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Rhodium(III)-catalysed decarbonylative coupling of maleic anhydrides with alkynes†

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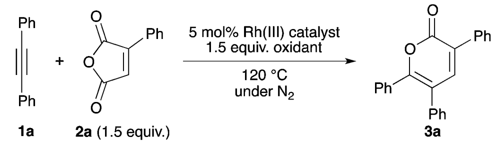
A formal [5 − 1 + 2] annulation for the preparation of substituted α-pyrones is reported. The reaction involves the decarbonylative coupling of substituted maleic anhydrides with internal alkynes in the presence of a rhodium(III) catalyst and a copper(II) salt, affording tri- and tetrasubstituted α-pyrones.

α-Pyrones (pyran-2-ones) are important substructures in many natural products and biologically active compounds[1] and also serve as dienes in Diels–Alder cycloadditions.[2] Transition-metal-catalysed annulation, cycloaddition, and ring expansion reactions have emerged as efficient strategies for the preparation of substituted pyrone derivatives.[3,4] The nickel-catalysed decarbonylative addition of cyclic anhydrides to alkynes, affording α-pyrones and isocoumarins, has been reported in 2008.[3m] During our investigations on the rhodium(III)-catalysed oxidative transformations of C–H bonds,[5] we discovered that maleic anhydrides and alkynes undergo a similar coupling reaction, producing α-pyrones under the rhodium(III)-catalysed conditions, which is reported herein.

When diphenylacetylene (**1a**) and phenylmaleic anhydride (**2a**, 1.5 equiv. to **1a**) were heated in *t*-amyl alcohol at 120 °C under a nitrogen atmosphere in the presence of 5 mol% $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (Cp* = pentamethylcyclopentadienyl) and 1.5 equiv. $Cu(OAc)_2$ for 2 h, the formal [5 − 1 + 2] annulation of **2a** with **1a** occurred to give 3,5,6-triphenyl-α-pyrone (**3a**) in 85% yield (Table 1, entry 1).[6] The reaction was regioselective, and the possible 4,5,6-triphenyl isomer was not observed in the crude reaction mixture. The reaction failed when the rhodium(III) catalyst was not used (entry 2); however, the reaction in the absence of the copper(II) salt afforded **3a** in 24% yield even when using 30 mol% Rh(III) catalyst (entry 3).[7] When $[Cp^*RhCl_2]_2$ was used instead of $[Cp^*Rh(MeCN)_3](SbF_6)_2$, the product was obtained in 42% yield, showing that the preformed cationic rhodium(III) catalyst is the most effective for this reaction (entry 4). A silver salt, Ag_2CO_3, also worked as the oxidant, albeit with a lower yield (entry 5). *t*-Amyl alcohol was found to be the best solvent. When the reaction was performed in DMF, **3a** was obtained in 69% yield (entry 6). The reaction was unsuccessful in toluene (entry 7). The optimal reaction temperature was found to be 120 °C (entry 8). The reaction was considerably less efficient when it was performed with a substoichiometric amount of $Cu(OAc)_2$ under an oxygen atmosphere (entry 9).

Then, the scope of alkynes **1** in this reaction with **2a** under the optimal reaction conditions was investigated (Table 2). The reactions of **2a** with diaryl alkynes **1b–e** reached completion within 5 h, affording the corresponding triaryl pyrones **3b–e** in good yields, whereas the reaction with di(2-thienyl)acetylene

Table 1 Optimisation of the rhodium(III)-catalysed pyrone synthesis[a]



Entry	Rh(III) catalyst	Oxidant	Solvent	Yield[b] (%)
1	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	$Cu(OAc)_2$	*t*-AmOH	85 (82)[c]
2	No Rh(III) catalyst	$Cu(OAc)_2$	*t*-AmOH	NR[d]
3[e]	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	No oxidant	*t*-AmOH	24
4	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	*t*-AmOH	42
5	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	Ag_2CO_3	*t*-AmOH	73
6	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	$Cu(OAc)_2$	DMF	69
7	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	$Cu(OAc)_2$	Toluene	Trace
8[f]	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	$Cu(OAc)_2$	*t*-AmOH	57
9[g]	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	$Cu(OAc)_2$	*t*-AmOH	29

[a] Alkyne **1a** (0.10 mmol), anhydride **2a** (0.15 mmol), Rh(III) catalyst (5.0 μmol) and oxidant (0.15 mmol) were reacted in solvent (1.0 mL) at 120 °C under N_2 atmosphere. [b] Isolated yield. [c] The reaction was performed on a 1.0 mmol scale. [d] No reaction. [e] 30 mol% Rh catalyst was used. [f] The reaction was performed at 100 °C. [g] The reaction was performed with 30 mol% $Cu(OAc)_2$ under O_2 atmosphere.

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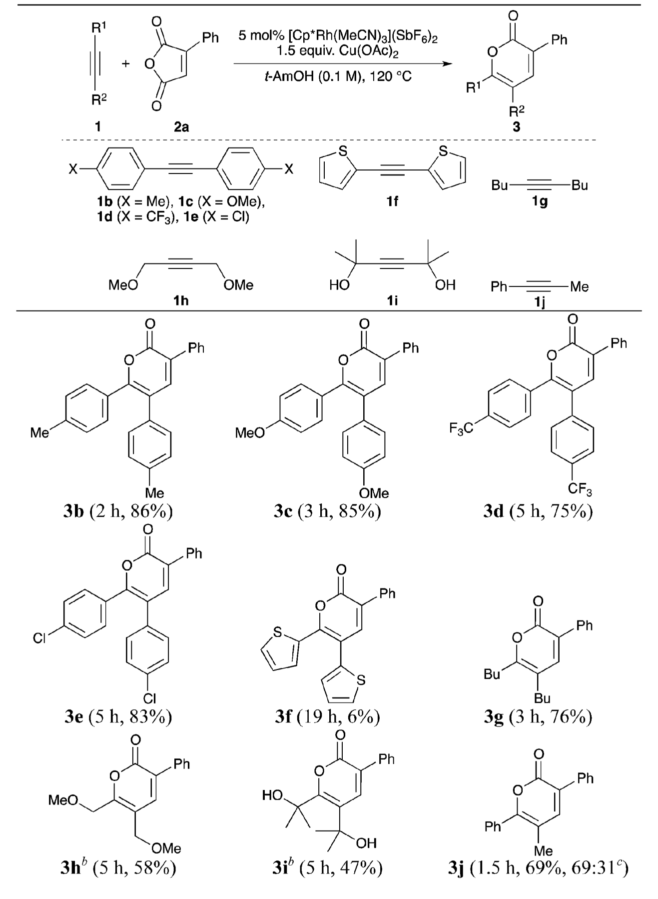
Table 2 Substrate scope of alkynes **1**[a]



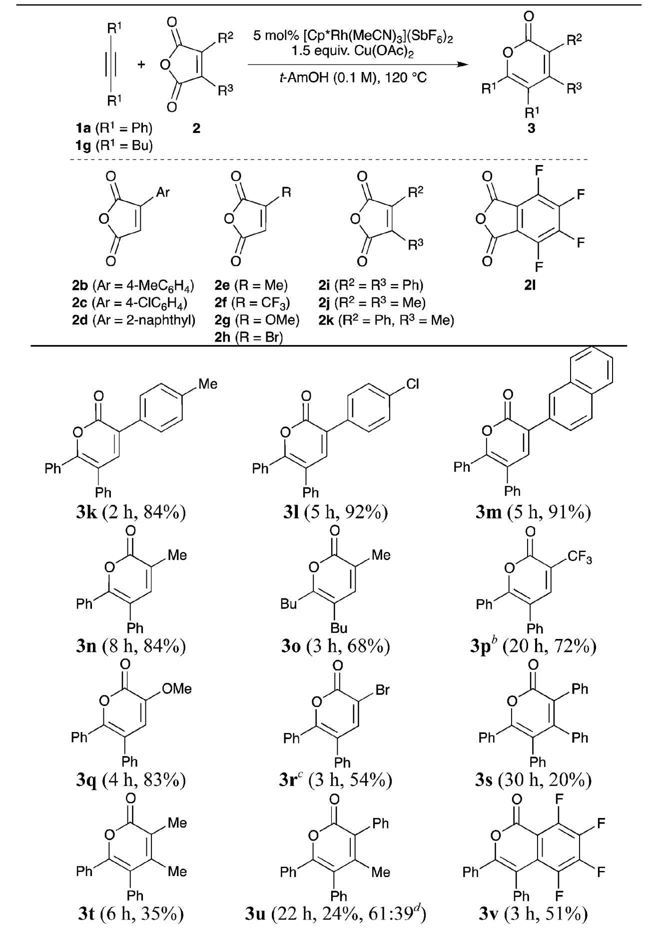
3b (2 h, 86%) **3c** (3 h, 85%) **3d** (5 h, 75%)

3e (5 h, 83%) **3f** (19 h, 6%) **3g** (3 h, 76%)

3h[b] (5 h, 58%) **3i**[b] (5 h, 47%) **3j** (1.5 h, 69%, 69:31[c])

[a] Alkyne **1** (0.10 mmol), anhydride **2a** (0.15 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5.0 μmol) and $Cu(OAc)_2$ (0.15 mmol) were reacted in *t*-amyl alcohol (1.0 mL) at 120 °C under N_2 atmosphere. [b] The reaction was performed in DMF using Ag_2CO_3 instead of $Cu(OAc)_2$. [c] Regioisomeric ratio (5-Me : 6-Me) determined by ^1H NMR.

Table 3 Substrate scope of maleic anhydrides **2**[a]



3k (2 h, 84%) **3l** (5 h, 92%) **3m** (5 h, 91%)

3n (8 h, 84%) **3o** (3 h, 68%) **3p**[b] (20 h, 72%)

3q (4 h, 83%) **3r**[c] (3 h, 54%) **3s** (30 h, 20%)

3t (6 h, 35%) **3u** (22 h, 24%, 61:39[d]) **3v** (3 h, 51%)

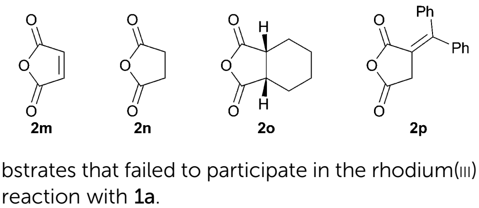
[a] See Table 2 for reaction conditions. [b] The reaction was performed using Ag_2CO_3 instead of $Cu(OAc)_2$. [c] 0.20 mmol **2h** was used. [d] Regioisomeric ratio (4-Me : 3-Me).

(**1f**) for 19 h afforded product **3f** in only 6% yield. Aliphatic alkynes were also compatible with this annulation. Although alkoxy- and hydroxy-substituted alkynes (**1h** and **1i**) did not react with **2a** under the optimal reaction conditions,[8] the reactions performed in DMF with Ag_2CO_3 as the oxidant afforded the corresponding products (**3h** and **3i**) in moderate yields. In the case of an unsymmetrical alkyne, 1-phenyl-1-propyne (**1j**), a 69 : 31 mixture of pyrone regioisomers were obtained, with the 5-methyl-6-phenyl isomer predominating.[9]

The substrate scope of diverse maleic anhydrides **2b–k** in this reaction with alkynes **1a** and **1g** was investigated (Table 3). Triaryl pyrones **3k–m** were obtained in excellent yields by the reaction of **1a** with monoaryl maleic anhydrides **2b–d**. The reaction of methylmaleic anhydride (**2e**) with **1a** and **1g** afforded **3n** and **3o** in 84% and 68% yields, respectively. The reaction of **1a** with CF_3-substituted anhydride **2f** required Ag_2CO_3 instead of $Cu(OAc)_2$ to achieve an acceptable yield. Methoxy- and bromo-substituted maleic anhydrides **2g** and **2h** also participated in the pyrone annulation, allowing an access to heteroatom-substituted pyrones **3q** and **3r**, respectively. However, the reactions of **1a** with the disubstituted maleic anhydrides **2i–k** were sluggish.[10] The reaction of unsymmetrically disubstituted anhydride **2k** with **1a** gave a mixture of 4-methyl and 3-methyl derivatives **3u** in 24% combined yield with a regioisomeric ratio of 61 : 39. The similar coupling of **1a** with 4,5,6,7-tetrafluorophthalic anhydride (**2l**) gave isocoumarin **3v** in 51% yield.

The decarbonylative coupling of **1a** with the parent maleic anhydride (**2m**) or the succinic anhydride derivatives **2n–p** failed (Fig. 1).

Miura and Satoh proposed a mechanism for the formation of pyrones from maleic acids and alkynes.[3r] Based on that mechanism, we propose a possible mechanism for the formation of pyrones from maleic anhydrides and alkynes in the presence of



2m **2n** **2o** **2p**

Fig. 1 Substrates that failed to participate in the rhodium(III)-catalysed coupling reaction with **1a**.

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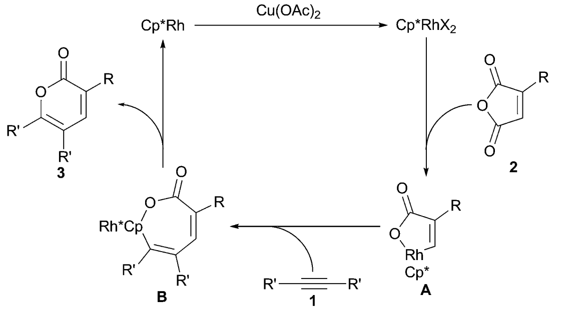
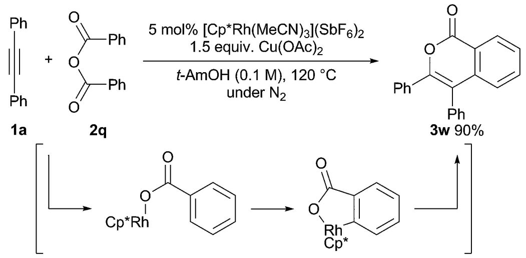


Scheme 1 Proposed catalytic cycle for the rhodium(III)-catalysed pyrone formation.



Scheme 2 Rh(III)-catalysed reaction of **1a** and **2q**.

a rhodium(III)/copper(II) catalyst system (Scheme 1). First, a five-membered oxarhodacycle **A** (ref. 3o, r and 4a–c, j, m) is formed from the Cp*Rh(III) species[11] and **2**, presumably by the decarbonylation of **2a**. The C–C bond cleavage occurs selectively at the less-substituted site of **2**. However, the detailed reaction mechanism for the formation of **A** remains unclear.[12] Next, the insertion of alkyne **1** to **A** generates **B**, and the subsequent reductive elimination furnishes pyrone **3**. Finally, the Cp*Rh(I) species is oxidised by the copper(II) salt to regenerate the catalytically active rhodium(III) species, thus completing the catalytic cycle.

We extended the rhodium(III)-catalysed pyrone-forming reaction to compounds other than cyclic anhydrides. The reaction of **1a** with benzoic anhydride (**2q**, **1a** : **2q** = 1 : 1) delivered isocoumarin **3w** in excellent yield (Scheme 2). Product **3w** may have been formed *via* the formation of rhodium(III) benzoate, intramolecular C–H bond activation, alkyne insertion, and reductive elimination.[13]

In summary, we developed a rhodium(III)-catalysed coupling reaction for preparing tri- and tetrasubstituted α-pyrones from substituted maleic anhydrides and internal alkynes. The formal [5 − 1 + 2] annulation reaction afforded a variety of α-pyrones, with diverse substitution patterns.

Acknowledgements

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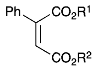
6 The corresponding diacid and monoester reacted with **1a** under the test conditions to give **3a** in 80% and 62% yields, respectively, whereas no reaction was observed using the diester. A reaction between maleic acids and alkynes under similar conditions was recently reported. See ref. 3r.



$R^1 = R^2 = H$ 80%
$R^1 = H, R^2 = Me$ (3:1) 62%
$R^1 = R^2 = Me$ no reaction

7 Cyclic anhydride **2a** remained largely unchanged (91% recovered after 3 h) after being heated in *t*-AmOH at 120 °C. In contrast, treatment with 1 equiv. $Cu(OAc)_2$ under the same conditions caused **2a** to be consumed, ring-opened products to be produced and the recovery of **2a** after 8 h to be only 6%.

8 **3h** (7h, 8%); **3i** (no reaction).

9 Use of phenylacetylene resulted in homocoupling to give 1,4-diphenyl-1,3-butadiyne.

10 The disubstituted anhydride **2k** was relatively reluctant to ring opening using the Cu(II) salt, and 63% of **2k** remained intact after 8 h. *cf.* ref. 7.

11 For effect of cyclopentadienyl ligands in the rhodium(III)-catalysed reactions, see: (*a*) T. Uto, M. Shimizu, K. Ueura, H. Tsurugi, T. Satoh and M. Miura, *J. Org. Chem.*, 2008, **73**, 298; (*b*) T. K. Hyster and T. Rovis, *Chem. Sci.*, 2011, **2**, 1606; (*c*) Y. Shibata and K. Tanaka, *Angew. Chem., Int. Ed.*, 2011, **50**, 10917; (*d*) T. K. Hyster and t. Rovis, *Chem. Commun.*, 2011, **47**, 11846; (*e*) B. Ye and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135**, 636.

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13 For a precedent work employing benzoic acids, see ref. 4a–c, j, m.