, a nearly quantitative yield of **6a** was obtained (entry 3). The basis for examining the effect of Pd(II) is that, in the envisioned multicomponent reaction, a Pd(II) species would be produced upon oxidative addition of either an aryl or alkenyl halide. Indeed, incorporating 5 mol % of alkenyl bromide **4a** in the presence of LiO-*t*Bu, $Pd_2(dba)_3$, and Q-Phos resulted again in a nearly quantitative yield of **6a** (entry 4). These results suggest that a Pd(II) catalyst, whether generated in situ from Pd(0) or added initially as a Pd(II) salt, is beneficial for the isomerization/lactonization portion of the envisioned sequence. In a related pathway for pyridine synthesis, thermal isomerization and cyclization were observed at higher temperatures (70−120 °C) but without a role of Pd being invoked,[11e] whereas, in other systems, alkene isomerization has been shown to be catalyzed by Pd(II).[12]

With conditions for isomerization and cyclization established, we next examined incorporation of the α-alkenylation step. Since enolates have been found to undergo alkenylation with highly activated α,β-unsaturated electrophiles such as alkylidenemalonate derivatives by a nonmetal-catalyzed addition/elimination pathway,[4a,b,13] we compared the reactions of our less activated bromoacrylate substrate in the absence and presence of a Pd catalyst. A very low yield of α-pyrone **6a** was obtained when the reaction was conducted with α-aryl ketone **3a**, β-bromoacrylate **4a** (1.05 equiv), and LiO*t*-Bu (3 equiv) in THF in the absence of Pd catalyst. When $Pd_2(dba)_3$ (0.5 mol %) and Q-Phos (1 mol %) were included, a 93% yield of **6a** was obtained after 10 h at 22 °C and a nearly quantitative yield after 16 h (Figure 2). For the experiments in Figure 2, the alkenylated intermediate **5a** was not observed in the crude reaction mixture. Overall, these results suggest that both a Pd-catalyzed α-alkenylation and a non-Pd-catalyzed Michael addition followed by elimination are feasible, but that the Pd-mediated process is more favorable, and that the isomerization/lactonization is faster than the alkenylation step. Several other examples of obtaining α-pyrones starting from α-substituted ketones (essentially a two-component rather than three-component procedure) can be found in the Supporting Information.

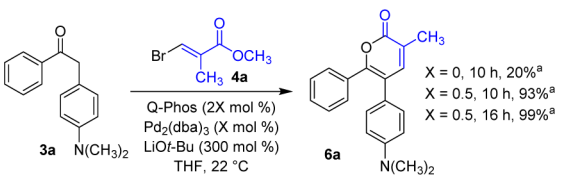



**Figure 2.** Examination of reaction conditions for the combination of α-alkenylation and subsequent isomerization/lactonization. [a] Yield based on NMR internal standard.

With an understanding of the latter steps, we were able to incorporate an initial α-arylation[14] reaction to achieve the envisioned multicomponent sequence. The resulting procedure consists of adding an aryl bromide (1 equiv) to a solution of LiO-*t*Bu (4 equiv), $Pd_2(dba)_3$ (0.5 mol %), Q-Phos (1 mol %), and a methyl ketone (1 equiv) at 22 or 40 °C. After TLC indicates full consumption of the starting ketone (1−4 h), a β-bromoacrylate (1.05 equiv) is added to the reaction mixture, which is stirred for 15 h at 22 or 40 °C. Following workup, the crude reaction mixtures are in many cases sufficiently pure for synthetic purposes (see Supporting Information). The reaction proved to be robust, reproducible, and easily conducted.

The scope was established for a range of methyl ketones undergoing reaction with 4-bromo-*N*,*N*-dimethylaniline and **4a** (Figure 3). Electron-rich to slightly electron-deficient aryl

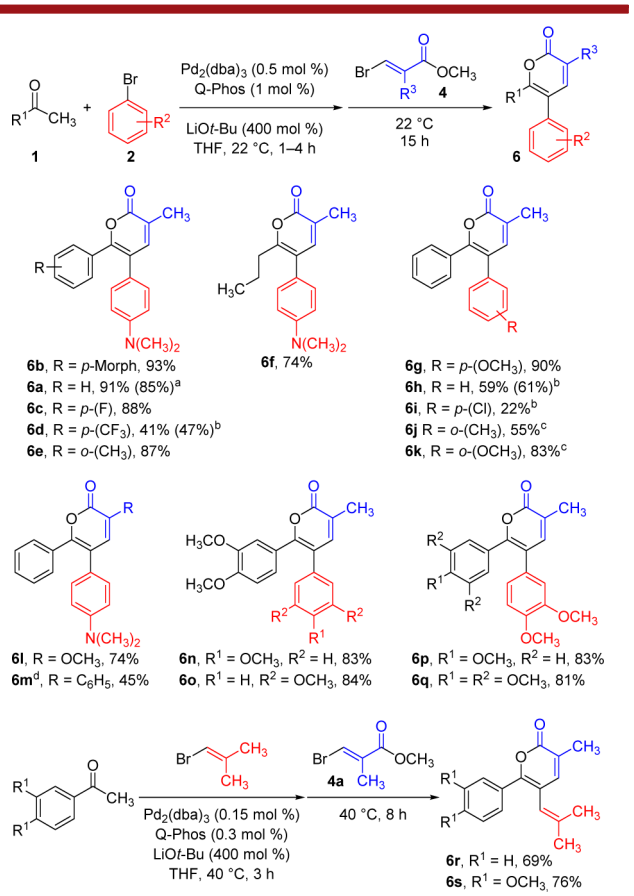



**Figure 3.** Investigation of the three-component synthesis of α-pyrones using methyl ketones with aryl or alkenyl bromides and bromoacrylates. Reactions were conducted on a 0.5 mmol scale. Isolated yields are reported. [a] Conducted on a 4.5 mmol scale. [b] The second part of the sequence was conducted at 40 °C. [c] The entire reaction sequence was conducted at 40 °C. [d] The corresponding ethyl acrylate was employed.



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ketones give excellent yields of the desired α-pyrones (**6b**, **6a**, and **6c**). A more electron-deficient aryl ketone results in moderate yields when conducted at either 22 or 40 °C (**6d**). The more sterically hindered *o*-tolyl ketone gives a high yield of **6e** at 22 °C. The aliphatic 2-pentanone affords a good yield of **6f** and is regioselective at the initially unsubstituted α-carbon for both coupling steps. The multicomponent reaction sequence is amenable to scale-up, producing 1.30 g (85%) of **6a**.

Next, a variety of aryl bromides was used with acetophenone and β-bromoacrylate **4a**. Electron-rich aryl bromides give excellent yields of **6a** and **6g**, while an electron-neutral substrate gives a moderate yield of **6h**. Aryl bromides that were even slightly more electron-deficient than bromobenzene react poorly, even at 40 °C, and result in low yields (**6i**) or no detectable quantity of the desired α-pyrones. The α-arylated ketone is isolated as the major product in these cases. Electronic effects were again apparent during the study of hindered aryl bromides. When 2-bromotoluene is employed at 40 °C, a moderate yield of **6j** is obtained, whereas the use of a more electron-rich but still sterically hindered aryl bromide results in higher yields at 40 °C (**6k**). An electron-rich α-methoxy acrylate affords a good yield of **6l**, while a moderate yield is obtained with a phenyl-substituted acrylate (**6m**). Several α-pyrones are obtained in high yields when both the methyl ketone and the aryl bromide are electron-rich due to varying methoxy substitution patterns (**6n**–**q**). The efficiency of the three-component sequence is comparable to the two-component process as illustrated in the formation of **6a** by the two procedures (Figures 2 and 3). The three-component coupling can be applied to the synthesis of alkenyl-substituted α-pyrones (**6r** and **6s**) by sequential use of two different alkenyl bromides.

With facile access to richly substituted α-pyrones, we have performed a brief, preliminary survey of some of their further transformations (Figure 4) to demonstrate utility of these diverse compounds. We focused on generation of highly substituted, extended aromatic systems, which are of significant interest for their physical and material properties.[15] A high yield of pyranophenanthrene **7** is obtained by intramolecular oxidative coupling of **6n**.[16] When α-pyrone **6o** is subjected to similar conditions, the initial intramolecular coupling is followed by a subsequent intermolecular coupling to afford an unexpected bis(pyranophenanthrene) **8** as the major product. Diels–Alder cycloadditions and decarboxylation[2a,d,f,13a] produce highly substituted teraryls **9a** and **9b** in excellent yields from α-pyrone **6q**. When subjected to $BF_3{\cdot}OEt_2$/$PhI(OCOCF_3)_2$ conditions, these teraryls yield fused tetracyclic compounds **10a** and **10b** in high yields. Subjecting **9b** to 2.1 equiv of iodonium salt and 4.2 equiv of $BF_3{\cdot}OEt_2$ provides another unexpected result whereby aryl–aryl oxidative coupling is accompanied by lactonization to afford **11** in excellent yield. The structures of **10a** and **11** were confirmed by X-ray diffraction. Finally, acid promoted electrophilic cyclization of a 5-alkenyl α-pyrone **6s** affords dihydronaphthopyrone **12** in high yield.

In conclusion, we have demonstrated that highly substituted α-pyrones are produced efficiently by an α-arylation/α-alkenylation/ketone enolate coupling strategy in a single-flask operation. Pd was found to have beneficial roles in all of the key steps of the sequence. A range of electronically and structurally diverse substrate combinations gives molecularly diverse α-pyrones with absolute control of regioselectivity under mild

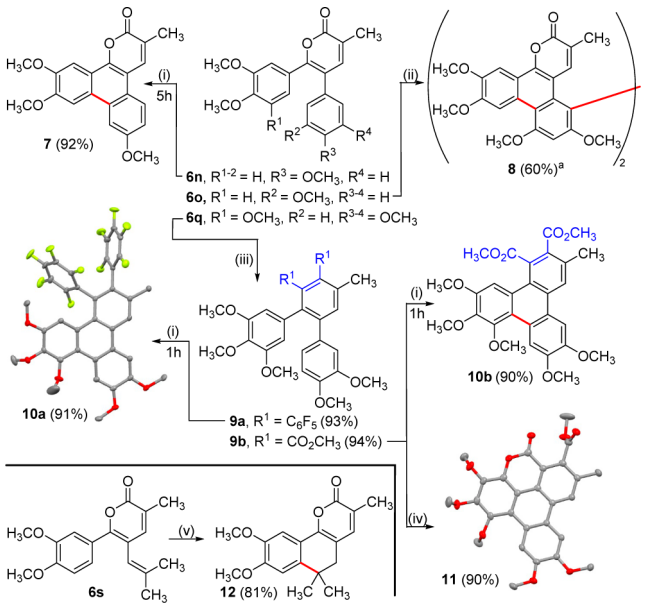


**Figure 4.** Further reactions of initially obtained α-pyrones. (i) $PhI(OCOCF_3)_2$ (1.1 equiv), $BF_3{\cdot}OEt_2$ (2.2 equiv), DCM, −40 °C. (ii) $PhI(OCOCF_3)_2$ (1.1 equiv), $BF_3{\cdot}OEt_2$ (2.2 equiv), DCM, −40–22 °C, 12 h. (iii) $R^1CCR^1$ (3 equiv), 1,2-dichlorobenzene, 200 °C, 48 h. (iv) $PhI(OCOCF_3)_2$ (2.1 equiv), $BF_3{\cdot}OEt_2$ (4.2 equiv), DCM, −40 °C, 5 h. (v) AcOH, $H_2SO_4$, 120 °C, 24 h. Isolated yields are shown. X-ray diffraction structures are shown for **10a** and **11** without hydrogens for clarity (red = O, green = F). [a] Yield is based on $PhI(OCOCF_3)_2$ as the limiting reagent.

conditions. The utility of the resulting α-pyrones is demonstrated in further transformations to access polyaromatic compounds, which have several applications in organic chemistry, supramolecular chemistry, polymers, and materials science. Furthermore, a two-component procedure may also be employed starting with substituted ketones (see Supporting Information). Extensions of the sequential reactions and other pathways for derivatization of the products are subjects of further investigations in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02969.

Crystallographic data (CIF, CIF)
Full experimental procedures, copies of spectral data, and X-ray crystal structures (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: phelquis@nd.edu.

### Notes

The authors declare no competing financial interest.

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## DEDICATION

This paper is dedicated to Professor Robert M. Carlson on the occasion of his 75th birthday and upon completion of 50 years of service on the faculty of the University of Minnesota Duluth.

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