Synthesis of 2-acylfurans from 3-(1-alkynyl)-2-alken-1-ones *via* the oxidation of gold–carbene intermediates by H_2O_2†

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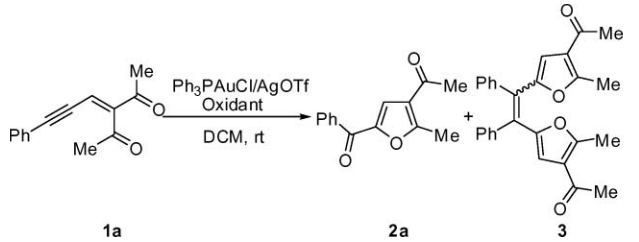
An efficient approach to 2,4,5-trisubstituted 2-acylfurans is described: treating 3-(1-alkynyl)-2-alken-1-ones with $AuCl_3$ in DCM at rt in the presence of H_2O_2 afforded good yields of 2-acylfurans.

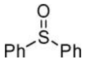
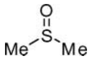
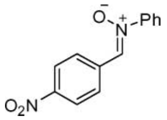
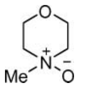
Polysubstituted furans play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals, but also as useful building blocks in synthetic chemistry.[1-2] Therefore, the development of new approaches to polysubstituted multi-functionalized furans from readily available starting materials still represents a continuing goal in the synthetic community.[3] Most recently, metal-catalyzed transformations have been reported among the cyclization of 3-alkyn-1-ones,[4-5] allenyl ketones,[5] 2-(1-alkynyl)-2-alken-1-ones[6] and (*Z*)-2-en-4-yn-1-ols[7] or cycloisomerization of alkylidenecyclopropyl ketones[8]/cyclopropenyl ketones.[9] Several examples for the synthesis of 2-acylfurans catalyzed by metals have been reported.[10] However, these methods often present low yield or require multi-step synthetic transformations.

Very recently, our group focused on developing novel reactions of 2-(1-alkynyl)-2-alken-1-ones for the synthesis of highly substituted furans.[11] During this course, we have become interested in the chemistry of 3-(1-alkynyl)-2-alken-1-ones. Herein we report a novel efficient, general gold-catalyzed oxidative cyclization of 3-(1-alkynyl)-2-alken-1-ones leading to trisubstituted 2-acylfurans.

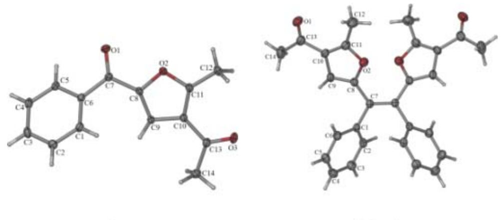
As indicated in Table 1, we started our studies by treating 3-(3-phenylprop-2-ynylidene) pentane-2,4-dione (**1a**) with various oxidants in the presence of Ph_3PAuCl and AgOTf in DCM. First, we tested O_2 as the oxidant. However, the reaction gave a *Z*/*E* mixture of furyl dimer **3** in 93% yield rather than the expected acyl furan **2a** (entry 1). Fortunately, other oxidants such as sulfoxides and nitrogen oxides[12] gave the expected 2-acylfuran **2a** in 15–86% yield (entries 2–5). For example, when the diphenyl sulfoxide[12b] (entry 2) or (*Z*)-*N*-(4-nitrobenzylidene)aniline oxide[12c] (entry 4) was used as oxidant, the reaction afforded **2a** in 86% and 79% yields, respectively. Further studies showed that environmentally friendly 30% H_2O_2 also works well to give **2a** in a relatively lower yield (entry 6). Since the by-product of the H_2O_2-oxidation reaction is H_2O, it is much greener than other oxidants. Thus, we next turned our examination on screening different catalysts and the results are summarized in Table 2. The structures of **2a** and **3** were confirmed by the X-ray crystallographic analysis (Fig. 1).[13]

Table 1 Scope of oxidants[a]



Entry	Oxidant	Time/h	Yield (%)[b] 2a	3
1	O_2	20	ND[c]	93
2		0.5	86	ND[c]
3		0.5	15	74
4		0.5	79	ND[c]
5		10	63	Trace
6	H_2O_2	20	69	Trace

[a] Unless otherwise noted, reactions were performed with 0.5 mmol of **1a**, 0.75 mmol of oxidant, and 5 mol% of Ph_3PAuCl and 5 mol% of AgOTf in 5.0 mL DCM at rt. [b] Yield of isolated product. [c] No product was detected.



2a (*Z*)-**3**

Fig. 1 ORTEP representation of **2a** and (*Z*)-isomer of **3**.

When three equivalents of H_2O_2 (30%) were used, the reaction gave a higher yield when using the same catalyst Ph_3PAuCl/AgOTf

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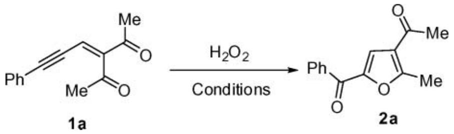
Table 2 Screening conditions for the tandem reaction of **1a** with H_2O_2[a]



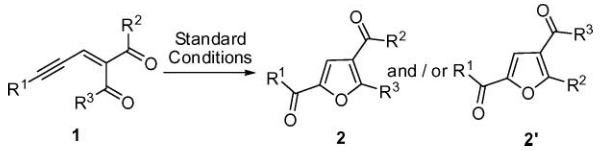
Entry	Catalyst	Solvent	H_2O_2 (equiv)	Time/h	Yield (%)[b]
1	$Ph_3PAuCl/AgOTf$	DCM	3	20	76
2	Ph_3PAuCl	DCM	3	24	23[c]
3	AgOTf	DCM	3	24	50[c]
4	$AgSbF_6$	DCM	3	20	32[c]
5	$Cu(OTf)_2$	DCM	3	6	NR
6	$AuCl_3$	DCM	3	2	88 (85)[c]
7	$AuCl_3$	DCM	1.5	3	83
8	$AuCl_3$	DCE	3	24	48[d]
9	$AuCl_3$	Toluene	3	24	85
10	$AuCl_3$	DMF	3	24	64

[a] Unless otherwise noted, reactions were performed with 0.5 mmol of **1a**, 1.5 mmol of oxidant, and 5 mol% of catalyst in 5.0 mL DCM at rt. [b] Yield of isolated product. [c] 3 mol% of $AuCl_3$ was used. [d] Furyl dimer were formed determined by TLC analysis.

(entry 1 in Table 2, comparing with entry 6 in Table 1). Interestingly, a silver(I) complex can also catalyze this reaction, but gives lower yields (entries 3–4). $Cu(OTf)_2$ is not effective for this reaction (entry 5). Finally, $AuCl_3$ was found to be the most effective catalyst providing **2a** in 88% yield within 2 h in DCM (entry 6). When H_2O_2 was reduced to 1.5 equivalents, the yield decreased slightly to 83% (entry 7). Other solvents failed to improve the yield (entries 8–10).

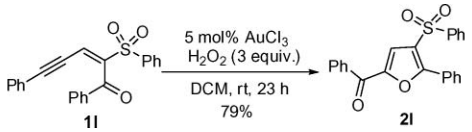
Under the optimal conditions, a wide variety of 3-(1-alkynyl)-2-alken-1-ones were examined and the results are summarized in Table 3. The substitute (R^1) on the alkynes can be aromatic or aliphatic groups. For example, the reaction of **1f** afforded 2-acylfuran **2f** in 63% yield (entry 5), in this case, 10 equivalents of H_2O_2 were used due to the potential β-hydride migration of the metal–carbene intermediate.[14] R^2, R^3 could also be aryl or alkyl groups. When they were the same groups, excellent yields of the single product were obtained (entries 6–7). But if R^2 and R^3 are alkyl and phenyl groups respectively, the *Z*-isomer of **1i** afforded a single product **2i** (entry 8) and the *E*-isomer gave a mixture of products **2i** and **2i′** (entry 9), indicating that the *E*-isomer could be converted into the *Z*-isomer in the presence of the gold catalyst.[15] Moreover, when the reaction of (*E*)-**1i** with H_2O_2 was carried out at 0 °C, the yield of **2i** increased to 37%. When one of R^2 and R^3 is an alkoxy group, both the *E*-isomer and *Z*-isomer of the substrates could be converted into 2-acylfurans **2** under the reaction conditions. For example, both the reactions of (*E*)-**1j** and (*Z*)-**1j** gave the same product **2j** (entry 11, **2j′** = entry 10, **2j**), albeit the latter one gave a relatively lower yield (entries 10–11). The phenylsulfonyl-substituted substrate **1l** could also afford 2-acylfuran **2l** in 79% yield under the reaction conditions (eqn (1)).

Table 3 Au(III)-catalyzed oxidative cyclization of 1[a]



Entry	Enyne **1** R_1, R_2/R_3	Time/h	Isolated yield (%)
1	4-MeOPh/Me/Me (**1b**)	17	**2b** (74)
2	4-MePh/Me/Me (**1c**)	11	**2c** (84)
3	$4\text{-}NO_2Ph$/Me/Me (**1d**)	10	**2d** (82)
4	1-naphthyl/Me/Me (**1e**)	14.5	**2e** (64)
5	n-Bu/Me/Me (**1f**)[b]	8	**2f** (63)
6	Ph/Et/Et (**1g**)	3.5	**2g** (83)
7	Ph/Ph/Ph (**1h**)	10	**2h** (87)
8	Ph/Me/Ph ((*Z*)-**1i**)	12	**2i** (89)
9	Ph/Ph/Me ((*E*)-**1i**)	12	**2i** (23), **2i′**(57)[c]
10	Ph/MeO/Me ((*E*)-**1j**)	36	**2j** (80)
11	Ph/Me/MeO ((*Z*)-**1j**)	53	**2j′** (66)
12	Ph/EtO/Ph (**1k**)	16	**2k** (73)

[a] Unless otherwise noted, reactions were performed with 0.5 mmol of **1**, 1.5 mmol of H_2O_2 (30%) and 5 mol% of $AuCl_3$ in 5.0 mL DCM at rt. [b] 10 equivalents of H_2O_2 were used. [c] When the reaction was carried out at 0 °C, the yield of **2i** and **2i′** was 37% and 44%, respectively.

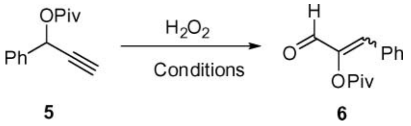


(1)

A proposed mechanistic pathway is shown in Scheme 1. The $AuCl_3$ coordination of the triple bond of **1** enhances the electrophilicity of the alkyne. Subsequent nucleophilic attack of the carbonyl oxygen to the gold-activated alkyne would form intermediate **B**, which was then converted into the gold–carbene intermediate **C**. In the presence of H_2O_2, the gold–carbene **C** would produce the 2-acylfuran and regenerate the catalyst to finish the catalytic cycle.[16] If R^3 is an alkoxy group, the reaction still could give the product but structured as **2′** due to the isomerization of the substrate in the presence of the gold catalyst.[15]

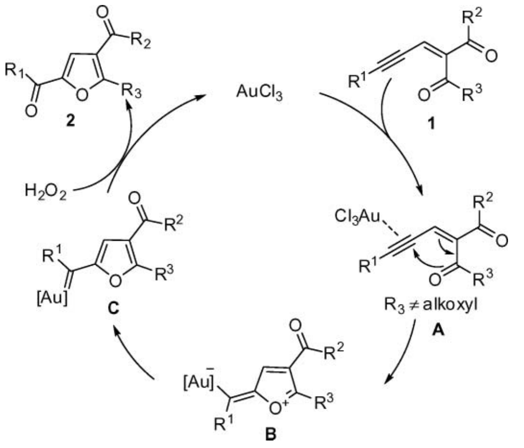
To further confirm the formation of gold–carbene intermediate **C** in the reaction, styrene was added instead of H_2O_2 (eqn (2)).[17] The reaction afforded the expected cyclopropane **4** *via* gold–carbene cyclopropanation in 56% yield as a mixture of two diastereomers (1/1.2).

Table 4 Oxidative rearrangement of propargyl esters[a]

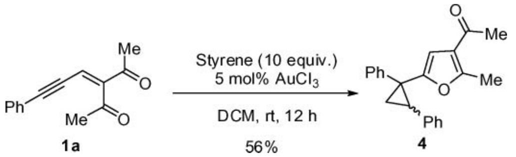


Entry	Catalyst	Solvent	Time/h	Yield (%)[b]	Z/E
1	$AuCl_3$	DCM	21	65	90/10
2	$AuCl_3$	DCE	10	77(65[c])	78/22
3[d]	$AuCl_3$	DCE	10	79	90/10
4	$AuCl_3$	Toluene	10	60	38/62
5	$AuCl_3$/AgOTf	DCM	0.5	50	86/14

[a] Unless otherwise noted, reactions were performed with 0.5 mmol of **1a**, 1.5 mmol of H_2O_2, and 5 mol% of catalysts in 5.0 mL DCM at rt. [b] NMR yield. [c] Isolated yield. [d] 0.75 mmol H_2O_2 was used.



Scheme 1 A plausible mechanistic pathway for the gold-catalyzed oxidative cyclization.

 (2)

Pleasingly, this H_2O_2–$AuCl_3$ system could be applied in other gold–carbene involved reactions. For example the oxidative rearrangement of propargyl ester **5** could give aldehyde **6** in a comparative yield with Toste's method in which $IPrAuSbF_6$–Ph_2SO were used (Table 4).[12b]

In conclusion, a novel efficient and general approach to trisubstituted 2-acylfurans has been developed through the oxidative cyclization of 3-(1-alkynyl)-2-alken-1-ones, in which H_2O_2 acts as an efficient and green oxidant for gold–carbene intermediate. This method can be also applied in other gold–carbene intermediate involved reactions. Further studies including scope, synthetic application, and mechanism are being carried out in this laboratory.

Acknowledgements

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