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Furan Synthesis

Sequential Synthesis of Furans from Alkynes: Successive Ruthenium(II)- and Copper(II)-Catalyzed Processes**

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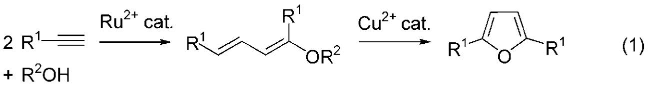
Functionalized furans are frequent subunits in a variety of biologically active molecules[1] and have also been used as communicating moieties in molecular materials.[2] Although these properties have motivated the development of efficient methods for furan synthesis,[3,4] there is still a need for new improved routes, which should be suitable for constructing molecular materials and avoid the use of stoichiometric reagents. In this respect synthetic innovations making use of atom-economical reaction cascades or one-pot multistep catalytic reactions are of special interest.[5]

In recent years the discovery of new activation processes and selective ruthenium-catalyzed multistep transformations of alkynes,[6,7] in parallel to the increasing availability of a variety of alkynes in particular by the use of catalytic Sonogashira reaction,[8] has significantly contributed to this field. The simple head-to-head dimerization of terminal alkynes is of special interest as a convenient way to build conjugated C_4 units.[9] Although the intramolecular oxidative coupling of nonconjugated diynes takes place readily with ruthenium complexes,[10] the catalytic intermolecular dimerization of alkynes could not be applied to the formation of dienyl ethers.[9] This apparently simple catalytic formation of 1,3-dienyl ethers remains a challenge as they are usually more easily obtained via enolates.[11] Noteworthy, the resulting 1,3-dienyl ethers are useful building blocks, such as for Diels–Alder reactions.[12]

Here, we report a novel synthesis of 2,5-disubstituted furans directly from terminal alkynes[13] by sequential one-pot reactions: 1) The ruthenium(II)-catalyzed "click" dimerization of terminal alkynes to produce stereoselectively 1,3-dienyl ethers and 2) the copper(II)-catalyzed cyclization of the in situ formed unsaturated ketones into furans [Eq. (1)].



(1)

It has been demonstrated that [RuCl(cod)Cp*] (cod = cyclooctadiene, Cp* = C_5Me_5) promotes the head-to-head dimerization of alkynes, leading to a bis(carbene)–ruthenium intermediate, and that subsequent 1,4-addition of carboxylic acids results in the catalytic formation of 1,3-dienyl esters.[9] Unfortunately, this catalytic system did not allow the addition of non-acidic pronucleophiles such as alcohols. Our search for a more electrophilic intermediate led us to evaluate the ionic catalyst $[Ru(NCMe)_3Cp^*][PF_6]$. This catalyst allowed a very fast reaction of phenylacetylene (**1a**) with methanol in THF at room temperature. After a reaction time of only 1 min the corresponding 1,3-dienyl methyl ether **3a** was isolated in 92% yield (Scheme 1).

As shown in Scheme 1 this catalytic reaction is highly stereoselective and appears to be quite general. It proceeded rapidly within a few minutes for a variety of terminal alkynes **1a**–**1e** in the presence of methanol, ethanol, and 2-methoxyethanol to produce the (1*E*,3*E*) 1,4-disubstituted 1,3-dienyl ethers **3a**–**3k** in good to excellent yields (75–92%). We believe that this reaction is one of the most facile routes to 1,4-disubstituted dienyl ethers.[11–12]

The catalytic alkyne dimerization is assumed to proceed by the head-to-head coupling of terminal alkynes to generate a bis(carbene)–Ru(Cp*)(NCMe)$^+$ complex with mixed Fischer- and Schrock-type behavior[9] (Scheme 2). This ionic intermediate is more reactive towards the alcohol addition than the intermediate arising from [RuCl(cod)Cp*].

Next, we were interested in the formation of the related β,γ-unsaturated ketones. The analogous reaction of aryl alkynes with water led to a complex mixture of products and not to the formation of ketones. Also attempts to hydrolyze the dienyl ether **3a** in situ under mild conditions failed. However, when $FeCl_3$ was used as Lewis acid in water at 80 °C, hydrolysis took place, and the β,γ-unsaturated ketone **4a** was formed together with a small amount of the α,β-unsaturated ketone **4b** (82% GC combined yield, **4a**/**4b** = 20:3). It is noteworthy that 2,5-diphenylfuran (**5a**) could be also isolated from the reaction mixture in 3% yield from the reaction mixture [Eq. (2)].

Inspired by the partial formation of furan **5a**, we investigated the hydrolysis/cyclization sequence for the conversion

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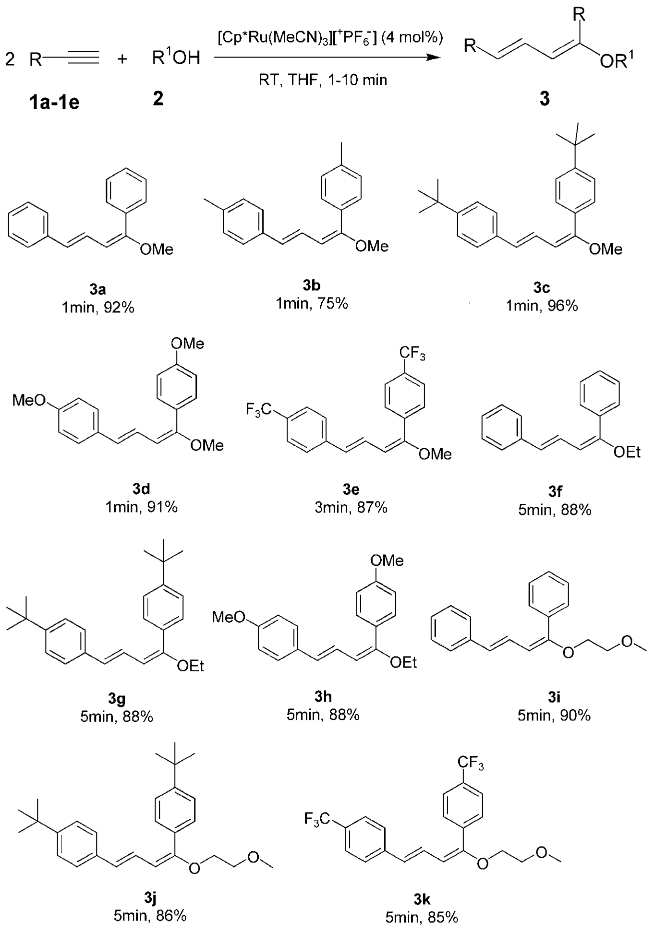
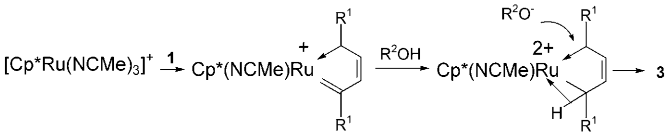
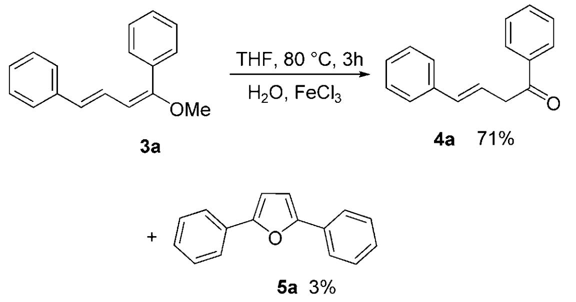


Scheme 1. Ruthenium-catalyzed synthesis of 1,3-dienyl ethers from terminal alkynes and alcohols. Reaction time and yield of isolated products are listed.



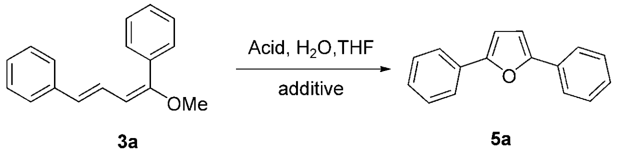
Scheme 2. Proposed mechanism for the formation of dienyl ethers **3**.



(2)

of **3a** into furan **5a** in more detail. For comparison, reactions in acidic media in the presence of Fe or Cu salts were performed under thermal conditions and microwave irradiation. Selected results are reported in Table 1. The best yields were obtained in the presence of *p*-toluenesulfonic acid (*p*-TSA) and a stoichiometric amount of an electrophilic salt in THF with one equivalent of water under microwave irradiation. Here, furan **5a** was formed in 87 % yield with $FeCl_3$ and in 99 % yield with $CuCl_2$ (Table 1, entries 2 and 8). Since in the absence of water (Table 1, entry 5) the formation of furan **5a** was not observed, the reaction is expected to proceed by formation of the unsaturated ketone **4a**. In agreement with this proposal the isolated ketone **4a** was fully converted into **5a** with $CuCl_2$ under microwave irradiation and the reaction conditions listed in Table 1, entry 8.

Table 1: Optimization of the intramolecular cyclization of dienyl ether **3a** to give furan **5a**.[a]



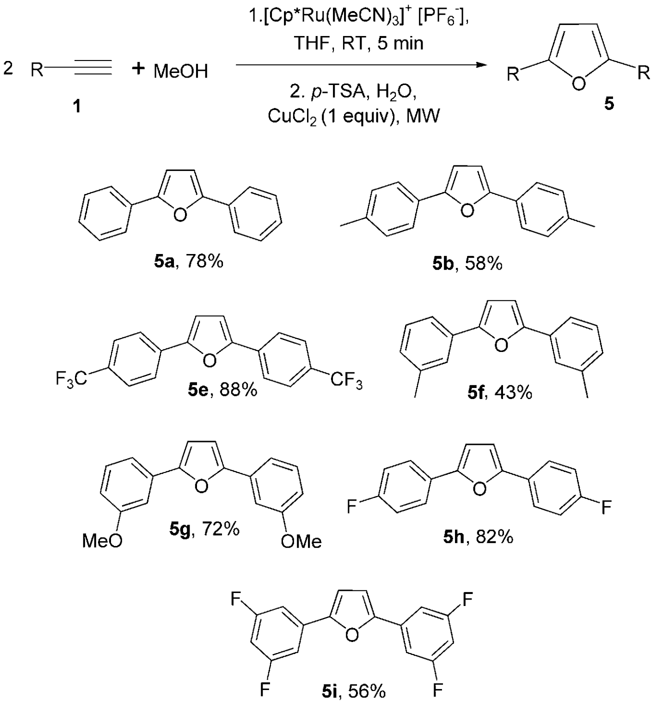
Entry	Acid	Additive	Yield [%][d]
1	*p*-TSA	$FeCl_3$	3[b]
2	*p*-TSA	$FeCl_3$	87[c]
3	*p*-TSA	$Cu(OAc)_2$	5[c]
4	*p*-TSA	CuO	37[c]
5	*p*-TSA[e]	$CuCl_2$	–[e]
6	none	$CuCl_2$	59[c]
7	*p*-TSA	$CuCl_2$	59[b]
8	*p*-TSA	$CuCl_2$	99[c]

[a] A solution of **3a** (0.5 mmol, 118 mg) in 2 mL of THF was treated with *p*-TSA·H_2O (0.1 mmol, 19 mg), H_2O (1 mmol), and additive (1 mmol); the resulting mixture was stirred. [b] The reaction was conducted at 80 °C for 3 h. [c] The reaction mixture was subjected to microwave irradiation (50 W, 150 °C) for 20 min. [d] Yields determined by GC with tetradecane as internal standard. [e] Without water in the reaction mixture.

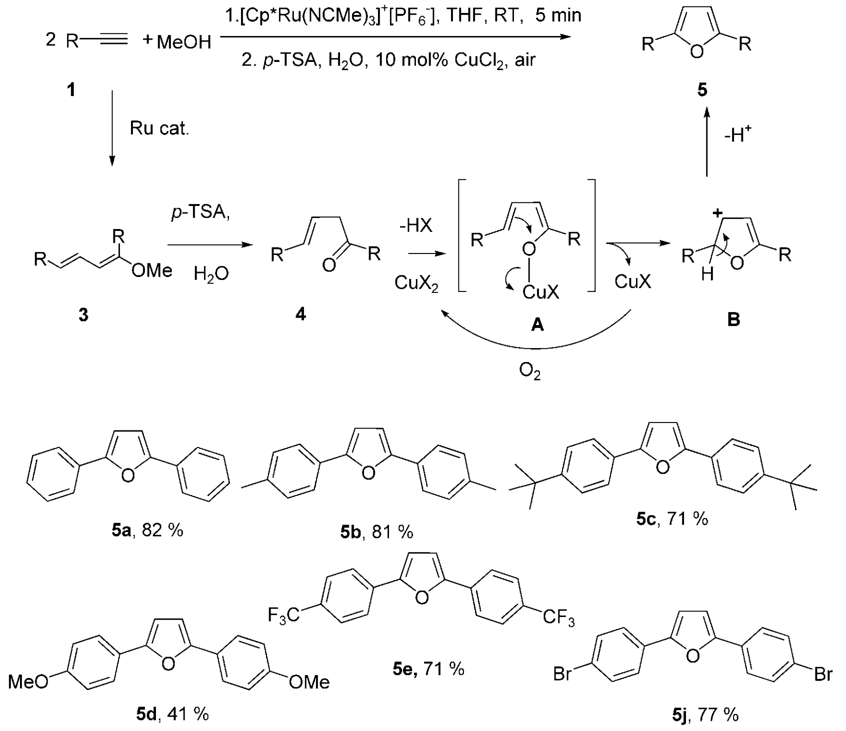
Having the optimized conditions in hand, we studied the synthesis of 2,5-disubstituted furans directly from terminal alkynes by one-pot combined successive ruthenium-catalyzed and copper(II)-promoted reactions. The results are listed in Scheme 3. In all cases studied—with alkynes **1a**–**1e** already used for the synthesis of dienyl ethers and the alkynes **1f**–**1i**—the cyclization reaction proceeded smoothly to give the 2,5-disubstituted furans **5a**–**5i** in good to excellent yields, including the fluorinated derivatives **5e**, **5h**, and **5i** (Scheme 3).[14]

The reaction mechanism has not yet been elucidated, but as Cu salts readily interact with the heteroatoms of ketones and imines,[15] the interaction of Cu^{2+} with the oxygen atom of **4** may promote deprotonation and formation of dienolate intermediate **A**, which is able to cyclize into **B** (Scheme 4). Alternatively, the interaction of Cu^{2+} with the C=C bond of **4** may also promote the formation of a π-carbon-bonded dienolate before cyclization into **B**. Such a cyclization would lead to the reduction of Cu^{II} to Cu^{I}.[15]

Consequently, we attempted to transform the Cu^{2+}-promoted stoichiometric cyclization into a catalytic reaction by regenerating the copper(II) species with oxygen. Thus, the



Scheme 3. One-pot synthesis of 2,5-disubstituted furans directly from alkynes.



Scheme 4. Copper(II)-catalyzed cyclization reaction and proposed mechanism.

second step of the reaction sequence was modified and performed with 10 mol % $CuCl_2$ in the presence of air in THF/toluene (10:1) at 70 °C. Indeed, formation of furans took place: reaction of terminal alkynes **1** provided the furans **5a**–**5e** in 70–82 % yield; **5d**, which contains electron-donating substituents, was formed in lower yield. Noteworthy, the furan formation tolerates aryl bromides, and **5j** was obtained in 77 % yield (Scheme 4). This reaction thus offers potential for further functionalization of furans by, for example, catalytic cross-coupling reactions.

In conclusion, we have established a facile and highly stereoselective method to synthesize 1,3-dienyl ethers from terminal alkynes in the presence of the $[Ru(NCMe)_3Cp^*][PF_6]$ catalyst, in only a few minutes at room temperature as a click reaction. Moreover, a novel method for the one-pot synthesis of 2,5-disubstituted furans from 1,3-dienyl alkyl ethers, and related unsaturated ketones, is described and takes place with catalytic amounts of $CuCl_2$ in the presence of air. Both catalytic reactions with ruthenium (II) and copper (II) can be performed successively in one pot directly from terminal alkynes. As the reaction tolerates aryl halides, it could potentially provide access to a variety of molecular materials, as well as mixed aryl–furan polymers from aromatic diynes.

Experimental Section

Typical procedure for the synthesis of the dienyl ether **3a**: Phenylacetylene (**1a**) (1 mmol, 102 mg) was added to a mixture of $[Cp^*Ru(MeCN)_3][PF_6]$ (20 mg, 0.04 mmol, 4 mol %) and MeOH (1 mmol, 32 mg) in distilled THF (2 mL). The mixture was stirred at RT for 1 min, the resulting mixture was concentrated and purified by flash column chromatography on silica, eluting with ethyl acetate/petroleum ether (1:10) to give **3a** as a white solid (109 mg, 92 %).

Typical procedure for the synthesis of 2,5-disubstituted furan **5a** from alkyne **1a**: Phenylacetylene (**1a**) (1 mmol, 102 mg) was added to a mixture of $[Cp^*Ru(MeCN)_3][PF_6]$ (20 mg, 0.04 mmol, 4 mol %) and MeOH (1 mmol, 32 mg) in distilled THF (2 mL). The mixture was stirred at RT for 5 min. Then *para*-toluenesufonic acid monohydrate (0.1 mmol, 19 mg), H_2O (1 mmol), $CuCl_2$ (0.1 mmol, 13.5 mg), and toluene (1 mL) were added. The resulting mixture was heated and aerated with air at 70 °C for 10 h. After cooling, the solution was diluted with diethyl ether (10 mL), washed with $NaHCO_3$, and dried with anhydrous $MgSO_4$. The solvent was removed, and the crude product was purified by flash column chromatography on silica, eluting with petroleum ether/diethyl ether (50:1) to give 2,5-diphenylfuran **5a** as a white solid (90 mg, 82 %).

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