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Ruthenium(II)-Catalyzed Alkene C–H Bond Functionalization on Cinnamic Acids: A Facile Synthesis of Versatile α-Pyrones

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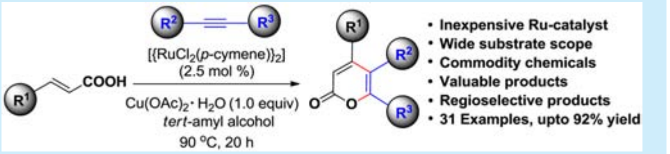
Supporting Information

ABSTRACT: An inexpensive ruthenium(II) complex enabled oxidative annulation of alkynes by using cinnamic acid derivatives to provide diversely decorated multisubstituted α-pyrones.

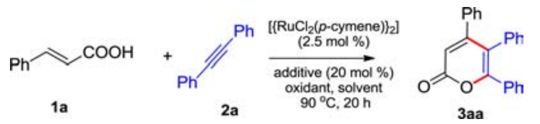


α-Pyrones with various substitution patterns are among the most abundant heterocycles found in bioactive natural products or pharmacologically active compounds.[1] Because of the importance of α-pyrones, there is a continued strong demand for new methods of construction of these heterocycles.[2]

In recent years, transition metal catalyzed annulation reactions which proceed via activation of a C–H bond have revolutionized the construction of cyclic compounds.[3] Miura and co-workers have used the rhodium-catalyzed C–H activation and functionalization of acrylic acids with alkynes for the synthesis of functionalized α-pyrones.[2e] Recently, the same group also disclosed a rhodium-catalyzed annulation of maleic acids with alkynes for the construction of α-pyrones.[2f] The high cost of the rhodium(III) catalysts used in these methods is the main limitation of these approaches. Recently, ruthenium(II) complexes, which are considerably less expensive than those of rhodium(III), were identified as viable catalysts for C–H activation and annulation reactions.[3b,4] In continuation of our work on the development of novel methods for the syntheses of important heterocycles,[5] herein, we report an unprecedented Ru(II) catalyzed C–H activation and annulation reaction of commercially available cinnamic acids with alkynes for the easy construction of a wide range of multisubstituted α-pyrones. Notably, the oxidative annulation reactions of cinnamic acid with some unsymmetrical alkynes are very regioselective in this Ru catalyzed reaction.

At the outset, the performance of the ruthenium(II) catalyst for the oxidative annulation reaction of cinnamic acid **1a** with diphenylacetylene **2a** for the synthesis of α-pyrone **3aa**[2g] was studied (Table 1). In the absence of either the oxidant or the ruthenium catalyst, the desired product **3aa** was not formed (entries 1 and 2). Among a set of representative solvents screened to perform this reaction (entries 3–7), *t*-AmOH provided the highest yield (88%) of **3aa**. The use of cocatalytic additives KPF_6 and $AgSbF_6$ that form cationic ruthenium(II) catalysts could not further improve the catalytic activity (entries 8–9). Moreover, the use of oxidants $CuBr_2$ and AgOAc instead of $Cu(OAc)_2{\cdot}H_2O$ delivered an inferior yield of **3aa** (entries 10–11).

Table 1. Optimization Study for α-Pyrone Synthesis[a]



entry	oxidant	additive	solvent	yield (%)[b]
1	–	–	*t*-AmOH	–
2	$Cu(OAc)_2{\cdot}H_2O$	–	*t*-AmOH	–[c]
3	$Cu(OAc)_2{\cdot}H_2O$	–	*t*-AmOH	88
4	$Cu(OAc)_2{\cdot}H_2O$	–	PhMe	61
5	$Cu(OAc)_2{\cdot}H_2O$	–	MeOH	80[d]
6	$Cu(OAc)_2{\cdot}H_2O$	–	H_2O	67
7	$Cu(OAc)_2{\cdot}H_2O$	–	MeCN	52
8	$Cu(OAc)_2{\cdot}H_2O$	KPF_6	*t*-AmOH	76
9	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	*t*-AmOH	70
10	$CuBr_2$	–	*t*-AmOH	15
11	AgOAc	–	*t*-AmOH	43

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (2.5 mol %), oxidant (1.0 mmol), solvent (5.0 mL), 90 °C, 20 h; unless otherwise mentioned. [b]Isolated yields. [c]No catalyst. [d]Temperature 64 °C.

With the optimized reaction conditions in hand, we first tested its scope in the oxidative annulation of cinnamic acid **1a**, utilizing representative disubstituted alkynes **2a–o** (Scheme 1). The diaryl-substituted alkynes bearing electron-donating and -withdrawing groups in the phenyl rings were well tolerated, providing 76–92% yields of α-pyrones **3aa–3ad**. Moreover, the annulation reaction of an alkyne substituted with a pair of heteroaromatic moieties proceeded well to afford corresponding α-pyrone **3ae** in 67% yield. Similarly, the dialkyl-substituted alkynes were also found to be suitable substrates in this annulation reaction, delivering the desired α-pyrones **3af** and **3ag** in 76–80% yields. The unsymmetrically substituted alkynes substituted with aryl, heteroaryl, and alkyl groups were also

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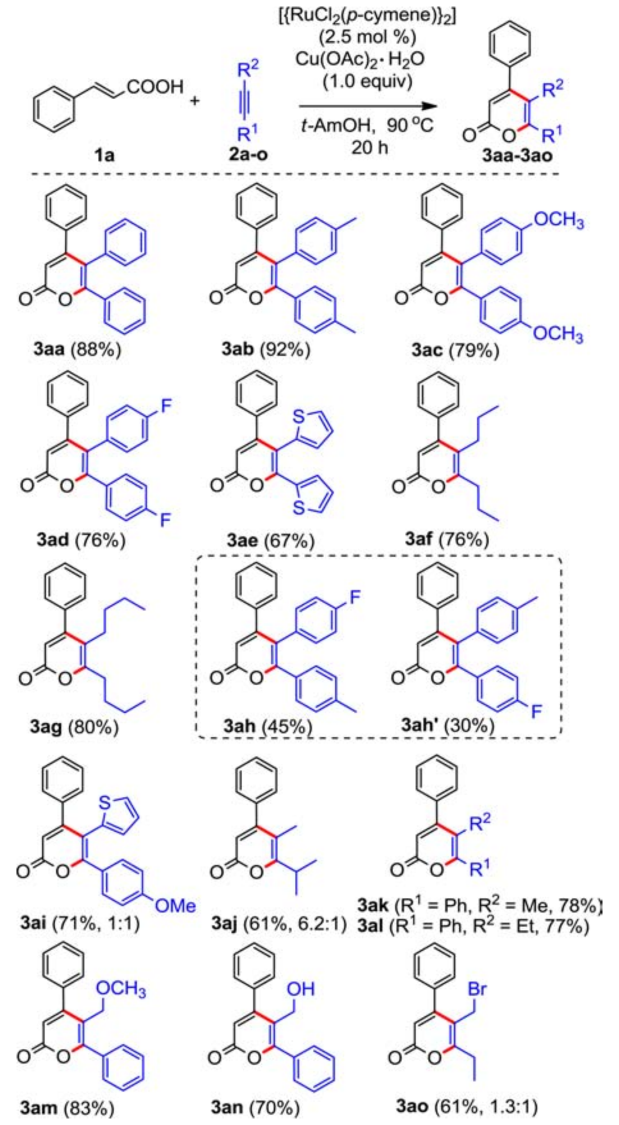
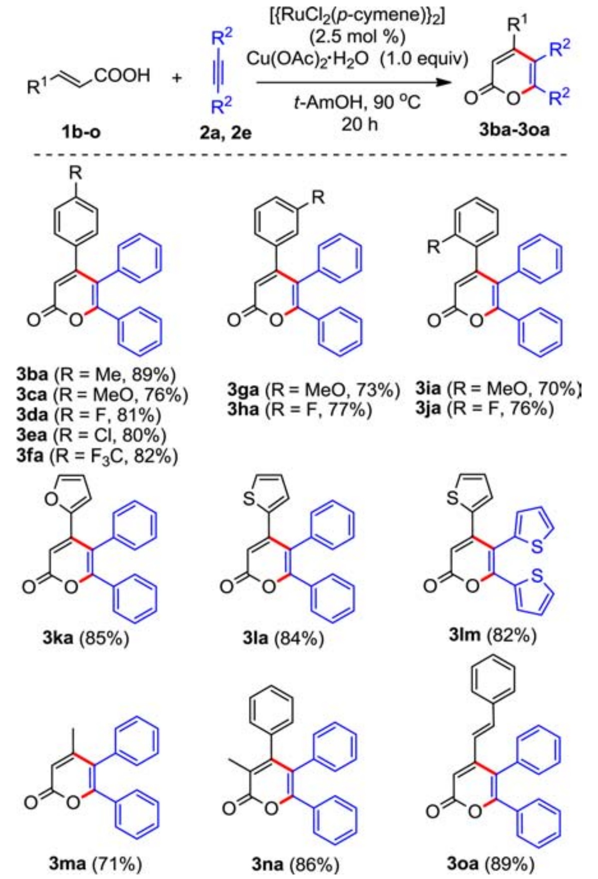
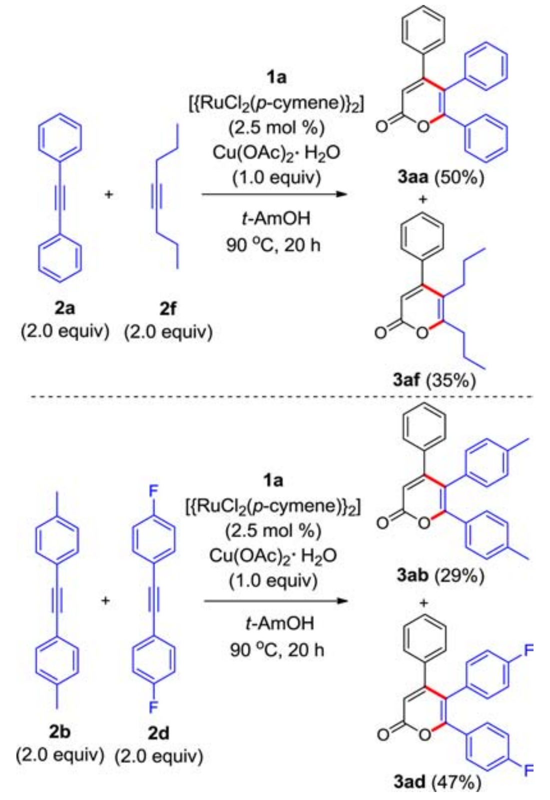
Scheme 1. Scope with Substituted Alkynes (2a–o)



Scheme 2. Synthesis of Various Substituted α-Pyrones



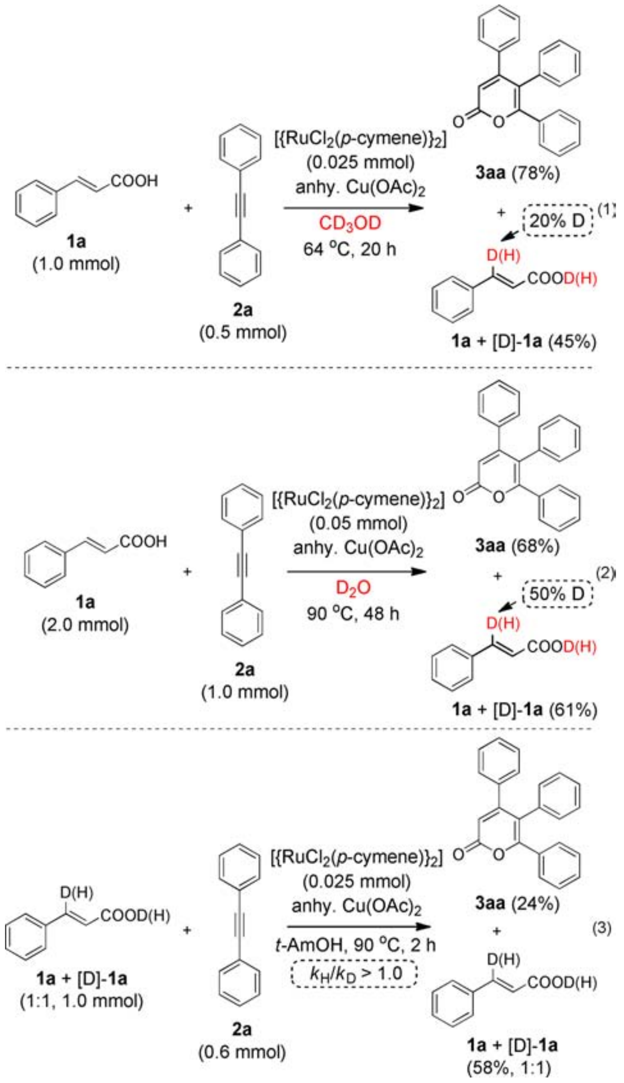
Scheme 3. Intermolecular Competition Reactions



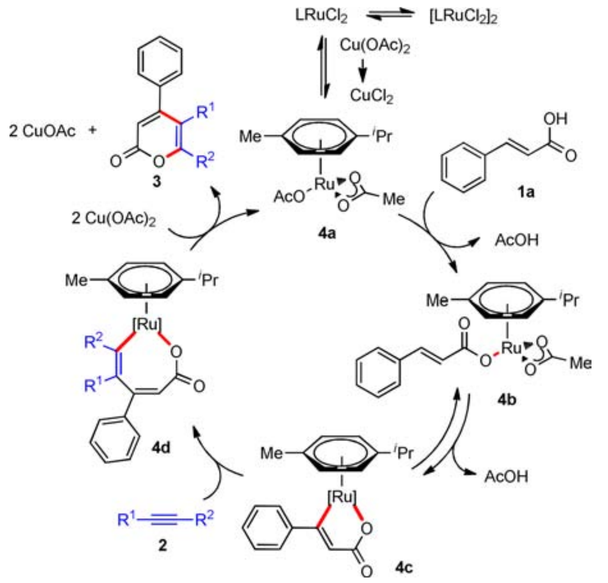
found to be good substrates for this annulation reaction. The reaction of **1a** with alkynes **2h**–**i** provided a mixture of α-pyrones **3ah**–**3ai** in 71–76% yields. The α-pyrones **3ah** and **3ah′** (1.5:1) were easily separated by silica gel column chromatography. We were pleased to observe that sensitive functional groups such as hydroxyl and bromo were well tolerated (**3an** and **3ao**). Remarkably, reactions of **1a** with unsymmetrical alkynes **2j**–**n** were highly regioselective to afford products **3aj**–**3an** in good yields (66–83%). The regioselectivity of the α-pyrones was proven by their NOE spectra. The selectivity pattern of the annulation products **3aj**–**3an** was similar to the case of the reported transition metal catalyzed annulation reactions, where insertion of alkyne into carbon–metal bonds occurred with the metal atom normally attacking the more negative carbon of the alkyne.[6]

Next, the annulation reaction was tested with alkyne **2a** using various functionalized cinnamic acids **1b**–**j** (Scheme 2). We were delighted to observe that numerous useful electron-donating and -withdrawing groups at different positions on the phenyl ring of the cinnamic acids were well tolerated to provide 70–89% yields of α-pyrones **3ba**–**ja** under the standard conditions. To observe the wide scope of the oxidative

Scheme 4. Isotopically Labelled Experiments



Scheme 5. Proposed Mechanism



annulation reaction, reactions of **2a** with various 3-heteroaryl/3-alkyl/2-alkyl-3-aryl substituted propenoic acids **1k−n** were also studied. The 3-heteroaryl substituted propenoic acids **1k−1l** reacted smoothly with **2a** to provide α-pyrones **3ka−3la** in 84−85% yields. Moreover, **1l** was converted easily to the 4,5,6-triheteroaryl α-pyrone **3lm** with alkyne **2e** in 82% yield. The 3-alkyl propenoic acid **1m** and 2,3-disubstituted propenoic acid **1n** also turned out to be very good substrates for this annulation reaction to provide 71−86% yields of **3ma−3na**[2a] with **2a**. Notably, 5-aryl substituted penta-2,4-dienoic acid **1o** also reacted with **2a** to selectively afford α-pyrone **3oa** in 89% yield.

The intermolecular competition experiments performed with differently substituted alkynes revealed an aryl substituted alkyne (**2a**) as well as an electron-poor alkyne (**2d**) to be preferentially converted to their corresponding α-pyrones (Scheme 3). In addition, the reaction between **1a** and **2a** performed under standard conditions in CD_3OD (20 h) and D_2O (48 h) employing an excess of **1a** resulted in a significant D/H exchange in the olefinic C−H of the recovered starting material [D]-**1a** (eqs 1−2, Scheme 4). This result provided evidence for a reversible C−H bond ruthenation step. The intermolecular kinetic isotope effect experiment performed between **1a** + D-**1a** (1:1) and **2a** provided a 1:1 mixture of unreacted **1a** + D-**1a** in 2 h (eq 3, Scheme 4). However, the β-hydrogen atom of cinnamic acid showed 2% exchange with the deuterium of the solvent CD_3OD, when the reaction between **1a** and **2a** mentioned in eq 1, Scheme 4 was performed under standard conditions for 2 h. Therefore, **1a** reacted with **2a** slightly faster than [D]-**1a** and the ratio of the recovered cinnamic acids (**1a**:[D]-**1a**) reached up to 1:1 after the hydrogen exchange with *t*-AmOH; as a result, $k_H/k_D > 1.0$.[7]

Based on our mechanistic studies and previous results on ruthenium metal catalyzed C−H activation and functionalization reactions,[4,8] we propose the mechanism for the formation of **3**, which is shown in Scheme 5. The catalytically active species **4a** on reversible cycloruthenation forms the complex **4c**. Subsequently, migratory insertion of alkyne **2**, followed by reductive elimination, furnishes desired compound **3**. The active catalyst is regenerated by the oxidation reaction with $Cu(OAc)_2$.

In summary, we have described the first use of rather inexpensive ruthenium catalysts for the oxidative annulation of cinnamic acids with disubstituted alkynes via a C−H/O−H functionalization strategy. The broad substrate scope, high regioselectivity with some unsymmetrical alkynes, and high yield of products α-pyrones are the noteworthy features of this reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02631.

Experimental procedures; characterization data; ^1H and ^{13}C NMR spectra for **3aa−3oa**, **3ba−3oa**; NOESY for **3aj**, **3am** (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) McGlacken, G. P.; Fairlamb, J. S. *Nat. Prod. Rep.* **2005**, *22*, 369−385. (b) Goel, A.; Ram, V. J. *Tetrahedron* **2009**, *65*, 7865−7913. (c) Kamano, Y.; Nogawa, T.; Yamashita, A.; Hayashi, M.; Inoue, M.; Drasar, P.; Pettit, G. R. *J. Nat. Prod.* **2002**, *65*, 1001−1005.

(2) (a) Kuninobu, Y.; Kawata, A.; Nishi, M.; Takata, H.; Takai, K. *Chem. Commun.* **2008**, 6360−6362. (b) Kondo, T.; Taguchi, Y.; Kaneko, Y.; Niimi, M.; Mitsudo, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5369−5372. (c) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770−8779. (d) Bu'Lock, J. D.; Smith, H. G. *J. Chem. Soc.* **1960**, 502−506. (e) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295−6298. (f) Itoh, M.; Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 11427−11432. (g) El-Kholy, I. E.-S.; Mishrikey, M. M.; Abdoul-Ela, S. L. *J. Heterocycl. Chem.* **1982**, *19*, 1329−1334.

(3) For recent reviews, see: (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622−1651. (b) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107−1295.

(4) For recent reviews on Ru-catalyzed C−H bond functionalization, see: (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918. (b) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886−896. (c) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281−295.

(5) (a) Shekarrao, K.; Kaishap, P. P.; Gogoi, S.; Boruah, R. C. *Adv. Synth. Catal.* **2015**, *357*, 1187−1192. (b) Prakash, R.; Shekarrao, K.; Gogoi, S.; Boruah, R. C. *Chem. Commun.* **2015**, *51*, 9972−9974. (c) Saikia, P.; Gogoi, S.; Boruah, R. C. *J. Org. Chem.* **2015**, *80*, 6885−6889 and references cited therein.

(6) (a) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042−8051. (b) Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179−5182. (c) Chang, K. J.; Rayabarapu, D. K.; Cheng, C. H. *Org. Lett.* **2003**, *5*, 3963−3966.

(7) (a) Simmons, E.; Hartwig, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072. (b) Shi, Z.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8092−8096.

(8) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416−3419.