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Tunable Synthesis of Indeno[1,2-*c*]furans and 3-Benzoylindenones via $FeCl_3$-Catalyzed Carbene/Alkyne Metathesis Reaction of *o*-Alkynylbenzoyl Diazoacetates

Bin Li,* Nana Shen, Yujie Yang, Xinying Zhang, and Xuesen Fan*

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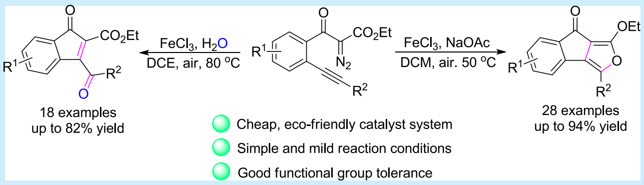
ABSTRACT: An efficient synthesis of indeno[1,2-*c*]furan and 3-benzoylindenone derivatives through a $FeCl_3$-catalyzed carbene/alkyne metathesis reaction of *o*-alkynylbenzoyl diazoacetates is presented. Mechanistically, the key intermediate, vinyl iron carbene, is formed by 5-*exo-dig* carbocyclization and terminated with a formal [3 + 2] cycloaddition or carbonylation. To the best of our knowledge, this is the first example in which $FeCl_3$ is used as a catalyst for a carbene/alkyne metathesis reaction. Finally, derivatization reactions were carried out to showcase the value of the products.



Indanones and indenones are important structural motifs found in a number of natural products and synthetically bioactive molecules.[1] For example, compound **A** (pauciflorol F, Figure 1), isolated from the stem bark of *Vatica pauciflora*, possesses diverse biological activities such as antibacterial, antiviral, and anti-HIV.[2] Compound **B** has been used for the treatment of Alzheimer's disease.[3] Compound **C**, isolated from the filamentous marine cyanobacterium *Lyngbya majuscula*, is a promising anticancer drug candidate.[4] Compound **D** is known for its applications as antiviral and antibacterial agents.[5] Compound **E** is isolated from the fruits of *Verola sebifera* and has unique biological activity.[6] Compound **F** was discovered as a unique template for the activation of peroxisome proliferator-activated receptor γ (PPAR γ).[7] Compound **G** and its derivatives are a novel class of anticancer agents with two of them in clinical trials[8] (Figure 1). In addition, a large number of indanone and indenone derivatives were used as organic functional materials.[9] While a variety of synthetic methods have been developed for the preparation of indanone and indenone derivatives,[1,9,10] conventional approaches still suffer from tedious multiple steps, harsh reaction conditions, and limited substrate scopes. Therefore, it is currently highly desirable to develop novel method to construct the indanone and indenone skeletons in a more convenient, sustainable, and green manner.

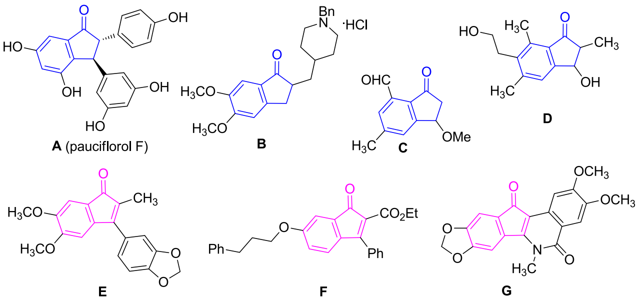


Figure 1. Biologically interesting indanones and indenones.

On the other hand, metal−carbene insertion serves as a powerful and useful method for C−X bond formation.[11] Among them, transition-metal-catalyzed carbene/alkyne metathesis (CAM) turns out to be a straightforward tool for the construction of complex polycyclic skeletons in one pot.[12] In this regard, CAM reactions using diazo compounds as the carbene precursors have attracted widespread attention due to its easy accessibility and high reactivity.[13−17] However, it was also noticed that most of these methods have to be accomplished in the presence of noble metal catalysts such as gold,[14] rhodium,[15] ruthenium,[16] and copper,[17] and the toxicity and scarcity of these catalysts could be the main restrictive factors for the sustainability of these methods, especially in large-scale applications. Therefore, finding low-cost yet still effective catalysts to promote the CAM reactions is urgently needed.

o-Alkynylaryl α-diazoester is a reactive substrate that is used to synthesize various functional molecules via metal-catalyzed carbocyclization. For example, in 2016, Zhang et al. reported a gold-catalyzed concise synthesis of functional indenes via

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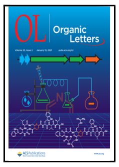

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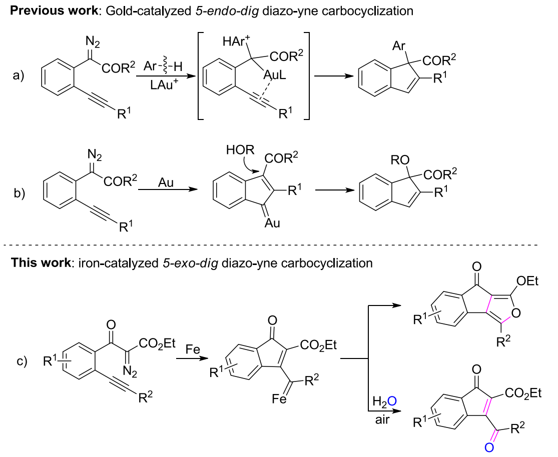
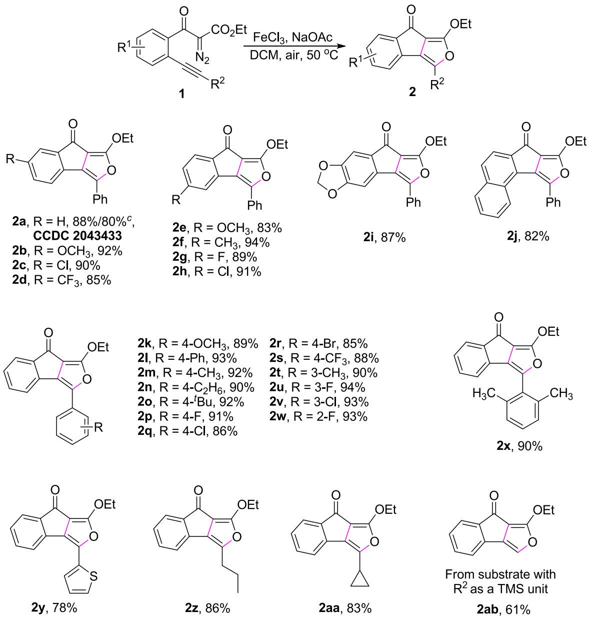
sequential C−H bond functionalization and 5-*endo-dig* carbocyclization of *o*-alkynylaryl *α*-diazoester and electron-rich aromatics[18] (Scheme 1a). More recently, Xu and co-workers reported a gold-catalyzed CAM reaction of *o*-alkynylaryl diazoacetates and protic nucleophiles for the synthesis of indenol derivatives with a tertiary center[14c] (Scheme 1b). As a continuation of our recent interest in using diazo compounds as carbene precursors to construct organic functional molecular skeletons via transition-metal-catalyzed C−H bond activation,[19] we have used *o*-alkynylbenzoyl diazoacetates (**1**) as coupling partners to synthesize naphthol compounds.[14d] During our study, we were surprised to find that under the promotion of $[Ir(cod)Cl]_2$ and NaOAc in dichloroethane (DCE) ethyl 2-diazo-3-oxo-3-(2-(phenylethynyl)phenyl)propanoate (**1a**) could be transformed into 1-ethoxy-3-phenyl-8*H*-indeno[1,2-*c*]furan-8-one (**2a**) in an excellent yield of 95%, and the structure of **2a** was confirmed by X-ray crystallography (see the Supporting Information). Considering that iron carbene has been frequently used for C−C or C−X bond (X = C, N, O, Si, S, etc.) formation and iron catalyst has advantages such as low price and environmental friendliness,[20] and in conjunction with our recent studies on iron-catalyzed reaction,[21] we tried to us $FeCl_3$ (0.2 equiv) to replace $[Ir(cod)Cl]_2$ as the catalyst for this interesting transformation. To our pleasure, **2a** could be obtained in a yield of 53%. In the absence of NaOAc, the yield of **2a** decreased to 22%. Meanwhile, ethyl 3-benzoyl-1-oxo-1*H*-indene-2-carboxylate (**3a**) was obtained in 28% yield (Scheme 1c). Bearing in mind the importance of products **2** and **3** and the fact that there is still no report on Fe-catalyzed CAM reaction, we realized that this reaction deserved a systematic study to explore its intriguing mechanism and its application scope on the synthesis related compounds. Herein, we report the detailed results obtained in this direction.

Scheme 1. Metal-Catalyzed Carbocyclization Reaction



Initially, the reaction parameters, including the solvent, base, catalyst, and temperature, were screened by using **1a** as model substrates. As shown in Table S1, we found that when **1a** was treated with $FeCl_3$ and NaOAc in dichloromethane (DCM) at 50 °C product **2a** was obtained in a higher 88% yield (Table S1, entry 17). In addition, the optimized reaction conditions for **3a** were found to be as follows: $FeCl_3$ (0.5 equiv) as a catalyst and 5 equiv of water in DCE at 80 °C under air (Table S1, entry 22). With the optimal reaction conditions in hand, we first focused on screening the substrate scope for the synthesis of **2**, and the results are listed in Scheme 2. Compound **1** bearing either an electron-donating group (EDG) such as methoxy and methyl or an electron-withdrawing group (EWG) including fluoro, chloro, or trifluoromethyl as the R^1 unit attached on different sites of the connecting benzene ring readily underwent this CAM reaction to afford **2b**−**2h** in excellent yields. Interestingly, the reactions of ethyl 2-diazo-3-oxo-3-(6-(phenylethynyl)benzo[*d*][1,3]dioxol-5-yl)propanoate (**1i**) and ethyl 2-diazo-3-oxo-3-(1-(phenylethynyl)naphthalen-2-yl)propanoate (**1j**) also proceeded smoothly to generate **2i** and **2j** in 87% and 82% yields, respectively. In addition, **1** bearing a phenyl unit attached a phenyl unit attached with either EDGs (methoxy, phenyl, methyl, ethyl, and *tert*-butyl) or EWGs (fluoro, chloro, bromo, and trifluoromethyl) on its *para*-, *meta*-, or *ortho*-position as the R^2 moiety took part in this reaction to give **2k**−**2w** in 85−94% yields. When *o*-alkynylbenzoyl diazoacetate **1** contained a sterically hindered 2,6-dimethyl-tethered alkyne group, the reaction could also take place smoothly to give **2x** in 90% yield. Delightfully, **1** bearing a thiophen-2-yl-tethered alkyne unit was also suitable for this cascade reaction to give **2y** in good yield. It is worth mentioning that **1** bearing a linear or cyclic alkane-tethered alkyne unit was found to be well tolerated, giving the corresponding products **2z** and **2aa** in 86% and 83% yields. Notably, **1** containing a TMS-tethered alkyne unit was found to be also suitable for the Fe(III)-catalyzed CAM reaction to give product **2ab** bearing no substituent at the 3-position.

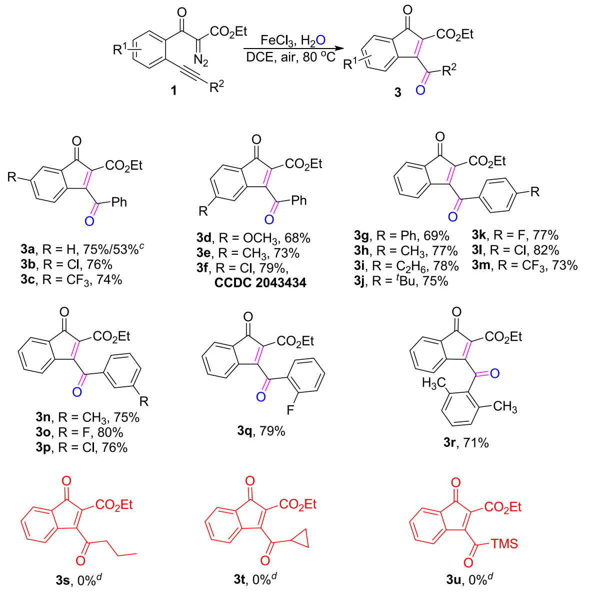
Scheme 2. Substrate Scope for the Synthesis of 2[*a,b*]



[*a*] Conditions: 0.2 mmol of **1**, 0.1 mmol of $FeCl_3$, 0.2 mmol of NaOAc, 1 mL of DCM, air, sealed tube, 15 h. [*b*] Isolated yield. [*c*] 4 mmol of **1a** was used.

Next, the substrate scope for the preparation of **3** was investigated. Thus, a range of **1** bearing various R^1 groups were all tolerated and gave the corresponding products **3b**−**3f** in good yields (Scheme 3). Notably, the structure of **3f** was unambiguously confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information). On the pendant alkyne, both electron-neutral and electron-rich aryl groups were subjected to the optimal reaction conditions to give the

Scheme 3. Substrate Scope for the Synthesis of 3[a,b]

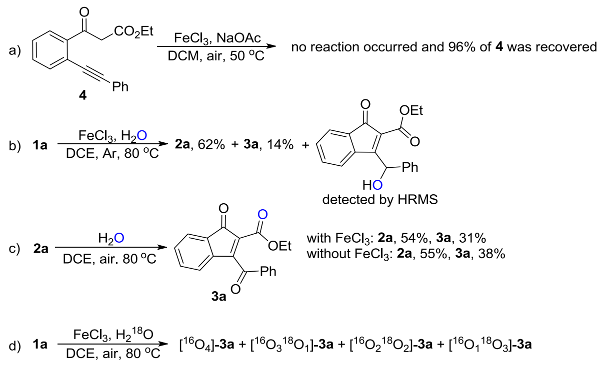


[a]Conditions: 0.2 mmol of **1**, 0.1 mmol of $FeCl_3$, 1 mmol of H_2O, 1 mL of DCE, air, sealed tube, 15 h. [b]Isolated yield. [c]4 mmol of **1a** was used. [d]The reaction became messy.

desired products **3g**−**3r** in 69−82% yields. Unfortunately, the reactions of substrates containing linear alkane- or cyclic alkane- or TMS-tethered alkyne failed to give the desired products **3s**−**3u** under the standard conditions.

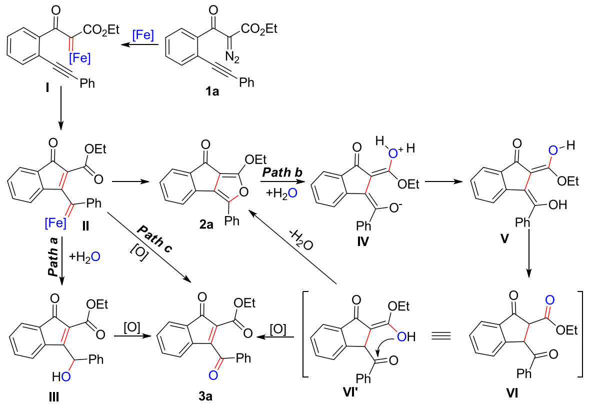
To gain insight into the mechanism of this reaction, a series of control experiments were carried out. First, ethyl 3-oxo-3-(2-(phenylethynyl)phenyl)propanoate (**4**) was subjected to the standard reaction conditions for the formation of **2**. It turned out that no reaction occurred and 96% of **4** was recovered (Scheme 4a), indicating that the reaction should be initiated with a iron carbene. Second, **2a** and **3a** were obtained in 62% and 14% yields, respectively, by treating substrate **1a** with $FeCl_3$ and H_2O in DCE under Ar at 80 °C for 15 h (Scheme 4b). Meanwhile, the unoxidized intermediate, ethyl 3-(hydroxy(phenyl)methyl)-1-oxo-1*H*-indene-2-carboxylate (HRMS (ESI) calcd for $C_{19}H_{15}O_3^+$: 291.1027 $[M - OH]^+$, found: 291.0997) was not obtained but was detected in the reaction mixture by HRMS analysis (for details, see Figures S1 and S2). These results indicate that air as an oxidant is indispensable for the efficient transformation of **3a**. Third, **2a** could be partially converted to **3a** in the presence of H_2O, with or without $FeCl_3$, revealing that the transition from **2a** to **3a** is a possible pathway (Scheme 4c). Fourth, to determine the source of oxygen atom on the benzoyl group, ^{18}O-labeling experiments with $H_2{}^{18}O$ for the formation of **3a** were carried out (Scheme 4d). From this reaction, $[^{16}O_4]$-**3a** vs $[^{16}O_3{}^{18}O_1]$-**3a** vs $[^{16}O_2{}^{18}O_2]$-**3a** vs $[^{16}O_1{}^{18}O_3]$-**3a** were obtained in a ratio of 0.09:0.64:1:0.24 as determined by HRMS analysis (see Figures S3 and S4 for details), revealing that the oxygen atom on the benzoyl group comes from water and there is a reversible reaction before forming of final product **3a**.

Scheme 4. Control Experiments



On the basis of the above control experiment results and related literature reports, two possible pathways for the preparation of **2a** and **3a** are described in Scheme 5. First, iron carbene **I** is formed through iron-catalyzed dinitrogen expulsion of *o*-alkynylbenzoyl diazoacetate **1a**.[22] This is followed by 5-*exo-dig* carbocyclization to afford vinyl iron carbene **II**.[14−17] Next, **II** is terminated with a formal [3 + 2] cycloaddition to give product **2a**.[10d,23] On the other hand, **II** is terminated with O−H insertion to form the intermediate **III**,[14c,16a] which undergoes an oxidant dehydrogenation to afford product **3a** (Scheme 5, path a). As an alternative pathway, **2a** might undergo a furan ring opening under the assistance of water to afford intermediate **IV**. Proton transfer of **IV** gives intermediate **V**. Subsequently, keto−enol tautomerization of **V** occurs to give intermediate **VI** or **VI′**, which undergoes an oxidation by air to afford product **3a** (Scheme 5, path b). Additionally, an intramolecular O-nucleophilic addition occurs with **VI′** to give **2a** by losing one molecule of water. Moreover, vinyl iron carbene **II** might be direct oxidized under the reaction conditions to give the product **3a** (Scheme 5, path c).[24]

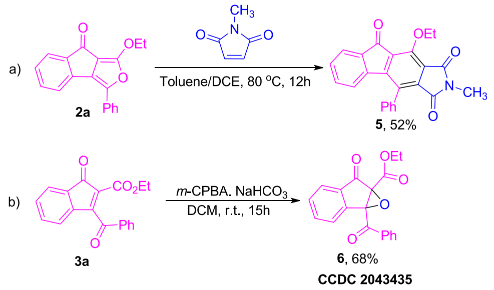
Scheme 5. Proposed Mechanism Accounting for the Formation of 2a and 3a



The synthetic utility of the products have been demonstrated in several derivatization reactions (Scheme 6). Treatment of **2a** with *N*-methylmaleimide in toluene/DCE at 80 °C for 12 h afforded maleimide-related polycyclic compound **5** in 52% yield via [4 + 2] cycloaddition and the following dehydration aromatization. In the presence of 3-chloroperbenzoic acid (*m*-CPBA), **3a** was oxidized to epoxide product **7** in 68% yield and its structural confirmation by X-ray crystallography (see the Supporting Information).

In summary, we have developed the first iron-catalyzed CAM reaction of *o*-alkynylbenzoyl diazoacetates, which provided an efficient and facile method to access indeno[1,2-*c*]furans and 3-benzoylindenones. Mechanistically, the in situ

Scheme 6. Derivatization of 2a and 3a



formed vinyl iron carbene as a key intermediate is terminated with a formal [3 + 2] cycloaddition to afford indeno[1,2-*c*]furans in the absence of water. On the other hand, vinyl iron carbene would undergo carbonylation in the presence of water and air to afford 3-benzoylindenones. Compared with literature protocols, these novel methods have notable features such use of cheap and green catalyst, mild reaction conditions, and an environmentally friendly nature. Further studies are currently underway to elucidate the mechanism and to develop more iron-catalyzed CAM reactions in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03882.

Experimental procedures, mechanism studies, data and spectra of the ^{1}H, ^{13}C and ^{19}F NMR of all products (PDF)

Accession Codes

CCDC 2043433−2043435 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Bin Li − *School of Environment, School of Chemistry and Chemical Engineering, Key Laboratory for Yellow River and Huai River Water Environmental Pollution Control and Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Collaborative Innovation Center of Henan Province for GreenManufacturing of Fine Chemicals, Henan Normal University, Xinxiang, Henan 453007, China;* orcid.org/0000-0002-0145-5926; Email: libin@htu.edu.cn

Xuesen Fan − *School of Environment, School of Chemistry and Chemical Engineering, Key Laboratory for Yellow River and Huai River Water Environmental Pollution Control and Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Collaborative Innovation Center of Henan Province for GreenManufacturing of Fine Chemicals, Henan Normal University, Xinxiang, Henan 453007, China;* orcid.org/0000-0002-2040-6919; Email: xuesen.fan@htu.cn

Authors

Nana Shen − *School of Environment, School of Chemistry and Chemical Engineering, Key Laboratory for Yellow River and Huai River Water Environmental Pollution Control and Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Collaborative Innovation Center of Henan Province for GreenManufacturing of Fine Chemicals, Henan Normal University, Xinxiang, Henan 453007, China*

Yujie Yang − *School of Environment, School of Chemistry and Chemical Engineering, Key Laboratory for Yellow River and Huai River Water Environmental Pollution Control and Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Collaborative Innovation Center of Henan Province for GreenManufacturing of Fine Chemicals, Henan Normal University, Xinxiang, Henan 453007, China*

Xinying Zhang − *School of Environment, School of Chemistry and Chemical Engineering, Key Laboratory for Yellow River and Huai River Water Environmental Pollution Control and Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory of Organic Functional Molecules and Drug Innovation, Collaborative Innovation Center of Henan Province for GreenManufacturing of Fine Chemicals, Henan Normal University, Xinxiang, Henan 453007, China;* orcid.org/0000-0002-3416-4623

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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