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Synthesis of Azulenopyridinones through Palladium-Catalyzed Oxidative [4 + 2] Cyclization Reactions of *N*-Methoxyazulene-1- and 2-carboxamides with Alkynes

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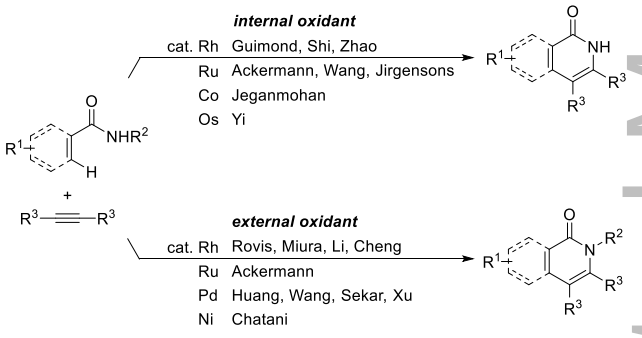
Abstract. Palladium-catalyzed oxidative [4 + 2] cyclization reactions were developed from the C−H activation reaction of *N*-methoxyazulene-1- and 2-carboxamides with symmetrical and unsymmetrical alkynes under a molecular oxygen atmosphere, producing azulenopyridinone derivatives with novel azulene skeletons in good to excellent yields with a wide substrate scope and excellent functional group tolerance.

Keywords: palladium; catalysis; C−H activation; azulene; azulenopyridinone

Azulenes, which are a class of nonbenzenoid aromatic hydrocarbons, have received prominent attention due to their importance as natural products,[1] bioactive compounds,[2] and molecular materials.[3] Accordingly, the establishment of streamlined synthetic approaches for azulene skeletons from easily accessible starting materials is continuously required.[4] Hafner and coworkers described an efficient method for azulene synthesis.[5] However, there is a barrier to the *de novo* introduction of useful substituents onto the azulene ring because of the abnormal reactivity induced by the polarized π-electron system. For this reason, the functionalization of azulene through the introduction of valuable functional groups onto the preformed azulene ring and its transformation is highly attractive strategies for the synthesis of azulene derivatives.

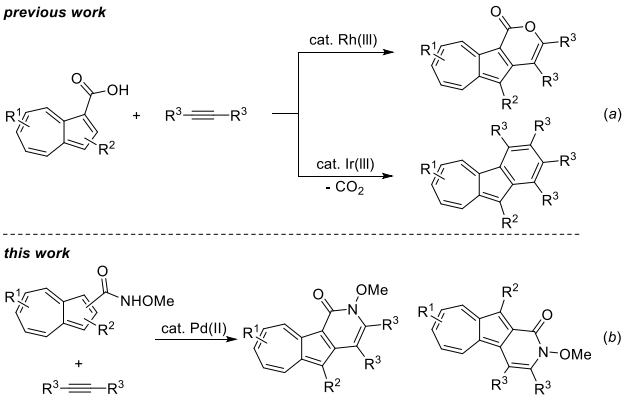
After Yu and coworkers reported for the first time C(sp^3)−H alkylation and arylation reaction using *N*-methoxyamide as a directing group,[6] many oxidative cyclization reactions of benzenoid aromatic compounds bearing amide directing groups with alkyne in the presence of external or internal oxidant have been reported (Scheme 1).[7,8] For example, Guimond and coworkers have developed a new synthetic method to oxidative [4 + 2] cyclization reaction from benzhydroxamic acids and alkynes without an external oxidant.[7a] Also, Huang and coworkers reported the first atom-economical synthesis of isoquinolinones and analogues via ligand-free Pd-catalyzed C–H and N–H double activation from *N*-methoxybenzamides and alkynes.[8e,8f,8g]



Scheme 1. Transition-Metal-Catalyzed Oxidative Cyclization Reactions of Substrates Containing an Amide Directing Group with Alkynes.

Recently, we developed for the first time Rh- and Ir-catalyzed oxidative [4 + 2] and [2 + 2 + 2] cyclization reactions of azulene-1-carboxylic acid and azulene-2-carboxylic acid, which are nonbenzenoid aromatic acids, with symmetrical and unsymmetrical alkynes, leading to the formation of a variety of azulenolactones and tetra(aryl)benzoazulenes with novel azulene skeletons (Scheme 2a).[9] Based on these results, we concluded that C−H activation is a very useful method for the functionalization of nonbenzenoid aromatic azulenes. However, no studies on C−H activation using amide directing groups have been described for azulene, a nonbenzenoid aromatic compound.[4e,10] Stimulated by the seminal results of Huang and coworkers[8e,8f,8g] and our results,[9] we envisioned that the development of C−H activation

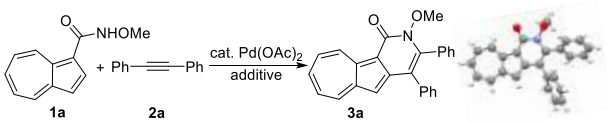
using azulene-bearing amide directing groups would be a significant milestone for the expansion of the C−H activation field. Although C−H activation has been applied to azulene for its functionalization, these are exclusively done at the 1,3-position, making use of their natural reactivity.[4e] As far as we know, there has been no attempt to make use of directed C−H activation to overcome the natural reactivity, so as to enable functionalization of azulene at other positions. Herein, we have developed Pd-catalyzed oxidative [4 + 2] cyclization reactions of *N*-methoxyazulene-1- and 2-carboxamides bearing nonbenzenoid aromatic azulene rings with symmetrical and unsymmetrical alkynes, leading to the formation of a number of azulenopyridinones bearing novel azulene frameworks (Scheme 2b).



Scheme 2. Transition-Metal-Catalyzed Oxidative Cyclization Reactions of Azulenes Containing a Directing Group with Alkynes.

First, we investigated the reaction of *N*-methoxyazulene-1-carboxamide (**1a**) with diphenylacetylene (**2a**) in the presence of $Pd(OAc)_2$ as a catalyst and potassium iodide (KI) as an additive under a molecular oxygen atmosphere (Table 1). A variety of solvents, including dichloroethane (DCE), EtOH, toluene, trifluoroethanol (TFE), and *N*,*N*-dimethylformamide (DMF), were screened (entries 1-5), and DMF was the solvent of choice. Although the desired azulenopyridinone (**3a**) was obtained in quantitative yield, the reaction time of 24 h was too long. When the reaction temperature was increased to 100 °C and 120 °C, the reaction time was dramatically decreased (entries 7 and 8). These results indicated that the efficiency of the present method is largely dependent on the reaction temperature. In addition, control reactions without KI were ineffective, suggesting that KI is essential for Pd-catalyzed oxidative [4 + 2] cyclization (entry 9). Accordingly, various additives performing a hard/soft ligand exchange process were investigated (entry 10-12). The anion of the additive has a greater effect on the reaction, and KI is the most effective additive in the reaction. When **1a** reacted with **2a** under an air atmosphere, the desired product (**3a**) and demethoxylated azulene-1-carboxamide were produced in 35 and 28% yields, respectively, indicating that the methoxy group does not act as an internal oxidant but that an external oxidant is required for this reaction to proceed (entry 13).[7b,8e] This is consistent with the optimum reaction conditions under a molecular oxygen atmosphere. *N*-Ethoxy and *N*-benzyloxyazulene-1-carboxamides yielded inferior results (entries 14 and 15). The best result of the cyclization reaction was obtained from the reaction of **1a** (0.15 mmol, 1.0 equiv) with **2a** (1.2 equiv) in the presence of $Pd(OAc)_2$ (4.0 mol %) and KI (1.0 equiv) in DMF at 120 °C for 4 h under a molecular oxygen atmosphere, providing **3a** in quantitative yield (entry 8). To demonstrate the applicability of the present method to larger-scale processes, 3.0 mmol of *N*-methoxyazulene-1-carboxamide (**1a**) (0.18 g) was treated with diphenylacetylene (**2a**) (1.2 equiv) under the optimal reaction conditions, providing the corresponding compound **3a** (0.18 g, 84%). The structure of **3a** was

Table 1. Reaction Optimization.[a]



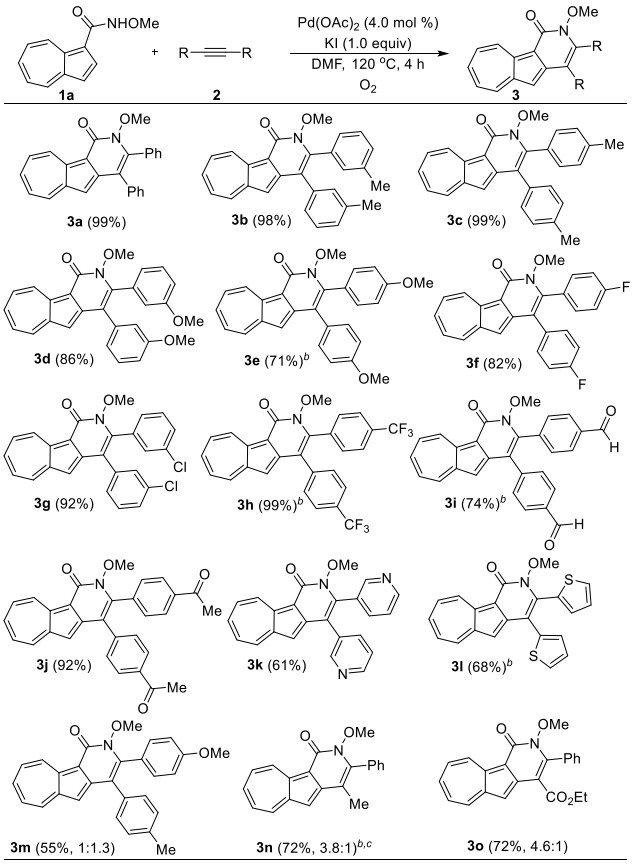
entry	additive	solvent	*T* [°C]	*t* [h]	yield [%][b]
1	KI	DCE	80	24	5
2	KI	EtOH	80	24	6
3	KI	toluene	80	24	0
4	KI	TFE	80	24	0
5	KI	DMF	80	24	99
6	KI	DMF	60	24	39
7	KI	DMF	100	12	99
8	KI	DMF	120	4	99 (84)[c]
9	-	DMF	120	24	13
10	KCl	DMF	120	12	64
11	LiI	DMF	120	4	86
12	LiCl	DMF	120	12	16
13[d]	KI	DMF	120	12	35 (28)[e]
14[f]	KI	DMF	120	4	30
15[g]	KI	DMF	120	4	27

[a] Reaction conditions: **1a** (0.15 mmol, 1.0 equiv) reacted with **2a** (1.2 equiv) in the presence of catalyst (4.0 mol %) and additive (1.0 equiv) in solvent (0.1 M) in a test tube under a molecular oxygen atmosphere.
[b] NMR yields using dibromomethane as an internal standard.
[c] Reaction scale is 3.0 mmol. Isolated yield.
[d] Air atmosphere.
[e] Numbers in parentheses are NMR yields of azulene-1-carboxamide.
[f] *N*-Ethoxy azulene was used.
[g] *N*-Benzyloxy azulene was used.

confirmed by X-ray crystallography and the redox potential of **3a** was obtained from electrochemical analysis results using cyclic voltammetry measurements (see the Supporting Information).

After these encouraging results were obtained, the scope and limitations of the alkynes (**2**) in the reaction with *N*-methoxyazulene-1-carboxamide (**1a**) were examined (Table 2). The reaction efficiency was not influenced by the electronic properties of the alkynes. C−H activation followed by cyclization also displays a wide functional group tolerance with respect to the alkyne substituent. Substrate **1a** was smoothly cyclized with a variety of symmetrical electron-rich diarylacetylenes **2** to afford 3,4-diarylazulenopyridinones **3b**-**3e** in good to excellent yields. Moreover, symmetrical electron-deficient diarylacetylenes with fluoro, chloro, and trifluoromethyl groups were reactive, and the corresponding 3,4-diarylazulenopyridinones **3f**-**3h** were obtained in good yields ranging from 82 to 99%. To our delight, the present oxidative cyclization proceeded despite the presence of labile formyl and acetyl groups on the phenyl ring, affording desired compounds **3i** and **3j** in good yield. Symmetrical di(heteroaryl)acetylenes with pyridine and thiophene moieties are also applicable to the present method,

Table 2. Substrate Scope of Alkynes.[a]



[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv) reacted with **2** (1.2 equiv) in the presence of $Pd(OAc)_2$ (4.0 mol %) and KI (1.0 equiv) in DMF (0.1 M) in a test tube under a molecular oxygen atmosphere.

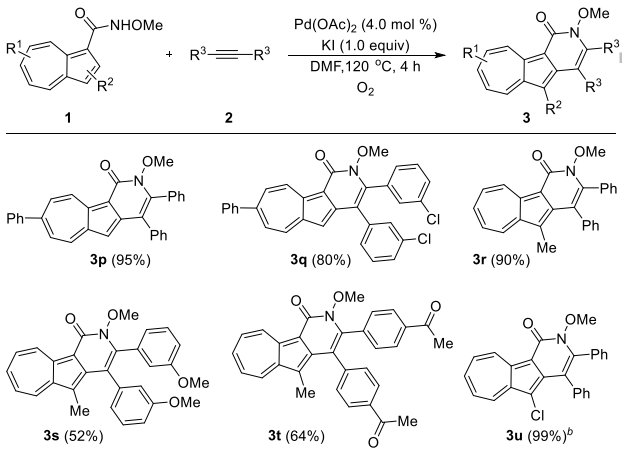
[b] **2** (2.0 equiv) was used.

[c] Molecular oxygen bubbling.

providing the corresponding 3,4-di(heteroaryl)azulenopyridinones (**3k** and **3l**) in 61 and 68% yields, respectively. Unsymmetrical disubstituted alkynes could be used to demonstrate the unique reactivity and effectiveness of the present reaction. When unsymmetrical diarylacetylenes with 4-methyl and 4-methoxy groups were used, the desired products (**3m**) were obtained in 55% (1:1.3) yield. 1-Phenyl-1-propyne was converted to desired product **3n** (72%, 3.8:1), indicating that azulenopyridinone with a phenyl group proximal to nitrogen was the major product due to the extended conjugation effect and the steric effect of the alkynes. In addition, ethyl but-2-ynoate reacted with **1a** to provide **3o** (72%, 4.6:1).

Next, the scope of *N*-methoxyazulene-1-carboxamides **1** and alkynes **2** was examined (Table 3). A substrate with a phenyl group attached to the 7-membered ring reacted with diphenylacetylene and di(3-chlorophenyl)acetylene, providing 3,4-diarylazulenopyridinones (**3p** and **3q)** in 95 and 80% yields, respectively. Azulene-1-carboxamides with a methyl group on the 5-membered ring worked equally well with a variety of alkynes, leading to the formation of 3,4-diarylazulenopyridinones **3r-3t** in moderate to good yields ranging from 52 to 90%. Electron-deficient azulene-1-carboxamide with a chloro group on the 5-membered ring underwent efficient C−H activation followed by cyclization with diphenylacetylene, affording the desired 3,4-diphenylazulenopyridinone **3u** in quantitative yield.

Table 3. Substrate Scope of Azulenes and Alkynes.[a]



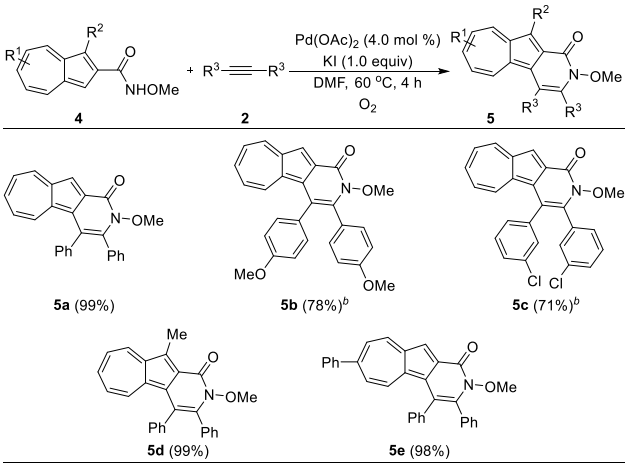
[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv) reacted with **2** (1.2 equiv) in the presence of $Pd(OAc)_2$ (4.0 mol %) and KI (1.0 equiv) in DMF (0.1 M) in a test tube under a molecular oxygen atmosphere.

[b] 8 h.

Stimulated by these results, *N*-methoxyazulene-2-carboxamide (**4a**) was investigated (Table 4). Substrate (**4a**) reacted with diphenylacetylene in the presence of $Pd(OAc)_2$ (4.0 mol %) and KI (1.0 equiv) in DMF at 60 °C for 4 h, providing azulenopyridinone **5a** in quantitative yield. When substrate (**4a**) reacted with di(4-methoxyphenyl)acetylene and di(3-

chlorophenyl)acetylene in DMF at 100 °C for 2 h, the desired products **5b** and **5c** were produced in 78 and 71% yields, respectively. Azulene-2-carboxamides with a methyl group on the 5-membered ring and a phenyl group on the 7-membered ring reacted with diphenylacetylene, leading to the formation of **5d** and **5e** in quantitatively yields. These results indicate that *N*-methoxyazulene-2-carboxamide is more reactive than *N*-methoxyazulene-1-carboxamide due to two reactive sites (1,3-positions) as well as the highly reactive 1,3-positions[11] caused by the polarized π-electron system of azulenes, making use of their natural reactivity.

Table 4. Substrate Scope of *N*-Methoxyazulene-2-Carboxamides.[a]

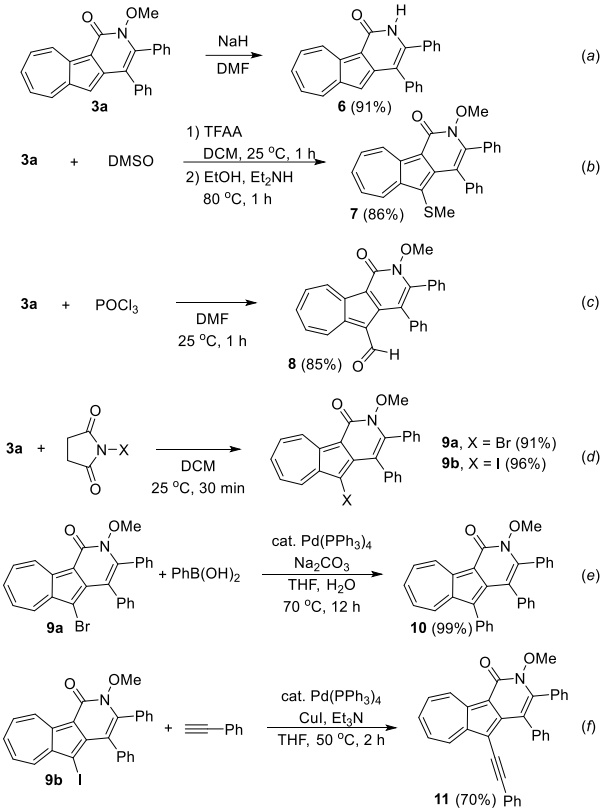


[a] Reaction conditions: **1e** (0.2 mmol, 1.0 equiv) reacted with **2** (1.2 equiv) in the presence of $Pd(OAc)_2$ (4.0 mol %) and KI (1.0 equiv) in DMF (0.1 M) in a test tube under a molecular oxygen atmosphere.

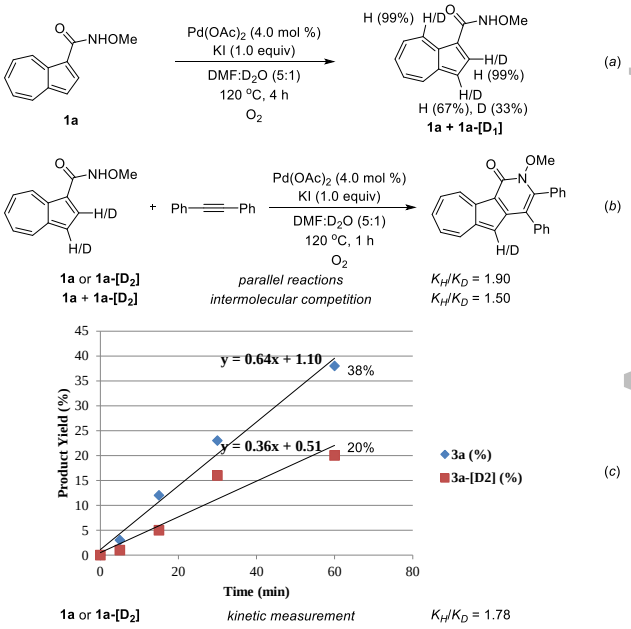
[b] The reaction was performed at 100 °C for 2 h.

The synthetic applications of azulenopyridinone (**3a**) were explored. As shown in Scheme 3, demethoxylation was performed with NaH in DMF, providing the desired N−H azulenopyridinone **6** in 91% yield (*a*).[8e,12] Additionally, **3a** reacted with DMSO in the presence of trifluoroacetic anhydride followed by diethyl amine to give methylsulfenylated azulenopyridinone (**7**) in 86% yield (*b*).[13] Formylated azulenopyridinone (**8**) was generated from **3a** and $POCl_3$ (*c*).[14] To our delight, **3a** was converted to the corresponding haloazulenopyridinones (**9a** and **9b**) with excellent yields using NBS and NIS (*d*).[15] Suzuki-Miyaura coupling of **9a** with phenyl boronic acid provided **10** in quantitative yield (*e*).[16] Additionally, iodoazulenopyridinone (**9b**) was transformed to desired compound **11** in 70% yield by the Sonogashira reaction (*f*).[17]

Catalytic C−H activation in DMF:D_2O (5:1) was conducted under the optimal reaction conditions, and mechanistic studies with isotopically labeled substrate **1a** revealed that the C(2)−H bond metalation was irreversible (Scheme 4a). Because the electron-rich C(3)-position of azulene is more reactive than the C(2) one, the deuterium exchange reaction occurred partly at the C(3)-position. Next, we performed kinetic isotope effect (KIE) studies to gain insight into the reaction mechanism. The KIE was obtained (K_H/K_D = 1.9) *via* parallel reactions and



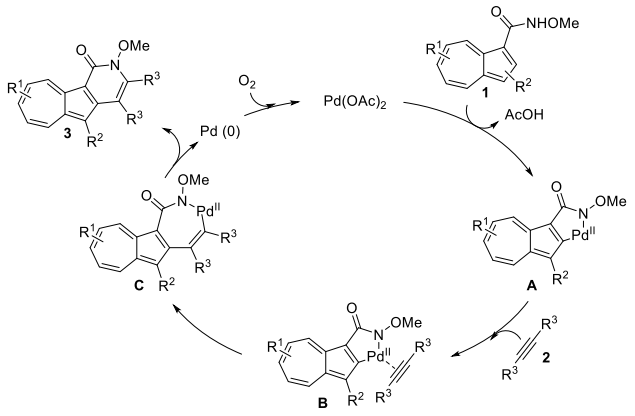
Scheme 3. Synthetic Application of Azulenopyridinones.



Scheme 4. Experiments with Isotopically Labeled Compounds.

was measured (K_H/K_D = 1.5) from the intermolecular competition reaction using **1a** and **1a**-[**D**$_2$] (Scheme 4b). Additionally, the KIE was observed (K_H/K_D = 1.78) by independent reactions using **1a** or **1a**-[**D**$_2$] as the substrate under standard conditions (Scheme 4c). These results suggested that the cleavage of the C−H bond at the 2-position of *N*-methoxyazulene-1-carboxamide is not involved in the rate-determining step.

A proposed mechanism for C−H activation followed by cyclization of *N*-methoxyazulene-1-carboxamide (**1**) with alkynes **2** is described in Scheme 5. Coordination of the amide to $Pd(OAc)_2$ yields five-membered palladacycle **A**, and alkyne insertion followed by reductive elimination delivers azulenopyridinones **3**. Finally, the oxidation of Pd(0) by molecular oxygen regenerates the catalytically active Pd(II) species. Potassium iodide seems to be an effective additive, possibly due to the soft ligand exchange processes.[8e,18]



Scheme 5. A Proposed Mechanism.

In conclusion, we have developed a novel synthetic method for the preparation of azulenopyridinone derivatives through a Pd-catalyzed oxidative [4 + 2] cyclization reaction of nonbenzenoid aromatic *N*-methoxyazulene-1- and 2-carboxamides with symmetrical as well as unsymmetrical alkynes under a molecular oxygen conditions. Broad substrate scope and excellent functional group tolerance were demonstrated. Thus, research on C−H functionalization will certainly expand to nonbenzenoid aromatic compounds in the future.

Experimental Section

General Procedure for the Palladium-Catalyzed C−H Activation of *N*-methoxyazulenecarboxamides with Alkynes. To a test tube were added *N*-methoxyazulene-1-carboxamide (**1**) (0.2 mmol, 1.0 equiv), alkyne (**2**) (0.24 mmol, 1.2 equiv), $Pd(OAc)_2$ (4.0 mol %), and KI (1.0 equiv) in DMF (1.0 mL, 0.2 M). The resulting mixture was stirred at corresponding temperature for 4 h under a molecular oxygen atmosphere. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel to afford product **3**.

CCDC-1894161 contains the supplementary crystallographic data for this paper (**3a**). 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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References

[1] T. Yanagisawa, K. Kosakai, T. Tomiyama, M. Yasunami, *Chem. Pharm. Bull.* **1990**, *38*, 3355-3358;

[2] a) W. Treibs, W. Schroth, *Liebigs Ann. Chem.* **1954**, *586*, 202-212; b) L.-Y. Zhang, F. Yang, W.-Q. Shi, P. Zhang, Li, Y. S.-F. Yin, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5722-5725; c) E. Rekka, M. Chrysselis, I. Siskou, A. Kourounakis, *Chem. Pharm. Bull.* **2002**, *50*, 904-907; d) T. Tomiyama, M. Yokota, S. Wakabayashi, K. Kosakai, T. Yanagisawa, *J. Med. Chem*. **1993**, *36*, 791-800.

[3] a) H. Xin, C. Ge, X. Yang, H. Gao, X. Yang, X. Gao, *Chem. Sci.* **2016**, *7*, 6701-6705; b) H. Xin, C. Ge, X. Jiao, X. Yang, K. Rundel, C. R. McNeill, X. Gao, *Angew. Chem., Int. Ed.* **2018**, *57*, 1322-1326; c) D. Lichosyt, S. Wasilek, P. Dydio, J. Jurczak, *Chem. Eur J.* **2018**, *24*, 11683-11692.

[4] a) A. L. Crombie, J. L. Kane, K. M., Jr. Shea, R. L. Danheiser, *J. Org. Chem.* **2004**, *69*, 8652-8667; b) S. Carret, A. Blanc, Y. Coquerel, M. Berthod, A. E. Greene, J.-P. Deprès, *Angew. Chem., Int. Ed.* **2005**, *44*, 5130-5133; c) T. Shibasaki, T. Ooishi, N. Yamanouchi, T. Murafuji, K. Kurotobi, Y. Sugihara, *J. Org. Chem.* **2008**, *73*, 7971-7977; d) I. B. Aumüller, J. Yli-Kauhaluoma, *Org. Lett.* **2009**, *11*, 5363-5365; e) X. Shi, A. Sasmal, J.-F. Soule, H. Doucet, *Chem. Asian J.* **2018**, *13*, 143-157.

[5] Hafner, K. *Organic Syntheses*, *Collect. Vol. VII*; Wiley: New York, **1990**, pp. 15.

[6] D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc*. **2008**, *130*, 7190-7191.

[7] a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908-6909; b) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449-6457; c) B. Li, Huiliang. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573-12577; d) L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548-6551; e) B. Su, J. Wei, W. Wu, Z. Shi, *ChemCatChem* **2015**, *7*, 2986-2990; f) B. Yu, Y. Chen, M. Hong, P. Duan, S. Gan, H. Chao, Z. Zhao, J. Zhao, C*hem. Commun.* **2015**, *51*, 14365-14368; g) G. Sivakumar, A. Vijeta, M. Jeganmohan, *Chem. Eur. J.* **2016**, *22*, 5899-5903; h) E. Petrova, D. Rasina, A. Jirgensons, *Eur. J. Org. Chem.* **2017**, 1773-1779; i) J. Yang, L. Wu, H. Xu, H. Gao, Z. Zhou, W. Yi, *Org. Lett.* **2019**, *21*, 9904-9908.

10.1002/adsc.202000587

[8] a) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc*. **2010**, *132*, 10565-10569; b) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett*. **2010**, *39*, 744-746; c) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487-7490; d) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed*. **2011**, *50*, 6379-6382; e) H. Zhong, D. Yang, S. Wang, J. Huang, *Chem. Commun.* **2012**, *48*, 3236-3238; f) N. Zhang, B. Li, H. Zhong, J. Huang, *Org. Biomol. Chem.* **2012**, *10*, 9429-9439; g) S. Lu, Y. Lin, H. Zhong, K. Zhao, J. Huang, *Tetrahedron Lett.* **2013**, *54*, 2001-2005; h) Z. Shu, W. Li, B. Wang, *ChemCatChem* **2015**, *7*, 605-608; i) N. Sharma, R. Saha, N. Parveen, G. Sekara, *Adv. Synth. Catal.* **2017**, *359*, 1947-1958; j) A. Obata, Y. Ano, N. Chatani, *Chem. Sci*. **2017**, *8*, 6650-6655; k) N. S. Upadhyay, V. H. Thorat, R. Sato, A. Pratheepkumar, S.-C. Chuang, C.-H. Cheng, *Green Chem.* **2017**, *19*, 3219-3224; l) X. Peng, W. Wang, C. Jiang, D. Sun, Z. Xu, C.-H. Tung, *Org. Lett*. **2014**, *16*, 5354-5357.

[9] C. Maeng, J.-Y. Son, S. C. Lee, Y. Baek, K. Um, S. H. Han, G. H. Ko, G. U. Han, K. Lee, K. Lee, P. H. Lee, *J. Org. Chem.* **2020**, *85*, 3824-3837.

[10] S. Park, W.-S. Yong, S. Kim, P. H. Lee, *Org. Lett*. **2014**, *16*, 4468-4471.

[11] a) A. G. Anderson, J. A. Nelson, *J. Am. Chem. Soc*. **1950**, *72*, 3824-3825; b) A. G. Anderson, J. A. Nelson, J. J. Tazuma, *J. Am. Chem. Soc*. **1953**, *75*, 4980-4989.

[12] General methods for the cleavage of N−O bond, see: S. P. Y. Cutulic, J. A. Murphy, H. Farwaha, S.-Z. Zhou, E. Chrystal, *Synlett* **2008**, 2132-2136.

[13] T. Shoji, J. Higashi, S. Ito, K. Toyota, T. Asao, M. Yasunami, K. Fujimori, N. Morita, *Eur. J. Org. Chem.* **2008**, 1242-1252.

[14] Y. Zhou, Y. Zhuang, X. Li, H. Agren, L. Yu, J. Ding, L. Zhu, *Chem. Eur. J*. **2017**, *23*, 7642-7647.

[15] J. Dubovik, A. Bredihhin, *Synthesis* **2015**, *47*, 538-548.

[16] F. Li, Q. Song, L. Yang, G. Wu, X. Zhang, *Chem. Commun.* **2013**, *49*, 1808-1810.

[17] T. Shoji, A. Maruyama, M. Tanaka, D. Nagai, E. Shimomura, K. Fujimori, S. Ito, T. Okujima, K. Toyota, M. Yasunami, *ChemistrySelect* **2016**, *1*, 49-56.

[18] a) R. G. Pearson, *J. Am. Chem. Soc*. **1963**, *85*, 3533-3539; b) R. G. Pearson, *Science* **1966**, *151*, 172-176.

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UPDATE

Synthesis of Azulenopyridinones through Palladium-Catalyzed Oxidative [4 + 2] Cyclization Reactions of *N*-Methoxyazulene-1- and 2-carboxamides with Alkynes

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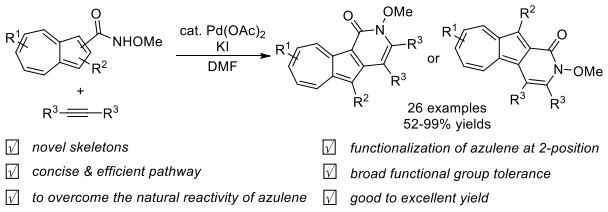

- ☑ *novel skeletons*
- ☑ *concise & efficient pathway*
- ☑ *to overcome the natural reactivity of azulene*
- ☑ *functionalization of azulene at 2-position*
- ☑ *broad functional group tolerance*
- ☑ *good to excellent yield*