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Versatile Synthesis of Isocoumarins and α-Pyrones by Ruthenium-Catalyzed Oxidative C–H/O–H Bond Cleavages

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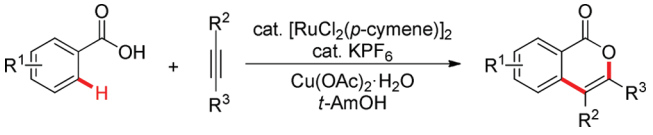
ABSTRACT



An inexpensive cationic ruthenium(II) catalyst enabled the expedient synthesis of isocoumarins through oxidative annulations of alkynes by benzoic acids. This C–H/O–H bond functionalization process also proved applicable to the preparation of α-pyrones and was shown to proceed by rate-limiting C–H bond ruthenation.

Isocoumarins and α-pyrones are key structural motifs of compounds with important biological activities.[1] One of the most general strategies for their synthesis involves palladium-catalyzed annulations of alkynes by *ortho*-halo-substituted carboxylic acid derivatives.[2] While this approach inherently requires prefunctionalized benzoic acids as substrates, a more atom- and step-economical access was elegantly devised by Miura and Satoh through rhodium-catalyzed[3] oxidative[4] annulations of alkynes by carboxylic acids.[5,6] We, in contrast, reported recently on the use of significantly less expensive ruthenium catalysts[7] for oxidative C–H/N–H bond functionalizations.[8] Further, Miura[9] and we[10] disclosed ruthenium-catalyzed oxidative alkenylations of carboxylic acid derivatives *via* twofold C–H bond cleavages. In continuation of our studies, we became interested in exploring cost-effective ruthenium catalysts for oxidative annulations of alkynes by carboxylic acids,[11] on which we report herein.

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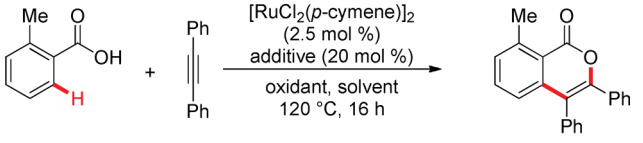
We initiated our studies by optimizing reaction conditions for the oxidative annulation of tolane (**2a**) by carboxylic acid **1a** (Table 1). Notably, the desired isocoumarin synthesis occurred with water[12] as the reaction medium, when using KPF_6 as a cocatalytic additive (entries 1 and 2). Yet, among a set of representative solvents, *t*-AmOH was found to be optimal (entries 1−8). The oxidative annulation proceeded efficiently under an atmosphere of ambient air (entry 9). It is noteworthy that the cationic[13] ruthenium(II) catalysts derived from KPF_6 proved to be more effective than the corresponding complexes generated from cocatalytic amounts of $AgBF_4$, $AgSbF_6$, AgOTf, CsOAc, HOPiv, or KOAc (entries 9−17). Furthermore, $Cu(OAc)_2 \cdot H_2O$ turned out to be the sacrificial oxidant of choice (entries 18−20).

Table 1. Optimization of Ruthenium-Catalyzed Oxidative Annulation[a]



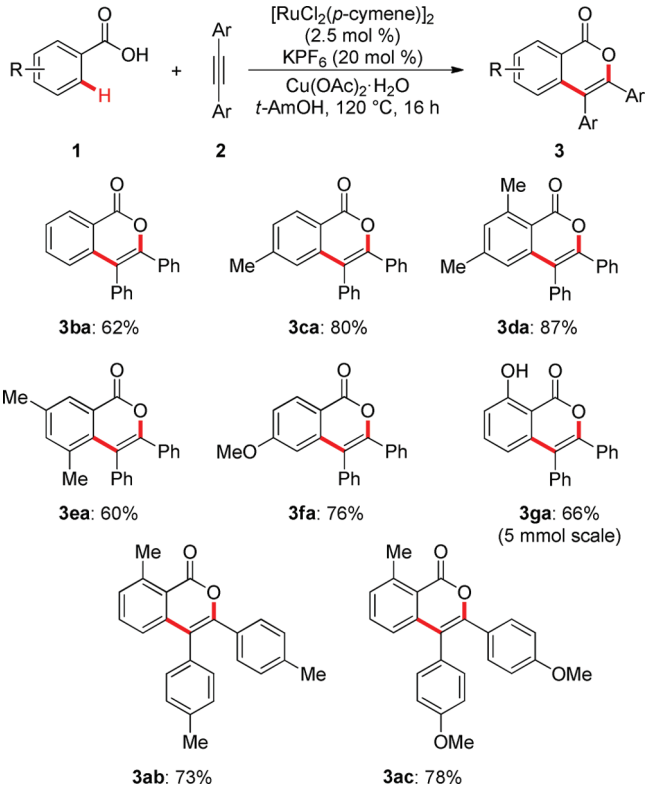
1a **2a** **3aa**

entry	oxidant	additive	solvent	*t* (°C)	yield
1	$Cu(OAc)_2 \cdot H_2O$	---	H_2O	80	15%[b]
2	$Cu(OAc)_2 \cdot H_2O$	KPF_6	H_2O	100	52%
3	$Cu(OAc)_2 \cdot H_2O$	KPF_6	DMF	120	34%[b]
4	$Cu(OAc)_2 \cdot H_2O$	KPF_6	NMP	120	30%[b]
5	$Cu(OAc)_2 \cdot H_2O$	KPF_6	PhMe	110	40%[b]
6	$Cu(OAc)_2 \cdot H_2O$	KPF_6	*o*-xylene	120	42%
7	$Cu(OAc)_2 \cdot H_2O$	KPF_6	*t*-AmOH	100	72%
8	$Cu(OAc)_2 \cdot H_2O$	KPF_6	*t*-AmOH	120	78%
9	$Cu(OAc)_2 \cdot H_2O$	KPF_6	*t*-AmOH	120	87%[c]
10	$Cu(OAc)_2 \cdot H_2O$	KPF_6	*t*-AmOH	120	84%[d]
11	$Cu(OAc)_2 \cdot H_2O$	$AgBF_4$	*t*-AmOH	120	27%[b,c]
12	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	*t*-AmOH	120	11%[b,c]
13	$Cu(OAc)_2 \cdot H_2O$	AgOTf	*t*-AmOH	120	50%[c]
14	$Cu(OAc)_2 \cdot H_2O$	CsOAc	*t*-AmOH	120	45%[b]
15	$Cu(OAc)_2 \cdot H_2O$	HOPiv	*t*-AmOH	120	34%[b]
16	$Cu(OAc)_2 \cdot H_2O$	KOAc	*t*-AmOH	120	17%
17	$Cu(OAc)_2 \cdot H_2O$	---	*t*-AmOH	120	16%
18	AgOAc	KPF_6	*t*-AmOH	120	41%
19	$CuBr_2$	KPF_6	*t*-AmOH	120	< 5%[b]
20	$Cu(OAc)_2 \cdot H_2O$	KPF_6	*t*-AmOH	120	84%[c,e]

[a] Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (20 mol %), oxidant (2.0 equiv), solvent (3.0 mL), 120 °C, 16 h; isolated yields, under N_2. [b] GC conversion. [c] Under air. [d] 5.0 mmol scale. [e] $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv).

With an optimized catalytic system in hand, we probed its scope in the ruthenium-catalyzed oxidative annulation of aryl-substituted alkynes **2** by benzoic acids **1** (Scheme 1). The cationic ruthenium(II) catalyst proved broadly applicable and, thus, enabled the synthesis of diversely decorated isocoumarins **3**. Notably, also salicylic acid **1g** bearing an unprotected hydroxyl group was chemoselectively converted to the desired product **3ga**. The oxidative annulation of electron-rich alkynes **2b** and **2c** occurred efficiently as well.

Scheme 1. Scope Using Aryl-Substituted Alkynes **2**



The ruthenium catalysts were not limited to the use of tolane derivatives but were also found to be applicable to alkyl-substituted alkynes **2** (Scheme 2). Again, valuable functional groups, such as free hydroxyl groups or fluoro- and bromo-substituents, were well tolerated by the catalytic system, the latter of which could be used for the subsequent elaboration of the obtained isocoumarins **3**.

Moreover, heteroaromatic carboxylic acids **1** turned out to be suitable substrates for the ruthenium-catalyzed C−H/O−H bond functionalization process, thereby delivering valuable indole derivatives **3** (Scheme 3).

Notably, unsymmetrically substituted alkynes **2f** and **2g** were converted with remarkably high regioselectivity, furnishing the desired isocoumarins **3** (Scheme 4).

The cationic ruthenium(II) catalyst further allowed the oxidative annulation of alkynes by acrylic acid derivative

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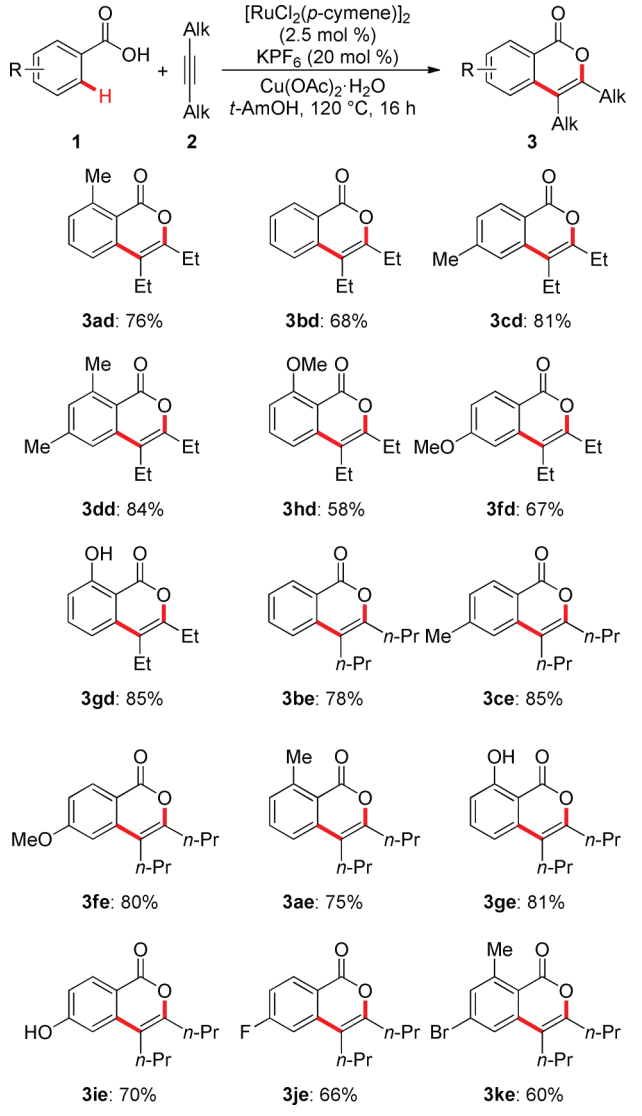
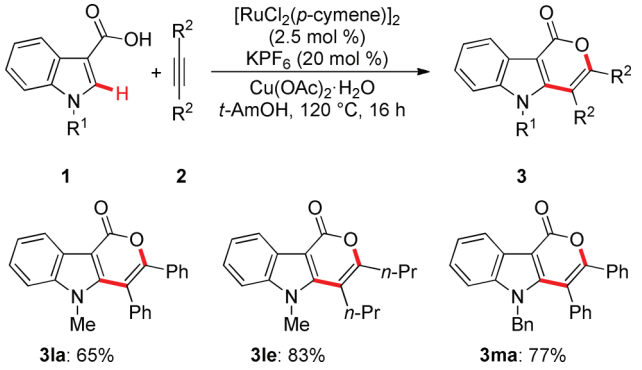
Scheme 2. Oxidative Annulation with Alkyl-Substituted Alkynes **2**

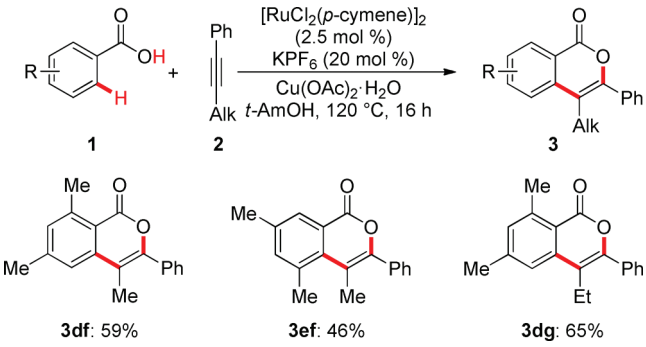


Scheme 3. Oxidative Annulations with Heteroarenes **1**

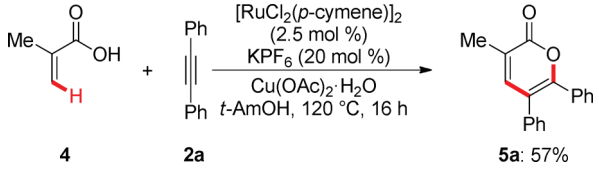


4, thus providing a step-economical access to α-pyrone **5a** (Scheme 5).

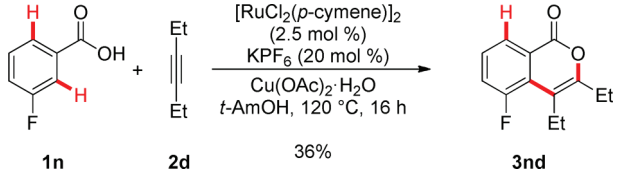
Scheme 4. Annulations of Unsymmetrically Substituted Alkynes **2**



Scheme 5. Oxidative α-Pyrone Synthesis



Scheme 6. Intramolecular Competition Experiment



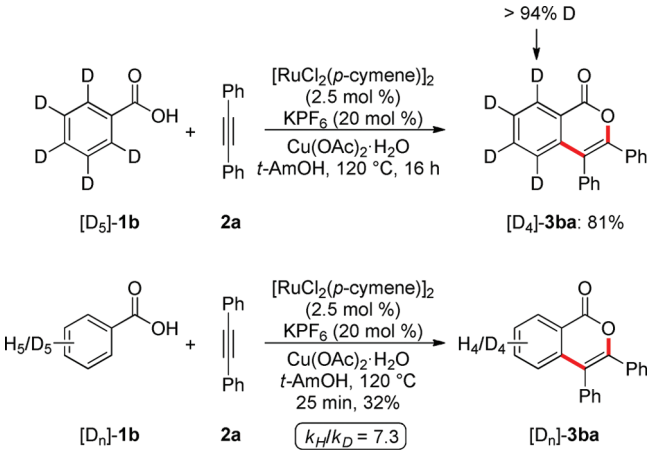
As to the catalyst's working mode, an intramolecular competition experiment with *meta*-substituted arene **1n** exclusively delivered product **3nd** through the site-selective functionalization of the C−H bond, displaying a higher kinetic acidity (Scheme 6). Moreover, additional competition experiments between differently substituted starting materials indicated aryl-substituted alkynes **2** and electron-rich carboxylic acids **1** to be preferentially converted.

Mechanistic studies with isotopically labeled substrate [D_5]-**1b** revealed the C−H bond metalation to be irreversible in nature, with a kinetic isotope effect of $k_H/k_D \approx 7.3$ (Scheme 7). These experimental findings are in good agreement with a reaction manifold involving a rate-limiting C−H bond metalation through acetate assistance.[14]

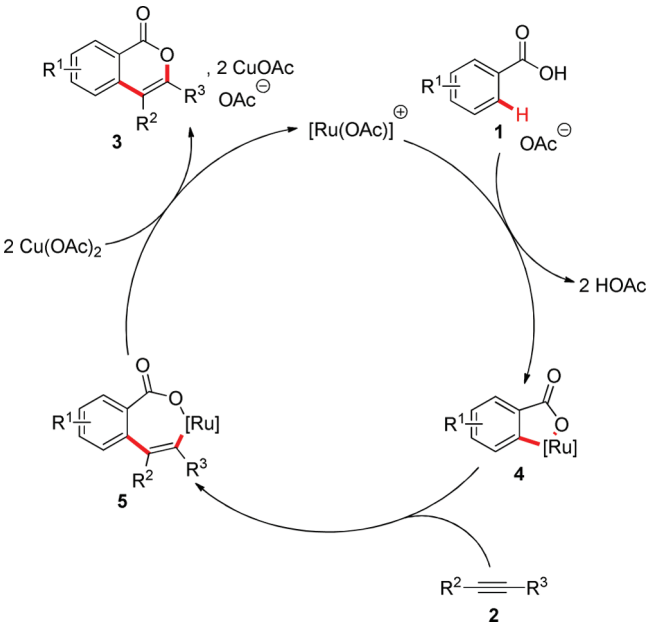
Thus, a proposed catalytic cycle initiates with an acetate-assisted irreversible cycloruthenation (Scheme 8), followed by coordination of alkyne **2**. Subsequent

(14) A review: Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345.

Scheme 7. Studies with Isotopically Labeled Compounds



Scheme 8. Proposed Catalytic Cycle



regioselective migratory insertion delivers key intermediate **5**, which upon reductive elimination furnishes desired isocoumarin **3**.

In summary, we have developed an atom- and step-economical synthesis of isocoumarins through oxidative annulations of alkynes by carboxylic acids using an inexpensive ruthenium catalyst. The optimized cationic ruthenium(II) complex proved widely applicable and, hence, allowed the direct preparation of α-pyrones *via* a rate-limiting C−H bond ruthenation as the key step. Further studies on oxidative ruthenium-catalyzed C−H bond functionalizations are ongoing in our laboratories and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.