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无金属催化的双 C—H 功能化 *N*-氰基苯并咪唑合成苯并咪唑并[1,2-*c*]喹唑啉衍生物

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摘要 在无金属、无任何添加剂的条件下, 通过过氧化物介导的双 C—H 功能化, 建立了一种绿色高效的合成苯并咪唑[1,2-*c*]喹唑啉的方法. 该方法经历了 C-中心自由基和 N-中心自由基之间的接力串联环化过程, 适用于多种环(硫)醚、乙二醇醚和环烷烃. 需要指出的是, 目标化合物具有良好的杀虫和杀菌活性, 特别是对粘虫具有显著的生物活性.

关键词 双 C—H 功能化; 自由基串联环化; 氰胺; 苯并咪唑; 喹唑啉

Metal-Free Synthesis of Benzimidazo[1,2-*c*]quinazolines from *N*-Cyanobenzimidazoles via Double C—H Functionalizations

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Abstract A green and efficient method for synthesis of privileged benzimidazo[1,2-*c*]quinazoline scaffolds is developed through the double C—H functionalizations mediated by peroxides under metal-free conditions without any additives. This protocol undergoes a radical cascade cyclization process involving the relay between C-centered radicals and N-centered radicals and is well applicable to a variety of cyclic (thio)ethers, glycol ethers and cyclic alkanes. Noteworthily, the title compounds display significant insecticidal and fungicidal activities, especially to armyworm.

Keywords double C—H functionalization; radical cascade cyclization; cyanamide; benzimidazole; quinazoline

1 Introduction

Benzimidazoles and quinazolines constitute two classes of important *N*-containing heterocycles, which prevail in an array of naturally-occurring products and bioactive molecules. Their tetracyclic hybrids, benzimidazo[1,2-*c*]-quinazolines, have exhibited prominent pharmaceutical activities such as anticancer, anti-inflammation and anti-tumor (Figure 1), and also possess wide applications in the areas of luminescent materials and fluorescent probes.[1]

Great progress has been made with respect to the synthesis of benzimidazo[1,2-*c*]quinazoline scaffold to date. Common strategies for construction of this scaffold include traditional-/oxidative-,[2] reductive-,[3] and Ullmann-coupling[4] followed by cyclization from 2-(*ortho*-aminophenyl)benzimidazoles, *ortho*-nitro and *ortho*-halo analogues, respectively (Scheme 1, a). Among these seminal

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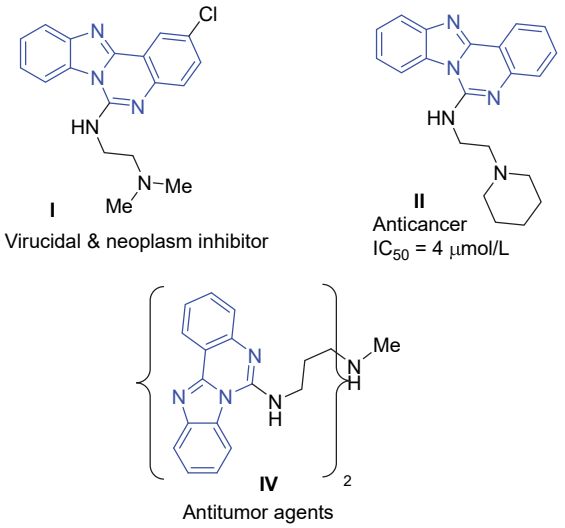
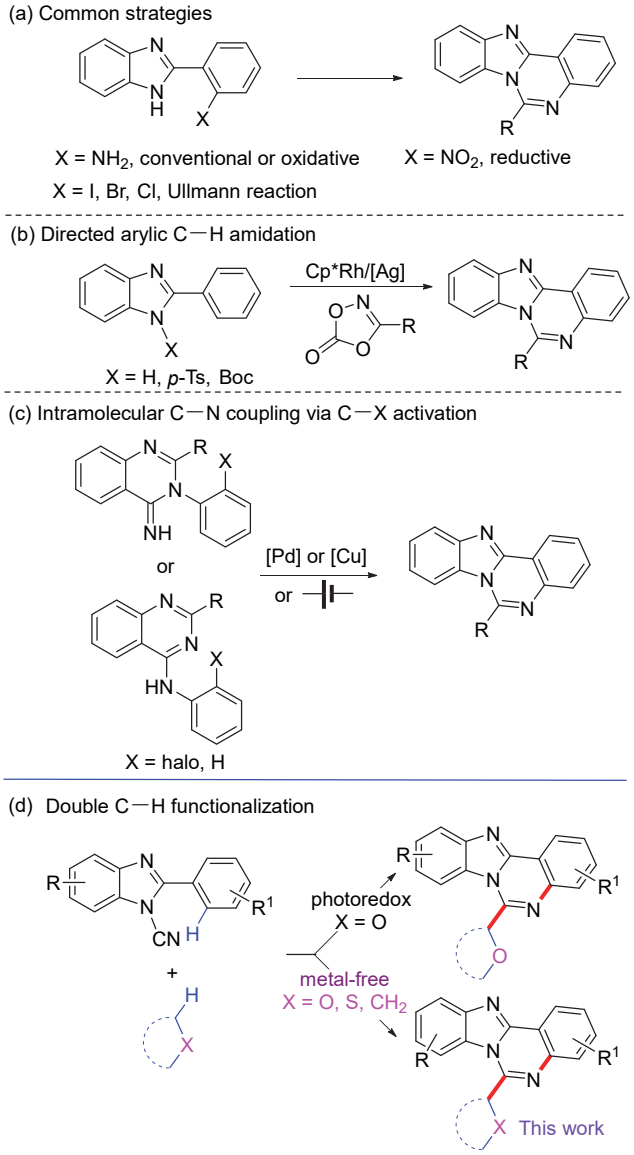


Figure 1 Representative bioactive molecules containing benzimidazo[1,2-*c*]quinazoline skeleton

works, Fu's[4d] method could enable ready access to C(6)-functionalized benzimidazoquinazolines, including the introduction of aryl, alkyl and amino groups. The second strategy involves transition metal-catalyzed arylic C—H activation-annulation (Scheme 1, b).[5] In 2018, Cheng *et al*.[5a] reported Rh(III)-catalyzed sequential *ortho*-C—H amidation and cyclization of 2-phenyl-1*H*-benzimidazole with 1,4,2-dioxazol-5-ones, but only one example on benzimidazoquinazoline was given. In 2019, Cui's group[5b] disclosed the use of *N*-LG-2-phenylbenzimidazoles (LG=Ts, Boc) as precursor for one-pot synthesis of benzimidazoquinazolines catalyzed by Cp*M(III)/AgNTf$_2$ (M=Rh, Ir). The third relates to intramolecular C—N bond formation via C—X activation (X=halo, H) through Cu-/Pd-/electrochemical catalysis (Scheme 1, c).[6] In 2015, Xi *et al*.[6a] disclosed CuI-catalyzed synthesis of C(6)-arylated benzimidazo[1,2-*c*]quinazolines via intramolecular amination of arylic C—Br bond. In 2019, Neuville *et al*.[6c] demonstrated Cu(OAc)$_2$-catalyzed access to this scaffold bearing an alkylamino group at the C(6) position under O_2 atmosphere. Recently, our group[7] has reported a photoredox-catalyzed synthesis of this skeleton, however, the substrate scope is limited to cyclic oxoethers (Scheme 1, d). Therefore, it remains desirable to develop an efficient method for the construction of benzimidazo[1,2-*c*]quinazoline derivatives from various C(sp^3)—H bonds.

The double C—H functionalizations[8] via a radical relay process constitutes a greener tactic and enables ready access to two C-based chemical bonds simultaneously, with the advantages of no need to install reactive functional groups on substrates, shorter reaction steps, higher atom-economy and less waste production. Importantly, this strategy allows for efficient construction of heterocycles through radical relay pathway,[9] involving the functionalization of sp^3 hybridized C—H bonds.[10] With our continuous interest in metal-free synthesis[11] and heterocyclic assembly,[12] we report herein an efficient and sustainable



Scheme 1 Previous methods and our work for synthesis of benzimidazo[1,2-*c*]quinazoline scaffolds

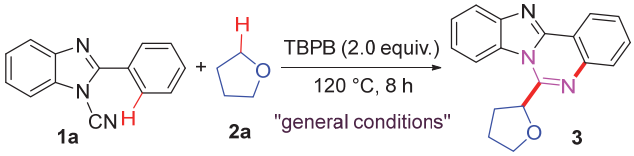
protocol to synthesize C(6)-functionalized benzimidazo-[1,2-*c*]quinazolines via radical cascade cyclization mediated by peroxides under metal- and additive-free conditions.

2 Results and discussion

We set about our research using *N*-cyano-2-phenylbenzimidazole (**1a**) and tetrahydrofuran (THF, **2a**) as model substrates under oxidation conditions. Delightingly, use of di-*tert*-butyl peroxide (DTBP) as oxidant delivered our desired product, 6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo-[1,2-*c*]quinazoline (**3**), in 83% yield at 120 ℃ for 8 h (Table 1, Entry 2). Utilization of other peroxides such as *tert*-butyl peroxybenzoate (TBPB) and benzoyl peroxide (BPO) smoothly afforded compound **3** (Table 1, Entries 1, 3). Notably, TBPB led to a superior yield of 85%. Slight elevation of reaction temperature helped improve the reaction

yields (Table 1, Entries 4, 5). Thus, the reaction carried out at 125 ℃ provided an 87% yield. Furthermore, it was found that either increasing or decreasing the equivalent of TBPB gave rise to a slight decline in the yield (Table 1, Entries 6, 7). Besides, optimization of reaction time indicated that the yield of product **3** amounted up to 90% when the reaction was run for 6 h (Table 1, Entries 8～10).

Table 1 Screening reaction conditions[a]



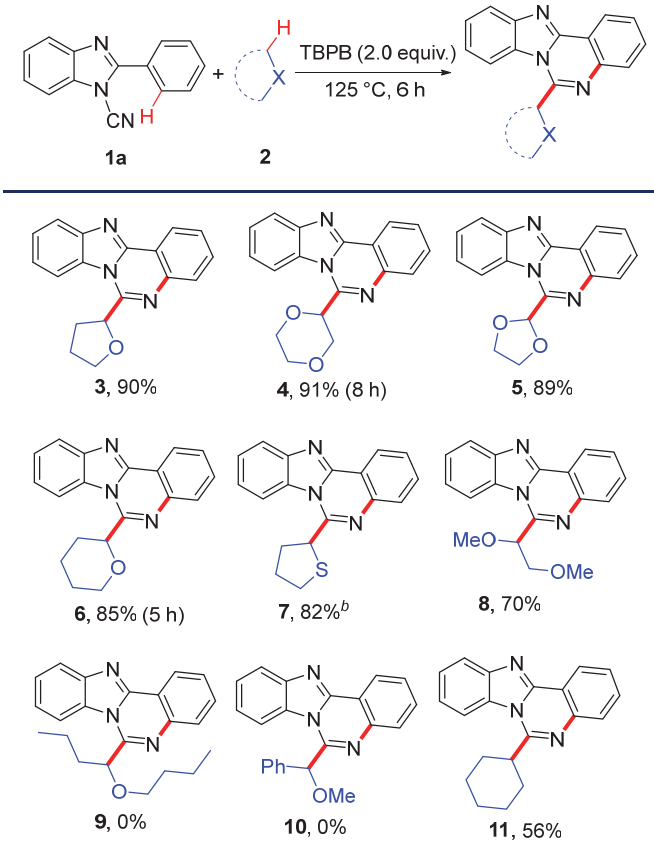
Entry	Variation from general conditions	Isolated yield/%
1	none	85
2	DTBP	83
3	BPO	58
4	125 ℃	87
5	130 ℃	86
6	1.5 equiv. at 125 ℃	84
7	2.3 equiv. at 125 ℃	86
8	5 h at 125 ℃	84
9	6 h at 125 ℃	90
10	7 h at 125 ℃	88

[a] General conditions: **1a** (0.1 mmol), **2a** (0.5 mL), TBPB (0.2 mmol), 120 ℃, 8 h. TBPB=*tert*-butyl peroxybenzoate, DTBP=di-*tert*-butyl peroxide, BPO=benzoyl peroxide.

After establishing the optimal conditions for the oxidative radical relay process, we shifted our attention to the scope of sp^3 hybridized C-centered radical precursors, and the results are depicted in Table 2. Evidently, an array of cyclic ethers including THF, 1,4-dioxane (**2b**), 1,3-dioxolane (**2c**) and tetrahydropyran (**2d**) smoothly underwent radical cascade cyclization to furnish fused quinazolines **3**～**6** in 85%～91% yields under the standard conditions. Cyclic thioether, tetrahydrothiophene (**2e**), failed to afford its corresponding product **7** with TBPB as oxidant, but succeeded with 82% yield using DTBP at 125 ℃ for 12 h. Linear ethers, including 1,2-dimethoxyethylene (DME, **2f**), di-*n*-butyl ether (**2g**) and benzylmethyl ether (**2h**), were attempted in this cascade reaction. It turned out that DME was an effective precursor with specific regioselectivity at ethylene carbon atom, thereby giving the product **8** in 70% yield, while ethers **2g** and **2h** were ineffective using either TBPB or DTBP, and even by adjusting reaction temperature, no products (**9**, **10**) were detected. Pleasingly, cyclic hexane (**2j**), an unactivated alkane, was subjected to this reaction, affording compound **11** in 56% yield using TBPB.

We next applied this radical relay protocol to a series of *N*-cyano-2-phenyl benzimidazoles in the case of THF. As shown in Table 3, almost all the benzimidazoles tested underwent this relay transformation to give their individual products in better yields than in the reported photoredox

Table 2 Scope of various C—H bonds[a]



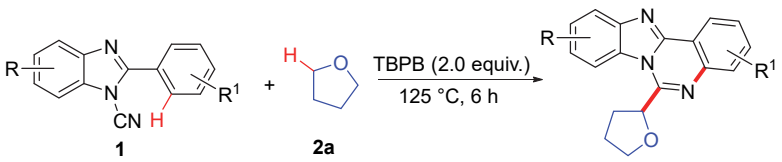
[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.75 mL), TBPB (0.3 mmol), 125 ℃, 6 h unless otherwise stated. [b] DTBP (2 equiv.) instead, 12 h.

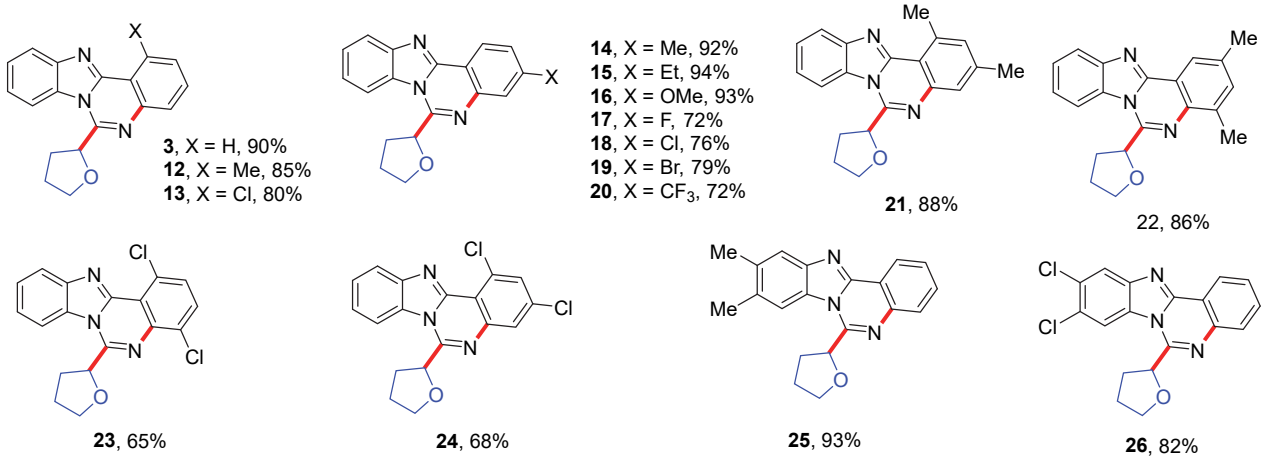
catalysis.[7] Various functional groups including Me, OMe, F, Cl, Br and CF_3 were well compatible for such an oxidative radical reaction. Electron effects of substituents imposed a remarkable impact on yields. Basically, electron-releasing groups connected to either aryl moiety, or fused benzene ring are more beneficial to reaction efficiencies than electron-pulling ones. For instance, alkyl or alkoxyl groups located at the *para*-position provided 92%～94% yields, while halo groups and CF_3 rendered 72%～79% yields (Table 3, compounds **14**～**16** vs **17**～**20**). Similarly, benzimidazoles bearing dimethyl groups gave higher yields than those having dichloro ones (Table 3, compounds **21**, **22**, **25** vs **23**, **24**, **26**). Steric effect of substituents exerted limited influence on reaction efficiencies (Table 3, compounds **12**, **13** vs **14**, **18**).

Furthermore, 2-methyltetrahydrofuran was examined as precursor to investigate regioselectivity. Under the standard conditions, an inseparable isomeric mixture was generated in 75% yield and the regioselective ratio of 1.95∶1 (Scheme 2).

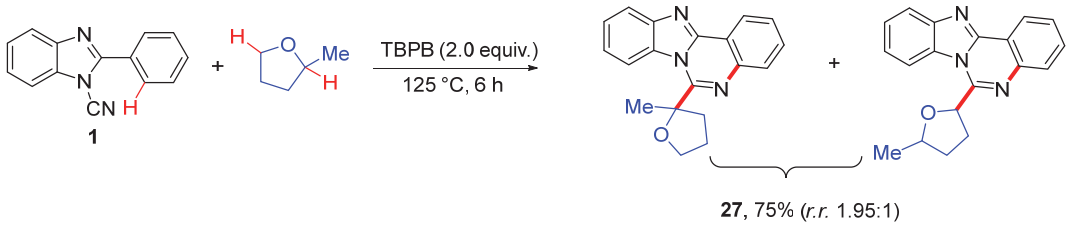
To certify the applicability of this radical cascade cyclization reaction, a gram-scale experiment was performed. Thus, 5 mmol of benzimidazole **1a** was reacted with 25 mL of ether **2b** to satisfactorily generate the target compound **4** in 84% yield (Scheme 3).

Table 3 Scope of *N*-cyanobenzimidazoles[a]

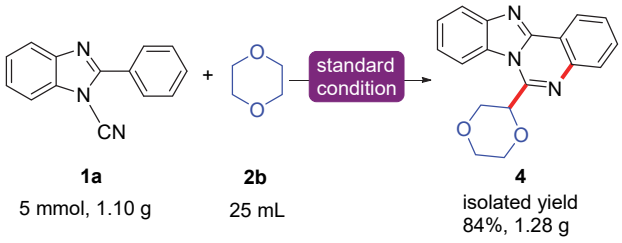




[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.75 mL), TBPB (0.3 mmol), 125 ℃, 6 h

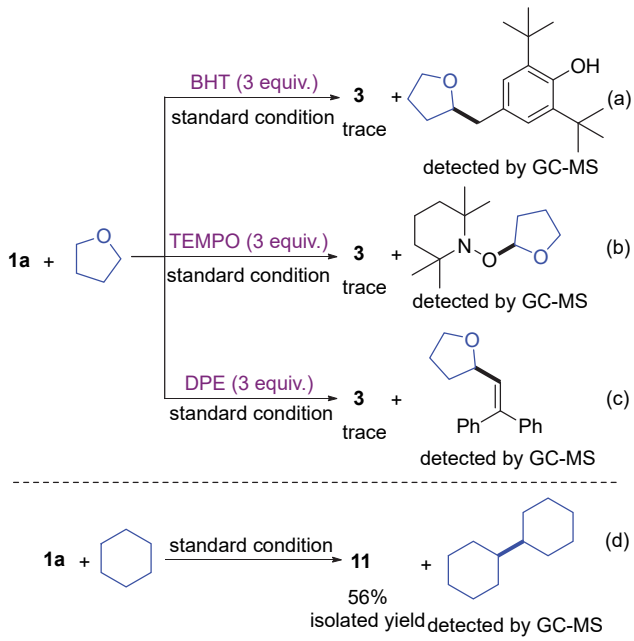


Scheme 2 Reaction with respect to 2-methyltetrahydrofuran



Scheme 3 Gram-scale experiment

To probe the mechanism for the present radical cascade cyclization reaction via the double C—H functionalizations, a set of control experiments were carried out (Scheme 4). The widely used radical inhibitors, 2,6-di(*tert*-butyl)-4-methyl phenol (BHT) and 1,1,6,6-tetramethyl-1-piperi-dinyloxyl (TEMPO), were added to the standard reactions in 3 equiv., respectively, and as a result the reactions were almost entirely shut down with the corresponding THF-related adducts being detected by gas chromatograph-mass spectrometer (GC-MS) (Scheme 4, a, b). When 3 equiv. of 1,1-diphenylethylene (DPE) as radical trapper was added under the standard conditions, a large amount of the THF-DPE adduct was detected with trace product **3** (Scheme 4, c). All the experimental results suggest that

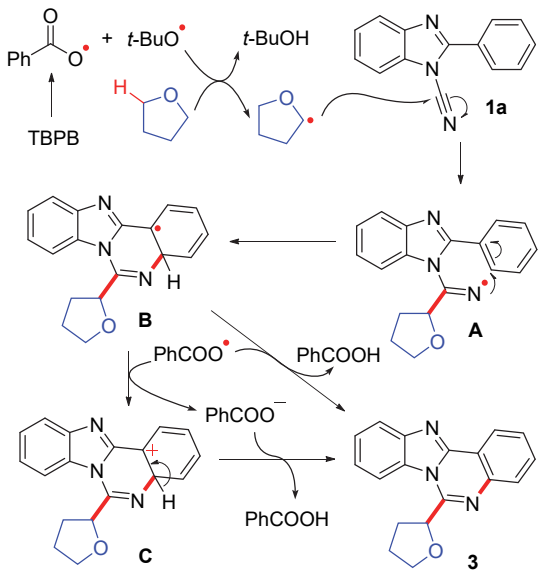


Scheme 4 Control experiments

the present peroxide-mediated reaction very likely involves

a radical process. It is worth noting that the formation of a considerable amount of 1,1'-bi(cyclo- hexane) was observed, implicating the probable participation of radicals in the process (Scheme 4, d). Besides, a great amount of benzoic acid generated in this transformation was observed by GC-MS.

Based on the previous work[7,13] and our experimental results mentioned above, a putative mechanism for the present radical relay reaction is illustrated in Scheme 5. Considering that the O—H bond dissociation energies (BDE) in benzoic acid (463.9±16.7 kJ/mol)[14] and *tert*-butanol (443.1±2.9 kJ/mol)[14] are comparable, both of which are greater than that of *α*-C—H bond in THF (384.9±6.7 kJ/mol),[14] either benzoxy or *tert*-butoxyl radicals could serve as hydrogen atom transfer (HAT) reagent. Thus, TBPB is homolyzed to benzoxy and *tert*-butoxy radicals. Oxyalkyl radicals are generated via a HAT process and react through nucleophilic addition to the *N*-cyano groups of **1a** to produce *N*-iminyl radicals **A**. Then N-centered radicals **A** participates in an *endo* cyclization to give radical species **B**. Finally, intermediate **B** undergoes another HAT process to yield product **3**. Alternatively, **B** is oxidized to species **C** and subsequently deprotonates to furnish quinazoline **3**.



Scheme 5 Plausible mechanism for thedouble C—H functionalizations

Due to the wide utility of *N*-heterocycles in pesticidefields, the insecticidal activities of products **3**, **12**, **18** and **24** were determined using standard operating procedures (SOP) (Table 4). The results of general screening showed that all the four compounds possess moderate to good insecticidal activities, especially against armyworm with the death rate of 100% (500 mg/L), while they display almost no activity against red spider (200 mg/L). Those compounds have remarkable fungicidal activities (25 mg/L) against phytophthora capsica in pepper, alternaria alternata in tobacco plants, and botrytis cinerea on cucumber.

3 Conclusions

In conclusion, a simple and efficient method for ready access to privileged heterocyclic benzimidazoquinazolines from *N*-cyano-2-arylbenzimidazoles was developed. A series of oxoethers, thioethers and cyclic alkanes are effective coupling partners. Our method undergoes a cascade cyclization process involving the C-/N-centered radicals relay through the double C—H functionalizations mediated by peroxides under metal- and additive-free conditions. Some compounds have considerable insecticidal and fungicidal activities. Further explorations regarding this relay protocol and bioactivity assay are under way in our laboratory.

4 Experimental section

4.1 General experimental information

All solvents and reagents were purchased from the suppliers and used without further purification unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 or JEOL 400 Ultrashield NMR spectrometers. The chemical-shift scale is based on internal TMS. High-solution mass spectra were acquired on a Waters UPLC/Xevo G2 quadrupole time-of-flight tandem mass spectrometry (Xevo G2 Q-TOF). The melting points were determined on an X-4 microscope melting point apparatus and uncorrected. Conversion was monitored by thin layer chromatography (TLC). Flash column chromatography was performed over silica gel (100～200 mesh).

4.2 General procedure for synthesis of benzo[4,5]imidazo[1,2-*c*]quinazolines

To a 10 mL glass vial was added **1** (0.15 mmol), TBPB (0.3 mmol, 2.0 equiv.) and 0.75 mL of ethers or alkanes. The reaction mixture was sealed with a polytetrafluoroethylene (PTFE) cap. The mixture was then stirred rapidly at preheated 125 ℃ (oil bath) for 6 h. After completion,

Table 4 Pesticide activity assay of selected products[a]

Compd.	Insecticidal activities			Fungicidal activities[d]			
	Armyworm[b]	Aphid[c]	Red spider[c]	Phytophthora	Alternaria	Fusarium	Botrytis
3	100	64.09	0	52.83	70.00	3.17	44.90
12	100	85.64	0	60.19	59.47	10.92	43.12
18	100	93.07	6.30	85.97	84.70	25.78	69.20
24	100	95.32	2.16	93.54	88.13	12.70	82.86

[a] Using the SOP, death rate for insecticide, %; inhibition rate for fungicide, %. [b] 500 mg/L. [c] 200 mg/L. [d] 25 mg/L.

the reaction mixture was extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography yielded desired products.

6-(Tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**3**):[7] 39.2 mg, yield 90%, white solid. m.p. 199～200 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, J=8.0 Hz, 1H), 8.25 (d, J=8.0 Hz, 1H), 8.01 (d, J=8.0 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.75 (t, J=8.0 Hz, 1H), 7.65 (t, J=8.0 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 5.78～5.72 (m, 1H), 4.13～4.07 (m, 2H), 3.13～3.10 (m, 1H), 2.42～2.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 148.1, 144.4, 141.6, 131.6, 129.00, 128.4, 128.3, 125.6, 124.2, 123.3, 120.0, 118.8, 115.5, 77.0, 69.4, 28.1, 25.9.

6-(1,4-Dioxan-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**4**):[7] 41.8 mg, yield 91%, white solid. m.p. 168～170 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (dd, J=8.0, 1.2 Hz, 1H), 8.04 (d, J=8.0 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 7.78 (t, J=8.0 Hz, 1H), 7.70 (t, J=8.0 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 5.36 (dd, J=8.8, 3.0 Hz, 1H), 4.51～4.39 (m, 2H), 4.23～4.17 (m, 1H), 4.10～4.06 (m, 1H), 3.99～3.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.8, 144.1, 143.3, 140.2, 130.7, 127.7, 127.6, 127.4, 124.7, 123.2, 122.4, 119.2, 117.9, 113.5, 72.2, 67.3, 66.1, 65.4.

6-(1,3-Dioxolan-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**5**):[7] 39.0 mg, yield 89%, white solid. m.p. 186～188 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (d, J=8.4 Hz, 1H), 8.21 (d, J=9.2 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.70 (t, J=8.0 Hz, 1H), 7.61 (t, J=8.0 Hz, 1H), 7.51 (t, J=8.0 Hz, 1H), 7.42 (t, J=8.0 Hz, 1H), 5.72～5.69 (m, 1H), 5.24～5.20 (m, 2H), 5.07 (d, J=3.2 Hz, 1H), 4.38～4.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.8, 144.2, 143.2, 140.1, 130.7, 127.7, 127.4, 124.8, 123.2, 122.5, 119.1, 117.8, 113.9, 95.1, 72.4, 65.4.

6-(Tetrahydro-2*H*-pyran-2-yl)benzo[4,5]imidazo[1,2-*c*]-quinazoline (**6**): 36.4 mg, yield 85%, white solid. m.p. 150～152 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, J=7.6 Hz, 1H), 8.15 (d, J=7.6 Hz, 1H), 7.98 (d, J=8.0 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.75 (t, J=8.0 Hz, 1H), 7.66 (t, J=7.6 Hz, 1H), 7.59 (t, J=8 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 5.12～5.15 (m, 1H), 4.22～4.16 (m, 1H), 3.90～3.85 (m, 1H), 2.46～2.41 (m, 1H), 219～2.16 (m, 2H), 1.85～1.72 (m, 2H), 1.26～1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.0, 143.5, 141.7, 133.7, 131.9, 130.3, 129.8, 128.5, 125.9, 124.5, 123.5, 119.9, 118.3, 115.1, 75.9, 69.1, 28.1, 25.7, 22.8; HRMS (ESI) calcd for $C_{19}H_{18}N_3O$ $[M+H]^+$ 304.1444, found 304.1447.

6-(Tetrahydrothiophen-2-yl)benzo[4,5]imidazo[1,2-*c*]-quinazoline (**7**): 37.6 mg, yield 82%, yellow solid. m.p. 185～187 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (d, J=8.0 Hz, 1H), 8.20 (d, J=8.4 Hz, 1H), 8.01 (d, J=8.0 Hz, 1H), 7.87 (d, J=8.0 Hz, 1H), 7.73 (t, J=8.0 Hz, 1H), 7.62 (t, J=8.0 Hz, 1H), 7.55 (t, J=7.6 Hz, 1H), 7.45 (d, J=7.6 Hz, 1H), 5.14 (s, 1H), 3.27～3.25 (m, 1H), 3.12～3.09 (m, 2H), 2.67～2.65 (m, 1H), 2.35～2.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.6, 148.1, 144.3, 141.9, 131.5, 128.6, 127.93, 127.85, 125.5, 124.1, 123.1, 120.1, 118.3, 114.9, 48.8, 33.8, 33.7, 31.5; HRMS (ESI) calcd for $C_{18}H_{16}N_3S$ $[M+H]^+$ 306.1059, found 306.1062.

6-(1,2-Dimethoxyethyl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**8**): 32.3 mg, yield 70%, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (d, J=8.8 Hz, 1H), 8.27 (d, J=8.4 Hz, 1H), 8.07～8.01 (m, 2H), 7.79 (t, J=7.6 Hz, 1H), 7.70 (t, J=7.6 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 5.49～5.46 (m, 1H), 4.21～4.16 (m, 1H), 4.10～4.06 (m, 1H), 3.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.0, 146.9, 144.2, 141.4, 131.9, 130.1, 128.7, 128.3, 125.9, 124.3, 123.6, 120.2, 118.7, 115.5, 79.5, 72.0, 59.7, 56.3; HRMS (ESI) calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1394, found 308.1396.

6-Cyclohexylbenzo[4,5]imidazo[1,2-*c*]quinazoline (**11**): 25.4 mg, yield 56%, white solid. m.p. 145～147 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (d, J=7.6 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.93 (t, J=8.0 Hz, 1H), 7.74 (t, J=8.0 Hz, 1H), 7.67～7.61 (m, 1H), 7.56 (t, J=8 Hz, 1H), 7.48 (t, J=8 Hz, 1H), 7.42 (d, J=7.6 Hz, 1H), 3.57～3.50 (m, 2H), 2.27 (d, J=13.2 Hz, 1H), 2.08～2.01 (m, 1H), 1.93～1.90 (m, 3H), 1.84～1.82 (m, 2H), 1.47～1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.1, 148.5, 142.7, 141.3, 137.5, 131.3, 129.7, 126.6, 125.9, 124.4, 119.0, 116.7, 113.5, 39.0, 33.4, 26.0, 25.3; HRMS (ESI) calcd for $C_{20}H_{20}N_3$ $[M+H]^+$ 302.1652, found 302.1664.

1-Methyl-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**12**):[7] 38.8 mg, yield 85%, white solid. m.p. 194～196 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J=8.0 Hz, 1H), 8.01 (d, J=8.4 Hz, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.50～7.60 (m, 2H), 7.46～7.42 (m, 2H), 5.73～5.69 (m, 1H), 4.11～4.05 (m, 2H), 3.20 (s, 3H), 3.13～3.08 (m, 1H), 2.39～2.26 (m, 2H), 2.18～2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 148.0, 144.5, 142.7, 138.1, 130.4, 130.3, 127.9, 126.1, 125.2, 123.2, 120.3, 117.7, 115.3, 76.9, 69.3, 28.1, 25.9, 23.7.

1-Chloro-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**13**):[7] 38.9 mg, yield 80%, white solid. m.p. 197～199 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J=8.4 Hz, 1H), 8.06 (d, J=8.0 Hz, 1H), 7.80 (dd, J=8.0, 1.2 Hz, 1H), 7.63 (dd, J=8.0, 1.2 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 7.43 (t, J=8.0 Hz, 1H), 5.70～5.67 (m, 1H), 4.05～4.00 (m, 2H), 3.06～3.99 (m, 1H), 2.35～2.19 (m, 2H), 2.13～2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.0, 144.9, 143.3, 142.5, 130.4, 129.7, 129.5, 126.9, 126.4, 124.6, 123.0, 120.0, 116.1, 114.3, 75.8, 68.4, 27.1, 24.9.

3-Methyl-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**14**):[7] 42.0 mg, yield 92%, white solid. m.p. 205～207 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, J=8.4 Hz, 1H), 8.25 (d, J=8.4 Hz, 1H), 7.99 (d, J=8.8 Hz, 1H), 7.77 (s, 1H), 7.57～7.45 (m, 2H), 7.26 (s, 1H)，5.77～5.73 (m, 1H), 4.13～4.06 (m, 2H), 3.16～3.10 (m, 1H), 2.57 (s, 3H), 2.43～2.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.2, 147.1, 143.2, 141.2, 140.6, 128.7, 127.8, 127.0,

124.4, 122.9, 122.0, 118.7, 115.1, 114.3, 75.85, 68.2, 26.9, 24.8, 20.9.

3-Ethyl-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**15**):[7] 44.9 mg, yield 94%, white solid. m.p. 203～205 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J=8.4 Hz, 1H), 8.22 (d, J=8.0 Hz, 1H), 7.99 (d, J=8.0 Hz, 1H), 7.78 (s, 1H), 7.50～7.55 (m, 2H), 7.45～7.42 (m, 1H), 5.74～5.73 (m, 1H), 4.12～4.07 (m, 2H), 3.12～3.07 (m, 1H), 2.85 (q, J=7.6 Hz, 2H), 2.41～2.15 (m, 3H), 1.36 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 148.3, 148.2, 144.4, 141.8, 128.84, 128.77, 126.9, 125.5, 124.0, 123.0, 119.8, 116.3, 115.4, 76.9, 69.3, 29.1, 28.1, 25.8, 15.3.

3-Methoxy-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo-[1,2-*c*]quinazoline (**16**):[7] 44.6 mg, yield 93%, white solid. m.p. 224～226 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, J=8.8 Hz, 1H), 8.19 (d, J=8.4 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.42 (d, J=7.6 Hz, 1H), 7.35 (s, 1H), 7.23 (d, J=9.2 Hz, 1H), 5.72 (t, J=4.8 Hz, 1H), 4.11 (t, J=6.8 Hz, 2H), 3.96 (s, 3H), 3.03 (t, J=6.2 Hz, 1H), 2.43～2.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5, 149.1, 148.3, 144.5, 143.5, 128.7, 125.5, 125.4, 122.7, 119.6, 118.2, 115.2, 112.1, 109.4, 76.9, 69.4, 55.7, 28.2, 25.8.

3-Fluoro-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**17**):[7] 33.3 mg, yield 72%, white solid. m.p. 212～214 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69～8.65 (m, 1H), 8.25 (d, J=8.4 Hz, 1H), 7.99 (d, J=8.0 Hz, 1H), 7.62～7.54 (m, 2H), 7.47 (t, J=7.8 Hz, 1H), 7.39 (t, J=8.4 Hz,1H), 5.74～5.72 (m, 1H), 4.13～4.06 (m, 2H), 3.11～3.09 (m, 1H), 2.42～2.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5 (C—F, $^1J_{CF}$=250 Hz), 149.5, 147.5, 144.1, 143.2 (C—F, $^3J_{CF}$=12 Hz), 128.7, 126.2 (C—F, $^3J_{CF}$=10 Hz), 125.8, 123.3, 119.8, 116.9 (C—F, $^2J_{CF}$=23 Hz), 115.5, 115.2 (C—F, $^4J_{CF}$=2 Hz), 113.7 (C—F, $^2J_{CF}$=21 Hz), 76.8, 69.4, 28.0, 25.8; ^{9}F NMR (376 MHz, $CDCl_3$) δ: −106.8.

3-Chloro-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**18**):[7] 37.0 mg, yield 76%, white solid. m.p. 221～223 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (d, J=8.4 Hz, 1H), 8.26 (d, J=8.4 Hz, 1H), 7.99 (d, J=8.0 Hz, 1H), 7.95 (s, 1H), 7.62～7.54 (t, J=8 Hz, 2H), 7.48 (t, J=8.0 Hz, 1H), 5.74～5.72 (m, 1H), 4.12～4.05 (m, 2H), 3.13～3.08 (m, 1H), 2.41～2.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.5, 147.3, 144.2, 142.4, 137.4, 128.8, 127.9, 125.9, 125.4, 123.6, 120.0, 117.1, 115.6, 76.9, 69.5, 28.0, 25.9.

3-Bromo-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**19**):[7] 43.6 mg, yield 79%, white solid. m.p. 189～191 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, J=8.4 Hz, 1H), 8.23 (d, J=8.4 Hz, 1H), 8.11 (s, 1H), 7.99 (d, J=8.0 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 7.57～7.53 (m, 1H), 7.46 (t, J=8 Hz, 1H), 5.72～5.69 (m, 1H), 4.11～4.03 (m, 2H), 3.12～3.07 (m, 1H), 2.40～2.25 (m, 2H), 2.19～2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 146.3, 143.2, 141.4, 130.4, 130.0, 127.8, 124.8, 124.5, 124.4, 122.6, 119.0, 116.5, 114.5, 75.84, 68.4, 26.9, 24.9.

3-Trifluoromethyl-6-(tetrahydrofuran-2-yl)benzo[4,5]-imidazo[1,2-*c*]quinazoline (**20**):[7] 38.7 mg, yield 72%, white solid. m.p. 199～201 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (d, J=8.4 Hz, 1H), 8.29 (d, J=8.0 Hz, 1H), 8.23 (s, 1H), 8.02 (d, J=8.0 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.59 (t, J=8.0 Hz, 1H), 7.51 (t, J=8.0 Hz, 1H), 5.74 (dd, J=7.2, 4.0 Hz, 1H), 5.13～.07 (m, 2H), 3.15～3.12 (m, 1H), 2.43～2.28 (m, 2H), 2.22～2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.8, 145.8, 143.3, 140.3, 132.2 (C—F, $^2J_{CF}$=33 Hz), 127.9, 125.1, 124.8 (C—F, $^3J_{CF}$=4 Hz), 124.1, 123.4 (C—F, $^3J_{CF}$=4 Hz), 123.2, 123.1, 122.6 (C—F, $^1J_{CF}$=270 Hz), 119.4, 114.8, 76.0, 68.6, 27.1, 25.0. ^{9}F NMR (376 MHz, $CDCl_3$) δ: −62.6.

1,3-Dimethyl-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**21**):[7] 42.0 mg, yield 88%, white solid. m.p. 206～209 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J=8.0 Hz, 1H), 7.93 (d, J=8.0 Hz, 1H), 7.51 (s, 1H), 7.44 (t, J=7.6 Hz, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.19 (s, 1H), 5.64 (d, J=4.4 Hz, 1H), 4.03～4.00 (m, 2H), 3.09 (s, 3H), 3.03～2.98 (m, 1H), 2.41 (s, 3H), 2.31～2.17 (m, 2H), 2.10～2.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.6, 146.9, 143.4, 141.7, 139.8, 136.6, 130.7, 126.8, 125.0, 124.0, 121.9, 119.0, 114.1, 75.8, 68.2, 27.0, 24.8, 22.4, 20.5.

2,4-Dimethyl-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**22**):[7] 41.0 mg, yield 86%, white solid. m.p. 213～215 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (s, 1H), 8.11 (d, J=8.0 Hz, 1H), 7.87 (d, J=8.0 Hz, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.32～7.28 (m, 2H), 5.54 (d, J=3.4 Hz, 1H), 4.00～3.89 (m, 2H), 3.11～3.04 (m, 1H), 2.56 (s, 3H), 2.41 (s, 3H), 2.23～2.17 (m, 2H), 2.09～2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.3, 144.7, 143.2, 137.0, 136.9, 135.3, 132.7, 127.8, 124.3, 121.8, 120.3, 118.6, 117.2, 114.3, 76.0, 68.1, 26.7, 24.8, 20.5, 16.4.

1,4-Dichloro-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**23**):[7] 35.0 mg, yield 65%, white solid. m.p. 203~205 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, J=8.0 Hz, 1H), 8.05 (d, J=8.0 Hz, 1H), 7.64 (dd, J=8.4, 2.2 Hz, 1H), 7.55～7.45 (m, 3H), 5.70～5.69 (m, 1H), 4.06～3.99 (m, 2H), 3.22～3.16 (m, 1H), 2.36～2.27 (m, 2H), 2.17～2.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.3, 144.3, 143.3, 138.5, 130.9, 129.9, 129.3, 128.8, 126.5, 124.9, 123.4, 119.94, 119.92, 114.4, 75.9, 68.5, 27.0, 24.9.

1,3-Dichloro-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**24**):[7] 36.5 mg, yield 68%, white solid. m.p. 206～208 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, J=8.0 Hz, 1H), 8.01 (dd, J=8.0, 2.6 Hz, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.51～7.40 (m, 2H), 5.64 (d, J=3.7 Hz, 1H), 4.04～3.97 (m, 2H), 3.02～2.97 (m, 1H), 2.33～2.18 (m, 2H), 2.13～2.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.1, 145.3, 144.3, 143.8, 136.1, 132.2, 130.4, 127.7, 127.0, 125.8, 124.3, 120.9, 115.3, 76.7, 69.5, 28.1, 25.9.

9,10-Dimethyl-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**25**):[7] 44.3 mg, yield 93%, white solid. m.p. 194～196 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ:

8.66 (d, J=8.0 Hz, 1H), 7.98 (s, 1H), 7.93 (d, J=8.4 Hz, 1H), 7.76 (s, 1H), 7.73 (t, J=8.0 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 5.76 (dd, J=7.4, 4.2 Hz, 1H), 4.15～4.06 (m, 2H), 3.11～3.06 (m, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 2.41～2.38 (m, 1H), 2.31～2.27 (m, 1H), 2.21～2.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.4, 146.3, 141.9 140.4 133.8, 131.5, 130.1, 127.2, 127.0, 126.2, 122.9, 118.8, 117.8, 114.3, 75.8, 68.3, 30.0, 24.7, 20.0, 19.5.

9,10-Dichloro-6-(tetrahydrofuran-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**26**):[7] 44.0 mg, yield 82%, white solid. m.p. 231～233 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (dd, J=8.0, 1.6 Hz, 1H), 8.46 (s, 1H), 8.06 (s, 1H), 7.97～7.94 (m, 1H), 7.80 (td, J=8.0, 1.2 Hz, 1H), 7.69 (t, J=8.0 Hz, 1H), 5.61～5.58 (m, 1H), 4.15～4.10 (m, 2H), 4.02～3.98 (m, 1H), 3.30～3.21 (m, 1H), 2.40～2.30 (m, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 147.6, 147.0, 143.4, 141.7, 139.8, 136.6, 130.7, 126.8, 125.0, 124.0, 121.9, 119.0, 114.1, 75.8, 68.2, 22.4, 20.5.

Mixture of 6-(5-Methyltetrahydrofuran-2-yl)benzo[4,5]-imidazo[1,2-*c*]quinazoline and 5-(2-methyltetrahydro furan-2-yl)benzo[4,5]imidazo[1,2-*c*]quinazoline (**27**):[7] 34.1 mg, yield 75% (for mixture), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (d, J=8.0 Hz, 1H), 8.25 (d, J=8.4 Hz, 0.5H), 8.19 (d, J=8.4 Hz, 0.5H), 7.95 (d, J=8.0 Hz, 1H), 7.89 (d, J=8.0 Hz, 1H), 7.69 (t, J=7.6 Hz, 1H), 7.59 (t, J=7.6 Hz, 1H), 7.49 (t, J=7.6 Hz, 1H), 7.41 (t, J=7.8 Hz, 1H), 5.78～5.58 (m, 1H), 4.39～4.28 (m, 1H), 3.15～3.05 (m, 1H), 2.41～2.29 (m, 2H), 1.90～1.80 (m, 1H), 1.73～1.66 (m, 1H), 1.31～1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.6, 147.5, 147.0, 143.2, 140.7, 140.5, 130.5, 127.9, 127.3, 127.2, 124.5, 123.1, 122.22, 122.20, 118.84, 118.80, 117.65, 117.60, 114.6, 76.9, 76.1, 75.7, 75.5, 32.2, 31.9, 27.5, 27.0, 20.4, 20.1.

Supporting Information MS spectra of mechanistical studies, the ^{1}H NMR and ^{13}C NMR spectra of all products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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