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Direct C−C Bond Cleavage of 1,3-Dicarbonyl Compounds as a Single-Carbon Synthon: Synthesis of 2-Aryl-4-quinolinecarboxylates

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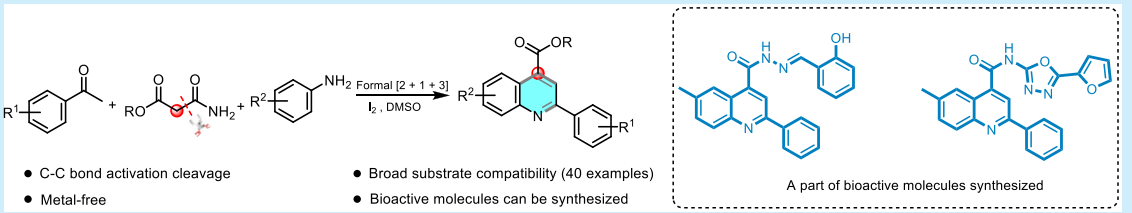

ABSTRACT: A novel [2 + 1 + 3] cyclization reaction for the synthesis of 2-aryl-4-quinolinecarboxylates from aryl methyl ketones, arylamines, and 1,3-dicarbonyl compounds has been established. This metal-free process achieved the C−C bond cleavage of 1,3-dicarbonyl compounds directly as a single-carbon synthon. The reaction is highly efficient and has good substrate compatibility while operating under mild conditions. This method has good practicability and successfully realized the synthesis of bioactive molecules.

The 2-arylquinoline-4-carboxylic acid derivatives have a wide range of physiological activities, some of which can be used as potential anticancer and antiviral drugs. (Figure 1).[1]

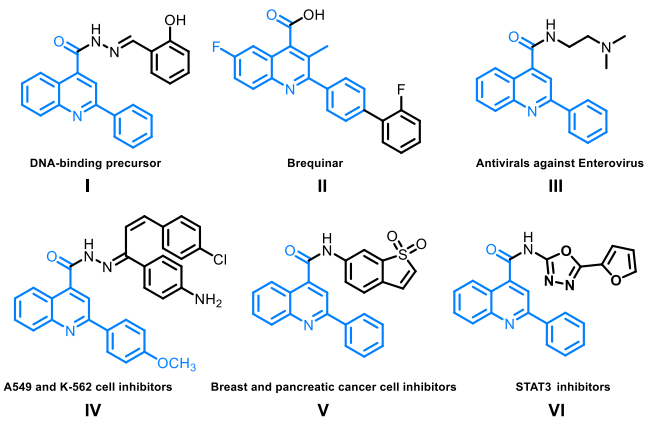

Figure 1. Bioactive molecules of 2-arylquinoline-4-carboxylic acid derivatives.

Some metal complexes of Compound **I** have a DNA-binding effect, which can be used for DNA structural probes and as potential anticancer drugs.[2] Brequinar (**II**) is an effective inhibitor of dihydroorotate dehydrogenase (DHODH).[3] Compound **III** has strong inhibitory activity against enterovirus EV-D68 and CVB3.[4] Compound **IV** has good activity against nonsmall cell lung cancer and chronic myeloid leukemia.[5] Compound **V** induces apoptosis in pancreatic and breast cancer cell lines.[6] Compound **VI** strongly inhibits STAT3 transcription in HeLa cells.[7] At present, the methods of 2-arylquinoline-4-carbon compound synthesis are mainly limited to the cyclization of isatins and arylmethyl ketones[1−5] and the [4 + 2] cycloaddition of aromatic imines and acrylates.[8] Therefore, it is essential to study new synthetic methods for these compounds.

Recently, functionalization reactions of the α-position of 1,3-dicarbonyl compounds have been widely reported.[9] In addition, many studies have focused on the cyclization of 1,3-dicarbonyl compounds as a multicarbon synthon.[10] Nevertheless, to realize the C−C bond activation cleavage of 1,3-dicarbonyl compounds is challenging, and the relevant reports are relatively rare. In the past 10 years, the Lei and Peng groups have reported the transition-metal-catalyzed cleavage activation reaction of 1,3-dicarbonyl compounds, achieving the formal arylation and phosphonation of the C−C bond at the carbonyl α-position (Scheme 1a).[11] Although some progress has been made in the C−C bond cleavage of 1,3-dicarbonyl compounds, cleavage processes in the cyclization reaction as a single-carbon synthon have rarely been reported. In 2017, the You group reported α-diazoesters that were prepared by 1,3-dicarbonyl compounds as substrates for the construction of indazole, realizing the rhodium-catalyzed C−C bond cleavage of 1,3-dicarbonyl compounds as a single-carbon synthon participating in the cyclization reaction (Scheme 1b).[12] However, to our knowledge, the direct involvement of 1,3-dicarbonyl compounds without preprepara-

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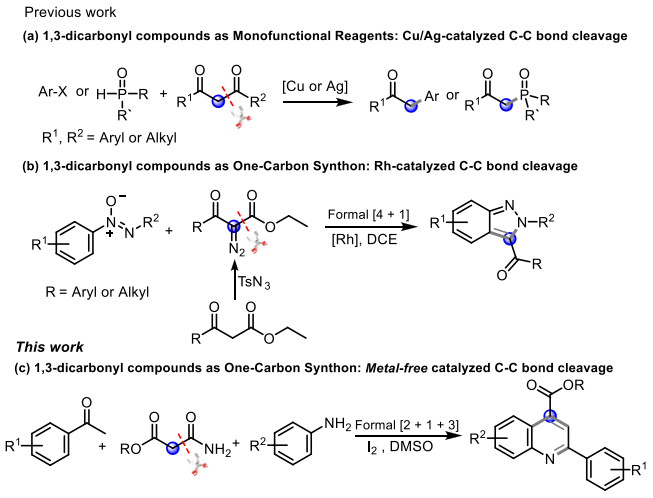
Scheme 1. Reaction of the C−C Bond Cleavage in 1,3-Dicarbonyl Compounds



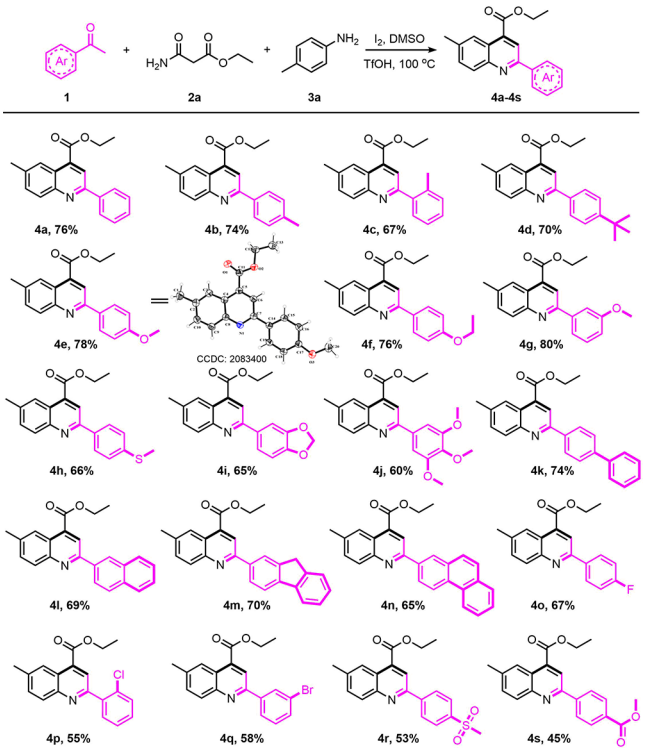
tion in the cyclization reaction via cleavage of the C−C bond as a single-carbon synthon has not been reported. Herein we realized 1,3-dicarbonyl compounds directly as a single-carbon synthon through the cleavage of the C−C bond for the synthesis of 2-aryl-4-quinolinecarboxylates without any metal catalyst (Scheme 1c). Simultaneously, we used our method to complete the multistep synthesis of several bioactive molecules, which further proves the practical value of our work.

To evaluate this proposal, we investigated the reaction conditions using acetophenone (**1a**), ethyl carbamoylacetate (**2a**), and *p*-toluidine (**3a**) as examples. (See the Supporting Information for details.) Through optimization of the acid, equivalent of I_2, and temperature, we found the following optimal conditions: I_2 (1.6 equiv) and TfOH (2.0 equiv) at 100 °C for 4 h under air.

After confirming the optimal conditions, we used aryl methyl ketones to investigate the applicability of a three-component reaction for the synthesis of the 2-aryl-4-quinolinecarboxylates (Scheme 2). Various alkyl-substituted acetophenones showed good compatibility under the optimal reaction conditions (**4a**−**4d**, 67−76%). Alkoxy- and methylthio-substituted products were obtained in excellent yields (**4e-4h**, 66−80%). Multi-substituted acetophenones **4i** and **4j** were also compatible with the reaction, achieving yields of 65 and 60%, respectively. Additionally, substrates containing large steric hindrance groups, including fused rings, achieved the target compounds in satisfactory yields (**4k**−**4n**, 65−74%). Pleasingly, halogen substituents and even acetophenones with electron-withdrawing groups could be converted into the target compounds in good yields (**4o**−**4s**, 45−67%).

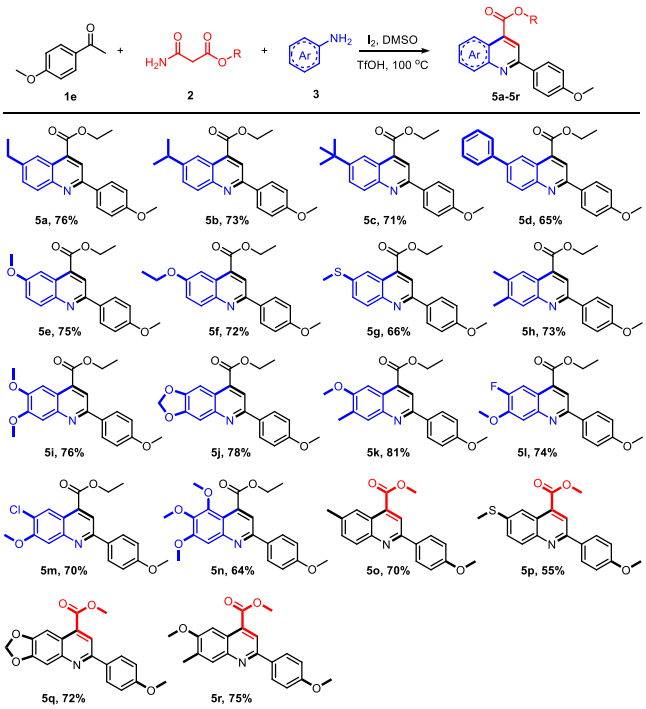
Subsequently, we investigated the compatibility of the substituents on both sides of the arylamines and carbamoyl acetates (Scheme 3). First, alkyl- and phenyl-substituted arylamines were converted into target compounds with great yields (**5a**−**5d**, 65−76%). The alkoxy group and methylthio group attached to the aryl group of arylamines were also compatible with the reaction (**5e**−**5g**, 66−75%). When the aryl group of the arylamine contained two substituents or even multiple substituents, the 2-aryl-4-quinoline esters were obtained in satisfactory yields (**5h**−**5n**, 64−81%). Finally, we replaced the ethyl ester in the substrate ethyl carbamoylacetate

Scheme 2. Scope of the Aryl Methyl Ketones[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), I_2 (1.6 mmol), TfOH (2.0 mmol), DMSO (4 mL), air, 100 °C, and 4 h. [b]Isolated yields.

Scheme 3. Scope of the Arylamines and Carbamoyl Acetates[a,b]



[a]Reaction conditions: **1e** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), I_2 (1.6 mmol), TfOH (2.0 mmol), DMSO (4 mL), air, 100 °C, and 4 h. [b]Isolated yields.

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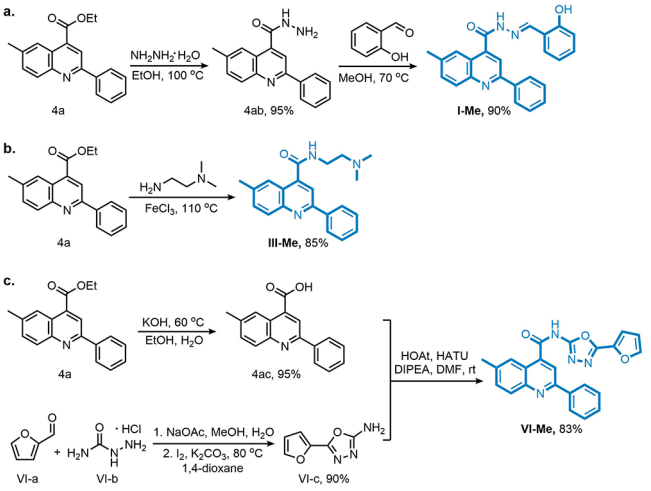
with a methyl ester to participate in the reaction and obtained the final products in relatively good yields (**5o**−**5r**, 55−75%).

To verify the practicability of our method, we completed the synthesis of three bioactive molecules (Scheme 4). First,

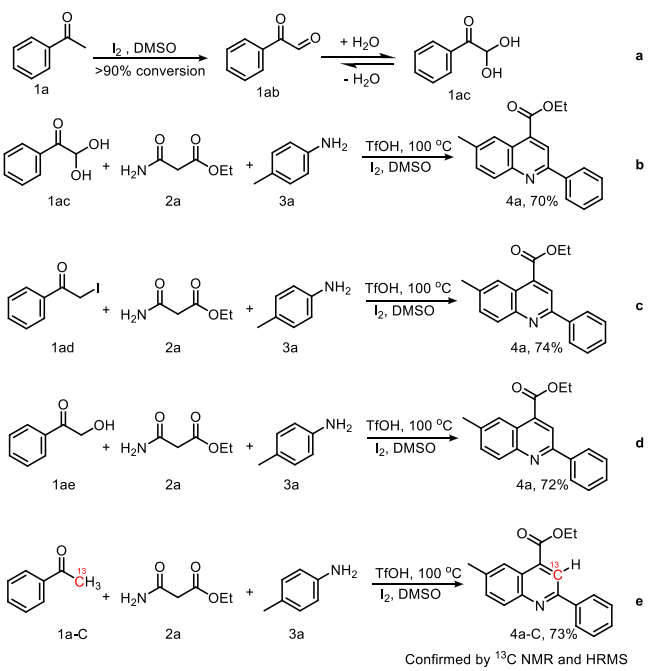
Scheme 4. Study on the Practicability of the Reaction



product **4a** was efficiently converted into **4ab** with hydrazine hydrate and then condensed with salicylaldehyde to produce the bioactive molecule **I-Me** (Scheme 4a).[2] Product **4a** was easily converted into amide **III-Me** with antiviral activity under the catalysis of $FeCl_3$ (Scheme 4b).[4,13] Finally, **4a** was hydrolyzed to carboxylic acid **4ac** and then reacted with preprepared amino-oxadiazole **VI-c** under the conditions of HOAt and HATU to produce **VI-Me**, which possessed anticancer activity (Scheme 4c).[7,14]

Control experiments were performed to obtain preliminary evidence of the reaction mechanism for this method (Scheme 5). First, acetophenone (**1a**) was converted to phenylglyoxal

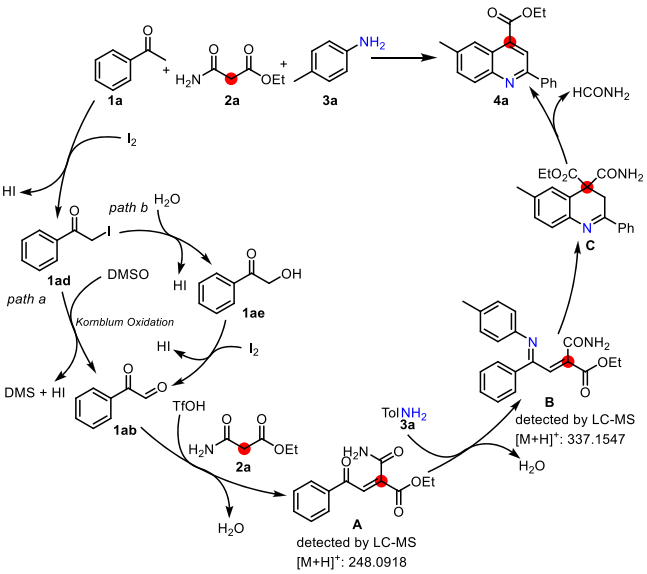
Scheme 5. Control Experiments



(**1ab**) in high yield under the promotion of the I_2-DMSO system (Scheme 5a). Subsequently, we confirmed that phenylglyoxal monohydrate (**1ac**), α-iodoacetophenone (**1ad**), and 2-hydroxyacetophenone (**1ae**) were the intermediates of the reaction (Scheme 5b−d). Finally, we used ^{13}C-labeled acetophenone as the substrate under standard conditions and found that the ^{13}C-labeled product could be successfully obtained, which proved that ethyl carbamoylacetate participated in the [2 + 1 + 3] cyclization process as a one-carbon synthon (Scheme 5e).

On the basis of the previously described results and the related literature,[15] we propose a plausible mechanism involving [2 + 1 + 3] cyclization (Scheme 6). First,

Scheme 6. Proposed Mechanism



acetophenone (**1a**) undergoes iodination and Kornblum oxidation under I_2-DMSO conditions to form phenylglyoxal (**1ab**). Subsequently, **1ab** reacts with ethyl carbamoylacetate (**2a**) to produce intermediate **A** under acid catalysis, and **A** is detected by LC-MS. Next, imine **B**, which is also detected by LC-MS, is afforded by intermediate **A** and *p*-toluidine (**3a**). Intermediate **B** may then undergo intramolecular cyclization to generate **C**. Finally, the C−C bond of amide intermediate **C** is cleaved to obtain the aromatization product **4a**.

In conclusion, we developed a method to directly cleave the C−C bond of 1,3-dicarbonyl compounds as a single-carbon synthon to construct 2-aryl-4-quinolinecarboxylates. This metal-free catalyzed reaction has good substrate compatibility and practicability and successfully achieved the synthesis of three biologically active molecules. Research on the direct cleavage of 1,3-dicarbonyl compounds promoted by iodine to construct other novel heterocycles is under further development 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.1c02267.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Accession Codes

CCDC 2083400 and 2098045 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.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Yu, X. Y.; Hill, J. M.; Yu, G.; Yang, Y.; Kluge, A. F.; Keith, D.; Finn, J.; Gallant, P.; Silverman, J.; Lim, A. A Series of Quinoline Analogues as Potent Inhibitors of C. Albicans Prolyl tRNA Synthetase. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 541−544. (b) Mohassab, A. M.; Hassan, H. A.; Abdelhamid, D.; Abdel-Aziz, M.; Dalby, K. N.; Kaoud, T. S. Novel Quinoline Incorporating 1,2,4-Triazole/Oxime Hybrids: Synthesis, Molecular Docking, Anti-inflammatory, COX Inhibition, Ulcerogenicity and Histopathological Investigations. *Bioorg. Chem.* **2017**, *75*, 242−259. (c) Kaoud, T. S.; Mohassab, A. M.; Hassan, H. A.; Yan, C.; Van Ravenstein, S. X.; Abdelhamid, D.; Dalby, K. N.; Abdel-Aziz, M. NO-Releasing STAT3 Inhibitors Suppress BRAF-Mutant Melanoma Growth. *Eur. J. Med. Chem.* **2020**, *186*, 111885.

(2) (a) Xi, P. X.; Xu, Z. H.; Chen, F. J.; Zeng, Z. Z.; Zhang, X. W. Study on Synthesis, Structure, and DNA-Binding of Ni, Zn Complexes with 2-Phenylquinoline-4-Carboylhydrazide. *J. Inorg. Biochem.* **2009**, *103*, 210−218. (b) Xu, Z. H.; Xi, P. X.; Chen, F. J.; Zeng, Z. Z. Synthesis, Characterization, and DNA-binding of Ln(III) Complexes with 2-Hydroxybenzylidene-2-Phenylquinoline-4-Carbonylhydrazone. *J. Coord. Chem.* **2009**, *62*, 2193−2202.

(3) (a) Schnellrath, L. C.; Damaso, C. R. Potent Antiviral Activity of Brequinar Against the Emerging Cantagalo Virus in Cell Culture. *Int. J. Antimicrob. Agents* **2011**, *38*, 435−441. (b) Boa, A. N.; Canavan, S. P.; Hirst, P. R.; Ramsey, C.; Stead, A. M.; McConkey, G. A. Synthesis of Brequinar Analogue Inhibitors of Malaria Parasite Dihydroorotate Dehydrogenase. *Bioorg. Med. Chem.* **2005**, *13*, 1945−1967.

(4) (a) Musharrafieh, R.; Kitamura, N.; Hu, Y.; Wang, J. Development of Broad-Spectrum Enterovirus Antivirals Based on Quinoline Scaffold. *Bioorg. Chem.* **2020**, *101*, 103981. (b) Musharrafieh, R.; Zhang, J.; Tuohy, P.; Kitamura, N.; Bellampalli, S. S.; Hu, Y.; Khanna, R.; Wang, J. Discovery of Quinoline Analogues as Potent Antivirals against Enterovirus D68 (EV-D68). *J. Med. Chem.* **2019**, *62*, 4074−4090.

(5) Abbas, S. H.; Abd El-Hafeez, A. A.; Shoman, M. E.; Montano, M. M.; Hassan, H. A. New Quinoline/Chalcone Hybrids as Anti-Cancer Agents: Design, Synthesis, and Evaluations of Cytotoxicity and PI3K Inhibitory Activity. *Bioorg. Chem.* **2019**, *82*, 360−377.

(6) Chen, H.; Yang, Z.; Ding, C.; Chu, L.; Zhang, Y.; Terry, K.; Liu, H.; Shen, Q.; Zhou, J. Fragment-Based Drug Design and Identification of HJC0123, a Novel Orally Bioavailable STAT3 Inhibitor for Cancer Therapy. *Eur. J. Med. Chem.* **2013**, *62*, 498−507.

(7) Matsuno, K.; Masuda, Y.; Uehara, Y.; Sato, H.; Muroya, A.; Takahashi, O.; Yokotagawa, T.; Furuya, T.; Okawara, T.; Otsuka, M.; Ogo, N.; Ashizawa, T.; Oshita, C.; Tai, S.; Ishii, H.; Akiyama, Y.; Asai, A. Identification of a New Series of STAT3 Inhibitors by Virtual Screening. *ACS Med. Chem. Lett.* **2010**, *1*, 371−375.

(8) (a) Yang, L.; Wan, J. P. Ethyl Lactate-Involved Three-Component Dehydrogenative Reactions: Biomass Feedstock in Diversity-Oriented Quinoline Synthesis. *Green Chem.* **2020**, *22*, 3074−3078. (b) Luo, Y.; Sun, H.; Zhang, W.; Wang, X.; Xu, S.; Zhang, G.; Jian, Y.; Gao, Z. Triple Zirconocene/Brønsted Acid/CuO Cooperative and Relay Catalysis System for Tandem Mannich Addition/C−C Formative Cyclization/Oxidation. *RSC Adv.* **2017**, *7*, 28616−28625.

(9) (a) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. Indium-Catalyzed 2-Alkenylation of 1,3-Dicarbonyl Compounds with Unactivated Alkynes. *J. Am. Chem. Soc.* **2007**, *129*, 5264−5271. (b) Li, X.; He, S.; Song, Q. Enantio- and Diastereoselective Diarylmethylation of 1,3-Dicarbonyl Compounds. *Chem. Sci.* **2020**, *11*, 5969−5973. (c) Li, T.; Liang, K.; Zhang, Y.; Hu, D.; Ma, Z.; Xia, C. Three-Component Minisci Reaction with 1,3-Dicarbonyl Compounds Induced by Visible Light. *Org. Lett.* **2020**, *22*, 2386−2390.

(10) (a) Tsuji, H.; Yamagata, K. I.; Fujimoto, T.; Nakamura, E. Manganese-Catalyzed Benzene Synthesis by [2 + 2+2] Coupling of 1,3-Dicarbonyl Compound and Terminal Acetylene. *J. Am. Chem. Soc.* **2008**, *130*, 7792−7793. (b) Komendantova, A. S.; Lyssenko, K. A.; Zavarzin, I. V.; Volkova, Y. A. Iodine-Promoted Synthesis of Pyrazoles from 1,3-Dicarbonyl Compounds and Oxamic Acid Thiohydrazides. *Org. Chem. Front.* **2020**, *7*, 1640−1646. (c) Raji Reddy, C.; Aila, M.; Subbarao, M.; Warudikar, K.; Grée, R. Domino Reaction of 2,4-Diyn-1-ols with 1,3-Dicarbonyl Compounds: Direct Access to Aryl/Heteroaryl-Fused Benzofurans and Indoles. *Org. Lett.* **2021**, *23*, 4882−4887.

(11) (a) He, C.; Guo, S.; Huang, L.; Lei, A. Copper Catalyzed Arylation/C-C Bond Activation: An Approach toward α-Aryl Ketones. *J. Am. Chem. Soc.* **2010**, *132*, 8273−8275. (b) Li, L.; Huang, W.; Chen, L.; Dong, J.; Ma, X.; Peng, Y. Silver-Catalyzed Oxidative C(sp^3) − P Bond Formation through C−C and P−H Bond Cleavage. *Angew. Chem., Int. Ed.* **2017**, *56*, 10539−10544. (c) Zhang, C.; Feng, P.; Jiao, N. Cu-Catalyzed Esterification Reaction via Aerobic Oxygenation and C−C Bond Cleavage: An Approach to α-Ketoesters. *J. Am. Chem. Soc.* **2013**, *135*, 15257−15262. (d) Zou, L. H.;

Priebbenow, D. L.; Wang, L.; Mottweiler, J.; Bolm, C. Copper-Catalyzed Synthesis of α-Thioaryl Carbonyl Compounds Through S−S and C−C Bond Cleavage. *Adv. Synth. Catal.* **2013**, *355*, 2558−2563.
(12) (a) Long, Z.; Wang, Z.; Zhou, D.; Wan, D.; You, J. Rh(III)-Catalyzed Regio- and Chemoselective [4 + 1]-Annulation of Azoxy Compounds with Diazoesters for the Synthesis of 2*H*-Indazoles: Roles of the Azoxy Oxygen Atom. *Org. Lett.* **2017**, *19*, 2777−2780. (b) Yong, W. S.; Park, S.; Yun, H.; Lee, P. H. Synthesis of 2H-Indazoles via Tandem Palladium-Catalyzed Deacylative Cross-Coupling and Denitrogenative Cyclization of 2-Iodoazoarenes and 2-Iodoaryltriazenes with Acyldiazoacetates in One-Pot. *Adv. Synth. Catal.* **2016**, *358*, 1958−1967.
(13) Mkhonazi, B. D.; Shandu, M.; Tshinavhe, R.; Simelane, S. B.; Moshapo, P. T. Solvent-Free Iron(III) Chloride-Catalyzed Direct Amidation of Esters. *Molecules* **2020**, *25*, 1040.
(14) Niu, P.; Kang, J.; Tian, X.; Song, L.; Liu, H.; Wu, J.; Yu, W.; Chang, J. Synthesis of 2-Amino-1,3,4-oxadiazoles and 2-Amino-1,3,4-thiadiazoles via Sequential Condensation and I_2-Mediated Oxidative C−O/C−S Bond Formation. *J. Org. Chem.* **2015**, *80*, 1018−1024.
(15) (a) Yin, G. D.; Zhou, B.; Meng, X.; Wu, A. X.; Pan, Y. J. Efficient C−C Double-Bond Formation Reaction via a New Synthetic Strategy: A Self-Sorting Tandem Reaction. *Org. Lett.* **2006**, *8*, 2245−2248. (b) Gao, Q.; Liu, S.; Wu, X.; Zhang, J.; Wu, A. X. Coproduct Promoted Povarov Reaction: Synthesis of Substituted Quinolines from Methyl Ketones, Arylamines, and α-Ketoesters. *J. Org. Chem.* **2015**, *80*, 5984−5991. (c) Wu, X.; Geng, X.; Zhao, P.; Zhang, J.; Gong, X.; Wu, Y. D.; Wu, A. X. I_2-Promoted Povarov-Type Reaction Using 1,4-Dithane-2,5-diol as an Ethylene Surrogate: Formal [4 + 2] Synthesis of Quinolines. *Org. Lett.* **2017**, *19*, 1550−1553. (d) Geng, X.; Wu, X.; Zhao, P.; Zhang, J.; Wu, Y. D.; Wu, A. X. Synergistic I_2/Amine Promoted Povarov-Type Reaction for the Synthesis of 2-Acyl-3-aryl(alkyl)quinolines Using Aryl(alkyl)acetaldehydes as Alkene Surrogates. *Org. Lett.* **2017**, *19*, 4179−4182. (e) Zhao, P.; Wu, X.; Zhou, Y.; Geng, X.; Wang, C.; Wu, Y. D.; Wu, A. X. Direct Synthesis of 2,3-Diaroyl Quinolines and Pyridazino[4,5-b]quinolines via an I_2-Promoted One-Pot Multicomponent Reaction. *Org. Lett.* **2019**, *21*, 2708−2711.

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