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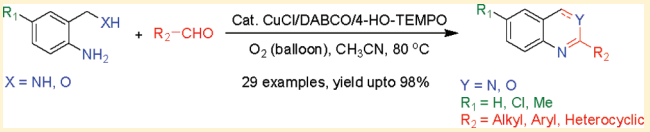
CuCl/DABCO/4-HO-TEMPO-Catalyzed Aerobic Oxidative Synthesis of 2-Substituted Quinazolines and 4*H*-3,1-Benzoxazines

Bing Han,* Xiu-Long Yang, Chao Wang, Yong-Wei Bai, Tai-Chao Pan, Xin Chen, and Wei Yu*

State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University, 222 Tianshui Street, Lanzhou 730000, P. R. China

Supporting Information

ABSTRACT: The Cu/*N*-ligand/TEMPO catalytic system was first applied to the aerobic oxidative synthesis of heterocycles. As demonstrated, 2-substituted quinazolines and 4*H*-3,1-benzoxazines were synthesized efficiently from the one-pot reaction of aldehydes with 2-aminobenzylamines and 2-aminobenzyl alcohols, respectively, by employing CuCl/DABCO/4-HO-TEMPO as the catalysts and oxygen as the terminal oxidant.



Heterocycle moieties, such as quinazolines and 4*H*-3,1-benzoxazines, are present in natural products and synthetic pharmaceutical compounds.[1] These compounds have been extensively studied for their biological and therapeutic activities (Figure 1). They have been used as α-adrenergic blockers for the treatment of high blood pressure, anxiety and panic disorder (prazosin),[2] tyrosine kinase inhibitor for the treatment of breast cancer and solid tumor (lapatinib),[3] GABA receptor inhibitor for anxiolytic and anticonvulsant (etifoxine),[4] and pancreatic lipase inhibitor to treat obesity (cetilistat).[5]

Substituted quinazolines have been synthesized by a number of methods involving several substrates such as 2-aminobenaldehydes and 2-aminobenzoketones or 2-amino-*N*-arylbenzamidines or 2-halophenylmethanamines (Scheme 1).[6] The condensation of 2-aminobenzylamines with aldehydes followed by subsequent oxidation with strong oxidants such as 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ),[7] MnO_2,[8] and NaClO[9] provides a conventional but simple method to synthesize quinazolines. However, despite the synthetic usefulness of this approach, the reported oxidizing conditions suffer from the drawbacks that a stoichiometric amount of nonrenewable oxidant has to be used and the yields are not satisfactory. Therefore, more efficient and environmentally friendly catalytic systems are needed to render this method to be synthetically more attractive.

Herein, we wish to report a facile and efficient approach for the aerobic oxidative synthesis of 2-substituted quinazolines and 4*H*-3,1-benzoxazines by using a one-pot reaction of aldehydes with 2-aminobenzylamines and 2-aminobenzyl alcohols, respectively, and CuCl/DABCO/4-HO-TEMPO as the catalysts under mild conditions (Scheme 2). The Copper/*N*-ligand/TEMPO catalytic system has been proven to be a powerful promoter for the aerobic oxidation of primary alcohols,[10] but its applications in the oxidative dehydrogenation synthesis of heterocycles have not been reported yet. This work provides the first example toward this goal.

Recently, catalytic oxidative reactions using oxygen as the terminal oxidant have received much attention because of their green chemistry and atom economy aspects. On a continuation of our research interest in developing aminoxyl radical-based catalytic oxidative processes[11] for the synthesis of *N*-heterocycles,[12] we reported very recently highly efficient aerobic oxidative approaches, which employ the stable aminoxyl radical TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as the catalyst, for the synthesis of benzoxazoles, benzothiazoles, benzimidazoles and 2-aryl quinazolines.[13] As an extension of this chemistry, we envisioned that TEMPO might also be utilized to promote the one-pot aerobic oxidative reaction of 2-aminobenzylamines with aldehydes. It was expected that after the condensation of 2-aminobenzylamines with aldehydes, the immediate product tetrahydroquinazolines **A** would undergo a TEMPO-catalyzed tandem aerobic oxidative dehydrogenation process to produce quinazolines.

The study was initiated by conducting the reaction of 2-aminobenzylamine **1a** (1 equiv) with 4-Cl-benzaldehyde **2a** (1 equiv). First, **1a** and **2a** were allowed to condensation in situ to give **A**; then 4-HO-TEMPO **4** (0.2 equiv) was added as the catalyst and the reaction system was charged with an oxygen balloon. As expected, the target molecule **3a** was obtained, but the yield was poor due to the oxidative decomposition of **A** (Table 1, entry 1).

To improve the yield, copper salts were employed together with TEMPO to catalyze the reaction. The catalytic systems based on copper and TEMPO has proved to be very effective for the aerobic oxidation of alcohols.[10] We hoped that these systems might work equally well to effect the dehydrogenation of **A**. To our delight, the reaction did improve when CuCl was used, and the yield of **3a** was raised up to 70% (Table 1, entry 3). The yield of **3a** was further improved by the addition of monodentate *N*-containing ligands such as Et_3N, DBU

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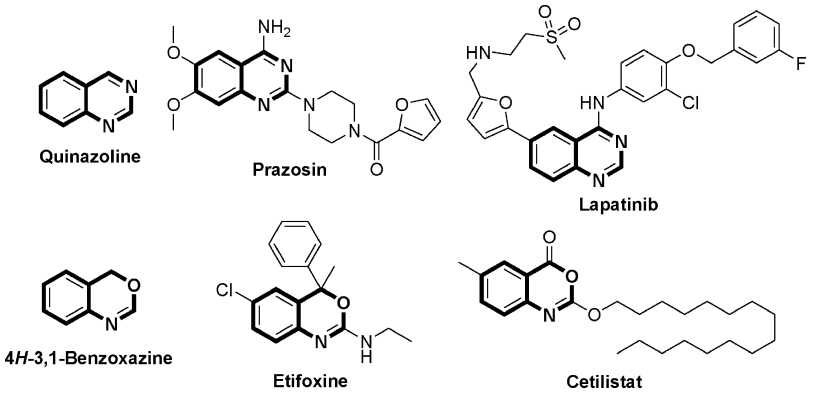
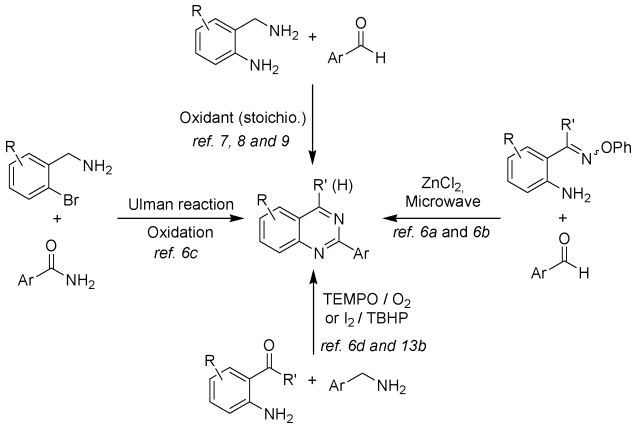
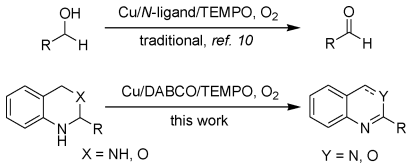


Figure 1. Quinazoline and 4*H*-3,1-benzoxazine moieties in drugs.

Scheme 1. Approaches for the Synthesis of Quinazolines

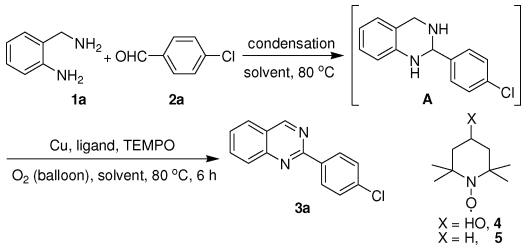


Scheme 2. Applications of Cu/*N*-Ligand/TEMPO Catalytic System



(1,8-diazabicyclo[5.4.0]undec-7-ene), HMTA (hexamethylenetetramine), TBD (1,5,7-triazabicyclo[4,4,0]dec-5-ene), DABCO (1,4-diazabicyclo[2.2.2]octane), and DMAP (*N*,*N*-dimethylpyridin-4-amine) (Table 1, entries 4–9). With DABCO as the ligand, the yield of **3a** reached as high as 98%. By comparison, bidentate ligands such as bipyridine and 1,10-phen (1,10-phenanthroline) are less active than the monodentate ones (Table 1, entries 10 and 11). Control experiments showed the oxidation could also be catalyzed by CuCl or $CuCl_2$ in the absence of TEMPO, but the yields were significantly lower (Table 1, entries 2, 3 and 12–15). On the other hand, excellent result was obtained when CuCl was used as the catalyst and TEMPO as the oxidant (Table 1, entry 24). These results demonstrated that TEMPO is necessary for an efficient reaction. Besides CuCl, several other salts, such as CuBr, $CuCl_2$ and $CuBr_2$, also exhibited good activity, but CuI was found to be much less effective (Table 1, entries 16–19). Among various solvents screened, CH_3CN gave the best result (Table 1, entries 8 and 20–22). When TEMPO **5** was used

Table 1. Optimization on the Catalytic Aerobic Oxidative Synthesis of 2-Aryl Quinazoline[a]



entry	copper	ligand	TEMPO	solvent	yield[b] (%)
1[c]			**4**	toluene	40
2[d]	CuCl			toluene	50
3	CuCl		**4**	CH_3CN	70
4	CuCl	Et_3N	**4**	CH_3CN	80
5	CuCl	DBU	**4**	CH_3CN	63
6	CuCl	HMTA	**4**	CH_3CN	81
7	CuCl	TBD	**4**	CH_3CN	78
8	**CuCl**	**DABCO**	**4**	**CH_3CN**	**98**
9	CuCl	DMAP	**4**	CH_3CN	86
10[e,f]	CuCl	Bipy	**4**	CH_3CN	80
11[e,f]	CuCl	Phen	**4**	CH_3CN	67
12	CuCl			CH_3CN	40
13	CuCl	DABCO		CH_3CN	60
14	$CuCl_2$			CH_3CN	35
15	$CuCl_2$	DABCO		CH_3CN	43
16	CuBr	DABCO	**4**	CH_3CN	95
17	CuI	DABCO	**4**	CH_3CN	65
18	$CuCl_2$	DABCO	**4**	CH_3CN	92
19	$CuBr_2$	DABCO	**4**	CH_3CN	93
20	CuCl	DABCO	**4**	toluene	85
21	CuCl	DABCO	**4**	DMF	85
22	CuCl	DABCO	**4**	DMSO	86
23	CuCl	DABCO	**5**	CH_3CN	95[g]
24[f,h,i]	CuCl	DABCO	**5**	CH_3CN	95
25[h]	CuCl	DABCO	**4**	CH_3CN	trace

[a]2-Aminobenzylamine (**1a**; 1 mmol) and 4-Cl-benzaldehyde (**2a**; 1 mmol) were dissolved in solvent (2 mL) in a 10 mL flask, and the mixture was stirred at 80 °C until the condensation completed (about 2 h). Then copper salts (0.05 mmol), ligand (0.10 mmol), and TEMPO (0.05 mmol) were added to the reaction mixture, and stirring was continued at 80 °C under oxygen until **A** was consumed completely as monitored by TLC (generally about 6 h unless otherwise specified). [b]Isolated yield. [c]At 110 °C after 12 h. [d]At 110 °C. [e]Ligand (0.05 mmol) was used. [f]After 24 h. [g]After 8 h. [h]Under argon. [i]TEMPO (3.0 mmol) was used.

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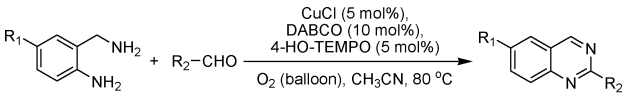
instead of 4-HO-TEMPO **4**, it took longer time for the reaction to complete (Table 1, entry 23). The cheaper 4-HO-TEMPO also showed to be more active than TEMPO in the aerobic oxidation of alcohols.[14] However, almost no desired product was generated when the reaction was performed under argon atmosphere in the same condition, demonstrating that oxygen is the terminal oxidant (Table 1, entry 25).

With the optimized catalytic system CuCl/DABCO/4-HO-TEMPO in hand, we synthesized a variety of substituted quinazolines next. As shown in Table 2, both of aryl aldehydes and alkyl aldehydes could be converted to the corresponding 2-substituted quinazolines in good to excellent yields. The method worked well with benzaldehydes of a range of electronic properties (Table 2, entries 1–9). Weak steric effects were observed for the *ortho*, *meta* and *para* substituted benzaldehydes (Table 2, entries 1, 8 and 9). When alkyl aldehydes or cinnamaldehyde were involved, the yields were a little bit lower (Table 2, entries 10–12). In addition, heterocyclic aldehydes, such as 3-picolylaldehyde and 2-furylaldehyde, could also be used as the substrates, resulting in the formation of the corresponding 2-(pyridin-3-yl)quinazoline and 2-(furan-2-yl)-quinazoline in excellent yields (Table 2, entries 13, 14 and 18). This protocol also showed broad scope for the substituted 2-aminobenzylamines (Table 2, entry 15–18). Notably, the aerobic oxidative reaction could be easily carried out on a gram scale without difficulty (Table 2, entry 1).

Table 2. CuCl/DABCO/TEMPO-Catalyzed One-Pot Aerobic Oxidative Synthesis of 2-Substituted Quinazolines[a]



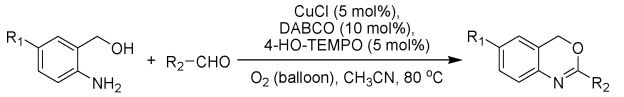
1 2 3

entry	R_1	R_2	time (h)	yield[b] (%)
1	H (**1a**)	4-ClC_6H_4 (**2a**)	8	95[c] (**3a**)
2	H (**1a**)	4-FC_6H_4 (**2b**)	6	96 (**3b**)
3	H (**1a**)	4-$NO_2C_6H_4$ (**2c**)	6	96 (**3c**)
4	H (**1a**)	C_6H_5 (**2d**)	6	95 (**3d**)
5	H (**1a**)	4-$CH_3C_6H_4$ (**2e**)	6	95 (**3e**)
6	H (**1a**)	4-$CH_3OC_6H_4$ (**2f**)	6	98 (**3f**)
7	H (**1a**)	3-BrC_6H_4 (**2g**)	10	86 (**3g**)
8	H (**1a**)	3-ClC_6H_4 (**2h**)	8	95 (**3h**)
9	H (**1a**)	2-ClC_6H_4 (**2i**)	10	86 (**3i**)
10	H (**1a**)	*E*-C_6H_5CH=CH (**2j**)	10	73 (**3j**)
11	H (**1a**)	$(CH_3)_3C$ (**2k**)	8	72 (**3k**)
12	H (**1a**)	$CH_3(CH_2)_2$ (**2l**)	14	40 (**3l**)
13	H (**1a**)	2-furyl (**2m**)	6	90 (**3m**)
14	H (**1a**)	3-pyridinyl (**2n**)	9	98 (**3n**)
15	Cl (**1b**)	4-$CH_3OC_6H_4$ (**2f**)	10	81 (**3o**)
16	Cl (**1b**)	4-ClC_6H_4 (**2a**)	10	90 (**3p**)
17	CH_3 (**1c**)	4-$CH_3OC_6H_4$ (**2f**)	10	89 (**3q**)
18	CH_3 (**1c**)	3-pyridinyl (**2n**)	10	88 (**3r**)

[a]See the Experimental Section. [b]Isolated yield. [c]On gram scale.

Having successfully achieved the aerobic oxidative synthesis of 2-substituted quinazolines, we expanded the catalytic system to the synthesis of 2-substituted 4*H*-3,1-benzoxazines by using 2-aminobenzyl alcohols **6** and aldehydes as the starting materials. As shown in Table 3, 2-substituted 4*H*-3,1-benzoxazines were produced as well in high yields.

Table 3. CuCl/DABCO/TEMPO-Catalyzed One-Pot Aerobic Oxidative Synthesis of 2-Substituted 4*H*-3,1-Benzoxazines[a]



6 2 7

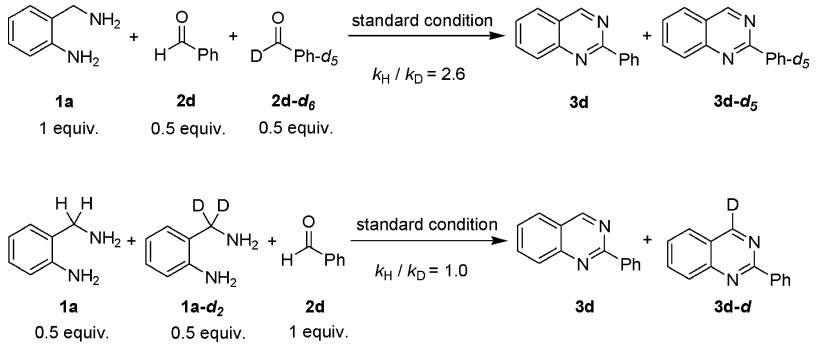
entry	R_1	R_2	time (h)	yield[b] (%)
1	H (**6a**)	4-ClC_6H_4 (**2a**)	12	87 (**7a**)
2	H (**6a**)	4-$NO_2C_6H_4$ (**2c**)	12	89 (**7b**)
3	H (**6a**)	C_6H_5 (**2d**)	11	87 (**7c**)
4	H (**6a**)	4-$CH_3OC_6H_4$ (**2f**)	12	86 (**7d**)
5	H (**6a**)	3-BrC_6H_4 (**2g**)	13	88 (**7e**)
6	H (**6a**)	*E*-C_6H_5CH=CH (**2j**)	12	84 (**7f**)
7	H (**6a**)	2-furyl (**2m**)	15	69 (**7g**)
8	Cl (**6b**)	4-$CH_3OC_6H_4$ (**2f**)	13	92 (**7h**)
9	Cl (**6b**)	4-FC_6H_4 (**2b**)	14	91 (**7i**)
10	CH_3 (**6c**)	4-$CH_3C_6H_4$ (**2e**)	10	79 (**7j**)
11	CH_3 (**6c**)	3-pyridinyl (**2n**)	14	79 (**7k**)

[a]See the Experimental Section. [b]Isolated yield.

To gain some insights into the mechanism of the above-mentioned process, the intermolecular kinetic isotopic effects (KIE) were measured through a competition process by subjecting **1a** to a 1:1 mixture of **2d** and **2d**-d_6, and **2d** to a 1:1 mixture of **1a** and **1a**-d_2, respectively (Scheme 3).[15] The relative rate constant of **2d** to **2d**-d_6 was determined to be 2.6, and that of **1a** to **1a**-d_2 was found to be 1.0. These results indicate that the hydrogen atom abstraction from the benzyl C–H bond derived from the benzaldehyde by Cu^I/DABCO/TEMPO is a rate determining step (RDS) during the oxidation process.

To account for the Cu/DABCO/TEMPO-catalyzed oxidative dehydrogenation process, a mechanism was proposed

Scheme 3. Kinetic Isotope Effects (KIE) Experiment



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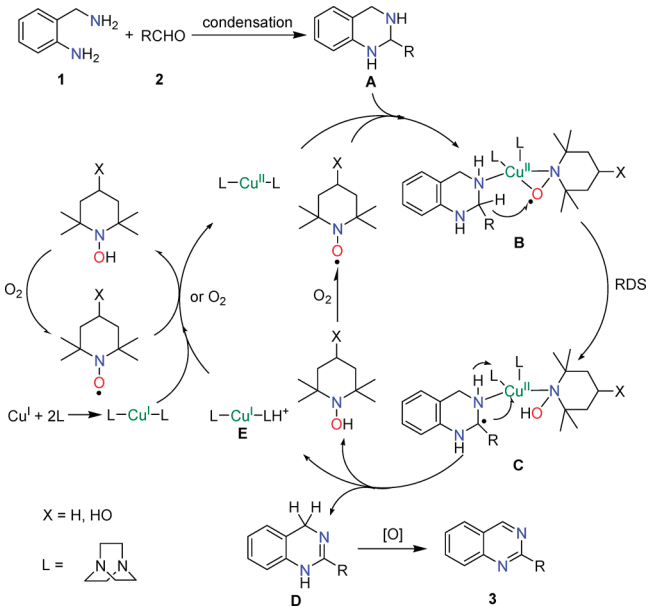
based on Sheldon's study and our experiments. We believe that Cu^{I}-$(DABCO)_2$ initially is oxidized by oxygen or TEMPO to produce Cu^{II}–$(DABCO)_2$ complex, which is further coordinated with *N*-atom of the substrate tetrahydroquinazolines **A** and TEMPO to Cu^{II}-$(DABCO)_2$ complex, which is further coordinated with *N*-atom of the substrate tetrahydroquinazolines **A** and TEMPO to produce an η-2 manner intermediate **B**, as reported by Rey et al.[16] The benzylic hydrogen atom is then transferred to TEMPO via a hydrogen abstraction step, resulting in a radical–TEMPOH copper species **C**. The benzyl radical in **C** is then further oxidized via Cu^{II}-mediated inner-sphere electron transfer to the corresponding carbocation, which deprotonates to afford dihydroquinazoline **D**, with Cu^{I} species **E** and TEMPOH being formed at the same time. TEMPOH is autoxidized to TEMPO, which then reoxidizes Cu^{I} species **E** to Cu^{II}–$(DABCO)_2$. Finally, the intermediate **D** is further oxidized to produce **3**. This later process is expected to be quite facile, as KIE was not observed for the further loss of hydrogen atoms. The proposed oxidative cycle is shown in Scheme 4.

Scheme 4. Plausible Mechanism for Cu^{I}/DABCO/TEMPO-Catalyzed Aerobic Oxidative Synthesis of Quinazolines



The proposed mechanism could also be used to explain why the bidentate ligands are less active than the monodentate ones. This phenomenon is probably due to the steric repulsion between the ligands and substrates which would affect the stability of intermediate **B** (Figure 2).

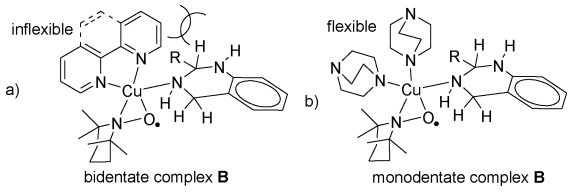


Figure 2. Comparison between mono- and bidentate ligands in catalytic oxidation. (a) Steric repulsion due to the rigidity of bidentate ligands hampers the formation of the intermediate **B** in the catalytic cycle. (b) Steric repulsion is relieved when the ligand is monodentate such as DABCO.

In conclusion, a simple, efficient, and environmentally friendly protocol for the oxidative synthesis of 2-substituted quinazolines and 4*H*-3,1-benzoxazines from easily accessible aldehydes and 2-aminobenzylamines or 2-aminobenzyl alcohols was successfully developed. This method features the use of CuCl/DABCO/TEMPO as the catalysts and oxygen as the terminal oxidant. This work represents the first application of Cu/*N*-ligand/TEMPO catalytic system to the oxidative dehydrogenation synthesis of heterocycles. The extension of this catalytic system to the preparation of other useful heterocycles is under way in our laboratory.

EXPERIMENTAL SECTION

General Experimental Procedure. *Synthesis of 2-Substituted Quinazolines from Aldehydes and 2-Aminobenzylamines (Table 2).* A solution of 2-aminobenzylamines (**1**, 1.0 mmol), aldehydes (**2**, 1.0 mmol) in 2 mL of CH_3CN was stirred at 80 °C until the condensation was complete (about 2 h). To the same solution were added CuCl (4.9 mg, 0.05 mmol), 4-HO-TEMPO (8.6 mg, 0.05 mmol), and DABCO (11.2 mg, 0.10 mmol), and the mixture was stirred at 80 °C for several hours under O_2 atmosphere (balloon). After completion of the reaction (monitored by TLC), the resulting residue was directly purified by silica gel column chromatography to give the product. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

Synthesis of 2-Substituted 4H-Benzo[d][1,3]oxazines from aldehydes and 2-Aminobenzyl Alcohols (Table 3). A solution of 2-aminobenzyl alcohols (**6**, 1.0 mmol) and aldehydes (**2**, 1.0 mmol) in 2 mL of CH_3CN was stirred at 80 °C until the condensation was complete (about 3 h). To the same solution were added CuCl (4.9 mg, 0.05 mmol), 4-HO-TEMPO (8.6 mg, 0.05 mmol), and DABCO (11.2 mg, 0.10 mmol), and the mixture was stirred at 80 °C for several hours under O_2 atmosphere (balloon). After completion of the reaction (monitored by TLC), the resulting residue was directly purified by silica gel column chromatography to give the product. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

Kinetic Isotope Effects (KIE) Experiment (Scheme 3). A solution of 2-aminobenzylamine (**1a**, 1.0 mmol), benzaldehyde (**2d**, 0.5 mmol) and benzaldehyde-d_6 (**2d**-d_6, 0.5 mmol) in 2 mL of CH_3CN was stirred at 80 °C until the condensation completed monitored by TLC (about 2 h). To the same solution were added CuCl (4.9 mg, 0.05 mmol), 4-HO-TEMPO (8.6 mg, 0.05 mmol), and DABCO (11.2 mg, 0.10 mmol), and the mixture was stirred at 80 °C under O_2 atmosphere (balloon) for 0.5 h (about ~15% conversion). The resulting residue was directly purified by silica gel column chromatography to give the mixed product **3d** and **3d**-d_5. The molar ratio of two products is determined by ^{1}H NMR analysis.

A solution of 2-aminobenzylamine (**1a**, 0.5 mmol), 2-aminobenzylamine-d_2 (**1a**-d_2, 0.5 mmol), and benzaldehyde (**2d**, 1 mmol) in 2 mL of CH_3CN was stirred at 80 °C until the condensation was complete as monitored by TLC (about 2 h). To the same solution were added CuCl (4.9 mg, 0.05 mmol), 4-HO-TEMPO (8.6 mg, 0.05 mmol), and DABCO (11.2 mg, 0.10 mmol), and the mixture was stirred at 80 °C under O_2 atmosphere (balloon) for 0.5 h (about ~15% conversion). The resulting residue was directly purified by silica gel column chromatography to give the mixed product **3d** and **3d**-*d*. The molar ratio of two products was determined by ^{1}H NMR analysis.

*2-(4-Chlorophenyl)-quinazoline (**3a**):* white solid; mp 133–135 °C (lit.[9] mp 130–131 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.55 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.87–7.90 (m, 2H), 7.57–7.61 (m, 1H), 7.48 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.9, 150.6, 136.7, 136.4, 134.1, 129.8, 128.5, 128.4, 127.4, 127.0, 123.5; MS m/z (relative intensity) 242 (32.5), 240 (100), 213 (29.9), 178 (29.0), 120 (10.9), 102 (15.8), 76 (10.5), 50 (6.8).

*2-(4-Fluorophenyl)quinazoline (**3b**):* white solid; mp 135–137 °C (lit.[9] mp 129–130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H),

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8.60−8.64 (m, 2H), 8.05 (d, J = 8.8 Hz, 1H), 7.89 (t, J = 7.6 Hz, 2H), 7.59 (t, J = 8.0, 7.6 Hz, 1H), 7.17−7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.4, 160.5, 160.1, 150.7, 134.22, 134.19, 134.15, 130.69, 130.60, 128.5, 127.2, 127.1, 123.5, 115.6, 115.4; MS m/z (relative intensity) 224 (100), 223 (27.9), 197 (52.6), 170 (5.6), 112 (5.3), 76 (10.0).

*2-(4-Nitrophenyl)quinazoline (**3c**):* yellow solid; mp 218−219 °C (lit.[9] mp 218−219 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.81−8.43 (m, 2H), 8.36−8.39 (m, 2H), 8.14 (t, J = 8.4, 0.8 Hz, 1H), 7.96−8.01 (m, 2H), 7.69−7.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 158.8, 150.6, 149.2, 143.8, 134.6, 129.4, 128.9, 128.3, 127.2, 123.9, 123.7; MS m/z (relative intensity) 252 (39.3), 251 (100), 205 (58.5), 115 (8.0), 102 (7.8), 77 (3.5).

*2-Phenylquinazoline (**3d**):* pale yellow solid; mp 97−98 °C (lit.[9] mp 97−98 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.62 (dd, J = 8.0 Hz, J = 2.0 Hz, 2H), 8.08 (d, J = 8.4 Hz, 1H), 7.88−7.92 (m, 2H), 7.50−7.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.4, 150.7, 138.0, 134.0, 130.6, 128.6, 128.5, 127.2, 127.1, 123.5; MS m/z (relative intensity) 207 (17.7), 206 (100), 205 (35.0), 179 (54.4), 103 (18.5), 76 (15.2).

*2-p-Tolylquinazoline (**3e**):* yellow solid; mp 107−109 °C (lit.[9] 97−98 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.51 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.88 (t, J = 8.4, 7.6 Hz, 2H), 7.57 (t, J = 8.0, 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 160.4, 150.7, 140.8, 135.3, 134.0, 129.4, 128.50, 128.48, 127.07, 126.97, 123.5, 21.5; MS m/z (relative intensity) 220 (100), 219 (42.8), 193 (22.0), 165 (9.0), 116 (4.6), 109 (8.0), 91 (5.2), 76 (3.8).

*2-(4-Methoxyphenyl)quinazoline (**3f**):* white solid; mp 91−93 °C (lit.[9] mp 90−91 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.58 (dd, J = 7.2, 2.0 Hz, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.87 (t, J = 8.4, 7.6 Hz, 2H), 7.56 (t, J = 7.6, 7.2 Hz, 1H), 7.03 (dd, J = 7.2, 2.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 160.9, 160.4, 150.8, 134.0, 130.7, 130.2, 128.4, 127.1, 126.8, 123.3, 114.0, 55.4; MS m/z (relative intensity) 236 (100), 235 (19.6), 221 (18.1), 209 (10.6), 193 (12.1), 166 (9.5), 118 (4.4), 97 (4.2), 90 (3.8), 77 (4.1).

*2-(3-Bromophenyl)quinazoline (**3g**):* yellow solid; mp 153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.78 (s, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.89−7.92 (m, 2H), 7.60−7.63 (m, 2H), 7.39 (t, J = 8.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.5, 150.6, 140.0, 134.2, 133.4, 131.5, 130.1, 128.6, 127.6, 127.10, 127.06, 123.7, 122.9; MS m/z (relative intensity) 286 (97.7), 284 (100), 257 (18.1), 205 (42.9), 178 (46.4), 151 (19.0), 102 (33.4), 76 (19.2), 50 (19.1). ESI-HRMS m/z calcd for $C_{14}H_9BrN_2$ + H^+ 285.0022, found:285.0025.

*2-(3-Chlorophenyl)quinazoline (**3h**):* pale yellow solid; mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.63 (t, J = 0.8, 1.2 Hz, 1H), 8.50−8.53 (m, 1H), 8.08 (dd, J = 8.4, 0.8 Hz, 1H), 7.90−7.94 (m, 2H), 7.62−7.66 (m, 1H), 7.44−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.7, 150.7, 139.9, 134.8, 134.3, 130.5, 129.8, 128.69, 128.66, 127.6, 127.1, 126.6, 123.8; MS m/z (relative intensity) 242 (33.3), 240 (100), 239 (20.4), 213 (30.4), 178 (41.1), 151 (11.0), 120 (10.9), 102 (28.3), 76 (14.9); ESI-HRMS m/z Calcd for $C_{14}H_9ClN_2$ + H^+ 241.0527, found 241.0526.

*2-(2-Chlorophenyl)quinazoline (**3i**):* yellow solid; mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.94−8.01 (m, 2H), 7.82−7.85 (m, 1H), 7.70 (t, J = 8.0, 7.2 Hz, 1H), 7.53−7.57 (m, 1H), 7.39−7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 160.1, 150.2, 138.2, 134.2, 132.8, 131.7, 130.4, 130.2, 128.5, 127.9, 127.0, 126.7, 123.1; MS m/z (relative intensity) 242 (22.4), 240 (66.3), 213 (16.9), 205 (100), 178 (31.0), 177 (11.0), 151 (10.6), 120 (9.8), 102 (19.3), 76 (13.4); ESI-HRMS m/z calcd for $C_{14}H_9ClN_2$ + H^+ 241.0527, found 241.0527.

*(E)-2-Styrylquinazoline (**3j**):* white solid; mp 120−121 °C (lit.[9] mp 120−121 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 9.37 (s, 1H), 8.17 (d, J = 15.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.86−7.90 (m, 2H), 7.68 (d, J = 7.2 Hz, 2H), 7.56−7.60 (m, 1H), 7.34−7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 160.2, 150.6, 138.5, 136.2, 134.2, 129.0, 128.8, 128.2, 128.0, 127.7, 127.2, 127.1, 123.4; MS m/z (relative intensity) 232 (39.3), 231 (100), 204 (8.5), 128 (4.4), 115 (8.1), 102 (7.8), 77 (3.5).

*2-tert-Butylquinazoline (**3k**):* yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.99 (m, 1H), 7.83−7.87 (m, 2H), 7.57 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 159.9, 150.2, 133.5, 128.4, 126.8, 126.7, 122.8, 39.6, 29.6; MS m/z (relative intensity) 186 (33.1), 185 (15.3), 171 (100), 144 (29.3), 103 (11.4), 77 (7.6), 57 (7.4).

*2-Propylquinazoline (**3l**):* yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.85−7.90 (m, 2H), 7.58 (m, 1H), 3.11 (t, J = 7.6 Hz, 2H), 1.97 (m, 2H), 1.05 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 160.3, 150.3, 133.9, 127.9, 127.0, 126.8, 123.0, 41.8, 22.2, 13.9; MS m/z (relative intensity) 172 (15.6), 161 (100), 157 (23.4), 144 (47.8), 132 (51.0), 118 (23.0), 77 (10.9).

*2-(Furan-2-yl)quinazoline (**3m**):* brown solid; mp 131−132 °C (lit.[9] mp 131−132 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.87−7.91 (m, 2H), 7.69 (t, J = 0.8, 0.8 Hz, 1H), 7.57−7.61 (m, 1H), 7.46 (dd, J = 2.8, 0.8 Hz, 1H), 6.63 (dd, J = 3.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 154.1, 152.5, 150.4, 145.3, 134.4, 128.4, 127.0, 123.3, 114.0, 112.3; MS m/z (relative intensity) 196 (100), 195 (25.4), 168 (23.3), 114 (10.6), 98 (7.3), 76 (6.8).

*2-(Pyridin-3-yl)quinazoline (**3n**):* yellow solid; mp 94−96 °C (lit.[6c] 94−96 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 9.46 (s, 1H), 8.46 (d, J = 7.6 Hz, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.93 (t, J = 8.0, 7.6 Hz, 2H), 7.64 (t, J = 7.6, 7.6 Hz, 1H), 7.45 (dd, J = 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 159.1, 151.2, 150.6, 150.2, 135.7, 134.3, 133.5, 128.6, 127.7, 127.1, 123.7, 123.3; MS m/z (relative intensity) 208 (14.8), 207 (100), 179 (29.0), 153 (6.1), 129 (2.9), 103 (7.2), 76 (11.2), 50 (6.4).

*6-Chloro-2-(4-methoxyphenyl)quinazoline (**3o**):* yellow solid; mp 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.55 (d, J = 8.8 Hz, 2H), 7.97(d, J = 9.2 Hz, 1H), 7.86 (d, J = 1.0 Hz, 1H), 7.80 (dd, J = 8.8, 1.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 161.1, 159.4, 149.3, 134.9, 132.2, 130.3, 130.25, 130.15, 125.8, 123.7, 114.0, 55.4; MS m/z (relative intensity) 272 (29.7), 270 (100), 255 (20.0), 227 (11.9), 194 (15.2), 149 (14.1), 106 (11.7), 71 (12.7), 57 (13.0); ESI-HRMS m/z calcd for $C_{15}H_{11}ClN_2O$ + H^+ 271.0633, found 271.0637.

*6-Chloro-2-(4-chlorophenyl)quinazoline (**3p**):* yellow solid; mp 207−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.55 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.85 (dd, J = 9.2, 2.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.6, 149.2, 137.2, 136.1, 135.2, 133.0, 129.9, 128.9, 125.8, 124.0; MS m/z (relative intensity) 278 (12.5), 276 (63.2), 274 (100), 247 (28.0), 214 (9.9), 212 (9.9), 177 (26.4), 106 (30.1), 75 (20.6), 57 (15.6); ESI-HRMS m/z calcd for $C_{14}H_8Cl_2N_2$ + H^+ 275.0137, found 275.0133.

*2-(4-Methoxyphenyl)-6-methylquinazoline (**3q**):* yellow solid; mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.55 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 160.2, 159.6, 149.4, 136.9, 136.3, 130.8, 130.0, 128.0, 125.8, 123.3, 113.9, 55.4, 21.6; MS m/z (relative intensity) 250 (100), 249 (14.1), 223 (21.3), 207 (11.3), 180 (6.7), 103 (7.0), 77 (2.3); ESI-HRMS m/z calcd for $C_{16}H_{14}N_2O$ + H^+ 251.1179, found 251.1181.

*6-Methyl-2-(pyridin-3-yl)quinazoline (**3r**):* yellow solid; mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 9.38 (s, 1H), 8.83 (m, 1H), 8.73 (dd, J = 4.8, 1.2 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.77 (dd, J = 8.8, 1.6 Hz, 1H), 7.70 (s, 1H), 7.45 (dd, J = 8.0, 4.8 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 159.9, 158.5, 151.0, 150.1, 149.2, 138.0, 136.7, 135.6, 133.6, 128.3, 125.8, 123.8, 123.3, 21.7; MS m/z (relative intensity) 221 (100), 220 (46.6), 194 (18.8), 179 (6.6), 110 (7.6), 89 (17.7), 78 (3.3), 40 (8.7); ESI-HRMS m/z calcd for $C_{14}H_{11}N_3$ + H^+ 222.1026, found: 222.1023.

*2-(4-Chlorophenyl)-4H-benzo[d][1,3]oxazine (**7a**):* white solid; mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.29−7.33 (m, 1H), 7.26 (m, 1H), 7.18 (m, 1H), 7.00 (d, J = 7.2 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 139.4, 137.6, 130.9, 129.0, 129.3, 129.0, 126.6, 124.7,

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123.7, 122.1, 66.5; MS *m*/*z* (relative intensity) 245 (33.7), 243 (100), 214 (14.6), 180 (5.7), 152 (4.7), 139 (63.0), 106 (16.0), 77 (10.8), 51 (7.2).

*2-(4-Nitrophenyl)-4H-benzo[d][1,3]oxazine (**7b**):* yellow solid; mp 158−159 °C (lit.[9] mp 158−159 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.361(m, 4H), 7.29−7.36 (m, 2H), 7.22−7.26 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 149.5, 138.9, 138.2, 129.2, 128.8, 127.5, 125.2, 123.8, 123.4, 121.9, 66.7; MS *m*/*z* (relative intensity) 254 (100), 225 (9.2), 207 (9.6), 179 (10.5), 150 (22.1), 120 (11.4), 106 (16.1), 76 (17.5), 51 (5.4).

*2-Phenyl-4H-benzo[d][1,3]oxazine (**7c**):* white solid; mp 92−93 °C (lit.[9] mp 92−93 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.2 Hz, 2H), 7.40−7.51 (m, 3H), 7.25−7.33 (m, 2H), 7.15−7.19 (m, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 139.7, 132.4, 131.4, 129.0, 128.2 128.0, 126.4, 124.6, 123.7, 122.3, 66.4; MS *m*/*z* (relative intensity) 209 (100), 208 (32.4), 180 (20.3), 152 (4.1), 105 (62.5), 77 (43.2), 51 (10.4).

*2-(4-Methoxyphenyl)-4H-benzo[d][1,3]oxazine (**7d**):* white solid; mp 138−139 °C (lit.[9] mp 140−141 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.10 (m, 2H), 7.24−7.32 (m, 2H), 7.13−7.16(m, 1H), 7.00 (d, *J* = 6.8 Hz, 1H), 6.91−6.95 (m, 2H), 5.34 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 157.6, 140.0, 129.8, 128.9, 126.0, 124.8, 124.3, 123.6, 122.3, 113.6, 66.4, 55.4; MS *m*/*z* (relative intensity) 239 (91.8), 210 (11.9), 135 (100), 107 (12.1), 92 (7.0), 77 (19.0).

*2-(3-Bromophenyl)-4H-benzo[d][1,3]oxazine (**7e**):* white solid; mp 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.6, 1.6 Hz, 1H), 8.06 (m, 1H), 7.61 (m, 1H), 7.26−7.33 (m, 3H), 7.17−7.21 (m, 1H), 7.00 (dd, *J* = 7.6, 0.4 Hz, 1H), 5.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 139.3, 134.4, 134.2, 130.9, 129.7, 129.1, 126.8, 126.5, 124.8, 123.7, 122.4, 122.1, 66.5; MS *m*/*z* (relative intensity) 289 (99.6), 287 (100), 260 (12.4), 258 (12.2), 185 (14.7), 183 (55.4), 152 (6.7), 132 (10.1), 106 (28.3), 77 (21.9); ESI-HRMS *m*/*z* Calcd for $C_{14}H_{10}BrNO + H^+$: 288.0019, found 288.0021.

*2-Styryl-4H-benzo[d][1,3]oxazine (**7f**):* yellow solid; mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.53 (m, 3H), 7.33−7.39 (m, 3H), 7.25−7.31 (m, 1H), 7.14−7.21 (m, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 139.8, 139.0, 135.4, 129.4, 129.0, 128.8, 127.6, 126.5, 124.4, 123.7, 122.4, 121.6, 66.1; MS *m*/*z* (relative intensity) 235 (100), 234 (58.6), 206 (14.5), 131 (25.2), 116 (6.1), 103 (39.0), 77 (21.3), 51 (6.4); ESI-HRMS *m*/*z* calcd for $C_{16}H_{13}NO + H^+$ 236.1070, found 236.1070.

*2-(Furan-2-yl)-4H-benzo[d][1,3]oxazine (**7g**):* yellow solid; mp 63−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 1H), 7.28−7.34 (m, 2H), 7.18 (m, 1H), 7.06 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.52 (dd, *J* = 3.2, 1.6 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 146.3, 145.6, 139.1, 129.1, 126.5, 124.8, 123.8, 122.2, 114.8, 111.8, 66.3; MS *m*/*z* (relative intensity) 199 (100), 170 (36.7), 143 (11.1), 115 (7.4), 106 (5.9), 95 (43.9), 77 (8.9), 51 (6.4).

*6-Chloro-2-(4-methoxyphenyl)-4H-benzo[d][1,3]oxazine (**7h**):* pale yellow solid; mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−8.08 (m, 2H), 7.26 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.91−6.95 (m, 2H), 5.30 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 157.8, 138.7, 130.9, 129.9, 128.9, 125.6, 124.4, 123.8, 123.7, 113.6, 65.8, 55.4; MS *m*/*z* (relative intensity) 275 (15.0), 273 (45.6), 238 (12.8), 149 (8.3), 135 (100), 107 (13.6), 77 (16.9); ESI-HRMS *m*/*z* calcd for $C_{15}H_{12}ClNO_2 + H^+$ 274.0629, found 274.0625 .

*6-Chloro-2-(4-fluorophenyl)-4H-benzo[d][1,3]oxazine (**7i**):* pale yellow solid, mp 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.14 (m, 2H), 7.27 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.08−7.14 (m, 2H), 7.00 (d, *J* = 2.0 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.8, 156.8, 138.2, 131.5, 130.3, 130.2, 129.1, 128.2, 128.1, 125.9, 123.9, 123.6, 115.5, 115.3, 66.0; MS *m*/*z* (relative intensity) 263 (17.0), 261 (57.4), 232 (10.5), 226 (24.7), 123 (100), 95 (41.2), 75 (18.8); ESI-HRMS *m*/*z* calcd for $C_{14}H_9ClFNO + H^+$ 262.0429, found 262.0430.

*6-Methyl-2-p-tolyl-4H-benzo[d][1,3]oxazine (**7j**):* pale yellow solid; mp 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 5.32 (s, 2H), 2.40 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 141.6, 137.4, 136.1, 129.7, 129.4, 128.9, 127.9, 124.4, 124.2, 122.1, 66.4, 21.5, 21.1; MS *m*/*z* (relative intensity) 237 (100), 222 (19.1), 208 (18.9), 194 (12.2), 119 (93.8), 91 (51.3), 65 (17.8); ESI-HRMS *m*/*z* Calcd for $C_{16}H_{15}NO + H^+$ 238.1226, found 238.1229.

*6-Methyl-2-(pyridin-3-yl)-4H-benzo[d][1,3]oxazine (**7k**):* pale yellow solid; mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 2.0 Hz, 1H), 8.69 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.37 (m, 1H), 7.35 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.82 (s, 1H), 5.38 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 151.7, 149.3, 137.0, 136.6, 135.1, 129.6, 128.4, 124.7, 124.4, 123.0, 121.9, 66.5, 21.2; MS *m*/*z* (relative intensity) 224 (100), 209 (26.5), 195 (18.4), 181 (5.8), 146 (9.2), 106 (28.5), 78 (36.5); ESI-HRMS *m*/*z* calcd for $C_{14}H_{12}N_2O + H^+$ 225.1022, found 225.1028.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR spectra of KIE experiment and copies of ^{1}H and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hanb@lzu.edu.cn, yuwei@lzu.edu.cn.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 4 contained errors in the version published ASAP on December 28, 2011. The correct version was reposted on January 3, 2012.