A Hg(OTf)₂-Catalyzed Enolate Umpolung Reaction Enables the Synthesis of Coumaran-3-ones and Indolin-3-ones

Zhouting Rong,* Weican Hu, Ning Dai, and Guoying Qian*

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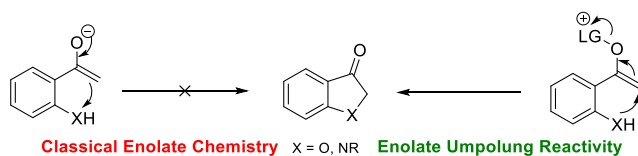ACCESS | ○ Metrics & More | ○ Article Recommendations | ○ Supporting Information

ABSTRACT: The potential of mercury catalysis has been extended to the arena of enolate umpolung reactions for the first time by the generation of enolonium species via Hg(OTf)₂-catalyzed *N*-oxide addition to alkynes. The enolonium species formed can undergo intramolecular nucleophilic attack by hydroxyl or amino groups, leading to the synthesis of various coumaran-3-ones and indolin-3-ones.

Synthesis of coumaran-3-ones and indolin-3-ones

Via: enolate umpolung reactivity
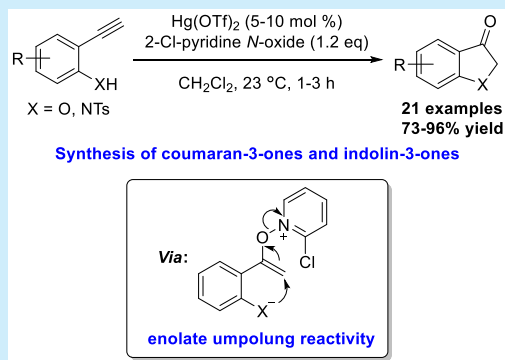
C oumaran-3-ones and indolin-3-ones are valuable synthetic targets because they are important building blocks for the construction of various natural products and pharmaceutical molecules.[1] We envisioned that coumaran-3-ones and indolin-3-ones could be synthesized via intramolecular α-etherification of *o*-hydroxyacetophenones or α-amination of *o*-aminoacetophenones. However, traditional methods for the α-functionalization of carbonyl compounds, by generating enolates with strong bases to attack electrophiles, can be ineffective because the electronegativity of oxygen and nitrogen atoms makes them unlikely to be attacked by nucleophilic enolates. In principle, an oxidation event is needed to complete the cyclization.[2] A less classical solution to this issue is to reverse the polarity of the enolate by forming an enolonium species. This enolonium species can display enolate umpolung reactivity to behave as an electrophile, which can be attacked by the hydroxyl or amino group in an S_N2′ manner to give our desired coumaran-3-one and indolin-3-one products (Scheme 1).

There have been a considerable number of reports on the generation of enolonium species.[3] For example, Maulide and co-workers developed an elegant metal-free method for the

treatment of amides with triflic anhydride, 2-I-pyridine, and 2,6-lutidine-*N*-oxide to access enolonium species **A**, which proved to be a versatile intermediate for the α-functionalization of amides.[4] Szpilman and co-workers used a TMS enolether with a hypervalent iodine to synthesize and characterize an enolonium species **B**, which can serve as an intermediate for the α-alkylation of carbonyl compounds.[5] Maulide also reported the generation of enolonium **C** by treating alkynes with sulfoxides in the presence of Brønsted acid, which undergo [3,3]-sigmatropic rearrangement to yield α-arylated ketones.[6] The combined system of Brønsted acids with pyridine *N*-oxides reported by Shin[7] and Hashmi[8] also converted alkynes into enolonium species **D** (Scheme 2a).

Compared with the metal-free methods mentioned above, transition metal-catalyzed generation of enolonium species and umpolung reactions are less developed.[9] Gold(I) complexes are known to catalyze the addition of pyridine *N*-oxides to alkynes to form α-oxo gold carbenes,[10] which have been applied to the synthesis of coumaran-3-ones and indolin-3-ones by Ye and co-workers (Scheme 2b).[11] In 2016, Zhang and co-workers isolated and characterized an *N*-alkenoxypyridinium salt **E** under their gold(I)-catalyzed conditions and demonstrated versatile enolate umpolung reactivities of this enolonium species (Scheme 2b).[12] We envisaged that other
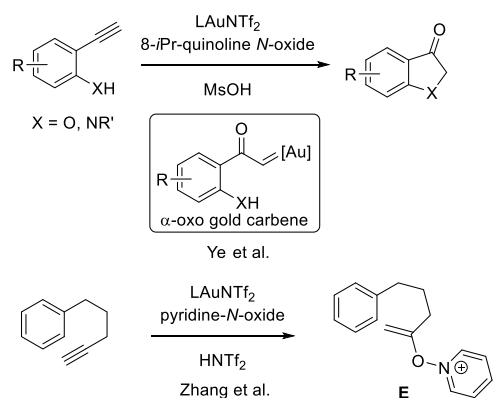
Scheme 1. Our Design for the Synthesis of Coumaran-3-one and Indolin-3-one

Classical Enolate Chemistry   X = O, NR   Enolate Umpolung Reactivity

Scheme 2. Precedents for the Generation of Enolonium Species, Synthesis of Coumaran-3-one and Indolin-3-one, and Our Work

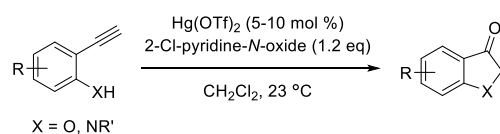(a) Metal-free Methods for the Access to Enolonium Species

Maulide et al.

Szpilman et al.

X = OH, OTs

Maulide et al.

Shin, Hashmi et al.
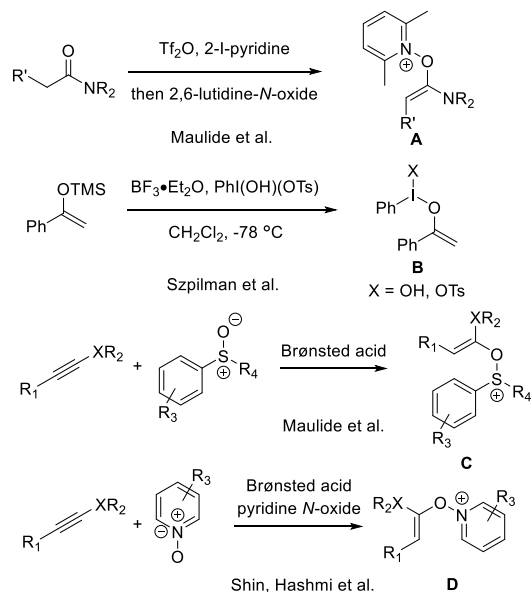
(b) Gold Catalysis in the Generation of Enolonium Species and Synthesis of Coumaran-3-ones and Indolin-3-ones

X = O, NR'

α-oxo gold carbene

Ye et al.

Zhang et al.

(c) This work: Hg(OTf)$_2$-catalyzed enolate umpolung reaction

X = O, NR'

Table 1. Optimization of the Reaction Conditions[a]

entry	catalyst	N-oxide	time (h)	yield[b] (%)
1	ZnCl$_2$	3a (H)	6	23
2	ZnBr$_2$	3a (H)	24	0
3	ZnI$_2$	3a (H)	24	0
4	CuCl	3a (H)	24	0
5	CuCl$_2$	3a (H)	24	0
6	CuBr$_2$	3a (H)	48	0
7	Zn(OTf)$_2$	3a (H)	48	0
8	Cu(OTf)$_2$	3a (H)	48	0
9	AgOAc	3a (H)	48	0
10	Hg(OTf)$_2$	3a (H)	1	64
11	Hg(OTf)$_2$	3b (2-Cl)	1	92
12	Hg(OTf)$_2$	3c (2-Br)	1	45
13	Hg(OTf)$_2$	3d (3-Br)	1	40
14	Hg(OTf)$_2$	3e (2,6-Cl$_2$)	1	90
15	Hg(OTf)$_2$	3f (2,6-Me$_2$)	1	49
16	Hg(OTf)$_2$	4a (H)	1	50
17	Hg(OTf)$_2$	4b (Me)	1	55
18	Hg(OTf)$_2$	4c (i-Pr)	1	53

[a]Unless otherwise noted, all reactions were performed with 1a (0.2 mmol), catalyst (0.01 mmol), and N-oxide (0.24 mmol) in CH$_2$Cl$_2$ (1 mL) at 23 °C. [b]The yield of 2a was determined by NMR with 1,3,5-trimethylbenzene as the internal standard.

metals that are more affordable than gold, as long as they could promote the addition of N-oxide to alkynes, could also catalyze the formation of N-alkenoxypyridinium species, which could serve as versatile intermediates for the synthesis of α-functionalized ketones. Herein, we report the first Hg(OTf)$_2$-catalyzed enolate umpolung reaction that enables the synthesis of various coumaran-3-ones and indolin-3-ones.

At the outset, we used commercially available 2-ethynylphenol 1a as the substrate to screen conditions, and the results are summarized in Table 1. Upon exposing 1a to 5 mol % ZnCl$_2$ in the presence of pyridine N-oxide (1.2 equiv) in dichloromethane at room temperature, we were able to isolate our desired product 2a, albeit in low yield (entry 1). Then, we continued to test other inexpensive transition metal salts, but to our disappointment, no reaction took place when other zinc
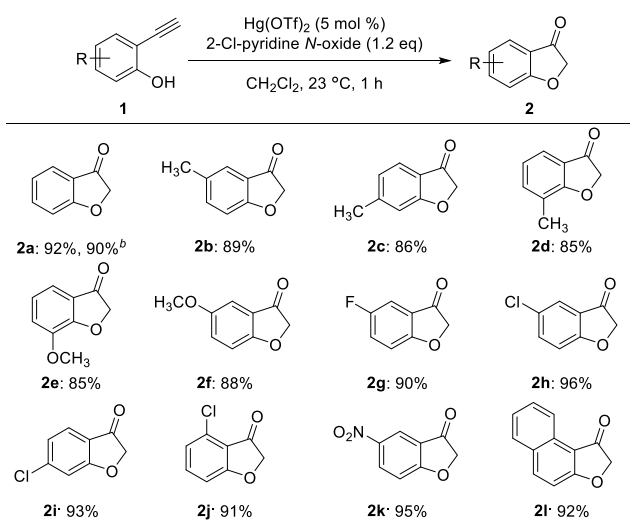
halides or copper halides were employed (entries 2−6). After Zn(OTf)$_2$, Cu(OTf)$_2$, and AgOAc failed to give any desired coumaran-3-one 2a, we turned our attention to Hg(OTf)$_2$,[13] an efficient inexpensive catalyst for alkyne activation, which successfully afforded 2a in 64% yield (entry 9). We also examined a variety of N-oxides and found that Cl-substituted pyridine N-oxides 3b and 3e outperformed other N-oxides with 2-Cl-pyridine N-oxide 3b giving the best yield (entries 10−17). The superiority of Cl-substituted pyridine N-oxides is presumably due to the nucleophilicity being stronger than those of other pyridine N-oxides, which accelerates the addition to the alkyne. It is noteworthy that our transformations can be completed in the absence of any Brønsted acid additive, which is usually essential in gold catalysis involving addition of N-oxide to alkynes.

With the optimal conditions in hand, we started to explore the substrate scope of this transformation, and a variety of 2-ethynylphenols were employed. In general, this reaction showed good functional group tolerance, and the results are listed in Scheme 3. 2-Ethynylphenols 1b−f bearing electron-donating substituents such as Me and OMe at different positions of the phenyl rings proved to be suitable substrates for producing the corresponding coumaran-3-ones 2b−f in good yields. Fluoro-, chloro-, and nitro-substituted coumaran-3-ones 2g−k can also be obtained under our standard conditions in excellent yields. 2-Ethynylnaphthol 1l reacted smoothly to furnish dihydronaphthofuran-1-one 2l in 92% yield. To our delight, when the reaction of 1a was carried out on a 10 mmol scale, the desired product 2a can be isolated in 90% yield, which indicated that our conditions were robust for large-scale preparations.

Scheme 3. Substrate Scope of Coumaran-3-one Synthesis[a]

2a: 92%, 90%[b]   **2b:** 89%   **2c:** 86%   **2d:** 85%

2e: 85%   **2f:** 88%   **2g:** 90%   **2h:** 96%

2i· 93%   **2j·** 91%   **2k·** 95%   **2l·** 92%

[a]All reactions were performed with **1** (0.5 mmol), Hg(OTf)$_2$ (0.025 mmol), and 2-Cl-pyridine N-oxide (0.6 mmol) in CH$_2$Cl$_2$ (2.5 mL) at 23 °C for 1 h. Isolated yields of **2** are listed. [b]Ten millimoles of **1a** was employed.

Next, we focused on the synthesis of indolin-3-ones under our standard conditions. Due to the fact that 2-ethynylaniline failed to afford the desired indolin-3-one, we decided to employ tosyl-substituted 2-ethynylaniline **5a**, as it can be more easily deprotonated under the reaction conditions, increasing its nucleophilicity. The reaction of substrate **5a** proceeded well to give N-Ts-indolin-3-one **6a** in 85% yield, with a slightly higher Hg(OTf)$_2$ loading (10 mol %) and a longer reaction time (3 h). Then various N-Ts-2-ethynylanilines were examined under these conditions, and the results are listed in Scheme 4. Similar to the synthesis of coumaran-3-ones, the synthesis of indolin-3-ones featured good functional group tolerance. Substrates **5b–d** bearing Me and OMe groups afforded the corresponding indolin-3-one products **6b–d**, respectively, in excellent yields. Halogen atoms and CO$_2$Me

Scheme 4. Substrate Scope of Indolin-3-one Synthesis[a]

6a: 85%   **6b:** 89%   **6c:** 88%

6d: 92%   **6e:** 80%   **6f:** 84%

6g: 79%   **6h:** 75%   **6i:** 73%
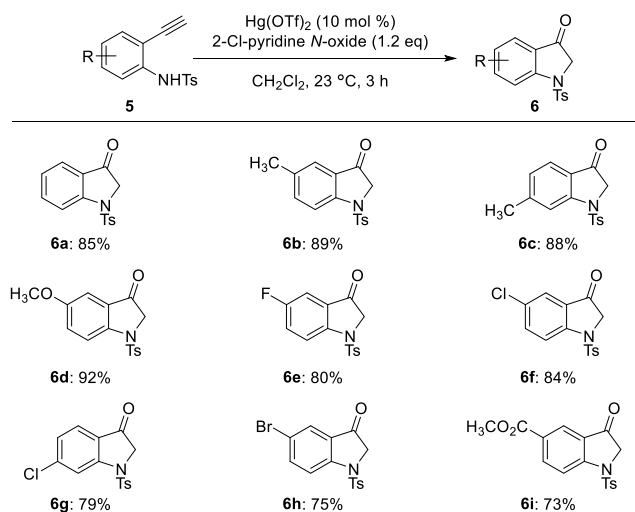
[a]All reactions were performed with **5** (0.5 mmol), Hg(OTf)$_2$ (0.05 mmol), and 2-Cl-pyridine N-oxide (0.6 mmol) in CH$_2$Cl$_2$ (2.5 mL) at 23 °C for 3 h. Isolated yields of **6** are listed.

can also be tolerated, and indolin-3-ones **6e–i** were obtained in 73–84% yields.

Then, we turned our attention to the reaction of disubstituted alkynes. Substrates **7a–c** were synthesized, but unfortunately, the desired 2-substituted coumaran-3-ones and indolin-3-ones **8** were not obtained. Instead, fast consumption of starting materials was observed in all cases, leading to the formation of 2-substituted benzofurans and indoles **8a′–c′** in good yields (Scheme 5).

## Scheme 5. Reaction of Disubstituted Alkynes under Standard Conditions

7a: X = O, R = Ph   **7b:** X = NTs, R = Ph   **7c:** X = NTs, R = n-Bu

8a′, 95%   **8b′,** 92%   **8c′,** 87%
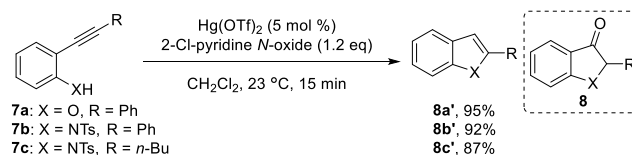
There is rational doubt about the mechanism of these transformations in terms of whether α-oxo mercury carbene **F** has formed during the catalytic process because the formation of α-oxo gold carbenes has frequently been found after alkynes are treated with N-oxides and gold(I) catalysts.[14] However, when phenylacetylene was treated with our standard conditions in the presence of trans-stilbene or cis-stilbene, no desired cyclopropane products **9** were detected (Scheme 6, eq

Scheme 6. Attempts to Trap Potential α-Oxo Mercury Carbene
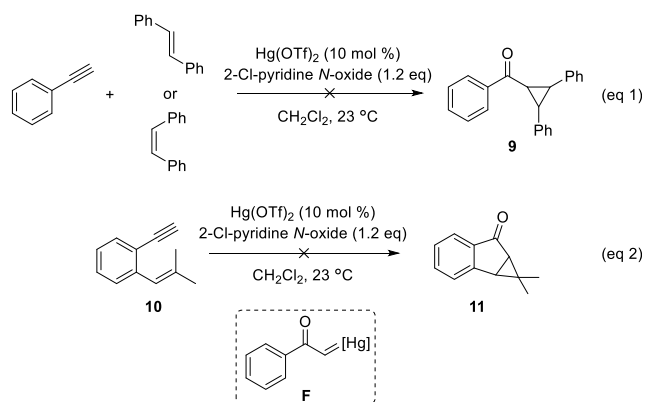
1). The intramolecular trapping of the potential mercury carbene was performed by exposing **10** to our standard conditions, but the expected cyclopropane product **11** could not be found (Scheme 6, eq 2). These results led us to propose a mechanism for our reactions without the formation of mercury carbene. With **1a** as an example, the alkynyl moiety can be activated by Hg(OTf)$_2$ and the addition of 2-Cl-pyridine N-oxide takes place to give intermediate **G**. Intramolecular proton transfer leads to the protodemercurization of intermediate **G** to generate enolonium species **H**. Then an intramolecular S$_N$2′ reaction occurs, which affords coumaran-3-one **2a** (Scheme 7).

In conclusion, we have demonstrated the first mercury-catalyzed enolate umpolung reaction that allows the efficient construction of various coumaran-3-ones and indolin-3-ones. This method features high yields and excellent functional group tolerance. Obviously, the formation of enolonium intermediates by mercury catalysis has the potential to be a

Scheme 7. Plausible Reaction Mechanism
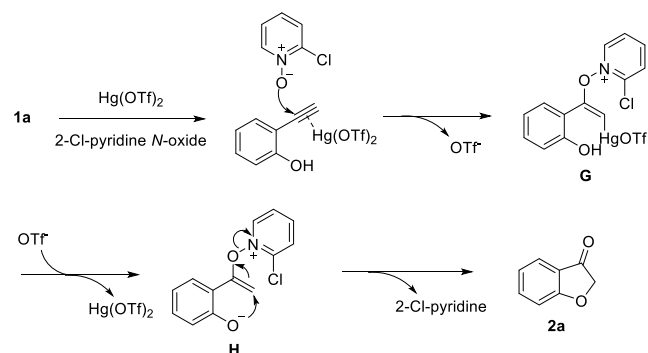
versatile strategy for the synthesis of α-functionalized carbonyl compounds.

■ ASSOCIATED CONTENT

ⓈⒾ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01096.

> Detailed experimental procedures, compound characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Zhouting Rong − *College of Biological and Environmental Sciences, Zhejiang Wanli University, Ningbo 315100, People's Republic of China;* ⓞ orcid.org/0000-0001-7811-4890; Email: zrong@zwu.edu.cn

Guoying Qian − *College of Biological and Environmental Sciences, Zhejiang Wanli University, Ningbo 315100, People's Republic of China;* Email: qiangy@zwu.edu.cn

Authors

Weican Hu − *College of Biological and Environmental Sciences, Zhejiang Wanli University, Ningbo 315100, People's Republic of China*

Ning Dai − *College of Biological and Environmental Sciences, Zhejiang Wanli University, Ningbo 315100, People's Republic of China*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.0c01096

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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