EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001561

Link to VoR: https://doi.org/10.1002/ejoc.202001561

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10.1002/ejoc.202001561

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Convergent Domino Cyclization: Oxidative [3+1+1] Annulation for One-pot Synthesis of 2-Quinoline-4,5-diaryl-oxazoles from Methyl Azaarenes, Benzoins and NH_4OAc

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Abstract: An oxidative [3+1+1] convergent domino cyclization is disclosed. This protocol enables to get quinoline, quinoxaline, quinazolin-4(3H)-one and benzo[d]thiazole attached 2,4,5-trisubstituted oxazoles from methyl azaarenes, benzoins and NH_4OAc in the presence of iodine and molecular sieves without any metal catalyst. The reaction features wide substrate scope, good functional group tolerance, mild reaction conditions, and easily available substrates.

Oxazoles derivatives are prevailing five-membered heterocyclic compounds, which have been found as key structural units in a great number of biologically active natural products, pharmaceuticals, agrochemicals and as functional materials.[1] In particular, 2,4,5-trisubstituted oxazole as privileged scaffold is widely presented in many natural products, drugs, and remarkably bioactive molecules, such as non-steroidal anti-inflammatory drug ditazo, anti-diabetic agent aleglitazar, antipancreatic cancer agent PC-046 and antimycobacterial natural product texaline (Figure 1).[2]

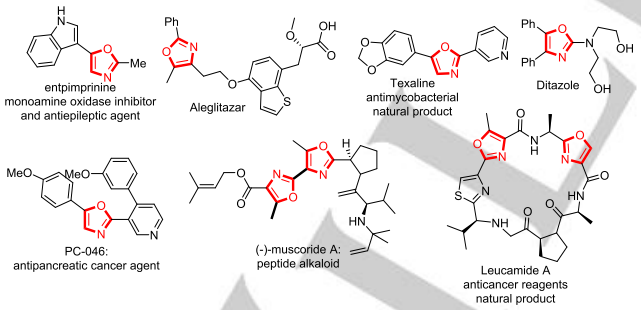


Figure 1. Oxazole contained important molecules.

Given the important biological and pharmaceutical activities of oxazoles, many synthetic strategies have been developed for the synthesis of functionalized oxazole skeletons, such as metal-catalyzed transformations, condensations, cyclization of α-acylamino ketones precursors, oxidation of oxazolines, transition-metal-catalyzed addition of diazo compounds to nitriles, rearrangements and Robinson−Gabriel type reaction.[3]

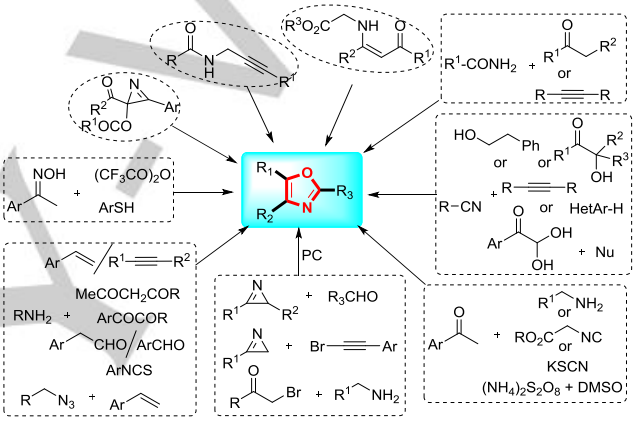


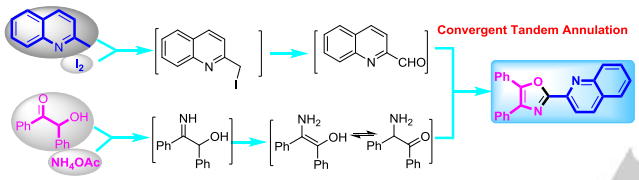
Figure 2. The protocols for substituted oxazoles synthesis.

Recently, some practical annulation reactions have been developed for the synthesis of oxazoles from commercial starting materials (Figure 2). For example, oxidative cyclization of amines or azides with alkenes, alkynes, ethyl acetoacetate, aldehydes and isothiocyanates were reported by the groups of Jiang, Wang, Jiao, and Pan et.al.[4] The groups of Wu, Liu and Guo reported a serials of elegant cascade cyclization reactions to afford oxazoles from simple aromatic ketones, thiocyanate salts, α-methylenyl isocyanides and $(NH_4)_2S_2O_8$/DMSO.[5] The annulation reactions of nitriles with alcohols, α-hydroxyl ketones, alkynes, electronic-rich heteroarenes, arylglyoxal monohydrates and various C-nucleophiles was also fully demonstrated.[6] The metal catalyzed annulation of amides with ketones or alkynes was also an efficient method.[7] Visible-light catalyzed approaches were achieved through the cyclization of 2H-azirines with aldehydes or alkynyl bromides, α-bromoketones with benzylamines.[8] Copper catalyzed three-component domino cyclization of oxime, arylthiol, and trifluoroacetic anhydride was demonstrated for the synthesis of trifluoromethyl attached oxazoles.[9] The intramolecular cyclization of 2H-azirines, enaminones and *N*-propargylamides was also efficient approach.[10]

Although the synthesis of substituted oxazole has received much interest, oxazole attached with quinoline, quinoxaline, quinazolin-4(3H)-one and benzo[d]thiazole at 2-position is rarely seen, because of the difficulty in introducing these heterocycles at the 2-position of oxazoles. Only very limited methods were available to get 2-position isoquinolin or 2-triazole attached oxazoles.[11] More importantly, quinoline, quinoxaline, quinazolin-

4(3H)-one and benzo[d]thiazolyl substituted oxozoles are new types of heterocyclic compounds, which had not been reported yet.

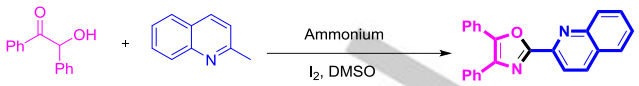
Convergent domino cyclization is a powerful synthetic strategy for quick and efficient construction of important compounds.[12] It enables two or more domino processes sequentially assembled in one-pot, improves steps economy and simplifies operational process. Herein, we would like to report a convergent domino annulation for the synthesis of quinoline, quinoxaline, quinazolin-4(3H)-one and benzo[d]thiazole attached 2,4,5-trisubstituted oxazoles from common and readily available benzoin derivatives, methyl azaarenes and NH_4OAc under mild conditions (schemes 1). Firstly, 2-methyl quinoline undergoes tandem iodination and oxidation to form 2-(iodomethyl)quinoline and quinoline-2-carbaldehyde via direct oxidative functionalization of sp^3 C–H bonds.[13] At the same time, benzoin undergoes condensation with NH_4OAc and isomerization to generate α-amino ketone and isomer. Finally, quinoline-2-carbaldehyde and α-amino ketone undergoes convergent annulation to give 2-quinoline-4,5-diphenyl-oxazole.



Scheme 1. The protocol for 2-quinoline-4,5-diphenyl-oxazole synthesis

With the idea in mind, we initially optimized the reaction conditions using benzoin (**1a**) and 2-methylquinoline (**2a)** as the model substrates (Table 1). As shown in entry 1, the reaction could give the product **3aa** in 43% yield under the condition of iodine (2.5 equiv), NH_4OAc (2.0 equiv) at 120 °C in DMSO for 12 h. Next, the dose of iodine was optimized. Increasing or decreasing the amount of iodine could not improve the yield (Table 1, entry 2-5). Various ammonium salts, such as NH_4Cl, $(NH_4)_2SO_4$ and HCO_2NH_4, were also screened in the presence of iodine in DMSO at 120 °C. The desired product could be obtained in only low yield (Table 1, entry 6-8). The effect of reaction temperature on the yield was subsequently examined; thus indicating that 120 °C was the optimal temperature (Table 1, entries 9–12). The mole ratios of benzoin (**1a**) /2-methylquinoline (**2a**) were screened from 1 : 2 to 6 : 1. Notably, the yield was significantly increased with the more amount of benzoin **1a** was used (Table 1, entry 13-18). The best result was obtained when the ratio of **1a** and **2a** is 5/1 (Table 1, entry 17). The further increase in the ratio of **1a** and **2a** did not give a better result, and the excess benzoin (**1a**) led to the lower yield of **3aa** (Table 1, entry 18). Interestingly, upon addition of molecular sieve, the yield was significantly increased (Table 1, entry 19 and 20). Finally, optimal conditions were identified, that is 2-methylquinoline **2a** (1.0 equiv), benzoin **1a** (5.0 equiv), ammonium acetate (2.0 equiv), and iodine (2.5 equiv) and molecular sieves (4 Å, 200 mg) in DMSO (3 mL) at 120 °C (Table 1, entry 20).

Table 1. Optimization studies for the preparation of **3aa**[a]



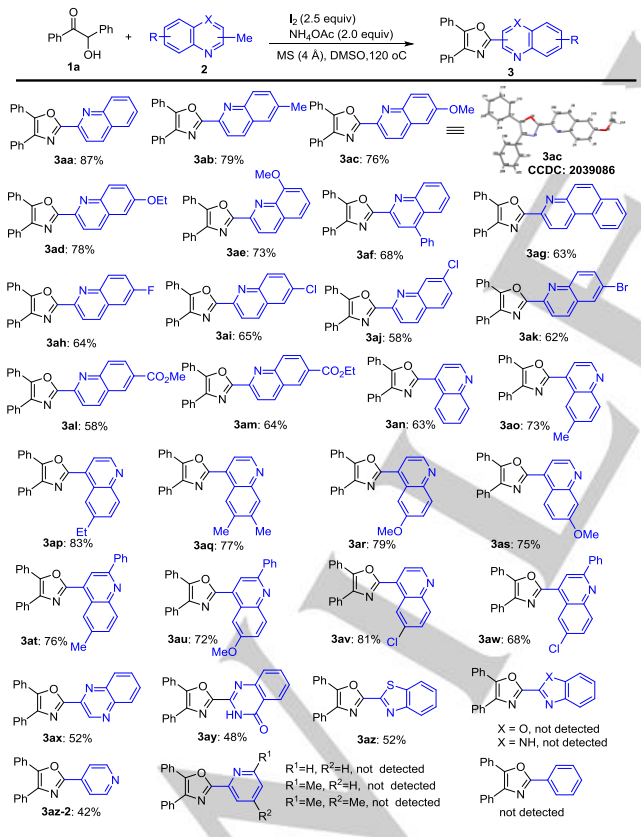
1a **2a** **3aa**

entry	I_2 (equiv)	**1a**:**2a**	Ammonium (2.0 equiv)	T/ °C	Yield (%) [b]
1	2.5	1.2:1	NH_4OAc	120	43
2	2.0	1.2:1	NH_4OAc	120	30
3	1.5	1.2:1	NH_4OAc	120	32
4	3.0	1.2:1	NH_4OAc	120	38
5	4.0	1.2:1	NH_4OAc	120	29
6	2.5	1.2:1	NH_4Cl	120	16
7	2.5	1.2:1	$(NH_4)_2SO_4$	120	32
8	2.5	1.2:1	HCO_2NH_4	120	36
9	2.5	1.2:1	NH_4OAc	110	30
10	2.5	1.2:1	NH_4OAc	100	34
11	2.5	1.2:1	NH_4OAc	130	17
12	2.5	1.2:1	NH_4OAc	140	14
13	2.5	1:2	NH_4OAc	120	29
14	2.5	2:1	NH_4OAc	120	39
15	2.5	3:1	NH_4OAc	120	56
16	2.5	4:1	NH_4OAc	120	70
17	2.5	5:1	NH_4OAc	120	74
18	2.5	6:1	NH_4OAc	120	62
19	2.5	5:1	NH_4OAc	120	80 [c],[d]
20	2.5	5:1	NH_4OAc	120	87 [c],[e],[f]

[a] Reaction conditions: benzoin **1a**, 2-methyl quinoline **2a** (0.3 mmol), I_2 and Ammonium were heated in DMSO (3 mL). [b] Isolated yields. [c] 200 mg of 4 Å molecular sieves was added. [d] Benzil was obtained in 81% yield. [e] **2a** (0.3 mmol) and I_2 in DMSO (3 mL) at 120 °C for 4 h, then added benzoin **1a**, NH_4OAc and 4 Å molecular sieves and stirred at 120 °C for another 2-3 h. [f] Benzil was obtained in 70% yield, which can be recycled by $NaBH_4$ to benzoin in quantitative yield.

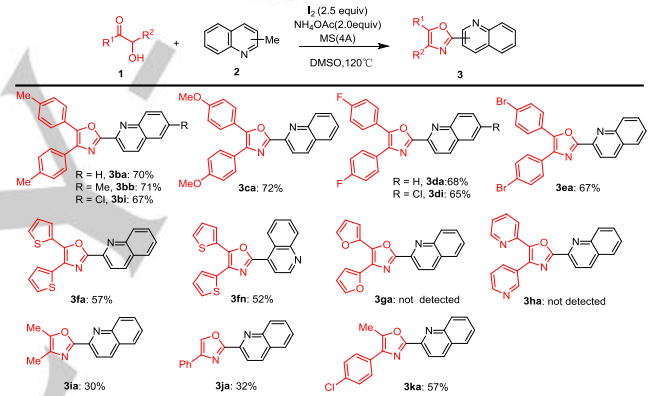
With the optimal reaction conditions in hand, the reaction scope was subsequently explored. We examined the steric and electronic effects of the substituents adjacent to the methyl quinoline **2** using benzoin (**1a**) as the model substrate (Scheme 2). First of all, 2-methyl quinolines attached with electron donating groups (6-Me, 6-OMe, 6-OEt, 8-OMe, 4-Ph) were tolerant for this reaction to afford the corresponding products (**3ab-3af**). The structure of **3ac** was further confirmed by X-ray crystallographic analysis. 3-Methylbenzo[f]quinoline was also suitable for the reaction to give the product **3ag** in 63% yield. 2-Methyl quinolines attached with halogen atoms (6-F, 6-Cl, 7-Cl, 6-Br) were also investigated, the corresponding products were generated in moderate to good yields (**3ah-3ak**). It was worth noting that the strongly electron-deficient substrates **2l** and **2m**

(with 6-methyl ester and 6-ethyl ester, respectively) could be applied to this protocol, giving the corresponding products in moderate yields (**3al** and **3am**). These results showed that 2-methyl quinolines bearing electron-donating groups could give high yields than those bearing halogen atoms or electron-deficient groups substrates. Intriguingly, 4-methyl quinoline and substituted 4-methylquinoline were similarly found to be suitable substrates for the transformation and giving the desired products in good to excellent yields. For example, 4-methylquinoline bearing electron-donating substituents on the aryl ring (e.g. 6-Me, 6-Et, 6,7-Me_2, 6-OMe, 7-OMe, 2-Ph-6-Me, 2-Ph-6-OMe) were all successfully cyclization into the desired compounds **3ao-3au** in 72%-83% yields. Molecules containing halogen atom substituents on the aryl ring (e.g. 6-Cl, 2-Ph-6-Cl) were all smoothly cyclization to the corresponding products **3av-3aw** with good yields. Moreover, three heteroatoms containing substrates 2-methylquinoxaline **2x**, 2-methylquinazolin-4(3H)-one **2y** and 2-methylbenzothiazole **2z** were also tolerant to react with benzoin, generating the desired products **3ax-3az** in moderate yields. However, 2-methylbenzo[d]oxazole and 2-methyl-1H-benzo[d]imidazole were not suitable for this reaction. Furthermore, 4-methylpyridine were successfully cyclization into the desired compounds **3az-2** in 42% yield. However, 2-methylpyridine, 2,6-dimethylpyridine, 2,4,6-trimethylpyridine and toluene were not suitable for this reaction.



Scheme 2. Scope of substituted methyl quinolines and derivatives. Reaction conditions: **2** (0.3 mmol), I_2 (0.75 mmol) in DMSO (3 mL) at 120 °C for 4-6 h, then added benzoin **1a** (1.5 mmol), NH_4OAc (0.6 mmol) and 4 Å molecular sieves (200 mg) and stirred at 120 °C for another 2-3 h. Isolated yields provided.

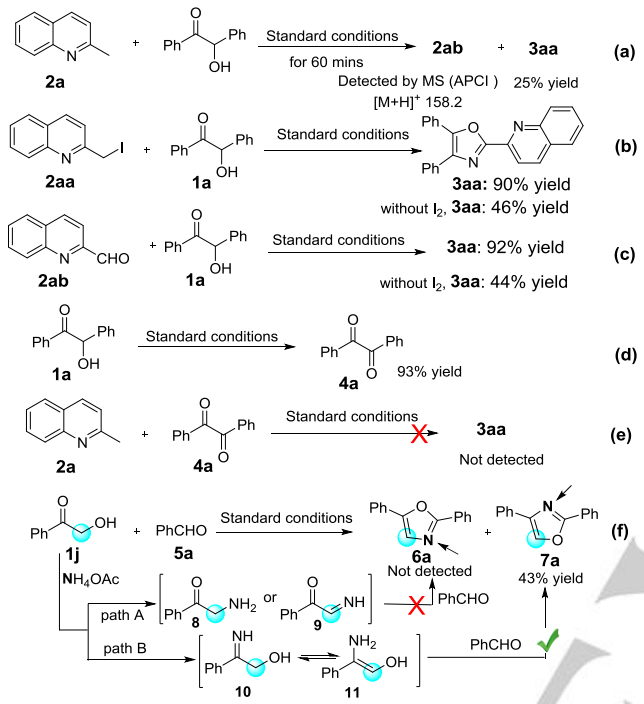
We next examined the scope of this reaction for benzoin derivatives **1** (Scheme 3). We firstly studied the benzoin in which on the phenyl ring had electron-rich substituents (e.g. 4,4'-$(Me)_2$, 4,4'-$(OMe)_2$), and the annulation reactions proceeded smoothly to deliver products **3ba-3ca** in 67-72% yields. Moreover, the phenyl ring of benzoin bearing halogen atoms (e.g. 4,4'-diF, 4,4'-diBr), the reactions could also afford the desired products (**3da**, **3di** and **3ea**) in good yields. In addition, it was worth noting that 2-hydroxy-1,2-di(thiophen-2-yl)ethan-1-one **1f** was also tolerant in this reaction with 2-methylquinoline and 4-methylquinoline to generate expected products **3fa** and **3fn** in moderate yields. However, furanyl and pyridyl contained substrates **1g** and **1h** could not perform the reaction. Moreover, aliphatic 3-hydroxybutan-2-one **1i** also suitable for the reaction to give desired product **3ia** in 30% yield. When 2-hydroxyacetophenone **1j** was reacted with 2-methylquinoline **2a** in this reaction, product **3ja** could be affored in 32% yield. In addition, 1-(4-chlorophenyl)-2-hydroxypropan-1-one **1k** was also tolerant under the standard conditions to generate the expected products **3ka** with a moderate yield.



Scheme 3. Scope of substituted benzoin derivatives and methylquinolines. Reaction conditions: **2** (0.3 mmol), I_2 (0.75 mmol) in DMSO (3 mL) at 120 °C for 4-6 h, then added benzoin derivatives **1** (1.5 mmol), NH_4OAc (0.6 mmol) and 4 Å molecular sieves (200 mg) and stirred at 120 °C for another 2-3 h. Isolated yields provided.

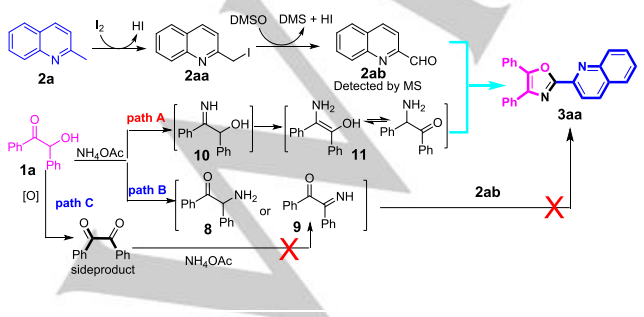
To obtain more information about the reaction mechanism, some control experiments were conducted (Scheme 4). When the standard reaction conducted for 60 mins, product **3aa** was obtained in 25% yield and quinoline-2-carbaldehyde **2ab** could be detected by MS (APCI). The two reactions, 2-(iodomethyl)quinoline **2aa** with benzoin **1a** and quinoline-2-carbaldehyde **2ab** with benzoin **1a**, could work smoothly under standard conditions to generate product **3aa** in 90% and 92% yields, respectively. When without iodine in these reactions, the yields were decreased. Benzoin **1a** could be oxidized to benzyl **4a** in high yield under standard conditions. However, the reaction of benzyl **4a** with 2-methylquinoline **1a** could not react to form product **3aa**. This result indicated that benzyl **4a** is not the potential intermediate in this reaction. In order to confirm the regioselectivity of this reaction, we chose 2-hydroxyacetophenone **1j** and benzaldehyde as model substrates to testify the result under standard conditions. The reaction maybe has two potential pathways to form product **6a** or **7a**. In path A, 2-hydroxyacetophenone **1j** reacted with NH_4OAc to form

intermediate **8** or **9**, which would further cyclization with benzaldehyde to generate **6a**. In path B, intermadiate **10** or **11** were firstly generated, then condensated with benzaldehyde to afford product **7a**. Through comparison with authentic samples **6a** and **7a**, **7a** could be isolated in 43% yield in reaction (f), **6a** was not observed. Further control experimental for **1j** with **2a** under standard conditions was also condected (See SI). Thses results disclosed that path B is the potential reaction process.



Scheme 4. Control experiments.

Based on the above results and previous works, a possible reaction mechanism is proposed in scheme 5. Initially, 2-methylquinoline **2a** undergoes iodination and oxidation to give intermediate 2-(iodomethyl)quinoline **2aa** and quinoline-2-carbaldehyde **2ab** in the presence of iodine and DMSO. At the same time, benzoin **1a** undergoes condensation with NH_4OAc to form intermediate **10** or **11** via path A. The potential path B and C are excluded via control experiments (Scheme 4) and result of product **3ja** (Scheme 3). In this process, benzyl **4a** is oxidazed as a sideproduct, which can be efficiently recycled to benzoin **1a** by $NaBH_4$ in quantitative yield. Finally, quinoline-2-carbaldehyde **1ab** will cyclization with intermediate **10** or **11** under standard conditions to generate the end product **3aa**.



Scheme 5. A plausible reaction mechanism for the preparation of 2-quinoline-4,5-diphenyl-oxazole.

In summary, we have developed an oxidative [3+1+1] convergent domino cyclization to prepare 2,4,5-trisubstituted oxazoles in the presence of iodine and molecular sieves. This process provides a new approach for one-pot synthesis of quinoline, quinoxaline, quinazolin-4(3H)-one and benzo[d]thiazole attached 2,4,5-trisubstituted oxazoles without any metal catalyst. It features wide substrate scope, good functional group tolerance, mild reaction conditions, and easily available substrates. Mechanism investigation uncovered that 2-(iodomethyl)quinoline, quinoline-2-carbaldehyde and 2-imino-1,2-diphenylethan-1-ol or isomer are the potential intermediates.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21702091), Science and Technology Innovation Development Plan of Yantai (2020MSGY114) and Yantai "Double Hundred Plan". The authors also thank Talent Induction Program for Youth Innovation Teams in Colleges and Universities of Shandong Province. The Graduate Innovation Foundation of Yantai University (YDZD2035) is gratefully acknowledged (for Z.-H. Shang). The College Students Innovation and Entrepreneurship Training Program (S202011066007) are gratefully acknowledged (for K.-X., Liu).

Keywords: 2-Quinoline-4,5-diaryl-oxazole • Iodine • Methyl azaarenes • Convergent domino cyclization

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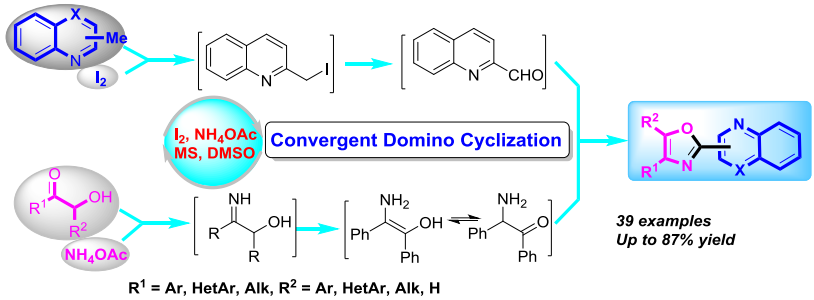

A metal-free oxidative [3+1+1] convergent domino annulation has been developed for the synthesis of 2,4,5-trisubstituted oxazoles. Compared with existing methods, this method has the advantages of wide substrate scope, mild reaction conditions, and obtaining raw materials.