JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

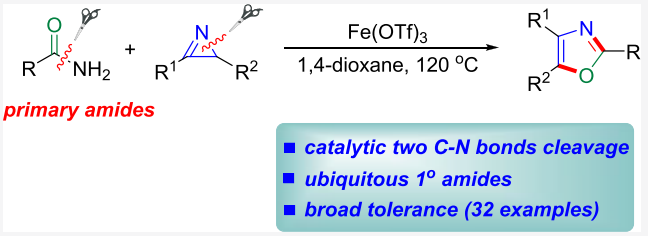
Iron-Catalyzed Cycloaddition of Amides and 2,3-Diaryl-2*H*-azirines To Access Oxazoles via C−N Bond Cleavage

Mi-Na Zhao,* Gui-Wan Ning, De-Suo Yang, Ming-Jin Fan, Sheng Zhang, Peng Gao, and Li-Fang Zhao

Cite This: *J. Org. Chem.* 2021, 86, 2957−2964 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A novel and efficient iron-catalyzed cycloaddition reaction using readily available 2,3-diaryl-2*H*-azirines and primary amides is reported. A wide range of trisubstituted oxazoles could be achieved in good yields with good functional group compatibility. In this transformation, two C−N bonds were cleaed and new C−N and C−O bonds were formed.

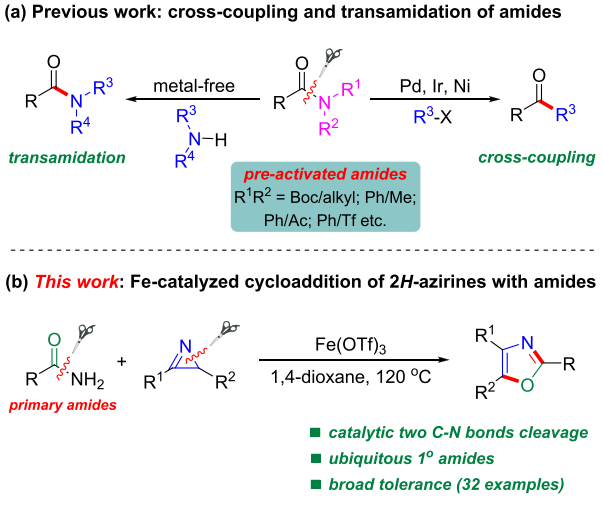


INTRODUCTION

The oxazole skeleton is an important *N*-heterocyclic structural unit widely found in natural products, biologically active compounds, pharmaceuticals, and materials science.[1] Examples include siphonazole,[2] aleglitazar,[3] and ulapualide C.[4] Owing to their significant value, numerous strategies have been developed to synthesize oxazole derivatives,[5] mainly involving oxidation of oxazoline,[6] intramolecular cyclization of *N*-propargylamide,[7] or transition-metal-catalyzed intermolecular cyclization.[8] Despite these significant achievements on the synthesis of oxazole derivatives, a concise and flexible method for the synthesis of this type of skeleton remains highly desirable.

Amides, which are key building blocks in organic synthesis,[9] have been widely applied in transition-metal-free transamidation via cleavage of an amide C−N bond to synthesize widely valuable amides (Scheme 1a, left).[10] Recently, transition-metal-catalyzed cross-coupling reactions by selective metal insertion into the inert N−C(O) bond have also been developed for the synthesis of various ketones (Scheme 1a, right).[11] However, preactivated amides are generally required for these reactions because N-substitution could facilitate metal insertion. Meanwhile, the cyclization reaction of amides via cleavage of C−N bond has rarely been reported[12] and remains a challenging task. 2*H*-Azirines are versatile synthetic intermediates for the synthesis of various azaheterocycles by a ring-opening reaction.[13,14] Our interest in the transition-metal-catalyzed transformation of 2*H*-azirines[15] prompted us to study the cycloaddition of 2*H*-azirines and primary amides. In this paper, we describe a novel iron-catalyzed cycloaddition of 2,3-diaryl-2*H*-azirines with primary amides (*N*-unsubstituted amides) via cleavage of two C−N bonds for the synthesis of trisubstituted oxazoles (Scheme 1b).

Scheme 1. Transformation of Amides by N−C(O) Bond Cleavage To Construct New Chemical Bonds



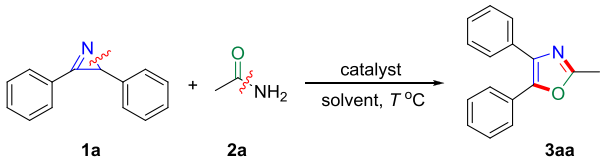
RESULTS AND DISCUSSION

We start our investigation by taking 2,3-diphenyl-2*H*-azirine **1a** and acetamide **2a** in DCE at 80 °C (Table 1). Initially, a wide range of different nickel and copper compounds were used as catalysts. Disappointingly, there is no result (Table 1, entries 1 and 2). To our delight, when $FeCl_2$ was used as catalyst, the 2-methyl-4,5-diphenyloxazole **3aa** was observed in 19% yield

Received: November 30, 2020
Published: January 14, 2021

https://dx.doi.org/10.1021/acs.joc.0c02843
J. Org. Chem. 2021, 86, 2957−2964

Table 1. Optimization of the Reaction Conditions[a]



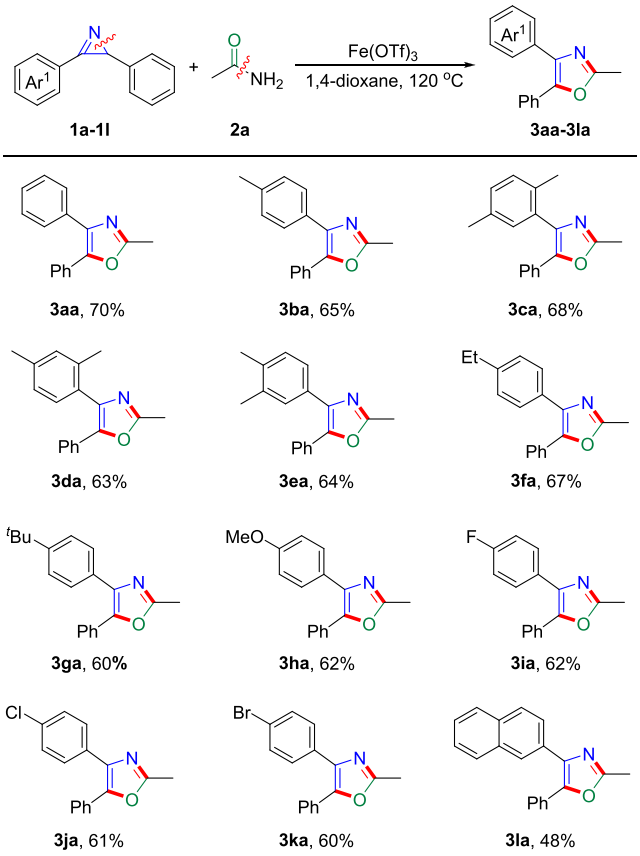
entry	catalyst	solvent	T (°C)	yield (%)
1[b]	[Ni]	DCE	80	0
2[c]	[Cu]	DCE	80	0
3	$FeCl_2$	DCE	80	19
4	$FeCl_3$	DCE	80	20
5	$Fe(acac)_2$	DCE	80	trace
6	$Fe(acac)_3$	DCE	80	trace
7	$Fe(OTf)_2$	DCE	80	35
8	$Fe(OTf)_3$	DCE	80	39
9		DCE	80	0
10	$Fe(OTf)_3$	toluene	80	20
11	$Fe(OTf)_3$	THF	80	20
12	$Fe(OTf)_3$	CH_3CN	80	24
13	$Fe(OTf)_3$	1,4-dioxane	80	45
14	$Fe(OTf)_3$	DMF	80	0
15	$Fe(OTf)_3$	1,4-dioxane	100	54
16	$Fe(OTf)_3$	1,4-dioxane	120	63
17[d]	$Fe(OTf)_3$	1,4-dioxane	120	61
18[e]	**$Fe(OTf)_3$**	**1,4-dioxane**	**120**	**70**

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (5 mol %), solvent (3 mL), 80 °C oil bath, 6 h. [b]$Ni(OAc)_2$, $Ni(acac)_2$, or $NiCl_2$ was screened. [c]$Cu(OAc)_2$ or $Cu(acac)_2$ was screened. [d]$Fe(OTf)_3$ (10 mol %) was added. [e]**2a** (0.6 mmol) was added.

(Table 1, entry 3). Therefore, screening of Fe catalysts is significant for this cycloaddition reaction. Gratifyingly, $Fe(OTf)_3$ was found to be an effective catalyst by screening different iron catalysts to give the desired oxazole **3aa** in 39% yield (Table 1, entries 4−8). Notably, iron catalyst plays a vital role in the reaction. No reaction occurred in the absence of the iron catalyst (Table 1, entry 9). For improving the reaction efficiency, various solvents such as toluene, THF, CH_3CN, 1,4-dioxane, and DMF were also screened (Table 1, entries 10−14). These results reveal that 1,4-dioxane was the best choice; the yield of **3aa** reached 45% (Table 1, entry 13). It was found that increasing the reaction temperature to 120 °C could improve the yield of **3aa** to 63% (Table 1, entries 15 and 16). However, increasing the amount of $Fe(OTf)_3$ resulted in no improvement (Table 1, entry 17). Pleasingly, the yield of the desired product **3aa** could be improved to 70% when a molar ratio of [**2a**]/[**1a**] = 3/1 was employed (Table 1, entry 18). Ultimately, the best conditions for the reaction were determined as **1a** (0.2 mmol), **2a** (0.6 mmol), and $Fe(OTf)_3$ (5 mol %) in 1,4-dioxane in a 120 °C oil bath.

With optimal reaction conditions in hand, we next turned our attention to the scope of 2*H*-azirines that can participate in this reaction (Scheme 2). Changing the Ar^1 group on the C=N double bond moiety of the 2*H*-azirines was studied first. 2*H*-Azirines bearing electron-donating groups on Ar^1, such as methyl, ethyl, *tert*-butyl, and methoxyl, all afforded the corresponding trisubstituted oxazoles **3aa**−**3ha** in 60−70% yields.[16] Of particular note, the required oxazoles **3ca** and **3da** were successfully obtained in 68% and 63% yields when the Ar^1 of 2*H*-azirines was ortho substituted, implying that the ring-forming process was insensitive to the steric hindrance of Ar^1. 2*H*-Azirines with an electron-withdrawing group, such as

Scheme 2. Substrate Scope with Respect to Ar^1 [a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $Fe(OTf)_3$ (5 mol %), 1,4-dioxane (3 mL), 120 °C oil bath, 6 h.

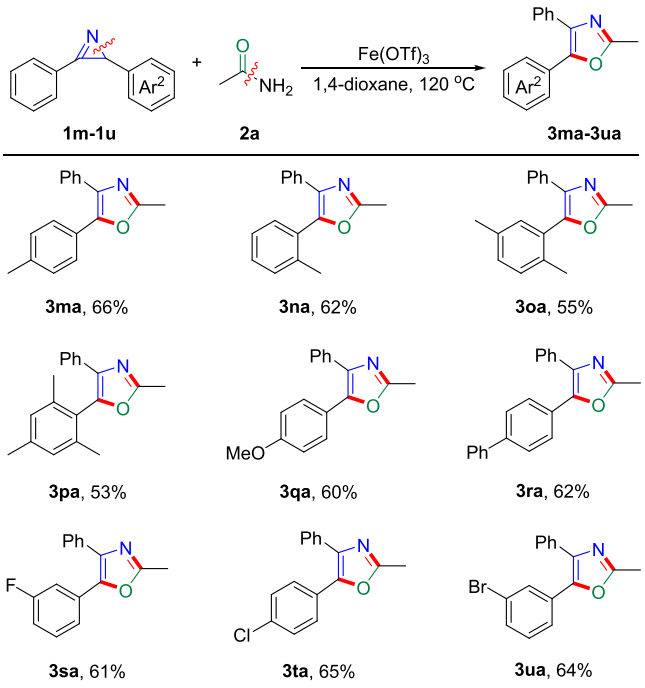
fluoro, chloro, and bromo, were well tolerated in this reaction, giving the desired oxazoles **3ia**−**3ka** in good yields. In addition, the desired oxazole **3la** was also obtained in 48% yield when 2-naphthyl-substituted 2*H*-azirine **1l** was used as the substrate, albeit in somewhat diminished yield. However, the alkyl-substituted 2*H*-azirine, such as 3-methyl-2-phenyl-2*H*-azirine, was incompatible under the reaction conditions.

Beyond variation of the substitution pattern at the Ar^1 moiety, the changes on Ar^2 were also tested (Scheme 3). Substituents such as methyl, methoxyl, phenyl, or halogen groups such as fluoro, chloro, and bromo at the Ar^2 group of 2*H*-azirines have not much impacted this transformation. The corresponding oxazoles **3ma**−**3ua** were obtained in 53−66% yields. From these results, the electronic nature effect of the substituents on Ar^2 is unconspicuous in this cycloaddition reaction. Nevertheless, 2,5-dimethyl-substituted and 2,4,6-trimethyl-substituted 2*H*-azirines **1o** and **1p** afforded the desired oxazoles **3oa** and **3pa** in 55% and 53% yields. This phenomenon indicates that the steric effect has a slight influence on the reaction.

Encouraged by the above results, we were committed to searching for other reactions with different substituents on Ar^1 and Ar^2 to further expand the range of substrates for the transformation (Scheme 4). We were pleased to find that 2*H*-azirines **1v**−**1y** proceeded smoothly to give the corresponding oxazoles **3va**−**3ya** in 50−66% yields. The structure of **3wa** was clearly confirmed by X-ray crystallographic analysis (CCDC 2036963, see Supporting Information for details). At the same

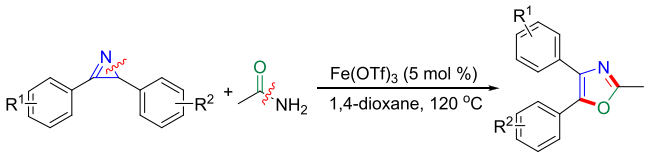
https://dx.doi.org/10.1021/acs.joc.0c02843
J. Org. Chem. 2021, 86, 2957−2964

Scheme 3. Substrate Scope with Respect to Ar^2 [a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), Fe(OTf)$_3$ (5 mol %), 1,4-dioxane (3 mL), 120 °C oil bath, 6 h.

Scheme 4. Fe-Catalyzed Cycloaddition of Various 2*H*-Azirines and Acetamide 2a



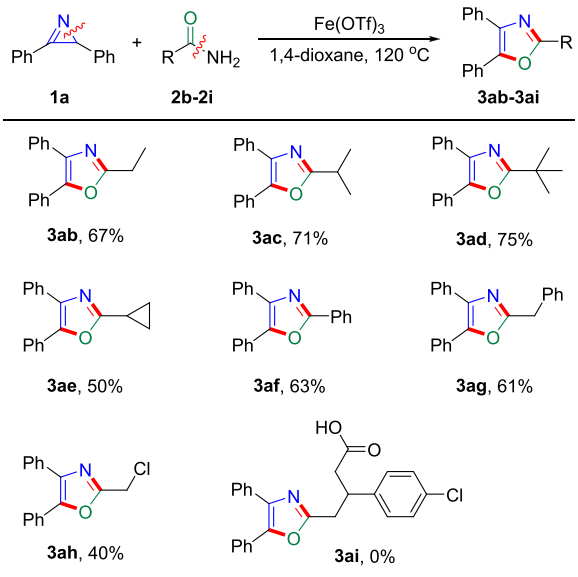
3va: R^1 = 4-Me, R^2 = 4-Me 63%
3wa: R^1 = 4-Cl, R^2 = 4-Me 66%
3xa: R^1 = 2,5-di-Me, R^2 = 4-Cl 62%
3ya: R^1 = 4-Br, R^2 = 4-Cl 50%

time, it was also confirmed that C−N single bond cleavage of the 2*H*-azirine was involved in the reaction.

In addition, to further investigate the scope and limitation of this cycloaddition reaction, a variety of amides with different substituents were examined (Scheme 5). Expectedly, when we replace the substrate acetamide (**2a**) with propamide (**2b**), isobutyramide (**2c**), pivalamide (**2d**), and cyclopropanecarboxamide (**2e**), the corresponding oxazoles **3ab**−**3ae** were obtained in 50−75% yields. Meanwhile, the R group of amide bearing phenyl **2f** and benzyl **2g** proceeded smoothly to afford the desired oxazoles **3af** and **3ag** in 63% and 61% yields, respectively. Strikingly, oxazole **3ah** was also obtained in 40% yield when R was substituted by an electron-withdrawing group (−CH_2Cl). However, no reaction occurred when the 5-amino-3-(4-chlorophenyl)-5-oxopentanoic acid **2i** was used as the substrate.

To achieve insights into the reaction mechanism, some control experiments were conducted (Scheme 6). Addition of a radical trapping reagent 2,2,6,6-tetramethylpiperidin-1-yl)-oxyl (TEMPO) or butylated hydroxytoluene (BHT) produced

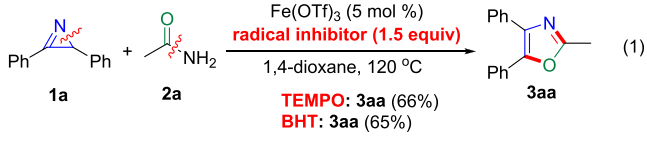
Scheme 5. Substrate Scope with Respect to Amides[a]



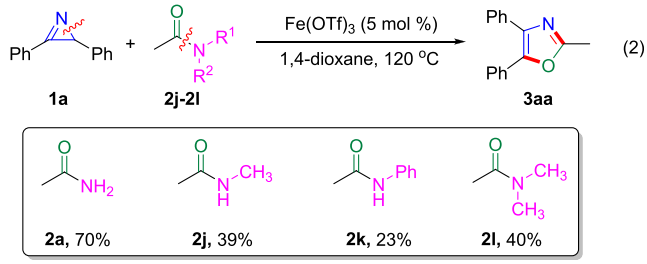
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), Fe(OTf)$_3$ (5 mol %), 1,4-dioxane (3 mL), 120 °C oil bath, 6 h.

Scheme 6. Investigation of the Reaction Mechanism

Radical trapping experiments



The source of nitrogen atom

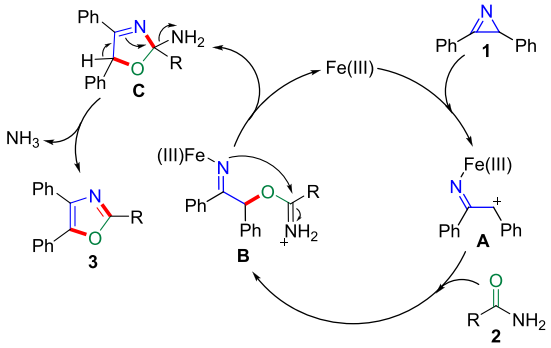


the desired product **3aa** in 66% or 65% yield, respectively (Scheme 6, eq 1). These results indicate that a radical pathway might not be involved in this transformation. Furthermore, when *N*-methylacetamide **2j**, *N*-phenylacetamide **2k**, or *N*,*N*-dimethylacetamide **2l** was used instead of acetamide **2a**, the oxazole **3aa** was obtained as well, albeit in low yield (Scheme 6, eq 2). This result confirmed that the nitrogen atom of the oxazole ring should indeed come from 2*H*-azirines rather than amides.

On the basis of the above experimental results and previous reports,[9−15] a plausible mechanism was postulated for the Fe-catalyzed cycloaddition reaction (Scheme 7). Initially, C−N bond cleavage of 2*H*-azirines **1** in the presence of Fe(III) generated intermediate **A**. Then the oxygen of the amides **2** attacked the electrophilic carbon of intermediate **A** to form intermediate **B**, which subsequently underwent intramolecular cyclization to give intermediate **C**. Simultaneously, the Fe(III) catalyst was released to facilitate the next catalytic cycle.

https://dx.doi.org/10.1021/acs.joc.0c02843
J. Org. Chem. 2021, 86, 2957−2964

Scheme 7. Proposed Mechanism for Fe-Catalyzed Cycloaddition of 2*H*-Azirines and Amides



Finally, elimination of intermediate **C** by release of ammonia gas (NH_3) resulted in formation of the oxazole product **3**.

CONCLUSION

In summary, we successfully developed a novel iron-catalyzed cycloaddition reaction of 2,3-diaryl-2*H*-azirines with primary amides, providing efficient access to valuable trisubstituted oxazoles in moderate to good yields. This transformation proceeds through cleavage of the C−N bond, followed by an intermolecular nucleophilic addition/intramolecular cyclization in one pot. The readily available starting materials, low-cost transition-metal catalysts, and good functional group tolerance make this protocol attractive for organic synthesis. Studies toward mechanistic investigations as well as on further developments of the Fe-catalyzed transformations of 2*H*-azirines are actively pursued in our laboratory.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Coupling constants, *J*, were reported in Hertz (Hz). Melting points were determined with a digital melting point measuring instrument. All products were characterized by HRMS; copies of their ^{1}H NMR and ^{13}C NMR spectra are provided in the Supporting Information. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification.

General Procedure. *Synthesis of 2,3-Diaryl-2H-azirines **1** According to the Known Procedure.*[15] Compounds **1a**−**1y** are known and were identified by comparison of their NMR data with the data reported in the literature.[15c]

*Synthesis of Trisubstituted Oxazoles **3** According to the Following Procedure.* In a 25 mL round-bottom flask, the 2,3-diaryl-2*H*-azirines **1** (0.2 mmol), amides **2** (0.6 mmol), and $Fe(OTf)_3$ (0.01 mmol, 0.0050 g) were stirred in 1,4-dioxane (3 mL) at 120 °C in an oil bath. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature. The solvent was evaporated under vacuum. The crude product was purified by column chromatography on silica gel to afford the corresponding oxazoles **3** with hexanes/ethyl acetate (v/v = 20:1) as the eluent.

*Preparation of **3aa** on Gram Scale.* In a 25 mL round-bottom flask, the 2,3-diphenyl-2*H*-azirine **1a** (6 mmol, 1.16 g), acetamide **2a** (18 mmol, 1.06 g), and $Fe(OTf)_3$ (0.3 mmol, 0.1509 g) were stirred in 1,4-dioxane (15 mL) at 120 °C in an oil bath. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature. The solvent was evaporated under vacuum. The crude product was purified by column chromatography on silica gel to afford the oxazole **3aa** in 64% yield (0.910 g) with hexanes/ethyl acetate (v/v = 20:1) as the eluent.

*2-Methyl-4,5-diphenyloxazole (**3aa**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3aa**. Yield 70% (32.9 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.63 (m, 2H), 7.59−7.56 (m, 2H), 7.37−7.29 (m, 6H), 2.54 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 145.2, 135.1, 132.4, 129.0, 128.5, 128.4, 128.3 127.9, 127.8, 126.3, 13.9. HRMS calcd (ESI-TOF) *m*/*z* for $C_{16}H_{14}NO$: $[M + H]^+$ 236.1099. Found: 236.1090.

*2-Methyl-5-phenyl-4-(p-tolyl)oxazole (**3ba**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ba**. Yield 65% (32.4 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.59−7.56 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.36−7.29 (m, 3H), 7.17−7.15 (m, 2H), 2.54 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 144.9, 137.8, 135.2, 129.5, 129.2, 128.5, 128.2, 127.7, 126.3, 21.3, 13.9. HRMS calcd (ESI-TOF) *m*/*z* for $C_{17}H_{16}NO$: $[M + H]^+$ 250.1226. Found: 250.1231.

*4-(2,5-Dimethylphenyl)-2-methyl-5-phenyloxazole (**3ca**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ca**. Yield 68% (35.9 mg); yellow solid; mp 50−51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.37 (m, 2H), 7.29−7.21 (m, 3H), 7.18−7.12 (m, 3H), 2.56 (s, 3H), 2.31 (s, 3H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.7, 145.5, 135.4, 135.0, 133.9, 132.2, 130.7, 130.3, 129.3, 129.0, 128.5, 127.6, 124.6, 20.8, 19.3, 14.0. HRMS calcd (ESI-TOF) *m*/*z* for $C_{18}H_{18}NO$: $[M + H]^+$ 264.1383. Found: 264.1390.

*4-(2,4-Dimethylphenyl)-2-methyl-5-phenyloxazole (**3da**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3da**. Yield 63% (33.2 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.37 (m, 2H), 7.28−7.20 (m, 4H), 7.09 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 2.55 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 145.5, 138.3, 136.9, 135.0, 131.2, 130.1, 129.4, 129.0, 128.5, 127.6, 126.8, 124.7, 21.3, 19.7, 14.0. HRMS calcd (ESI-TOF) *m*/*z* for $C_{18}H_{18}NO$: $[M + H]^+$ 264.1383. Found: 264.1391.

*4-(3,4-Dimethylphenyl)-2-methyl-5-phenyloxazole (**3ea**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ea**. Yield 64% (33.8 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.45 (s, 1H), 7.35−7.28 (m, 4H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.54 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0, 144.8, 136.8, 136.4, 135.3, 130.0, 129.7, 129.3, 129.0, 128.5, 128.1, 126.3, 125.2, 19.6, 19.6, 13.9. HRMS calcd (ESI-TOF) *m*/*z* for $C_{18}H_{18}NO$: $[M + H]^+$ 264.1383. Found: 264.1393.

*4-(4-Ethylphenyl)-2-methyl-5-phenyloxazole (**3fa**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3fa**. Yield 67% (35.2 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.54 (m, 4H), 7.36−7.29 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.69−2.63 (m, 2H), 2.54 (s, 3H), 1.25 (t, *J* = 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0, 144.9, 144.1, 135.2, 129.8, 129.2, 128.5, 128.2, 128.0, 127.7, 126.4, 28.6, 15.3, 13.9. HRMS calcd (ESI-TOF) *m*/*z* for $C_{18}H_{18}NO$: $[M + H]^+$ 264.1383. Found: 264.1390.

*4-(4-(tert-Butyl)phenyl)-2-methyl-5-phenyloxazole (**3ga**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ga**. Yield 60% (34.9 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.56 (m, 4H), 7.38−7.30 (m, 5H), 2.53 (s, 3H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0, 151.0, 144.9, 135.1, 129.5, 129.3, 128.6, 128.2, 127.4, 126.4, 125.4, 34.6, 31.3, 13.9. HRMS calcd (ESI-TOF) *m*/*z* for $C_{20}H_{22}NO$: $[M + H]^+$ 292.1696. Found: 292.1706.

*4-(4-Methoxyphenyl)-2-methyl-5-phenyloxazole (**3ha**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 15/1, v/v) to afford **3ha**. Yield 62% (32.9 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.54 (m, 4H), 7.36−7.29 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 2.54 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0, 159.4, 144.5, 134.9, 129.3, 129.1, 128.6, 128.1, 126.2, 124.9, 114.0, 55.2, 13.9. HRMS calcd (ESI-TOF) *m*/*z* for $C_{17}H_{16}NO_2$: $[M + H]^+$ 266.1176. Found: 266.1183.

*4-(4-Fluorophenyl)-2-methyl-5-phenyloxazole (**3ia**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to

https://dx.doi.org/10.1021/acs.joc.0c02843
J. Org. Chem. 2021, 86, 2957−2964

afford **3ia**. Yield 62% (31.2 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H), 7.56−7.53 (m, 2H), 7.38−7.31 (m, 3H), 7.07−7.02 (m, 2H), 2.54 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5 (C−F, d, J_{C-F} = 246.0 Hz), 160.2, 145.2, 134.2, 129.6 (C−F, d, J_{C-F} = 8.0 Hz), 128.9, 128.7, 128.6, 128.6, 128.4, 126.4, 115.5 (C−F, d, J_{C-F} = 21.0 Hz), 13.9. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{13}FNO$: $[M + H]^+$ 254.0976. Found: 254.0980.

*4-(4-Chlorophenyl)-2-methyl-5-phenyloxazole (**3ja**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ja**. Yield 61% (32.7 mg); yellow solid; mp 43−45 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.53 (m, 4H), 7.38−7.30 (m, 5H), 2.54 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 145.6, 134.0, 133.7, 131.0, 129.0, 128.8, 128.7, 128.7, 128.6, 126.5, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{13}ClNO$: $[M + H]^+$ 270.0680. Found: 270.0687.

*4-(4-Bromophenyl)-2-methyl-5-phenyloxazole (**3ka**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ka**. Yield 60% (37.6 mg); yellow solid; mp 54−57 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.46 (m, 6H), 7.38−7.32 (m, 3H), 2.53 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 145.6, 134.0, 131.7, 131.4, 129.3, 128.8, 128.7, 128.6, 126.5, 121.9, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{13}BrNO$: $[M + H]^+$ 314.0175. Found: 314.0185.

*2-Methyl-4-(naphthalen-2-yl)-5-phenyloxazole (**3la**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3la**. Yield 48% (27.3 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.83−7.79 (m, 3H), 7.70−7.67 (m, 1H), 7.62−7.59 (m, 2H), 7.47−7.45 (m, 2H), 7.36−7.31 (m, 3H), 2.58 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 145.7, 135.1, 133.5, 133.0, 129.9, 129.1, 128.6, 128.4, 128.2, 128.0, 127.6, 126.9, 126.5, 126.2, 126.1, 125.6, 14.0. HRMS calcd (ESI-TOF) m/z for $C_{20}H_{16}NO$: $[M + H]^+$ 286.1226. Found: 286.1235.

*2-Methyl-4-phenyl-5-(p-tolyl)oxazole (**3ma**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ma**. Yield 66% (33.1 mg); yellow solid; mp 49−51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.62 (m, 2H), 7.47−7.45 (m, 2H), 7.37−7.29 (m, 3H), 7.15 (d, J = 8.0 Hz, 2H), 2.53 (s, 3H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 145.5, 138.4, 134.5, 132.6, 129.3, 128.4, 127.8, 127.7, 126.4, 126.2, 21.3, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{17}H_{16}NO$: $[M + H]^+$ 250.1226. Found: 250.1228.

*2-Methyl-4-phenyl-5-(o-tolyl)oxazole (**3na**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3na**. Yield 62% (30.8 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.38−7.33 (m, 2H), 7.30−7.21 (m, 5H), 2.54 (s, 3H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 145.1, 137.9, 135.6, 132.1, 130.7, 130.5, 129.5, 129.0, 128.4, 127.4, 126.4, 126.0, 19.9, 14.0. HRMS calcd (ESI-TOF) m/z for $C_{17}H_{16}NO$: $[M + H]^+$ 250.1226. Found: 250.1235.

*5-(2,5-Dimethylphenyl)-2-methyl-4-phenyloxazole (**3oa**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3oa**. Yield 55% (28.9 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.28−7.16 (m, 6H), 2.54 (s, 3H), 2.32 (s, 3H), 2.11 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 145.2, 135.5, 135.4, 134.7, 132.1, 130.9, 130.6, 130.3, 128.8, 128.4, 127.4, 126.3, 20.8, 19.4, 14.0. HRMS calcd (ESI-TOF) m/z for $C_{18}H_{18}NO$: $[M + H]^+$ 264.1383. Found: 264.1386.

*5-Mesityl-2-methyl-4-phenyloxazole (**3pa**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3pa**. Yield 53% (29.4 mg); brown solid; mp 51−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.26−7.18 (m, 3H), 6.96 (s, 2H), 2.54 (s, 3H), 2.35 (s, 3H), 2.06 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 144.0, 139.6, 138.8, 135.6, 132.1, 128.6, 128.5, 127.2, 125.8, 125.4, 21.3, 19.9, 14.0. HRMS calcd (ESI-TOF) m/z for $C_{19}H_{20}NO$: $[M + H]^+$ 278.1539. Found: 278.1548.

*5-(4-Methoxyphenyl)-2-methyl-4-phenyloxazole (**3qa**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 15/1, v/v) to afford **3qa**. Yield 60% (31.7 mg); yellow solid; mp 51−53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.62 (m, 2H), 7.51−7.49 (m, 2H), 7.37−7.29 (m, 3H), 6.89−6.87 (m, 2H), 3.82 (s, 3H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.6, 159.6, 145.3, 133.8, 132.6, 128.4, 128.0, 127.7, 127.5, 121.6, 114.0, 55.2, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{17}H_{16}NO_2$: $[M + H]^+$ 266.1176. Found: 266.1183.

*5-([1,1′-Biphenyl]-4-yl)-2-methyl-4-phenyloxazole (**3ra**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ra**. Yield 62% (38.4 mg); yellow solid; mp 55−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.61−7.56 (m, 4H), 7.45−7.32 (m, 6H), 2.56 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 145.1, 141.0, 140.3, 135.3, 132.6, 128.8, 128.5, 128.0, 128.0, 127.9, 127.6, 127.2, 126.9, 126.7, 14.0. HRMS calcd (ESI-TOF) m/z for $C_{22}H_{18}NO$: $[M + H]^+$ 312.1383. Found: 312.1393.

*5-(3-Fluorophenyl)-2-methyl-4-phenyloxazole (**3sa**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3sa**. Yield 61% (30.8 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.60 (m, 2H), 7.41−7.34 (m, 4H), 7.32−7.26 (m, 2H), 7.01−7.69 (m, 1H), 2.55 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.8 (C−F, d, J_{C-F} = 244.0 Hz), 160.5, 144.0, 136.2, 132.2, 131.0 (C−F, d, J_{C-F} = 8.0 Hz), 130.2 (C−F, d, J_{C-F} = 8.0 Hz), 128.6, 128.3, 128.0, 121.8, 115.1 (C−F, d, J_{C-F} = 21.0 Hz), 113.1 (C−F, d, J_{C-F} = 24.0 Hz), 13.9. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{13}FNO$: $[M + H]^+$ 254.0976. Found: 254.0982.

*5-(4-Chlorophenyl)-2-methyl-4-phenyloxazole (**3ta**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ta**. Yield 65% (35.0 mg); yellow solid; mp 33−35 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.59 (m, 2H), 7.52−7.49 (m, 2H), 7.39−7.30 (m, 5H), 2.54 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 144.2, 135.6, 134.1, 132.2, 128.9, 128.6, 128.2, 127.8, 127.5, 127.5, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{13}ClNO$: $[M + H]^+$ 270.0680. Found: 270.0679.

*5-(3-Bromophenyl)-2-methyl-4-phenyloxazole (**3ua**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ua**. Yield 64% (40.1 mg); yellow solid; mp 66−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.75 (m, 1H), 7.62−7.60 (m, 2H), 7.50−7.47 (m, 1H), 7.44−7.34 (m, 4H), 7.18 (t, J = 8.0 Hz, 1H), 2.55 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 143.7, 136.2, 132.1, 131.2, 131.0, 130.1, 129.0, 128.6, 128.4, 127.9, 124.7, 122.7, 14.0. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{13}BrNO$: $[M + H]^+$ 314.0175. Found: 314.0180.

*2-Methyl-4,5-di-p-tolyloxazole (**3va**).*[5i] Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3va**. Yield 63% (33.2 mg); brown solid; mp 77−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.16−7.13 (m, 4H), 2.52 (s, 3H), 2.35 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 145.1, 138.2, 137.6, 134.6, 129.7, 129.2, 129.1, 127.6, 126.4, 126.4, 21.3, 21.3, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{18}H_{18}NO$: $[M + H]^+$ 264.1383. Found: 264.1391.

*4-(4-Chlorophenyl)-2-methyl-5-(p-tolyl)oxazole (**3wa**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3wa**. Yield 66% (37.3 mg); yellow solid; mp 127−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.33−7.30 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.53 (s, 3H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 145.7, 138.7, 133.5, 133.4, 131.1, 129.4, 128.9, 128.7, 126.5, 125.9, 21.4, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{17}H_{15}ClNO$: $[M + H]^+$ 284.0837. Found: 284.0838.

*5-(4-Chlorophenyl)-4-(2,5-dimethylphenyl)-2-methyloxazole (**3xa**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3xa**. Yield 62% (36.7 mg); yellow solid; mp 70−73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.25−7.22 (m, 2H), 7.17−7.11 (m, 3H), 2.55 (s, 3H), 2.31 (s, 3H), 2.10 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 144.6, 135.6, 135.5, 133.8, 133.4, 131.9, 130.5, 130.4, 129.5, 128.8, 127.4, 125.8, 20.8, 19.2, 14.0. HRMS calcd (ESI-TOF) m/z for $C_{18}H_{17}ClNO$: $[M + H]^+$ 298.0993. Found: 298.0996.

*4-(4-bromophenyl)-5-(4-chlorophenyl)-2-methyloxazole (**3ya**).* Flash column chromatography on silica gel (eluent: PE/EtOAc = 20/1, v/v) to afford **3ya**. Yield 50% (34.6 mg); yellow solid; mp 156−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.46 (m, 6H), 7.33 (d, J = 8.0 Hz, 2H), 2.54 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ

https://dx.doi.org/10.1021/acs.joc.0c02843
J. Org. Chem. 2021, 86, 2957−2964

160.6, 144.5, 134.6, 134.5, 131.8, 131.2, 129.3, 129.0, 127.7, 127.3, 122.2, 13.9. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{12}BrClNO$: $[M + H]^+$ 347.9785. Found: 347.9790.

*2-Ethyl-4,5-diphenyloxazole (**3ab**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 60/1, v/v) to afford **3ab**. Yield 67% (33.3 mg); yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.63 (m, 2H), 7.60−7.57 (m, 2H), 7.39−7.30 (m, 6H), 2.91−2.85 (m, 2H), 1.42 (t, J = 8.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.5, 145.0, 134.9, 132.6, 129.1, 128.6, 128.5, 128.2, 127.9, 127.9, 126.3, 21.7, 11.4. HRMS calcd (ESI-TOF) m/z for $C_{17}H_{16}NO$: $[M + H]^+$ 250.1226. Found: 250.1237.

*2-Isopropyl-4,5-diphenyloxazole (**3ac**).*[8h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 70/1, v/v) to afford **3ac**. Yield 71% (37.5 mg); yellow solid; mp 30−33 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.38−7.27 (m, 6H), 3.21−3.14 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.6, 144.7, 134.8, 132.7, 129.2, 128.5, 128.5, 128.2, 127.9, 127.9, 126.3, 28.5, 20.5. HRMS calcd (ESI-TOF) m/z for $C_{18}H_{18}NO$: $[M + H]^+$ 264.1383. Found: 264.1390.

*2-(tert-Butyl)-4,5-diphenyloxazole (**3ad**).*[5h] Flash column chromatography on silica gel (eluent: PE/EtOAc = 80/1, v/v) to afford **3ad**. Yield 75% (41.6 mg); yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.64 (m, 2H), 7.59−7.57 (m, 2H), 7.38−7.29 (m, 6H), 1.48 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 144.6, 134.8, 132.8, 129.3, 128.5, 128.5, 128.1, 128.1, 127.9, 126.3, 33.7, 28.7. HRMS calcd (ESI-TOF) m/z for $C_{19}H_{20}NO$: $[M + H]^+$ 278.1539. Found: 278.1547.

*2-Cyclopropyl-4,5-diphenyloxazole (**3ae**).*[5i] Flash column chromatography on silica gel (eluent: PE/EtOAc = 40/1, v/v) to afford **3ae**. Yield 50% (26.2 mg); yellow solid; mp 61−63 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64−7.61 (m, 2H), 7.56−7.53 (m, 2H), 7.38−7.29 (m, 6H), 2.18−2.12 (m, 1H), 1.19−1.17 (m, 2H), 1.11−1.06 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.7, 144.3, 135.1, 132.6, 129.1, 128.5, 128.5, 128.1, 127.9, 127.9, 126.2, 8.95, 8.25. HRMS calcd (ESI-TOF) m/z for $C_{18}H_{16}NO$: $[M + H]^+$ 262.1226. Found: 262.1234.

*2,4,5-Triphenyloxazole (**3af**).*[5i] Flash column chromatography on silica gel (eluent: PE/EtOAc = 70/1, v/v) to afford **3af**. Yield 63% (37.3 mg); yellow solid; mp 100−103 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17−8.14 (m, 2H), 7.74−7.72 (m, 2H), 7.69−7.66 (m, 2H), 7.49−7.45 (m, 3H), 7.42−7.33 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 145.5, 136.8, 132.6, 130.3, 129.0, 128.7, 128.7, 128.6, 128.5, 128.2, 128.1, 127.4, 126.5, 126.4. HRMS calcd (ESI-TOF) m/z for $C_{21}H_{16}NO$: $[M + H]^+$ 298.1226. Found: 298.1224.

*2-Benzyl-4,5-diphenyloxazole (**3ag**).*[8e] Flash column chromatography on silica gel (eluent: PE/EtOAc = 40/1, v/v) to afford **3ag**. Yield 61% (37.8 mg); yellow solid; mp 75−77 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.63 (m, 2H), 7.56−7.53 (m, 2H), 7.42−7.26 (m, 11H), 4.20 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.6, 145.7, 135.5, 135.3, 132.5, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 127.0, 126.5, 34.8. HRMS calcd (ESI-TOF) m/z for $C_{22}H_{18}NO$: $[M + H]^+$ 312.1383. Found: 312.1379.

*2-(Chloromethyl)-4,5-diphenyloxazole (**3ah**).*[5j] Flash column chromatography on silica gel (eluent: PE/EtOAc = 40/1, v/v) to afford **3ah**. Yield 40% (21.4 mg); yellow solid; mp 35−38 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4H), 7.40−7.35 (m, 6H), 4.70 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.6, 147.0, 135.8, 131.8, 129.0, 128.7, 128.6, 128.4, 128.3, 127.9, 126.7, 36.0. HRMS calcd (ESI-TOF) m/z for $C_{16}H_{13}ClNO$: $[M + H]^+$ 270.0680. Found: 270.0685.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02843.

^1H and ^{13}C NMR spectra for products (PDF)

Accession Codes

CCDC 2036963 contains 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 Author

Mi-Na Zhao − *Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China;* orcid.org/0000-0001-7937-9284; Email: zhaomina@bjwlxy.edu.cn

Authors

Gui-Wan Ning − *Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China*

De-Suo Yang − *Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China;* orcid.org/0000-0002-7190-3122

Ming-Jin Fan − *Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China;* orcid.org/0000-0003-4343-4514

Sheng Zhang − *Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China;* orcid.org/0000-0001-9370-0548

Peng Gao − *Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China;* orcid.org/0000-0003-1292-0691

Li-Fang Zhao − *Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji 721013, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02843

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by generous grants from the Natural Science Foundation of Shaanxi Province (No. 2018JQ2031), Scientific Research Foundation of Shaanxi Provincial Key Laboratory (No. 19JS006), the Baoji University of Arts and Sciences (No. ZK2018057), and the China Postdoctoral Science Foundation (No. 2019T120936).

■ REFERENCES

(1) (a) Chen, S.; Ji, X.; Gao, M.; Dedkova, L. M.; Hecht, S. M. In Cellulo Synthesis of Proteins Containing a Fluorescent Oxazole Amino Acid. *J. Am. Chem. Soc.* **2019**, *141*, 5597−5601. (b) Guo, J.; Hao, Y.; Ji, X.; Wang, Z.; Liu, Y.; Ma, D.; Li, Y.; Pang, H.; Ni, J.; Wang, Q. Optimization, Structure-Activity Relationship, and Mode of Action of Nortopsentin Analogues Containing Thiazole and Oxazole Moieties. *J. Agric. Food Chem.* **2019**, *67*, 10018−10031. (c) Childress, E. S.; Garrison, A. T.; Sheldon, J. R.; Skaar, E. P.; Lindsley, C. W. Total Synthesis of Hinduchelins A-D, Stereochemical Revision of

Hinduchelin A, and Biological Evaluation of Natural and Unnatural Analogues. *J. Org. Chem.* **2019**, *84*, 6459−6464. (d) Shen, S.; Hadley, M.; Ustinova, K.; Pavlicek, J.; Knox, T.; Noonepalle, S.; Tavares, M. T.; Zimprich, C. A.; Zhang, G.; Robers, M. B.; Barinka, C.; Kozikowski, A. P.; Villagra, A. Discovery of a New Isoxazole-3-hydroxamate-Based Histone Deacetylase 6 Inhibitor SS-208 with Antitumor Activity in Syngeneic Melanoma Mouse Models. *J. Med. Chem.* **2019**, *62*, 8557−8577.

(2) (a) Zhang, J.; Ciufolini, M. A. Total Synthesis of Siphonazoles by the Use of a Conjunctive Oxazole Building Block. *Org. Lett.* **2009**, *11*, 2389−2392. (b) Nett, M.; Erol, O.; Kehraus, S.; Köck, M.; Krick, A.; Eguereva, E.; Neu, E.; König, G. M. Siphonazole, an Unusual Metabolite from Herpetosiphon sp. *Angew. Chem., Int. Ed.* **2006**, *45*, 3863−3867.

(3) Charbonnel, B. PPAR-α and PPAR-γ Agonists for Type 2 Diabetes. *Lancet* **2009**, *374*, 96−98.

(4) Parrish, S. M.; Yoshida, W.; Yang, B.; Williams, P. G. Ulapualides C-E Isolated from a Hawaiian Hexabranchus Sanguineus Egg Mass. *J. Nat. Prod.* **2017**, *80*, 726−730.

(5) (a) Xiao, F.; Yuan, S.; Huang, H.; Zhang, F.; Deng, G.-J. Copper-Catalyzed Three-Component Domino Cyclization for the Synthesis of 4-Aryl-5-(arythio)-2-(trifluoromethyl)oxazoles. *Org. Lett.* **2019**, *21*, 8533−8536. (b) Sun, M.; Zhao, L.; Ding, M.-W. One-Pot-Three-Component Synthesis of 2-(1,2,3,4-Tetrahydroisoquinolin-1-yl)-oxazoles via DEAD-Promoted Oxidative Ugi/Wittig Reaction. *J. Org. Chem.* **2019**, *84*, 14313−14319. (c) Liao, L. H.; Zhang, H.; Zhao, X. D. Selenium-π-Acid Catalyzed Oxidative Functionalization of Alkynes: Facile Access to Ynones and Multisubstituted Oxazoles. *ACS Catal.* **2018**, *8*, 6745−6750. (d) Cheng, Y.; Xiang, J. C.; Wang, Z. X.; Ma, J. T.; Wang, M.; Tang, B. C.; Wu, Y. D.; Zhu, Y. P.; Wu, A. X. Dimerization of Phenylalanine: An Approach to Thiazoles and Oxazoles Involved S/O-Insertion. *Adv. Synth. Catal.* **2018**, *360*, 550−555. (e) Yang, W.; Zhang, R.; Yi, F.; Cai, M. A Heterogeneous Gold(I)-Catalyzed [2 + 2 + 1] Annulation of Terminal Alkynes, Nitriles, and Oxygen Atoms Leading to 2,5-Disubstituted Oxazoles. *J. Org. Chem.* **2017**, *82*, 5204−5211. (f) Zhou, R.-R.; Cai, Q.; Li, D.-K.; Zhuang, S.-Y.; Wu, Y.-D.; Wu, A.-X. Acid-Promoted Multicomponent Tandem Cyclization to Synthesize Fully Substituted Oxazoles via Robinson-Gabriel-Type Reaction. *J. Org. Chem.* **2017**, *82*, 6450−6456. (g) Yagyu, T.; Takemoto, Y.; Yoshimura, A.; Zhdankin, V. V.; Saito, A. Iodine(III)-Catalyzed Formal [2 + 2 + 1] Cycloaddition Reaction for Metal-Free Construction of Oxazoles. *Org. Lett.* **2017**, *19*, 2506−2509. (h) Yamamoto, C.; Takamatsu, K.; Hirano, K.; Miura, M. A. A Divergent Approach to Indoles and Oxazoles from Enamides by Directing-Group-Controlled Cu-Catalyzed Intramolecular C-H Amination and Alkoxylation. *J. Org. Chem.* **2017**, *82*, 9112−9118. (i) Li, X.; Huang, L.; Chen, H.; Wu, W.; Huang, H.; Jiang, H. Copper-Catalyzed Oxidative [2 + 2 + 1] Cycloaddition: Regioselective Synthesis of 1,3-Oxazoles from Internal Alkynes and Nitriles. *Chem. Sci.* **2012**, *3*, 3463−3467. (j) Patil, P. C.; Luzzio, F. A.; Demuth, D. R. Oxazoles for Click Chemistry II: Synthesis of Extended Heterocyclic Scaffolds. *Tetrahedron Lett.* **2015**, *56*, 3039−3041.

(6) For selected examples, see: (a) Meyers, A. I.; Tavares, F. X. Oxidation of Oxazolines and Thiazolines to Oxazoles and Thiazoles. Application of the Kharasch-Sosnovsky Reaction. *J. Org. Chem.* **1996**, *61*, 8207−8215. (b) Huang, Y.; Ni, L.; Gan, F.; He, Y.; Xu, J.; Wu, X.; Yao, H. Environmental-Benign Oxidation of 2-Oxazolines to Oxazoles by Dioxygen as the Sole Oxidant. *Tetrahedron* **2011**, *67*, 2066−2071. (c) Li, X.; Li, C.; Yin, B.; Liu, P.; Li, J.; Shi, Z.; Li, C. DDQ-Induced Dehydrogenation of Heterocycles for C-C Double Bond Formation: Synthesis of 2-Thiazoles and 2-Oxazoles. *Chem. - Asian J.* **2013**, *8*, 1408−1411.

(7) For recent examples, see: (a) Herszman, J. D.; Berger, M.; Waldvogel, S. R. Fluorocyclization of *N*-Propargylamides to Oxazoles by Electrochemically Generated $ArIF_2$. *Org. Lett.* **2019**, *21*, 7893−7896. (b) An, H.; Mai, S.; Xuan, Q.; Zhou, Y.; Song, Q. Gold-Catalyzed Radical-Involved Intramolecular Cyclization of Internal *N*-Propargylamides for the Construction of 5-Oxazole Ketones. *J. Org. Chem.* **2019**, *84*, 401−408. (c) Weng, Y.-X.; Lv, W.-W.; Yu, J.; Ge, B.-L.; Cheng, G.-L. Preparation of 2,4,5-Trisubstituted Oxazoles through Iodine-mediated Aerobic Oxidative Cyclization of Enaminones. *Org. Lett.* **2018**, *20*, 1853−1856. (d) Ma, J.-W.; Wang, Q.; Wang, X.-G.; Liang, Y.-M. Palladium-Catalyzed Cascade Difluoroalkylation/Cyclization of N-Propargylamides: Synthesis of Oxazoles and Oxazolines. *J. Org. Chem.* **2018**, *83*, 13296−13307. (e) Nalivela, K. S.; Rudolph, M.; Baeissa, E. S.; Alhogbi, B. G.; Mkhalid, I. A. I.; Hashmi, A. S. K. Sequential Au/Cu Catalysis: A Two Catalyst One-Pot Protocol for the Enantioselective Synthesis of Oxazole α-Hydroxy Esters via Intramolecular Cyclization/Intermolecular Alder-Ene Reaction. *Adv. Synth. Catal.* **2018**, *360*, 2183−2190. (f) Suzuki, S.; Saito, A. Single-Step Synthesis of Iodinated Oxazoles from *N*-Propargyl Amides Mediated by I_2/Iodosylbenzene/Trimethylsilyl Trifluoromethanesulfonate Systems. *J. Org. Chem.* **2017**, *82*, 11859−11864. (g) Okamura, Y.; Sato, D.; Yoshimura, A.; Zhdankin, V. V.; Saito, A. Iodine(III)-Mediated/Catalyzed Cycloisomerization-Amination Sequence of *N*-Propargyl Carboxamides. *Adv. Synth. Catal.* **2017**, *359*, 3243−3247.

(8) For recent examples, see: (a) Zhang, D.; Song, H.; Cheng, N.; Liao, W.-W. Synthesis of 2,4,5-Trisubstituted Oxazoles via Pd-Catalyzed C-H Addition to Nitriles/Cyclization Sequences. *Org. Lett.* **2019**, *21*, 2745−2749. (b) Tian, X.; Song, L.; Han, C.; Zhang, C.; Wu, Y.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Gold(III)-Catalyzed Formal [3 + 2] Annulations of *N*-Acyl Sulfilimines with Ynamides for the Synthesis of 4-Aminooxazoles. *Org. Lett.* **2019**, *21*, 2937−2940. (c) Zhang, X.; He, Y.; Li, J.; Wang, R.; Gu, L.; Li, G. CO_2/Photoredox-Cocatalyzed Tandem Oxidative Cyclization of α-Bromo Ketones and Amines To Construct Substituted Oxazoles. *J. Org. Chem.* **2019**, *84*, 8225−8231. (d) Pan, J.; Li, X.-Y; Qiu, X.; Luo, X.; Jiao, N. Copper-Catalyzed Oxygenation Approach to Oxazoles from Amines, Alkynes, and Molecular Oxygen. *Org. Lett.* **2018**, *20*, 2762−2765. (e) Qi, C.; Peng, Y.; Wang, L.; Ren, Y.; Jiang, H. Copper-Catalyzed [2 + 3] Cyclization of α-Hydroxyl Ketones and Arylacetonitriles: Access to Multisubstituted Butenolides and Oxazoles. *J. Org. Chem.* **2018**, *83*, 11926−11935. (f) Niu, B.; Liu, R.; Wei, Y.; Shi, M. Catalyst-Controlled Synthesis of 4-Amino-Isoquinolin-1(2*H*)-One and Oxazole Derivatives. *Org. Chem. Front.* **2018**, *5*, 1466−1470. (g) Reddy, R. J.; Ball-Jones, M. P.; Davies, P. W. Alkynyl Thioethers in Gold-Catalyzed Annulations to Form Oxazoles. *Angew. Chem., Int. Ed.* **2017**, *56*, 13310−13313. (h) Zhang, W.; Yu, W.; Yan, Q.; Liu, Z.; Zhang, Y. Synthesis of Substituted Oxazoles via Pd-Catalyzed Tandem Oxidative Cyclization. *Org. Chem. Front.* **2017**, *4*, 2428−2432.

(9) For reviews, see: (a) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide Activation: an Emerging Tool for Chemoselective Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899−7925. (b) Takise, R.; Muto, K.; Yamaguchi, J. Cross-Coupling of Aromatic Esters and Amides. *Chem. Soc. Rev.* **2017**, *46*, 5864−5888. (c) Chaudhari, M. B.; Gnanaprakasam, B. Recent Advances in the Metal-Catalyzed Activation of Amide Bonds. *Chem. - Asian J.* **2019**, *14*, 76−93. (d) Dander, J. E.; Garg, N. K. Breaking Amides using Nickel Catalysis. *ACS Catal.* **2017**, *7*, 1413−1423.

(10) For selected examples, see: (a) Chen, J.; Xia, Y.; Lee, S. Transamidation for the Synthesis of Primary Amides at Room Temperature. *Org. Lett.* **2020**, *22*, 3504−3508. (b) Nandi, J.; Vaughan, M. Z.; Sandoval, A. L.; Paolillo, J. M.; Leadbeater, N. E. Oxidative Amidation of Amines in Tandem with Transamidation: A Route to Amides Using Visible-Light Energy. *J. Org. Chem.* **2020**, *85*, 9219−9229. (c) Li, G.; Ji, C.-L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N-C/O-C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161−11172. (d) Ghosh, T.; Jana, S.; Dash, J. KO^{t}Bu-Promoted Transition-Metal-Free Transamidation of Primary and Tertiary Amides with Amines. *Org. Lett.* **2019**, *21*, 6690−6694. (e) Rahman, M. M.; Li, G.; Szostak, M. Metal-Free Transamidation of Secondary Amides by N-C Cleavage. *J. Org. Chem.* **2019**, *84*, 12091−12100. (f) Dander, J. E.; Baker, E. L.; Garg, N. K. Nickel-Catalyzed Transamidation of Aliphatic Amide Derivatives. *Chem. Sci.* **2017**, *8*, 6433−6438.

https://dx.doi.org/10.1021/acs.joc.0c02843
J. Org. Chem. 2021, 86, 2957−2964

(11) For selected examples, see: (a) Buchspies, J.; Rahman, M. M.; Szostak, R.; Szostak, M. *N*-Acylcarbazoles and *N*-Acylindoles: Electronically Activated Amides for N-C(O) Cross-Coupling by N_{lp} to Ar Conjugation Switch. *Org. Lett.* **2020**, *22*, 4703−4709. (b) Gao, P.; Szostak, M. Highly Selective and Divergent Acyl and Aryl Cross-Couplings of Amides via Ir-Catalyzed C-H Borylation/N-C(O) Activation. *Org. Lett.* **2020**, *22*, 6010−6015. (c) Kadam, A. A.; Metz, T. L.; Qian, Y.; Stanley, L. M. Ni-Catalyzed Three-Component Alkene Carboacylation Initiated by Amide C-N Bond Activation. *ACS Catal.* **2019**, *9*, 5651−5656. (d) Zhou, T.; Ji, C.-L.; Hong, X.; Szostak, M. Palladium-Catalyzed Decarbonylative Suzuki-Miyaura Cross-Coupling of Amides by Carbon-Nitrogen Bond Activation. *Chem. Sci.* **2019**, *10*, 9865−9871. (e) Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Triflamides: Highly Reactive, Electronically Activated *N*-Sulfonyl Amides in Catalytic N-C(O) Amide Cross-Coupling. *Org. Lett.* **2019**, *21*, 1253−1257. (f) Liu, C.; Li, G.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, R.; Szostak, M. Acyl and Decarbonylative Suzuki Coupling of *N*-Acetyl Amides: Electronic Tuning of Twisted, Acyclic Amides in Catalytic Carbon-Nitrogen Bond Cleavage. *ACS Catal.* **2018**, *8*, 9131−9139. (g) Liu, X.; Hsiao, C.-C.; Guo, L.; Rueping, M. Cross-Coupling of Amides with Alkylboranes via Nickel-Catalyzed C-N Bond Cleavage. *Org. Lett.* **2018**, *20*, 2976−2979. (h) Medina, J. M.; Moreno, J.; Racine, S.; Du, S.; Garg, N. K. Mizoroki-Heck Cyclizations of Amide Derivatives for the Introduction of Quaternary Centers. *Angew. Chem., Int. Ed.* **2017**, *56*, 6567−6571. (i) Meng, G.; Szostak, M. Site-Selective C-H/C-N Activation by Cooperative Catalysis: Primary Amides as Arylating Reagents in Directed C-H Arylation. *ACS Catal.* **2017**, *7*, 7251−7256.

(12) (a) Walker, J. A.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. Ni-Catalyzed Alkene Carboacylation via Amide C-N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 10228−10231. (b) Medina, J. M.; Moreno, J.; Racine, S.; Du, S.; Garg, N. K. Mizoroki-Heck Cyclizations of Amide Derivatives for the Introduction of Quaternary Centers. *Angew. Chem., Int. Ed.* **2017**, *56*, 6567−6571.

(13) For reviews, see: (a) Khlebnikov, A. F.; Novikov, M. S.; Rostovskii, N. V. Advances in 2*H*-Azirine Chemistry: A Seven-Year Update. *Tetrahedron* **2019**, *75*, 2555−2624. (b) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. Transition-Metal-Catalyzed Cleavage of C-N Single Bonds. *Chem. Rev.* **2015**, *115*, 12045−12090. (c) Huang, C.-Y.; Doyle, A. G. The Chemistry of Transition Metals with Three-Membered Ring Heterocycles. *Chem. Rev.* **2014**, *114*, 8153−8198. (d) Khlebnikov, A. F.; Novikov, M. S. Recent Advances in 2*H*-Azirine Chemistry. *Tetrahedron* **2013**, *69*, 3363−3401.

(14) For selected examples, see: (a) Jiang, Y.; Chan, W. C.; Park, C.-M. Expedient Synthesis of Highly Substituted Pyrroles via Tandem Rearrangement of α-Diazo Oxime Ethers. *J. Am. Chem. Soc.* **2012**, *134*, 4104−4107. (b) Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M. Synthesis of Pyridines by Carbenoid-Mediated Ring Opening of 2*H*-Azirines. *Angew. Chem., Int. Ed.* **2013**, *52*, 2212−2216. (c) Prechter, A.; Henrion, G.; Faudot dit Bel, P.; Gagosz, F. Gold-Catalyzed Synthesis of Functionalized Pyridines by Using 2*H*-Azirines as Synthetic Equivalents of Alkenyl Nitrenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 4959−4963. (d) Xuan, J.; Xia, X.-D.; Zeng, T.-T.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. Visible-Light-Induced Formal [3 + 2] Cycloaddition for Pyrrole Synthesis under Metal-Free Conditions. *Angew. Chem., Int. Ed.* **2014**, *53*, 5653−5656. (e) Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. Gold-Catalyzed Intermolecular Nitrene Transfer from 2*H*-Azirines to Ynamides: A Direct Approach to Polysubstituted Pyrroles. *Org. Lett.* **2015**, *17*, 30−33. (f) Li, T.; Xu, F.; Li, X.; Wang, C.; Wan, B. Ruthenium-Catalyzed C-C Bond Cleavage of 2*H*-Azirines: A Formal [3 + 2 + 2] Cycloaddition to Fused Azepine Skeletons. *Angew. Chem., Int. Ed.* **2016**, *55*, 2861−2865. (g) Ding, H.; Wang, Z.; Bai, S.; Lu, P.; Wang, Y. Rh-Catalyzed Conversion of 3-Diazoindolin-2-imines to 5*H*-Pyrazino[2,3-b]indoles with Photoluminescent Properties. *Org. Lett.* **2017**, *19*, 6514−6517. (h) Xu, F.; Si, X.-J.; Song, Y.-Y.; Wang, X.-D.; Liu, C.-S.; Geng, P.-F.; Du, M. Palladium-Catalyzed C-N Bond Cleavage of 2*H*-Azirines for the Synthesis of Functionalized α-Amido Ketones. *J. Org. Chem.* **2019**, *84*, 2200−2208. (i) Zhang, J.; Yang, M.; Liu, J.-B.; He, F.-S.; Wu, J. A Copper-Catalyzed Insertion of Sulfur Dioxide via Radical Coupling. *Chem. Commun.* **2020**, *56*, 3225−3228.

(15) (a) Zhao, M.-N.; Ren, Z.-H.; Yang, D.-S.; Guan, Z.-H. Iron-Catalyzed Radical Cycloaddition of 2*H*-Azirines and Enamides for the Synthesis of Pyrroles. *Org. Lett.* **2018**, *20*, 1287−1290. (b) Zhao, M.-N.; Ning, G.-W.; Yang, D.-S.; Gao, P.; Fan, M.-J.; Zhao, L.-F. Nickel-Catalyzed Formal [3 + 2]-Cycloaddition of 2*H*-Azirines with 1,3-Dicarbonyl Compounds for the Synthesis of Pyrroles. *Tetrahedron Lett.* **2020**, *61*, 152319−152323. (c) Zhao, M.-N.; Zhang, W.; Wang, X.-C.; Zhang, Y.; Yang, D.-S.; Guan, Z.-H. Modular 2,3-Diaryl-2*H*-Azirine Synthesis from Ketoxime Acetates via Cs_2CO_3-Mediated Cyclization. *Org. Biomol. Chem.* **2018**, *16*, 4333−4337.

(16) The reaction yields are always moderate due to the residue of the starting materials.

https://dx.doi.org/10.1021/acs.joc.0c02843
J. Org. Chem. 2021, 86, 2957−2964