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# Ru(II)-catalyzed synthesis of poly-substituted furans via intermolecular oxidative annulation reaction of ethyl 3-oxo-3-phenylpropanoates with aryl alkynes/heteroaryl alkynes†

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The oxidative annulation reaction of ethyl 3-oxo-3-phenylpropanoates with internal alkynes proceeds efficiently in the presence of a Ru(II)-catalyst, a copper oxidant and an additive such as AgSbF6 to give poly-substituted furans, which offers a novel method for the selective construction of poly-substituted furans. The reaction has wider substrate scope with simple starting materials, and the desired tetrasubstituted furans were prepared in good to excellent yields.

Polyfunctionalized furans constitute an important class of five-membered O-heterocycles with widespread applications.[1] Furans are extremely important heterocyclic compounds (Fig. 1)[2–5] and worthy of attention as they exhibit a wide range of biological activities.[6,7] Transition metal-catalyzed cyclization reactions, especially intermolecular cyclizations of structurally simple starting materials, are among the most direct and practical methods for the construction of substituted furans.[8] Ma and co-workers reported a method for the synthesis of 3-alkynyl polysubstituted furans by gold-catalyzed $C_{(sp^3)}$–H/$C_{(sp^2)}$–H coupling/cyclization/oxidative alkynylation sequentially.[9] Cao and co-workers synthesized α-carbonyl furan derivatives by Pd-catalyzed cyclization reaction between benzoylacetates and propargyl vinyl ethers.[10] Wang and co-workers developed a method for the synthesis of sulfonyl-substituted furans via copper-mediated annulation between acetylenic sulfones and activated methylenes.[11] Cui and co-workers described the cobalt-catalyzed synthesis of substituted furans from alkynes and α-diazocarbonyls.[12] The Wang group has reported a novel method for the synthesis of polysubstituted furans via sequential Rh-catalyzed arylation and cycloisomerization of cyclopropane.[13] Recently, a Rh(III)-catalyzed cyclization of acrylic acids with α-diazocarbonyls led to the synthesis of furans.[14]

Inspired by these reactions, we envisaged a novel strategy for the synthesis of polysubstituted furans via annulation reaction of ethyl 3-oxo-3-phenylpropanoates and diphenylacetylenes using Rh-catalyzed reaction conditions. Unlike previously reported methods (Scheme 1(a) and (b))[15,16] our work on the catalytic $C_{(sp^3)}$–H bond functionalization of ethyl 3-oxo-3-phenylpropanoate with diphenyl-acetylene via oxidative annulation reaction resulted in the synthesis of tetra-substituted furans (Scheme 1(c)).

Initially, we started an annulation reaction between ethyl 3-oxo-3-phenylpropanoate 1a and diphenylacetylene 2a, which were selected as a model substrate for screening of the reaction conditions for the synthesis of substituted furans. When we examined the reaction between 1a and 2a in the presence of catalysts such as Pd(OAc)2, PtBr2, and RuO2, at 5 mol% loading, Cu(OAc)2·H2O (1.0 equiv.) as an oxidant, AgSbF6 as an additive and K2CO3 (2.0 equiv.) as a base in dichloroethane at 120 °C for 6 h did not afford the desired product 3aa (Table 1, entries 1–3). Then, we tried a reaction with RuCl2(PPh3)3 as a catalyst for the annulation reaction of 1a and 2a using similar reaction conditions and as a result traces of product formation were observed (Table 1, entry 4). When we used [RuCl2(pcymene)]2 as a catalyst in place of RuCl2(PPh3)3 and carried out a reaction between 1a and 2a, it fortunately afforded the
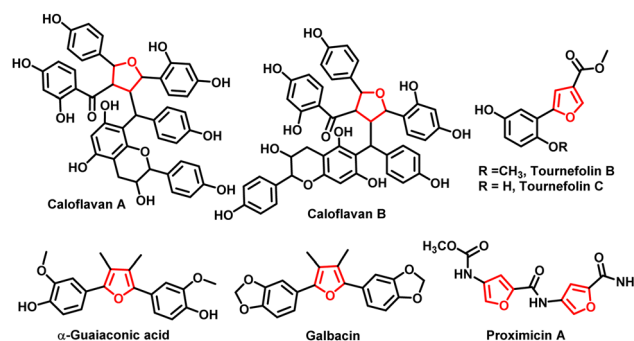
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Fig. 1 The presence of a substituted furan moiety in various natural products and biologically active compounds.
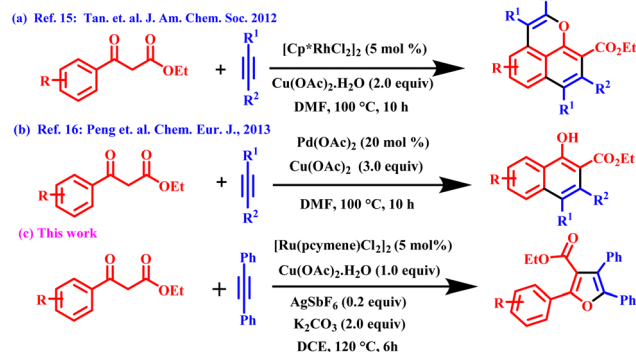
## Previous work



**Scheme 1** Previously reported methods (a) and (b) and our work (c) with ethyl 3-oxo-3-phenylpropanoates and diphenylacetylenes.

**Table 1** Optimization of the reaction conditions



| Entry | Catalyst (5 mol%) | Oxidant (1.0 equiv.) | Base (2.0 equiv.) | Solvent | Yield[d] (%) |
|---|---|---|---|---|---|
| 1[ab] | Pd(OAc)$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | NR |
| 2[ab] | PtBr$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | NR |
| 3[ab] | RuO$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | NR |
| 4[ab] | RuCl$_2$(PPh$_3$)$_3$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | Trace |
| 5[a] | [RuCl$_2$(pcymene)] | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | 67 |
| 6[a] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | 13 |
| 7[ab] | [RuCl$_2$(pcymene)]$_2$ | — | K$_2$CO$_3$ | DCE | NR |
| 8[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | — | DCE | 21 |
| 9[b] | — | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | NR |
| 10[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OTf)$_2$ | K$_2$CO$_3$ | DCE | 47 |
| 11[ab] | [RuCl$_2$(pcymene)]$_2$ | AgOAc | K$_2$CO$_3$ | DCE | 32 |
| 12[ac] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DCE | 52 |
| 13[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | Na$_2$CO$_3$ | DCE | 64 |
| 14[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | Cs$_2$CO$_3$ | DCE | 44 |
| 15[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | Toluene | 28 |
| 16[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | t-BuOH | 16 |
| 17[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | tAmOH | Trace |
| 18[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DMF | Trace |
| 19[ab] | [RuCl$_2$(pcymene)]$_2$ | Cu(OAc)$_2$·H$_2$O | K$_2$CO$_3$ | DMSO | Trace |

Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), at 120 °C. [a] 6 h. [b] AgSbF$_6$. [c] AgBF$_4$. [d] Isolated yields, NR = no reaction.

desired product **3aa** in 67% yield (Table 1, entry 5). A few more experiments were performed in the absence of catalyst, oxidant, additive and base to explore their roles in the reaction (Table 1, entries 6–9). We next screened a few oxidants such as Cu(OTf)$_2$ and AgOAc which yielded 47% and 32% of the desired product, respectively (Table 1, entries 10–11); hence, we concluded that the oxidant Cu(OAc)$_2$·H$_2$O may provide the best yield (Table 1, entry 5). Similarly, we examined another additive i.e., AgBF$_4$, which also did not increase the yield (Table 1, entry 12). The role of other bases such as Na$_2$CO$_3$ and Cs$_2$CO$_3$ (Table 1, entries 13–14) and different solvents was also screened and there was no improvement in the yield of the reaction (Table 1, entries 15–19). With the optimized reaction conditions in hand, we tested the substrate scope between various substituted/un-substituted ethyl 3-oxo-3-phenylpropanoates

**1a–1k** and diaryl-acetylenes **2a–2g** to synthesize tetra-substituted furans **3aa–3kd**, **3ag**, **3gg** and **3hg** with the yields ranging from 59 to 81% (Scheme 2). When, we examined the compatibility of unsubstituted ethyl 3-oxo-3-phenylpropanoate **1a** with unsubstituted/substituted diaryl-acetylenes **2a**, **2c** and **2d** afforded the desired products **3aa**, **3ac**, and **3ad** in good yields with 63–74% (Scheme 2). Furthermore, we explored the substrate scope between electron releasing groups on the *ortho*, and *meta*-position of substituted ethyl 3-oxo-3-phenylpropanoates **1b–1d** reacted with substituted/unsubstituted diarylalkynes **2a**, **2c** and **2e** to give products **3ba**, **3ca**, **3da**, **3dc** and **3de** in better yields than an electron withdrawing group (F) on the *ortho*-position of ethyl 3-oxo-3-phenylpropanoate **1c** (Scheme 2). Electron releasing groups (OMe, Me, and C–(CH$_3$)$_3$) on the *para*-position of diphenyl alkyne produced the desired product in slightly better yields than electron withdrawing groups (F, Cl and Br) on the *para*-position of diphenyl alkyne (Scheme 2). Electron releasing groups on the *para*-position of ethyl 3-oxo-3-phenylpropanoate **1e–1f** reacted with **2a–2c** providing the products **3ea**, **3eb**, **3ec** and **3fa** with good yields (Scheme 2). When we screened the electron withdrawing groups (F, Cl and Br) on the *para*-position of ethyl 3-oxo-3-phenylpropanoate **1g–1i** with unsubstituted/substituted diaryl alkyne **2a**, **2c** and **2f** it gave **3ga**, **3gc**, **3gf**, **3ha**, **3hc**, **3hd** and **3ia** in good to moderate yields (Scheme 2). Furthermore, we focused on electron-releasing groups containing disubstituted ethyl 3-oxo-3-phenylpropanoate **1j**, which was reacted with **2a**, **2b**, **2d** and **2f** to obtain products **3ja**, **3jb**, **3jd**, and **3jf** in good yields (Scheme 2). A reaction of the 3,4,5-OMe group containing ethyl 3-oxo-3-phenylpropanoate **1k** with substituted/unsubstituted diaryl alkynes **2a**, **2b** and **2d** resulted in the products **3ka**, **3kb** and **3kd** in better yields (Scheme 2). We also explored the substrate scope for the reaction between ethyl 3-oxo-3-phenylpropanoate **1a**, **1g** and **1h** with **2g** to afford the products **3ag**, **3gg**, and **3hg** in 70%, 63% and 65% yields, respectively. When we examined the substrate scope between substituted ethyl 3-oxo-3-phenylpropanoate **1g** and **1k** and unsymmetrical substituted diarylalkyne **2h** and **2i** under the optimized reaction conditions, it produced a mixture of compounds **3gh** (65:35), **3kh** (60:40), and **3ki** (63:37) (Scheme 2).
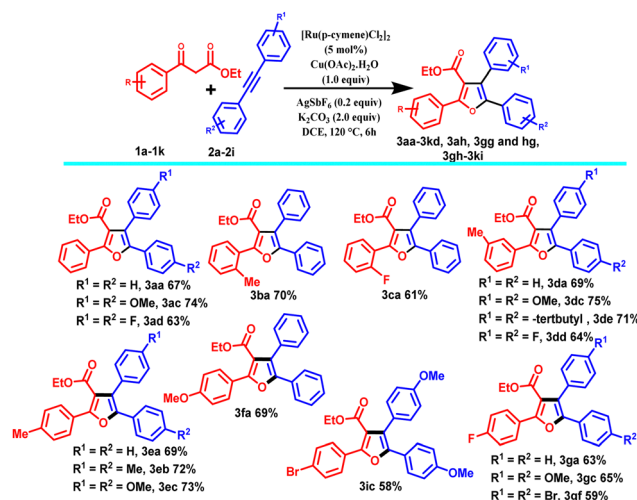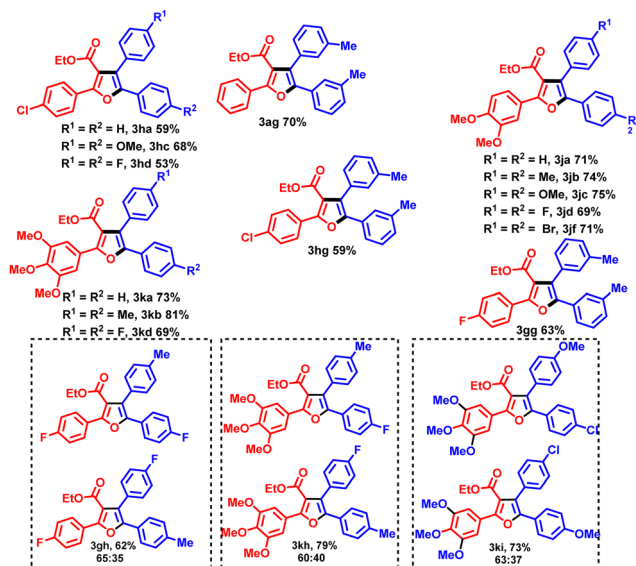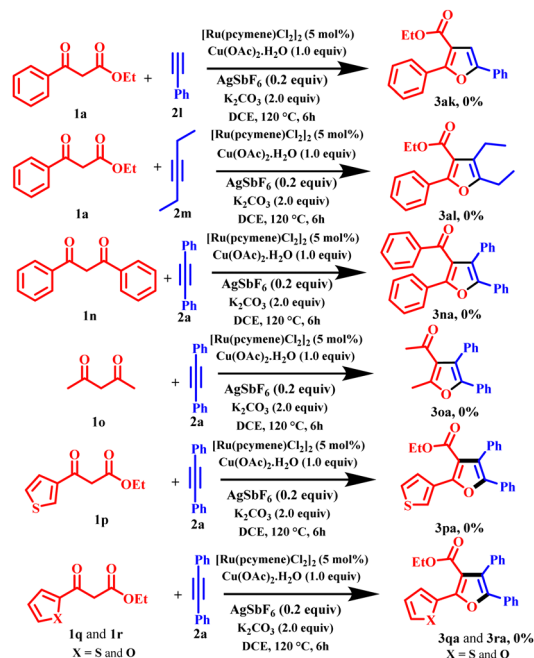
**Scheme 2** The substrate scope of the reaction between ethyl 3-oxo-3-phenylpropanoates **1a–1k** (1.0 mmol) and symmetrical diphenylacetylenes **2a–2g** (1.0 mmol) and unsymmetrical diphenylacetylenes **2h–2i** (1.0 mmol) in the synthesis of tetra-substituted furans.

We also tested a reaction with internal alkyne **2j** bearing both aliphatic and aromatic substituents and heteroaryl alkyne **2k** with ethyl 3-oxo-3-phenylpropanoates/3,4,5-trimethoxy substituted ethyl 3-oxo-3-phenylpropanoate **1a/1k** and obtained the respective tetrasubstituted furans **3aj** (86 : 14 mixture)/**3kj** (90 : 10 mixture) and **3kk**. A reaction with an aliphatic ester **1l** and methyl 3-(4-chlorophenyl)-3-oxopropanoate **1m** with diaryl alkyne **2a** using the optimized conditions also gave the desired
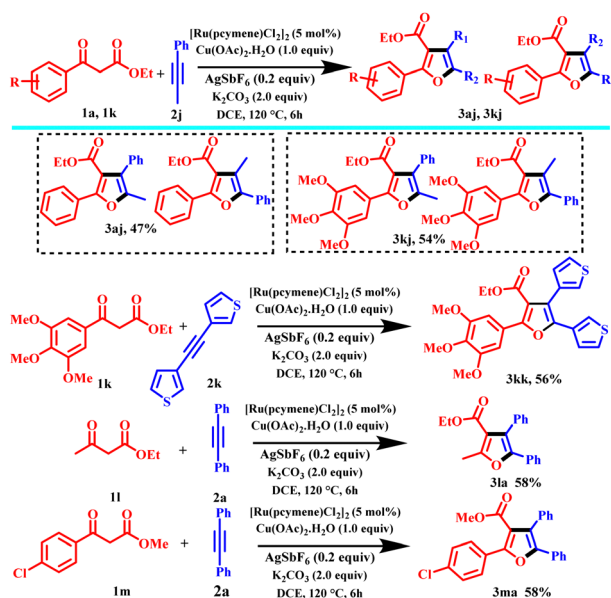


**Scheme 3** The substrate scope of the reaction between ethyl 3-oxo-3-phenylpropanoates **1a/1k** (1.0 mmol), ethyl 3-oxobutanoate **1l** (1.0 mmol), methyl 3-(4-chlorophenyl)-3-oxopropanoate **1m** (1.0 mmol) and prop-1-yn-1-ylbenzene **2j** (1.0 mmol), 1,2-di(thiophen-3-yl)ethyne **2k** (1.0 mmol) and 1,2-diphenylethyne **2a** (1.0 mmol) in the synthesis of tetra-substituted furans.



**Scheme 4** Exploration of the substrate scope of the reaction with ethyl 3-oxo-3-phenylpropanoate **1a** (1.0 mmol) and terminal alkyne **2k** (1.0 mmol) and aliphatic internal alkyne **2l** (1.0 mmol) and 1,3-diphenyl-propane-1,3-dione **1m** (1.0 mmol), and pentane-2,4-dione **1n** (1.0 mmol) and heterocyclic propanoates **1p–1r** (1.0 mmol) with 1,2-diphenylethyne **2a** (1.0 mmol) for the synthesis of tetra substituted furans.

tetrasubstituted furan; however, the yields were low in all these reactions (**3aj**: 47%; **3kj**: 57%; **3kk**: 56%; **3la**: 58%; **3ma**: 58%) (Scheme 3).

Furthermore, we attempted a few more reactions between ethyl 3-oxo-3-phenylpropanoate **1a** and phenylacetylene **2l** (terminal alkyne) and aliphatic internal alkyne **2m** and 1,3-diphenylpropane-
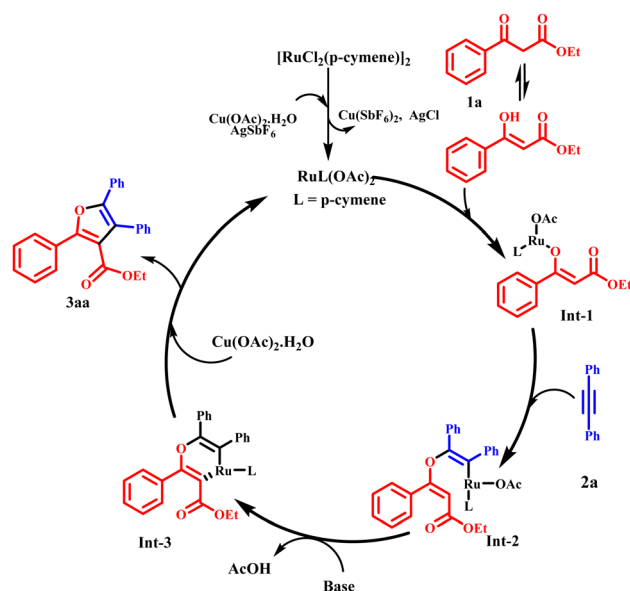


**Scheme 5** Plausible mechanism of the reaction.
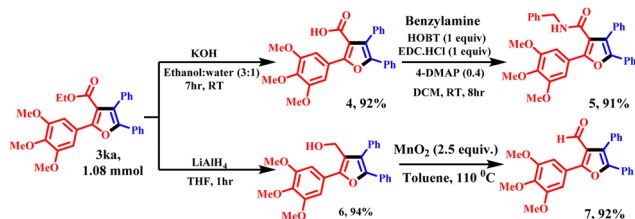
**Scheme 6** Scale up studies and chemical transformation of **3ka**.

1,3-dione **1n** and pentane-2,4-dione **1o**, heterocyclic propanoates such as ethyl 3-oxo-3-(thiophen-3-yl)propanoate **1p**, ethyl 3-oxo-3-(thiophen-2-yl)propanoate **1q**, and ethyl 3-(furan-2-yl)-3-oxopropanoate **1r** with 1,2-diphenylethyne **2a**, which failed to produce the desired product **3ak/3al**, **3ma/3na** and **3pa/3qa/3ra** under the standard reaction conditions (Scheme 4). Liu and co-workers could synthesize polysubstituted furans by oxidative cyclization of diethylbut-2-yne dioate with **1a**, **1n** and **1o** in the presence of Ag(I)/SnCl$_2$–CuI, which indicates the necessity of electron withdrawing groups on alkynes to react with diketoester **1a** aliphatic and aromatic diketones **1n** and **1o** to produce polysubstituted furans.[8j,l] In the case of furan **3pa** and **3qa** synthesis from heterocyclic propanoates **1p–1r**, the carbonyl might have strongly stabilized to restrict the formation of the enol tautomer.

A possible reaction mechanism for polysubstituted furan synthesis appears to be oxidative annulation of ethyl 3-oxo-3-phenylpropanoate **1a** with diaryl alkyne **2a** (Scheme 5). Initially, the base can promote the reaction of ethyl 3-oxo-3-phenylpropanoate **1a** with the Ru(II)-catalyst to generate intermediate-1 (**Int-1**). Subsequent coordinative insertion of diarylalkyne **2a** gives alkenyl Ru(II) intermediate-2 (**Int-2**), which would undergo intramolecular C–H activation to form cyclic intermediate-3 (**Int-3**) with the aid of the base. Then, a reductive elimination of **Int-3** gives substituted furan **3aa** and regenerates the catalyst for the next catalytic cycle. Our control experiments (Table 1; entries 1–4 and 6–9 and ESI†) also support the proposed reaction mechanism. Further studies, however, are required to confirm the exact reaction mechanism.

To demonstrate the practicality of the reaction, we prepared **3ka** in larger quantities and transformed it to acid **4** and alcohol **5**, and subsequently amide **5** and aldehyde **7**, respectively (Scheme 6).

In summary, we have developed a new method for the synthesis of polysubstituted furans by Ru(II)-catalyzed oxidative annulation reaction between ethyl 3-oxo-3-phenylpropanoates/ethyl 3-oxobutanoate and diaryl alkynes/diheteroaryl/prop-1-yn-1-ylbenzene for the first time in the presence of Cu(OAc)$_2$·H$_2$O and additive AgSbF$_6$ and demonstrated its broader substrate scope. In addition, the synthetic practicality of this protocol has been demonstrated by the construction of diverse useful functionalized furan derivatives. Moreover, simple and readily available reagents and starting materials are additional advantages of this strategy.

## Conflicts of interest

There are no conflicts of interest to declare.

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