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FULL PAPER

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Base-promoted cycloisomerization for the synthesis of oxazoles and imidazoles

Lidan Zhang,[a] Ke Xiao,[a] Yan Qiao,[b] Xin Li,[a] Chuanjun Song,*[, a] and Junbiao Chang*[, a, c]

Abstract: A cesium carbonate promoted, transition metal and halogen-free 5-exo-dig type cyclization reaction for the synthesis of oxazoles and imidazoles has been developed.

Introduction

Substituted oxazoles, imidazoles and related heterocycles are important structural motifs present in many bioactive natural products[1,2] (Figure 1) and pharmaceuticals[3] that display antitumor, antiviral, antifungal, antibacterial, and antiproliferative activities. They also serve as useful synthetic intermediates and ligands in organic synthesis.[4] Therefore, development of efficient strategies toward the synthesis of these heterocyclic compounds from easily available starting materials is an active research area.[5,6] Among these, the transition metal catalyzed cycloisomerization of propargylamides and propargylamidines has emerged as a popular method in recent years to access the corresponding oxazoles and imidazoles.[7,8] However, the majority of these methods face drawbacks such as harsh reaction conditions, limited substrate scope, and poor functional group tolerance. Also, removal of trace amount of toxic metal catalysts from the desired products (often used as ligands) is difficult. Recently, we have become interested in the base-mediated cyclization reaction for the synthesis of structurally interesting heterocyclic compounds.[9] Herein, we report an efficient, general, and environmentally benign protocol for the synthesis of oxazoles and imidazoles via cesium carbonate promoted cycloisomerization of propargylamides and propargylamidines. To the best of our knowledge, these represent the first examples of base-mediated cyclization of propargylamidines for the assembly of imidazoles. [10]

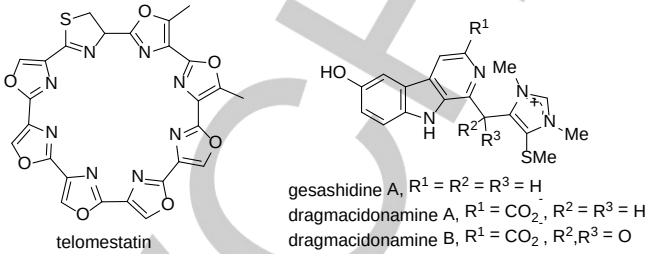
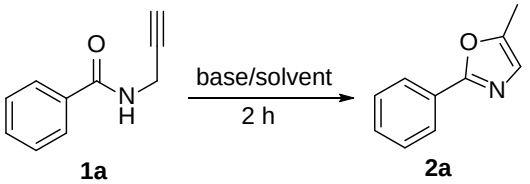


Figure 1. Examples of natural products that incorporate oxazoles and imidazoles

Results and Discussion

Optimization of reaction conditions was carried out with propargyl benzamide **1a** and the results were collected in Table 1. The reaction was complete within two hours in the presence of 2 equiv of sodium hydride at 100 °C in DMSO. However, the desired product **2a** was isolated in 30% yield only (entry 1). The product yield could be improved to 80% when potassium *tert*-butoxide was applied (entry 2). No reaction occurred in the presence of organic bases (entries 3, 4) or weak inorganic base (entry 5). The reaction was sluggish in the presence of potassium carbonate, and **2a** was obtained in 21% isolated yield after 2 hours, together with large amount of the unreacted starting material recovered (entry 6). However, delightfully, the reaction proceeded efficiently and cleanly when cesium carbonate was used, and **2a** was isolated in 89% yield (entry 7). Therefore, we chose cesium carbonate as the base for further optimization. Solvent screening indicated that polar solvent favored product formation. **2a** was isolated in 80% and 66% yields, respectively, in acetonitrile and DMF (entries 10, 11), while no reaction occurred in THF, 1,4-dioxane, toluene, or DCE (entries 8, 9, 12, 13). Next, the base-to-substrate ratio and reaction temperature were briefly explored (entries 14–17), and the best result remained by employing 2 equiv of cesium carbonate in DMSO at 100 °C.

Table 1. Optimization of reaction conditions for the base promoted synthesis of oxazole **2a**



1a **2a**

entry	base (equiv)	solvent	temp. (°C)	isolated yield
1	NaH (2.0)	DMSO	100	30%
2	KO^{t}Bu (2.0)	DMSO	100	80%

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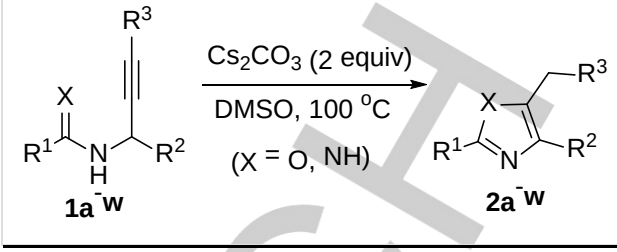
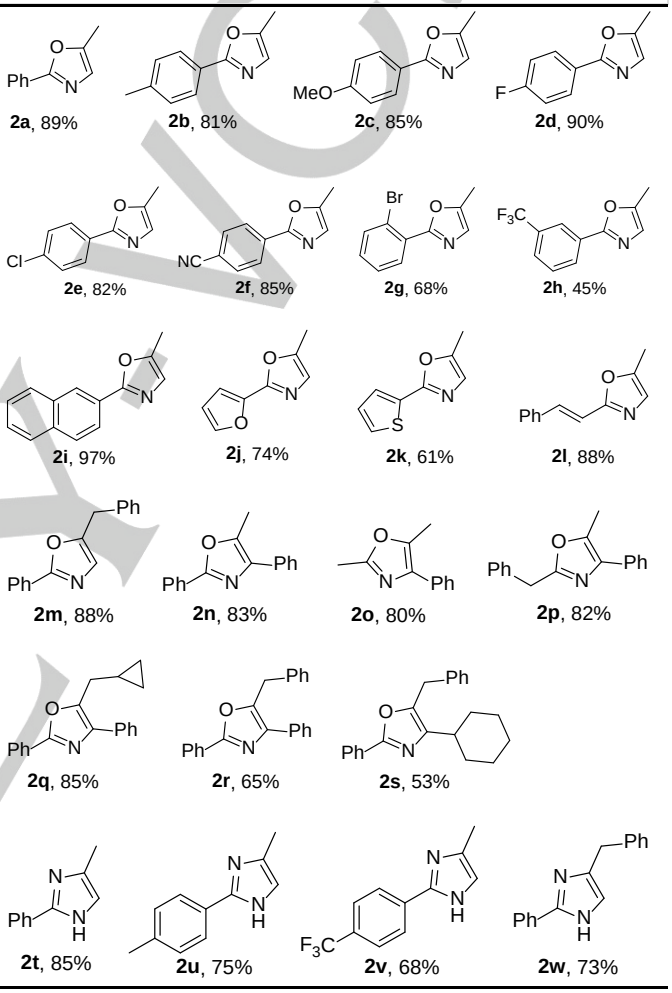
3	NMM (2.0)	DMSO	100	–[a]
4	DBU (2.0)	DMSO	100	–[a]
5	$NaHCO_3$ (2.0)	DMSO	100	–[a]
6	K_2CO_3 (2.0)	DMSO	100	21%[b]
7	**Cs_2CO_3 (2.0)**	**DMSO**	**100**	**89%**
8	Cs_2CO_3 (2.0)	THF	100	–[a]
9	Cs_2CO_3 (2.0)	1,4-dioxane	100	–[a]
10	Cs_2CO_3 (2.0)	CH_3CN	100	80%
11	Cs_2CO_3 (2.0)	DMF	100	66%
12	Cs_2CO_3 (2.0)	toluene	100	–[a]
13	Cs_2CO_3 (2.0)	DCE	100	–[a]
14	Cs_2CO_3 (1.0)	DMSO	100	75%
15	Cs_2CO_3 (3.0)	DMSO	100	85%
16	Cs_2CO_3 (2.0)	DMSO	90	75%
17	Cs_2CO_3 (2.0)	DMSO	110	88%

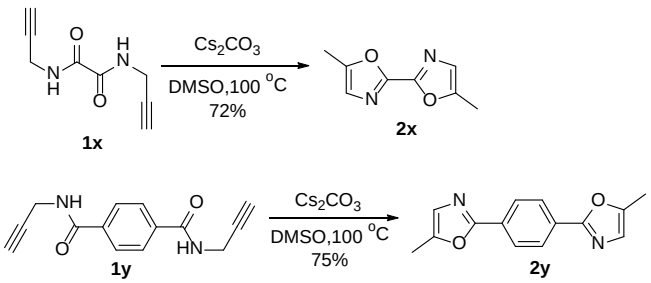
[a] No reaction. [b] incomplete reaction.

With the optimized reaction conditions in hand, the reaction scope of various propargylamides and propargylamidines were investigated, and the results were collected in Table 2. A series of unsubstituted aryl propargylamides (R^1 = Ar, R^2 = R^3 = H) with either a para-, ortho-, or meta-substituted phenyl ring (**1b**-**h**) reacted smoothly to give the corresponding oxazolines **2b**-**h** in moderate to good isolated yields. Under the reaction conditions, naphthalenyl, as well as heteroaryl substituted oxazolines **2i**-**k** could also be obtained. Delightfully, the base-sensitive α,β-unsaturated propargylamide **1l** proceeded cleanly to give **2l** eventlessly. Further explorations indicated that internal (**1m**), α-substituted (**1n**), and doubly substituted aryl acetylenic amide moieties (**1q**-**s**) could all cyclize as expected to provide the desired products (**2m**, **n**, **q**-**s**). The cyclization of aliphatic propargylamides (**1o**, **p**) also proceeded efficiently, resulting in the formation of **2o** and **2p**, respectively. Inspired by the results, we then explored the cyclization reaction of propargylamidines **1t**-**w**, which could be successfully conducted under the reaction conditions to yield imidazoles **2t**-**w** in good isolated yields. Finally, bisamides **1x** and **1y** could also be persuaded to cyclize, providing bisoxazolines **2x** and **2y** in 72% and 75% isolated yields, respectively (Scheme 1).

Table 2. Substrate scope







Scheme 1. Synthesis of bisoxazolines **2x** and **2y**

Two possible mechanisms were proposed for the base-mediated oxazoline formation. The first (mechanism A) involves a 5-exo-dig cyclization via direct nucleophilic attack of the triple bond by the deprotonated amide, followed by isomerization of the formed exocyclic double bond. In the second mechanism (mechanism B), rearrangement of acetylene occurs first to give an allenic intermediate, which is then attacked by the amide moiety. In the present work, a DFT study on the transformation of compound **1d** to **2d** was performed, as no theoretical calculations on this kind of reaction have been carried out previously. According to the calculated results, mechanism A consists of three reaction steps, including deprotonation of the NH group, intramolecular cyclization and double bond isomerization. As shown in Figure 2, the first reaction step is a barrier-less process, and the second reaction step is rate-determining with free energy barrier of 21.3 kcal/mol. The isomerization of the carbon-carbon double bond in **m2A** to the thermodynamically more stable product **2d** is believed to be an easy process and thus was not considered in the calculation. Mechanism B consists of five reaction steps, including two consecutive proton transfer processes giving rise to the allenic intermediate m2B, NH- deprotonation followed by intramolecular cyclization and proton transfer to form the final product. The intramolecular cyclization is rate-determining with the highest free energy barrier of 18.6 kcal/mol. In comparison, the free energy barrier of mechanism B is 2.7 kcal/mol lower than that of mechanism A, indicating that mechanism B is more energetically favorable.

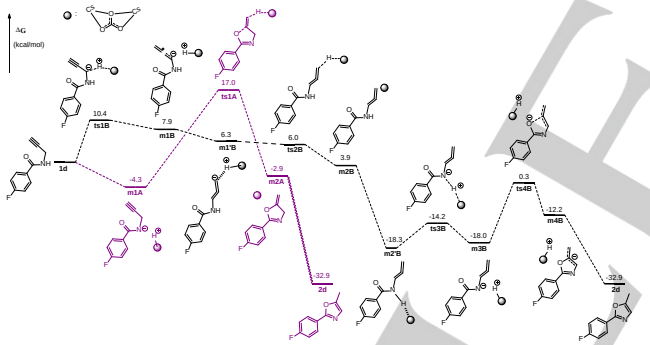


Figure 2. The free energy profile for the two possible reaction mechanisms on the transformation of 1d to 2d

Conclusions

In summary, we have developed an efficient and practical approach toward the synthesis of oxazoles and imidazoles via Cs_2CO_3-mediated cycloisomerization of propargylamides and propargylamidines. A large variety of substrates with various functional groups are tolerated. Moreover, the reaction does not require the aid of halogen or transition metal catalyst, and is thus environmentally friendly.

Experimental Section

Experimental Details. Melting points were determined on a hot-stage apparatus and were uncorrected. Infrared spectra were obtained using an FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer. High-resolution mass spectra were recorded on a Q-TOF mass spectrometer. Flash column chromatography was performed over silica gel 200—300 mesh.

General procedure for the preparation oxazoles and imidazoles 2a-2y. A mixture of propargylamides/propargylamidines **1a-1y** (1.0 mmol), Cs_2CO_3 (2.0 mmol), and DMSO (5 mL) was stirred at 100 °C for 2 h and cooled. Water (2 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), then dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to afford oxazoles and imidazoles **2a-2y**.

5-Methyl-2-phenyloxazole (2a)[7f]: The title compound was prepared according to the general produce by stirring a mixture of **1a** (80 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (12% EtOAc in petroleum ether) to afford **2a** (71 mg, 89% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (dd, J = 8.2, 2.0 Hz, 2H), 7.46–7.38 (m, 3H), 6.83 (q, J = 1.3 Hz, 1H), 2.38 (d, J = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.7, 148.9, 129.9, 128.7, 127.8, 125.9, 124.2, 11.1 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{10}NO$ 160.0757, found 160.0764.

5-Methyl-2-(p-tolyl)oxazole (2b)[7f]: The title compound was prepared according to the general produce by stirring a mixture of **1b** (87 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2b** (70 mg, 81% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.80 (q, J = 1.2 Hz, 1H), 2.38 (s, 3H), 2.37 (d, J = 1.2 Hz, 3H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ = 160.9, 148.5, 140.0, 129.4, 125.9, 125.1, 124.0, 21.5, 11.0 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{12}NO$ 174.0913, found 174.0916.

2-(4'-Methoxyphenyl)-5-methyloxazole (2c)[7f]: The title compound was prepared according to the general produce by stirring a mixture of **1c** (95 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2c** (80 mg, 85% yield) as a colorless oil: ^{1}H NMR (400 MHz,$CDCl_3$) δ = 7.93 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 6.78 (q, J = 1.2 Hz, 3H), 3.85 (s, 3H), 2.37 (d, J = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9, 160.8, 148.2, 127.5, 123.9, 120.7, 114.1, 55.4, 11.0 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{12}NO_2$ 190.0863, found 190.0864.

2-(4'-Fluorophenyl)-5-methyloxazole (2d): The title compound was prepared according to the general produce by stirring a mixture of **1d** (89 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (12% EtOAc in petroleum ether) to afford **2d** (80 mg, 90% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99–7.96 (m, 2H), 7.14–7.10 (m, 2H), 6.81 (q, J = 1.3 Hz, 1H), 2.38 (d, J = 1.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.7 (d, $J_{F\text{-}C}$ = 248.6 Hz), 159.9, 148.9, 128.0 (d, $J_{F\text{-}C}$ = 8.5 Hz), 124.2, 124.2, 115.9 (d, $J_{F\text{-}C}$ = 21.9 Hz), 11.0 ppm; IR (neat) ν_{max}/cm^{-1} 1625, 1562, 1405, 1370, 1274, 1030; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_9FNO$ 178.0663, found 178.0668.

2-(4'-Chlorophenyl)-5-methyloxazole (2e): The title compound was prepared according to the general produce by stirring a mixture of **1e** (97

mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2e** (79 mg, 82% yield) as a white solid: mp 36–37 °C; ^{1}H NMR (400 MHz,$CDCl_3$) δ = 7.92 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 6.83 (q, *J* = 1.2 Hz, 1H), 2.38 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8, 149.2, 135.9, 129.0, 127.2, 126.3, 124.4, 11.1 ppm; IR (neat) ν_{max}/cm^{-1} 1635, 1582, 1408, 1380, 1278, 1090; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{10}H_9{}^{35}ClNO$ 194.0367, found 194.0371.

4-(5'-Methyloxazol-2'-yl)benzonitrile (2f): The title compound was prepared according to the general produce by stirring a mixture of **1f** (92 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (12% EtOAc in petroleum ether) to afford **2f** (78 mg, 85% yield) as a white solid: mp 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 6.92 (q, *J* = 1.2 Hz, 1H), 2.43 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8, 150.4, 132.6, 131.5, 126.3, 125.1, 118.5, 113.1, 11.2 ppm; IR (neat) ν_{max}/cm^{-1} 2227, 1599, 1449, 1408, 1346, 1260, 1125; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{11}H_9N_2O$ 185.0709, found 185.0718.

2-(2'-Bromophenyl)-5-methyloxazole (2g)[7i]: The title compound was prepared according to the general produce by stirring a mixture of **1g** (119 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2.0 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (16% EtOAc in petroleum ether) to afford **2g** (81 mg, 68% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39 (td, *J* = 7.5, 1.2 Hz , 1H), 7.28–7.24 (m, 1H), 6.93 (q, *J* = 1.2 Hz, 1H), 2.41 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0, 149.4, 134.5, 130.9, 130.8, 128.6, 127.3, 124.2, 120.8, 11.1 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{10}H_9{}^{79}BrNO$ 237.9862, found 237.9857.

5-Methyl-2-[3'-(trifluoromethyl)phenyl]oxazole (2h)[11]: The title compound was prepared according to the general produce by stirring a mixture of **1h** (114 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (14% EtOAc in petroleum ether) to afford **2h** (51 mg, 45% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H) 6.88 (q, *J* = 1.2 Hz, 1H), 2.42 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.3, 149.7, 131.3 (q, $J_{F\text{-}C}$ = 32.5 Hz), 129.3, 129.0 (q, $J_{F\text{-}C}$ = 1.4 Hz), 128.5, 126.3 (q, $J_{F\text{-}C}$ = 3.6 Hz), 124.6, 123.8 (q, $J_{F\text{-}C}$ = 270.7 Hz) , 122.8 (q, $J_{F\text{-}C}$ = 4.0 Hz), 11.1 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{11}H_9F_3NO$ 228.0631, found 228.0631.

5-Methyl-2-(naphthalen-2'-yl)oxazole (2i): The title compound was prepared according to the general produce by stirring a mixture of **1i** (105 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2i** (101 mg, 97% yield) as a white solid: mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (s, 1H), 8.11 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.94–7.83 (m, 3H), 7.54–7.50 (m, 2H), 6.89 (q, *J* = 1.2 Hz, 1H), 2.44 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9, 149.1, 133.9, 133.1, 128.6, 128.6, 127.9, 127.0, 126.7, 125.6, 125.1, 124.4, 123.2, 11.2 ppm; IR (neat) ν_{max}/cm^{-1} 1599, 1508, 1439, 1368, 1260, 1111; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{14}H_{12}NO$ 210.0913, found 210.0918.

2-(Furan-2'-yl)-5-methyloxazole (2j)[7f]: The title compound was prepared according to the general produce by stirring a mixture of **1j** (75 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (8% EtOAc in petroleum ether) to afford **2j** (55 mg, 74% yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 1.7, 0.8 Hz, 1H), 6.93 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.80 (q, *J* = 1.2 Hz, 1H), 6.51–6.49 (m, 1H), 2.36 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ = 153.6, 148.5, 143.9, 143.2, 124.0, 111.7, 110.4, 10.9 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_8H_8NO_2$ 150.0550, found 150.0548.

5-Methyl-2-(thiophen-2'-yl)oxazole (2k)[7b]: The title compound was prepared according to the general produce by stirring a mixture of **1k** (83 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2k** (50 mg, 61% yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (dd, *J* = 3.7, 1.2 Hz ,1H), 7.36 (dd, *J* = 5.1, 1.2 Hz ,1H), 7.09–7.07 (m, 1H), 6.77 (q, *J* = 1.2 Hz, 1H), 2.36 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.9, 148.4, 130.5, 127.8, 127.5, 126.8, 124.1, 11.0 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for C_8H_8NOS 166.0321, found 166.0334.

(*E*)-5-Methyl-2-styryloxazole (2l)[7f]: The title compound was prepared according to the general produce by stirring a mixture of **1l** (93 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2l** (81 mg, 88% yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53–7.50 (m, 2H), 7.44–7.35 (m, 3H), 7.31 (tt, *J* = 7.1, 1.4 Hz, 1H), 6.90 (d, *J* = 16.4 Hz, 1H), 6.79 (q, *J* = 1.2 Hz, 1H), 2.36 (d, *J* = 1.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6, 148.6, 135.7, 134.7, 128.9, 128.8, 127.0, 124.4, 114.2, 11.1 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}NO$ 186.0913, found 186.0915.

5-Benzyl-2-phenyloxazole (2m)[7d]: The title compound was prepared according to the general produce by stirring a mixture of **1m** (118 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2m** (103 mg, 88% yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.98 (m, 2H), 7.44–7.39 (m, 3H), 7.35–7.24 (m, 5H), 6.86 (t, *J* = 1.1 Hz, 1H), 4.06 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.3, 151.4, 136.7, 130.1, 128.7, 128.7, 128.7, 127.7, 127.0, 126.1, 124.9, 32.2 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1074.

5-Methyl-2,4-diphenyloxazole (2n)[12]: The title compound was prepared according to the general produce by stirring a mixture of **1n** (118 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (20% EtOAc in petroleum ether) to afford **2n** (98 mg, 83% yield) as a white solid: mp 72–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12–8.09 (m, 2H), 7.77–7.75 (m, 2H), 7.50–7.42 (m, 5H), 7.36–7.32 (m, 1H), 2.26 (s, 3H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ = 159.4, 144.0, 136.0, 132.4, 130.0, 128.7, 128.6, 127.7, 127.3, 126.8, 126.2, 12.1 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1075.

2,5-dimethyl-4-phenyloxazole (2o)[13]: The title compound was prepared according to the general produce by stirring a mixture of **1o** (87 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (13% EtOAc in petroleum ether) to afford **2o** (69 mg, 80% yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64–7.61 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.1, 143.3, 134.3, 132.5, 128.6, 127.0, 126.5, 13.8, 11.8 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{11}H_{12}NO$ 174.0913, found 174.0917.

2-Benzyl-5-methyl-4-phenyloxazole (2p): The title compound was prepared according to the general produce by stirring a mixture of **1p** (125 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2p** (102 mg, 82% yield) as an orange oil : ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.65 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36–7.30 (m, 6H), 4.12 (s, 2H), 2.48 (s, 3H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ = 160.6, 144.0, 135.8, 134.5, 132.4, 128.8, 128.7, 128.6, 127.1, 127.0, 126.7, 34.7, 11.9 ppm; IR (neat) v_{max}/cm^{-1} 1585, 1571, 1448, 1287, 1163, 1014, 1111; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{17}H_{16}NO$ 250.1226, found 250.1226.

5-(Cyclopropylmethyl)-2,4-diphenyloxazole (2q): The title compound was prepared according to the general produce by stirring a mixture of **1q** (138 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (15% EtOAc in petroleum ether) to afford **2q** (117 mg, 85% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.74 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.50–7.42 (m, 5H), 7.36–7.32 (m, 1H), 2.91 (d, *J* = 6.6 Hz, 2H), 1.19–1.15 (m, 1H), 0.61–0.56 (m, 2H), 0.35–0.31 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.6, 147.5, 136.0, 132.4, 130.0, 128.7, 128.6, 127.8, 127.5, 127.1, 126.2, 30.4, 9.8, 4.5 ppm; IR (neat) v_{max}/cm^{-1} 1596, 1494, 1448, 1338, 1259, 1156; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{19}H_{18}NO$ 276.1383, found 276.1385.

5-Benzyl-2,4-diphenyloxazole (2r)[14]: The title compound was prepared according to the general produce by stirring a mixture of **1r** (156 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (15% EtOAc in petroleum ether) to afford **2r** (101 mg, 65% yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10–8.08 (m, 2H), 7.77–7.74 (m, 2H), 7.48–7.42 (m, 5H), 7.38–7.27 (m, 6H), 4.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.2, 145.6, 137.3, 137.3, 132.1, 130.2, 128.8, 128.7, 128.3, 127.7, 127.6, 127.1, 126.8, 126.3, 32.0; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{22}H_{18}NO$ 312.1383, found 312.1383.

5-Benzyl-4-cyclohexyl-2-phenyloxazole (2s)[14]: The title compound was prepared according to the general produce by stirring a mixture of **1s** (159 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (18% EtOAc in petroleum ether) to afford **2s** (84 mg, 53% yield) as a white solid: mp 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99–7.97 (m, 2H), 7.41–7.31 (m, 5H), 7.26–7.24 (m, 3H), 4.07 (s, 2H), 2.57 (tt, *J* = 11.8, 3.6 Hz, 1H), 1.88–1.68 (m, 7H), 1.36–1.33 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8, 144.0, 142.2, 138.0, 129.7, 128.6, 128.5, 128.3, 128.0, 126.6, 126.1, 35.7, 32.4, 31.2, 26.6, 25.9 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{22}H_{24}NO$ 318.1852, found 318.1851.

4-Methyl-2-phenyl-1H-imidazole (2t)[15]: The title compound was prepared according to the general produce by stirring a mixture of **1t** (79 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (30% EtOAc in petroleum ether) to afford imidazole **2t** (67 mg, 85% yield) as a yellow solid: mp 184–185 °C [lit[15], mp 180.5–181.6 °C]; ^{1}H NMR (400 MHz, DMSO) δ = 7.89 (d, *J* = 7.1 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.83 (s, 1H), 2.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 145.1, 131.4, 129.1, 128.0, 124.9, 12.4 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{10}H_{11}N_2$ 159.0917, found 159.0922.

4-Methyl-2-(p-tolyl)-1H-imidazole (2u)[16]: The title compound was prepared according to the general procedure by stirring a mixture of **1u** (86 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (40% EtOAc in petroleum ether) to afford imidazole **2u** (65 mg, 75% yield) as a yellow solid: mp 210–211 °C [lit[16], mp 214 °C]; ^{1}H NMR (400 MHz, DMSO) δ = 7.78 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.68 (s, 1H), 2.31 (s, 3H), 2.19 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 145.3, 137.3, 129.6, 128.8, 124.9, 21.3, 12.4 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{11}H_{13}N_2$ 173.1073, found 173.1075.

4-Methyl-2-(4-(trifluoromethyl)phenyl)-1H-imidazole (2v): The title compound was prepared according to the general procedure by stirring a mixture of **1v** (113 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (30% EtOAc in petroleum ether) to afford imidazole **2v** (77 mg, 68% yield) as a white solid: mp 211–212 °C; ^{1}H NMR (400 MHz, DMSO) δ = 12.51 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 6.90 (s, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 143.7, 135.0, 127.9 (q, $J_{F\text{-}C}$ = 31.7 Hz), 126.1 (q, $J_{F\text{-}C}$ = 4.0 Hz), 125.2, 124.32 (q, $J_{F\text{-}C}$ = 270.1 Hz), 14.49; IR (neat) v_{max}/cm^{-1} 1605, 1536, 1444, 1322, 1248, 1095; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{11}H_{10}F_3N_2$ 227.0791, found 227.0790.

4-Benzyl-2-phenyl-1H-imidazole (2w)[8a]: The title compound was prepared according to the general procedure by stirring a mixture of **1w** (117 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (30% EtOAc in petroleum ether) to afford imidazole **2w** (85 mg, 73% yield) as a yellow solid: mp 170–171 °C ; ^{1}H NMR (400 MHz, DMSO) δ = 7.90 (d, *J* = 7.1 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 2H), 7.32–7.28 (m, 5H), 7.22–7.16 (m, 1H), 6.86 (s, 1H), 3.90 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 145.6, 140.9, 131.3, 129.1, 129.0, 128.7, 128.2, 126.4, 125.1, 33.5 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{11}H_{15}N_2$ 235.1230, found 235.1230.

5,5'-Dimethyl-2,2'-bioxazole (2x): The title compound was prepared according to the general produce by stirring a mixture of **1t** (82 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2x** (59 mg, 72% yield) as a white solid: mp 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.91 (q, *J* = 1.2 Hz, 2H), 2.41 (d, *J* = 1.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.7, 150.5, 124.8, 11.0 ppm; IR (neat) v_{max}/cm^{-1} 1600, 1473, 1442, 1288, 1132, 1008; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_8H_9N_2O_2$ 165.0659, found 165.0669.

1,4-Bis(5'-methyloxazol-2'-yl)benzene (2y)[7b]: The title compound was prepared according to the general produce by stirring a mixture of **1y** (120 mg, 0.5 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), and DMSO (2 mL) at 100 °C for 2 h. The crude product was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) to afford **2y** (90 mg, 75% yield) as a white solid: mp 174–175 °C [lit[7b], mp 170 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (s, 4H), 6.85 (q, *J* = 1.2 Hz, 2H), 2.39 (d, *J* = 1.2 Hz, 6H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) δ = 160.1, 149.3, 128.7, 126.2, 124.6, 11.1 ppm; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O_2$ 241.0972, found 241.0972.

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Keywords: oxazoles • imidazoles • cyclization • alkynes • transition metal free

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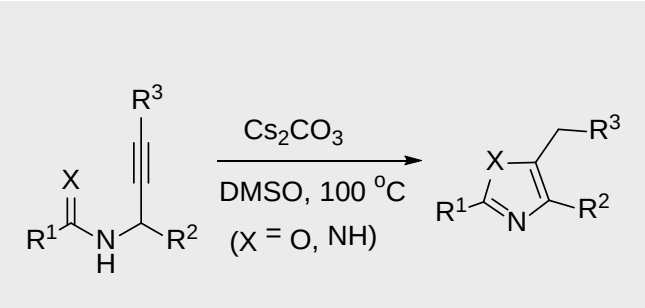

Heterocycle synthesis

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Base-promoted cycloisomerization for the synthesis of oxazoles and imidazoles

Treatment of propargylamides or propargylamidines with cesium carbonate in DMSO results in the formation of the corresponding oxazoles or imidazoles in good yields. A large variety of substrates with various functional groups are tolerated. DFT study on a model substrate reveals that the reactions proceed via a sequence involving allene formation, intramolecular cyclization, and double-bond isomerization.