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Heterocycle Synthesis

Metal-Free Oxidative Cyclization of Alkynyl Aryl Ethers to Benzofuranones**

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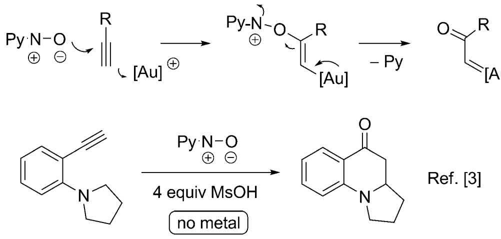
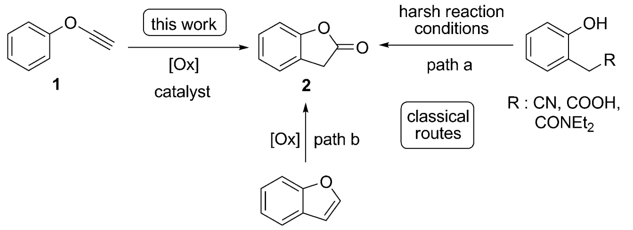
Dedicated to Professor Teruaki Mukaiyama

Recently, reactions of *N*-oxides with alkynes have attracted significant attention; several groups were involved and many synthetically useful transformations have been reported.[1] In nearly all of the reactions gold catalysts are used as π-activators for the triple bond. After oxygen transfer and release of pyridine, α-oxo gold carbenes[2] are obtained as intermediates (Scheme 1, upper part). These highly reactive species can be used to generate a diverse set of valuable target molecules. Apart from these transition-metal-catalyzed reactions only one report was published by the Gong group in which a metal-free process for this kind of chemistry was presented (Scheme 1, lower part).[3] For this particular transformation stoichiometric amounts of MsOH turned out to be crucial to promote the reaction, and the authors speculate that a nitrogen-assisted protonation of the alkyne initiates the reaction cascade.



Scheme 1. Top: Gold-catalyzed generation of α-oxo carbenoids. Bottom: Metal-free *N*-oxide/alkyne reaction with stoichiometric amounts of acid.

Herein we present a new and unusual metal-free *N*-oxide transformation that can even be performed without any additives or with only catalytic amounts of an acid. Our initial aim was to use alkynyl aryl ethers **1** (substrates that are easily available from inexpensive phenol derivatives) for the gold-catalyzed oxidative cyclization providing benzofuranone derivatives **2** (Scheme 2). The target structure is of great interest, since it is a subunit in many natural products.[4] Recent approaches for the synthesis of benzofuranones use 2-hydroxyphenylacetic acid[5] or substrates derived from this structure as starting materials.[6] However, these reactions require harsh conditions (Scheme 2, path a). Alternative strategies comprise the oxidation of benzofurans with *N*-oxides or oxone (Scheme 2, path b).[7]



Scheme 2. Overview of previous synthetic routes to benzofuranones and our new approach.

For an initial screening (Table 1), we applied alkynyl aryl ether **1a** which is predestined to form a carbenoid that is prone to be attacked by a nucleophile or to undergo C–H insertion. The desired product **2a** was detected by GC-MS in 43 % yield following application of the well-established combination of IPrAuCl and AgNTf$_2$ (Table 1, entry 1). In a series of experiments with different silver salts as halide scavengers no strong influence was evident and yields ranged from 31 % to 48 % (Table 1, entries 2–6). To our surprise even better yields were obtained by the use of AgNTf$_2$ in the absence of a gold catalyst (Table 1, entry 7). Even more interesting for us was the fact that HBF$_4$ diethyl etherate was also able to mediate a conversion, even when only catalytic amounts of acid were applied (Table 1, entry 11). This is remarkable, as to the best of our knowledge this is the first case in which a metal-free intermolecular *N*-oxide/alkyne reaction takes place with only catalytic amounts of an acid as

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[+] Crystallographic investigation.

[**] We thank Umicore AG & Co. KG for the generous donation of gold salts. We dedicate this work to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

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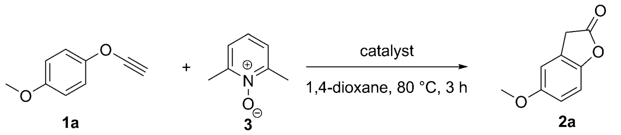
Table 1: Catalyst screening.



1a **3** **2a**

Entry	Catalyst	Catalyst loading	Yield[a]
1[b]	IPrAuCl/AgNTf$_2$	5 mol%	43%
2[b]	IPrAuCl/AgSbF$_6$	5 mol%	31%
3[b]	IPrAuCl/AgOTs	5 mol%	43%
4[b]	IPrAuCl/AgOTf	5 mol%	37%
5[b]	IPrAuCl/AgPF$_6$	5 mol%	40%
6[b]	IPrAuCl/AgBF$_4$	5 mol%	48%
7[b]	AgNTf$_2$	5 mol%	55%
8[b]	HBF$_4$·OEt$_2$	5 mol%	55%
9	IPrAuCl/AgOTf	10 mol%	70%
10	AgNTf$_2$	10 mol%	82%
11	HBF$_4$·OEt$_2$	10 mol%	86%
12	*p*-toluene-sulfonic acid	10 mol%	36%
13	TFA	10 mol%	26%
14	–	–	42%[c]

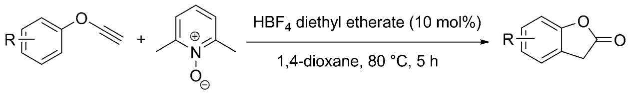
[a] Determined by GC analysis. [b] Under anhydrous reaction conditions (dry glassware, molecular sieves). [c] Yield of the isolated product after 18 h.

a promoter. Increasing the catalyst loading had a positive effect on all of the tested catalyst systems (Table 1, entries 9–13). HBF$_4$ diethyl etherate turned out to be the catalyst of choice while other tested Brønsted acids were less effective (Table 1, entries 12 and 13). Even in the absence of catalyst a significant amount of product could be obtained but yields were lower for this uncatalyzed transformation and the reaction time was longer (Table 1, entry 14).

Changing the *N*-oxide to 8-isopropylquinoline *N*-oxide or 3,5-dibromopyridine *N*-oxide did not improve the yield but resulted in rather unselective transformations. Furthermore, neither *meta*-chloroperoxybenzoic acid nor *N*-methylmorpholine *N*-oxide were suitable oxidants for this reaction. DCE and benzene were tested as alternative solvents. Whilst DCE showed slightly lower conversion, benzene and 1,4-dioxane gave equally good results.

Next we evaluated the substrate scope of this transformation (Table 2). It should be mentioned that interpretation of yields is not easy due to the fact that the starting alkynyl aryl ethers were used directly after elimination from the corresponding dichloro vinyl ethers and some of the elimination reactions did not deliver totally pure starting materials. (Unfortunately column chromatography was not suitable for the purification of the terminal aryl alkynyl ethers; thus the yields pertain to two steps.) All of the reactions were performed under the optimized conditions using HBF$_4$ diethyl etherate (10 mol%) as the catalyst and 2,6-dimethylpyridine *N*-oxide (**3**) as the oxygen donor (1 equiv). Substrate **1b**, bearing an unsubstituted phenyl group, smoothly delivered the corresponding benzofuranone **2b** in high yield (Table 2, entry 1). Even when one of the *ortho* positions was blocked, the expected product **2c** was still obtained (Table 2, entry 2). When both of the *ortho* positions

Table 2: Scope of the reaction.



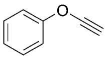
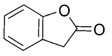
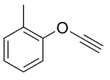
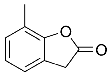
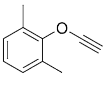
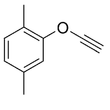
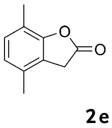
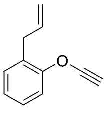
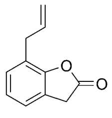
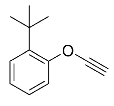
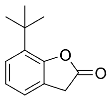
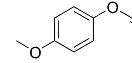
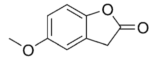
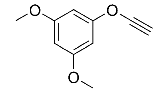
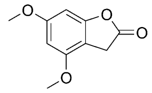
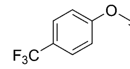
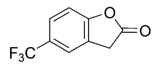
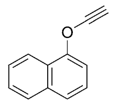
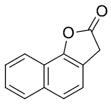
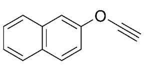
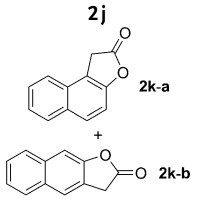
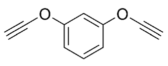
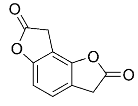
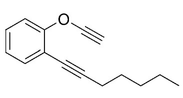
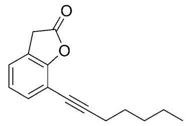
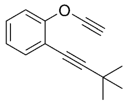
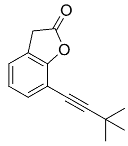
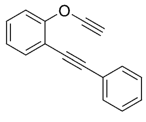
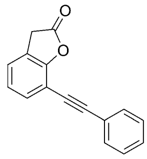
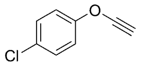
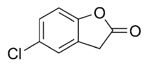
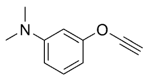
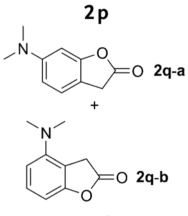
Entry	Substrate	Product	Yield[a]
1	 **1b**	 **2b**	81%
2	 **1c**	 **2c**	51%
3	 **1d**	–	complex mixture
4	 **1e**	 **2e**	42%
5	 **1f**	 **2f**	63%
6	 **1g**	 **2g**	78%
7	 **1a**	 **2a**	68%
8	 **1h**	 **2h**	64%
9	 **1i**	 **2i**	30%
10	 **1j**	 **2j**	83%
11	 **1k**	 **2k-a/2k-b** (5:1)	77%[b]
12	 **1l**	 **2l**	17%

Table 2: (Continued)

Entry	Substrate	Product	Yield[a]
13	 **1m**	 **2m**	56% 28%[c]
14	 **1n**	 **2n**	37% 34%[c]
15	 **1o**	 **2o**	18% 10%[c]
16	 **1p**	 **2p**	43%
17	 **1q**	 **2q-a/2q-b** (2:1)	64%[b]

[a] Yields of isolated products. [b] Combined yield of both isomers; isomers were separable. [c] Yields for reaction catalyzed by IPrAuCl/AgNTf$_2$.

were blocked (**1d**), only a complex mixture was obtained and no selective C–H insertion of the benzylic position took place (Table 2, entry 3). Shifting one of the blocking methyl groups to the *meta* position (**1e**) restored good reactivity but yields were slightly lower (Table 2, entry 4). A substrate with an alkene unit (**1f**) delivered no cyclopropanation product; once again exclusive formation of benzofuranone **2f** was observed (Table 2, entry 5). A *tert*-butyl group in *ortho* position was also well tolerated and product **2g** was obtained in a good yield of 78% (Table 2, entry 6). The yield of isolated product generated from test substrate **1a** was slightly lower, which might be explained by the instability of the starting material (Table 2, entry 7). The even more electron-rich substrate **1h** could also be converted in reasonable yield (Table 2, entry 8). Shifting to an electron-withdrawing trifluoromethyl group (**1i**) led to a significant decrease in yield but once again the interpretation is difficult as the starting alkynyl ether **1i** turned out to be fairly unstable (Table 2, entry 9). Starting materials containing a naphthyl moiety proved to be more stable and as a consequence yields of the final products were high (Table 2, entries 10 and 11). For substrate **1j**, bearing the alkynyloxy group in the α-position of the naphthyl system, only one regioisomer was formed, whereas in the case of substrate **1k** a mixture of isomers (**2k-a**, **2k-b**) was obtained in a 5:1 ratio favoring the α-attack of the naphthyl system (Table 2, entry 11). Attempts to perform the reaction in a bidirectional fashion turned out to be difficult as the starting materials were unstable. However, product **2l** could be isolated in poor yields (Table 2, entry 12). Next we investigated diynes **1m–o** as starting materials. Owing to the second alkynyl moiety, these starting materials could alternatively follow a dual activation pathway in the presence of a gold catalyst;[8] thus these compounds were transformed with gold as well as with the Brønsted acid catalysts. No dual activation pathway was observed with the gold catalysts; instead the oxidation pathway took place, but yields were lower than in the corresponding conversions with Brønsted acid (Table 2, entries 13–15) for all three cases. Finally, we wanted to evaluate the compatibility with other functional groups. A chloro substituent in *para* position of the arene was well tolerated and the corresponding product **2p** could be isolated in moderate yield (Table 2, entry 16). Aniline derivative **1q** could also be converted in good yield but the *ortho*/*para* selectivity was poor (Table 2, entry 17). In addition to the NMR-based structure assignments, X-ray crystal structure analyses for compounds **2l** and **2n** were conducted. The solid-state structures (Figure 1) provide the final proof for the formation of the benzofuranone structures.[9]

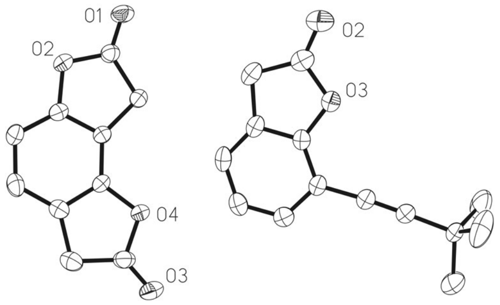
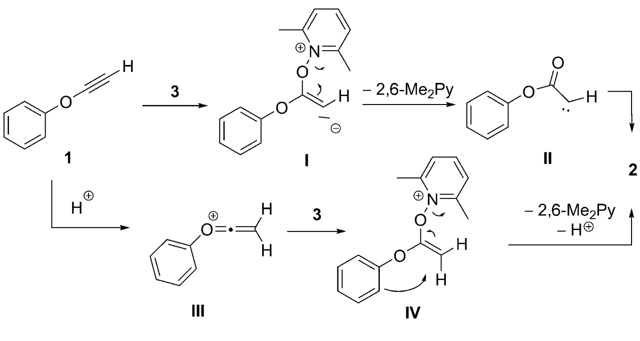


Figure 1. Solid-state molecular structure of **2l** (left) and **2n** (right). Thermal ellipsoids at 50% probability.

Our proposed mechanism for this transformation, which is highly speculative, can be divided into the uncatalyzed and an acid-catalyzed pathway (Scheme 3). For the uncatalyzed case the alkyne can react as an electrophile with the *N*-oxide without further activation. This is based on the high reactivity of the alkynyl ethers due to the effect of the adjacent oxygen atom which increases the electrophilicity at the internal

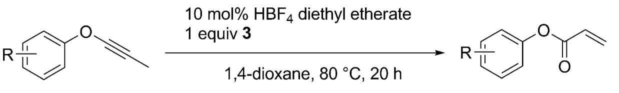


Scheme 3. Proposed mechanism (**3** = 2,6-dimethylpyridine *N*-oxide).

alkyne position to form intermediate **I**. In the next step the pyridine is released and a highly reactive carbene intermediate **II** is generated which can then insert into the aryl–hydrogen bond. A related mechanism was discussed by the Zhang group for an in situ generated *N*-oxide (generated by the oxidation of an aniline derivative with *m*CPBA) which then reacted in an intramolecular fashion.[10] Attempts to trap the free carbene intermolecularly with external alkenes only resulted in the formation of unseparable mixtures.

For the catalyzed pathway the alkynyl aryl ether is protonated by the acid, which increases the electrophilicity and leads to the formation of the highly reactive ketenium intermediate **III**. After attack of the *N*-oxide, intermediate **IV** is formed which releases 2,6-dimethylpyridine and a proton to generate the product **2**.

Our proposed mechanism is endorsed by an experiment with the non-terminal alkynyl aryl ether substrates **4**. In this case the 2,6-dimethylpyridine *N*-oxide **3** also attacks the more electrophilic alkyne carbon next to the heteroatom to form the highly reactive carbenoid intermediate. In contrast to the previously described mechanism, these systems now have the possibility of a competing 1,2-hydride shift onto the carbene center which is the favored reaction step.[11] After this hydride shift, phenyl acrylates **5** were obtained in 27 % and 50 % yield (Scheme 4).



4
4a: R = H
4b: R = OMe

5
50 %
27 %

Scheme 4. Conversion of non-terminal aryl alkynyl ethers **4** to phenyl acrylates **5**.

In conclusion, we herein report a convenient metal-free synthesis of benzofuranones using starting materials derived from inexpensive phenol derivatives. The reaction proceeds with only catalytic amounts of the Brønsted acid HBF$_4$ diethyl etherate and can even be performed without any additives. 2,6-Dimethylpyridine *N*-oxide was used as an oxidant and oxygen donor. To the best of our knowledge this is the first example of the generation of an α-oxy carbene in an intermolecular reaction by application of an *N*-oxide without the use of any additives or with only catalytic amounts of acid. This demonstrates that highly activated alkynes can be used as α-oxy carbene precursors even in the absence of a transition metal. The easy accessibility of the starting materials and the mild reaction conditions combined with the importance of benzofuranone as target molecule make this new reaction a useful advancement of recent synthetic approaches.

Experimental Section

General procedure: A round-bottomed flask was charged with a solution of the HBF$_4$ diethyl etherate (13.7 mg, 84.7 µmol; 10 mol %) in 1.0 mL 1,4-dioxane. 2,6-Dimethylpyridine *N*-oxide (104 mg, 847 µmol; 1.0 equiv) was added to this solution. Afterwards ethynyloxybenzene (100 mg, 847 µmol; 1.0 equiv) was added and the resulting mixture was stirred at 80 °C. After completion of the reaction after 5 h the crude product was adsorbed onto Celite and subjected to flash column chromatography over silica gel with petroleum ether (PE)/ethyl acetate (EA)/dichloromethane (DCM) (40:1:1). The product obtained was a yellow oil (91.3 mg, 681 µmol, 81 %). R_f (PE/EA/DCM 10:1:1) = 0.22; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 3.74$ (s, 2H), 7.05–7.17 (m, 2H, 7.27–7.37 ppm (m, 2H). The spectroscopic data are in agreement with the data in reference [7a].

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[9] CCDC 942521 (**2l**) and 942522 (**2n**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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