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Indium-mediated one-pot synthesis of benzoxazoles or oxazoles from 2-nitrophenols or 1-aryl-2-nitroethanones

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ABSTRACT

One-pot reduction-triggered heterocyclizations from 2-nitrophenols to benzoxazoles and from 1-aryl-2-nitroethanones to oxazoles were investigated. In the presence of indium/AcOH in benzene at reflux, 2-nitrophenols and R–C(OMe)$_3$ (R=H, Me, Ph) produced excellent yields of corresponding benzoxazoles within an hour. Similarly, 1-aryl-2-nitroethanones and Ph–C(OMe)$_3$ in the presence of indium/AcOH in acetonitrile transformed into the corresponding oxazoles with good yields.

1. Introduction

N,*O*-Heteroatom-containing oxazole or benzoxazole ring systems occur occasionally in nature and oxazole moiety is a popular heterocyclic unit of biologically active and pharmaceutically interesting compounds.[1] It has been claimed that oxazole and its derivatives act as diverse medicinal mediators, such as anti-inflammatory agents, fungicides, adrenergic antagonists, anti-hypertensive agents, and anti-ulcer agents.[1b] More recently, benzoxazole derivatives, such as UK-1 and their analogs, have been actively investigated as they exhibit a wide range of potent anticancer activities against leukemia, lymphoma, and certain solid tumor-derived cell lines.[2]

Thus, various synthetic methods of oxazole and benzoxazole derivatives have been developed, including one of the most reliable methods, the Robinson–Gabriel synthesis.[1,3] Recent examples of the oxazole or benzoxazole ring formations include the combinatorial library synthesis via the condensation of aldehydes with 2-aminophenols/subsequent DDQ-promoted oxidative cyclization reactions,[4a] solvent-free microwave irradiation of ketones,[4b] ruthenium and/or gold-catalyzed one-pot reactions of propargylic alcohols with amides[4c] or propargylic amides,[4d] copper-catalyzed cyclizations of *o*-halobenzanilides,[4e] and Cu-nanoparticle catalyzed oxidative cyclization of Schiff's bases.[4f]

The applications of indium metal for a wide range of organic transformations have been receiving increasing interest in the past decade because of the metal's eco-friendly green chemistry characteristics.[5] Indium metal is stable in air, moreover, the toxicity observed with many metals acting as a single-electron transfer (SET) agent is little known in indium. Thus, we have been continuously working to utilize indium for efficient reductive organic transformations[6] that include various indium-mediated reductive heterocyclizations via the reductive cyclization reaction of nitroarenes toward nitrogen-containing heterocycles, such as 2,1-benzisoxazoles,[6a] benzimidazoles,[6e] quinolines,[6f] indazoles,[6g,h] and indoles[6i] when there is a proper functional group at the *ortho* position.

Among the indium-mediated reactions we have previously developed, most are intramolecular heterocyclization reactions that are preceded by a reduction-triggered one-pot reaction of nitroarenes. The intermolecular reaction with 2-nitroanilines/benzaldehyde in the presence of indium and 2-bromo-2-nitropropane was not very successful, resulting in a mixture of two products.[6e] More recently, we discovered an interesting reaction that is a one-pot reaction of a reduction-triggered aza-Michael type addition of nitroarenes to vinyl sulfones,[7] which is triggered by the reductive reaction of the nitro group followed by the 1,4-addition of an in situ formed nitrogen nucleophile to the α,β-unsaturated vinyl sulfones. This implies that the intermolecular one-pot reductive heterocyclizations of nitroarenes should be possible if the reduction of the nitroarene versus the coupling reaction between the nitroarene substrate and coupling reagent is properly controlled. Herein we report the one-pot reaction of indium-reduction-triggered intermolecular heterocyclizations toward benzoxazoles or oxazoles starting from 2-nitrophenols or 1-aryl-2-nitroethanones and proper orthoesters as a counter-part coupling reagent.

2. Results and discussion

2.1. Indium-mediated reductive reaction toward benzoxazoles

For the reductive intermolecular reaction toward benzoxazole ring formation, orthoesters such as trimethyl orthoformate (**1**),

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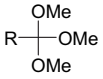
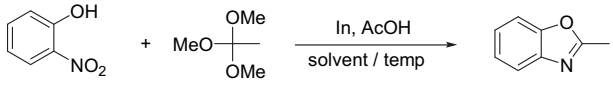
trimethyl orthoacetate (**2**), and trimethyl orthobenzoate (**3**) were elected as the counter-part of the 2-nitrophenols. In the literature, there are several examples of benzimidazole production starting from arylenediamines and orthoesters,[8] which were done in the presence of catalysts such as KSF clay,[8a] $Yb(OTf)_3$,[8b] Zeolite,[8c] iodine,[8d] Lewis acids,[8e] and sulfamic acid.[8f] Thus, orthoesters should be good candidates for the coupling reaction if the nitro group on the 2-nitrophenols that is timely reduced prior to cyclization.



1; R = H
2; R = Me
3; R = Ph

Various control experiments were examined to determine the proper reaction condition for the reduction-initiated heterocyclization of 2-nitrophenols with orthoesters using indium and wide ranges of Lewis acid or acid additives, such as $InCl_3$, I_2, AcOH, and HI or radical anion-producing 2-bromo-2-nitropropane[6a] in various solvent systems. Reactions of 2-nitrophenol and orthoester in the presence of indium/iodine or indium/2-bromo-2-nitropropane usually produce low yields with the starting 2-nitrophenol recovered. Reactions of 2-nitrophenol and orthoester in the presence of the indium/HI, neither organic products nor starting 2-nitrophenol were recovered from the reactions of 2-nitrophenol and orthoester as well. Meanwhile, reactions of 2-nitrophenol and orthoester in the presence of indium/$InCl_3$ in THF/H_2O (v/v=5/1) at 50 °C for 4 h produced 2-aminophenol in low yield (~10–15%), instead of the desired benzoxazole product. However, 2-nitrophenol and orthoester in the presence of indium with a weak acid such as acetic acid produced the desired benzoxazole within a short reaction time. For our indium-mediated intermolecular heterocyclizations, acetic acid seemed to be the best candidate as an additive for our reductive heterocyclization. To obtain the optimum conditions for benzoxazole formation, various reaction conditions in the presence of indium/acetic acid were examined, as shown in Table 1.

Table 1
Indium-mediated reductive heterocyclizations of 2-nitrophenol (1 mmol) to trimethyl orthoacetate under various conditions



4 **2**

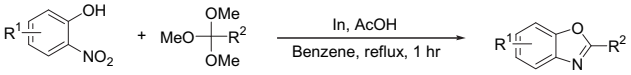
Entry	Molar equiv				Solvent (mL)/Temp (°C)	Time (h)	Yield[a] (%)
	4	**2**	In	AcOH			
1	1	4	4	10	Benzene(5)/reflux	6	95
2	1	6	4	10	Benzene(5)/reflux	1	95
3	1	4	4	10	Benzene(5)/reflux	1	96(92[b])
4	1	2	4	10	Benzene(5)/reflux	1	73
5	1	4	5	10	Benzene(5)/reflux	1	94
6	1	4	3	10	Benzene(5)/reflux	1	93c
7	1	4	4	5	Benzene(5)/reflux	1	89c
8	1	4	4	20	Benzene(5)/reflux	1	96
9	1	4	4	10	Benzene(5)/50	1	Trace[c]
10	1	4	4	10	Toluene(5)/reflux	1	84
11	1	4	4	10	*p*-Xylene(5)/reflux	1	82
12	1	4	4	10	$CHCl_3$(5)/reflux	1	89
13	1	4	4	10	CH_3CN(5)/reflux	1	93
14	1	4	4	10	THF(5)/reflux	1	Trace[c]
15	1	4	4	10	MeOH(5)/reflux	1	Trace[c]
16	1	4	4	10	MeOH(5), satd NH_4Cl(3)/reflux	1	Trace

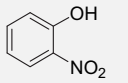
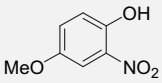
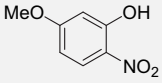
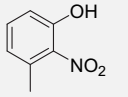
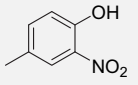
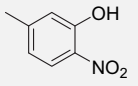
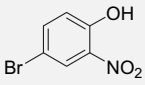
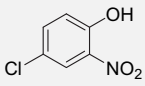
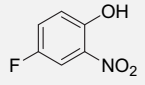
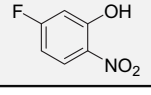
[a] GC yield with an internal standard.
[b] Isolated yield.
[c] Substrate (**4**) remained (entry 9: 94%, entry 14: 82%, entry 15: 91%).

As shown in Table 1, most reactions in an aprotic solvent, such as benzene, toluene, *p*-xylene, chloroform, and acetonitrile did proceed well at reflux (entries 1–13), whereas the reactions in THF (entry 14) or protic solvents (entries 15 and 16) proceeded poorly. After the various reaction conditions were examined, the reaction condition with 2-nitrophenol (1 equiv)/orthoester (4 equiv)/indium (4 equiv)/AcOH (10 equiv) in benzene at reflux (entry 3) was elected as the most optimized condition.

With the optimum reaction condition obtained, the indium/acetic acid-promoted intermolecular heterocyclization of 2-nitrophenol with orthoester to benzoxazole was applied to heterocyclizations of variously substituted 2-nitrophenols with orthoesters to verify the synthetic utilization. Thus, heterocyclizations of variously substituted 2-nitrophenols with orthoesters were

Table 2
Indium/acetic acid-mediated reductive heterocyclization of various 2-nitrophenols (1 mmol) to trimethyl orthoesters (4 equiv) in the presence of indium (4 equiv) and acetic acid (10 equiv) in benzene at reflux for 1 h



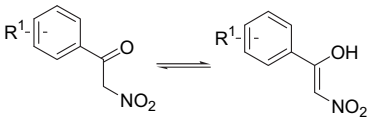
Entry	Substrate	R^2	Product	Yield[a] (%)
1		H	(**5**)	69
2		Me	(**6**)	92
3		Ph	(**7**)	97
4		H	(**8**)	83
5		Me	(**9**)	86
6		Ph	(**10**)	97
7		H	(**11**)	87
8		Me	(**12**)	98
9		Ph	(**13**)	98
10		H	(**14**)	71
11		Me	(**15**)	88
12		Ph	(**16**)	96[b]
13		H	(**17**)	73
14		Me	(**18**)	89
15		Ph	(**19**)	98
16		H	(**20**)	77
17		Me	(**21**)	95
18		Ph	(**22**)	98
19		H	(**23**)	81[c]
20		Me	(**24**)	94[c]
21		Ph	(**25**)	98[b,c]
22		H	(**26**)	81
23		Me	(**27**)	87
24		Ph	(**28**)	95[b]
25		H	(**29**)	50
26		Me	(**30**)	70
27		Ph	(**31**)	92[b]
28		H	(**32**)	53
29		Me	(**33**)	84
30		Ph	(**34**)	94

[a] Isolated yield.
[b] After satd aq NH_4Cl work-up, the concentrated organic layer was added to MeOH/10 M aq NaOH solution (8 mL/2 mL), stirred for 0.5 h at room temperature for the methyl benzoate removal that overlapped with the product on TLC, and extracted with CH_2Cl_2/satd aq NH_4Cl.
[c] Debrominated benzoxazole trace was detected on GC–MS.

examined using the optimized reaction conditions. In most cases, the heterocyclization reaction appeared to be generally applicable, as most of the reactions were completed within 1 h to produce the corresponding benzoxazoles with reasonable yields (Table 2). In general, reactions of 2-nitrophenols with trimethyl orthoacetate (**2**) or trimethyl orthobenzoate (**3**) produced excellent yields of benzoxazoles without any electronic effect from the substituent. On the contrary, the reactions of 2-nitrophenols with trimethyl orthoformate (**1**) produced relatively lower yields of benzoxazoles compared to the reactions of 2-nitrophenols with **2** or **3**. Moreover, the strong inductive effect significantly lowered the yields (Table 2, entries 25 and 28), which was not much observed in the reactions of 2-nitrophenols with **2** or **3**. This implies the possibility of modified intermediate formation prior to cyclization, changes of rate-determining step in the reaction path, and/or interferences by undesired intermediate formation. Mechanistic considerations will be discussed in detail in Section 3.

2.2. Indium-mediated reductive reaction toward oxazoles

As reduction-initiated heterocyclizations of 2-nitrophenols with orthoesters using indium/acetic acid were successful, it may be worth attempting to carry out the syntheses not only with benzoxazoles, but also with oxazoles from proper substrates using a similar reaction condition. One of the important key points of success would be the reduction potential of the substrate, as the nitro group should first be reduced properly to form the imidate intermediate prior to heterocyclization. Aliphatic nitro compounds have less chance for the well-timed reduction, as their reduction potentials are more negative than those of aromatic nitro compounds. However, aliphatic compounds such as 1-aryl-2-nitroethanones could be good candidates for our reduction-triggered oxazole ring formation. As shown in Eq. 1, 1-aryl-2-nitroethanones could be in equilibrium with enol-form via tautomerization because of the conjugation effect with the aryl group, which may result in a reduction potential change that would be similar in value to that of nitroarenes. From the cyclic voltammetric response of 2-nitrophenol (0.10 M) obtained in 0.10 M tetrabutylammonium tetrafluoroborate in acetonitrile solution (platinum electrode, scan rate 50 mV/s), the reduction potential of 2-nitrophenol was observed at −0.99 V (Fig. 1). Similarly, 2-nitro-1-phenylethanone showed a reduction peak at −1.08 V at the same cyclic voltammetric condition, probably because of the enol-form contribution as shown in Eq. 1, which implies the possibility of successful heterocyclization of reduction-triggered oxazole ring formation similar to that of benzoxazole ring formation.



(1)

Thus, a reaction condition similar to that applied to benzoxazole ring formation was attempted with 2-nitro-1-phenylethanone with orthoesters. Unfortunately, 2-nitro-1-phenylethanone with orthoesters in the presence of indium/AcOH in benzene did not work well and mostly resulted in poor yields of the desired oxazoles. However, 2-nitro-1-phenylethanone with trimethyl orthobenzoate did start working after the reaction condition was varied, particularly by changing the solvent. After the various reactions were examined, the optimum reaction condition was determined: 2-nitro-1-phenylethanone (1 mmol) with trimethyl orthobenzoate (4 equiv) in the presence of indium (4 equiv)/AcOH (10 equiv) in acetonitrile (15 mL) at reflux, which was analogous to the optimum reaction condition of benzoxazole synthesis, except for the solvent. This condition produced the 2,5-diphenyl-substituted oxazole with a good yield (60%, Scheme 1, Eq. 4), whereas the reactions of 2-nitro-1-phenylethanone with trimethyl orthoformate or trimethyl orthoacetate failed to produce a reasonable yield of oxazole formation. The reaction failure with trimethyl orthoformate or trimethyl orthoacetate presumably arises from the thermodynamic driving force difference of the produced oxazoles or the difficulties of the desired intermediate formation, since the conjugative effect of the 5-aryloxazoles (products from trimethyl orthoformate or trimethyl orthoacetate) is not as strong as that of 5-aryl-2-phenyl-substituted oxazoles (products from trimethyl orthobenzoate). Despite the failure with trimethyl orthoformate (**1**) or trimethyl orthoacetate (**2**), the methodology with

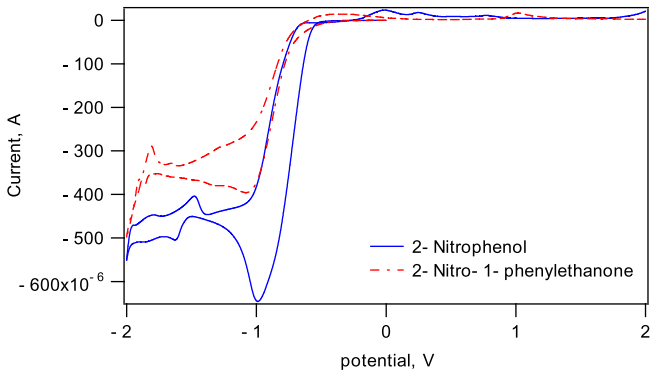
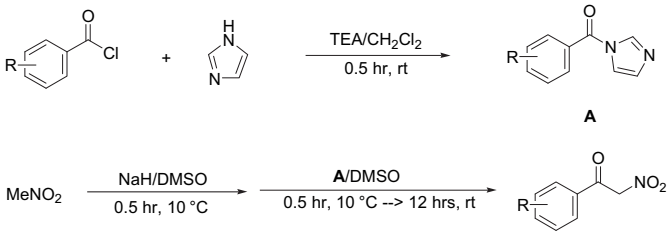
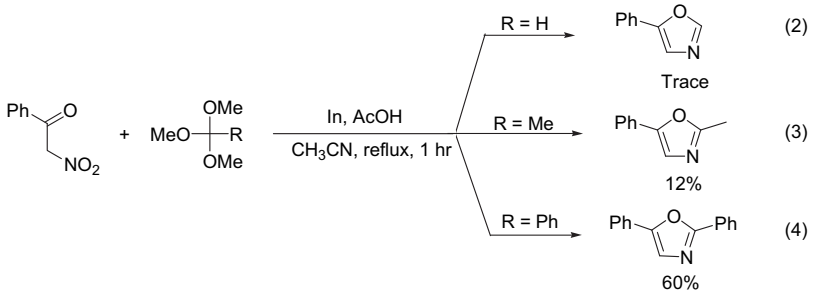


Figure 1. Cyclic voltamograms (50 mV/s) of 2-nitrophenol and 2-nitro-1-phenylethanone (0.10 M) at a Pt electrode in MeCN containing in 0.10 M tetrabutylammonium tetrafluoroborate electrolyte (reference electrode, Ag/Ag^{+}).

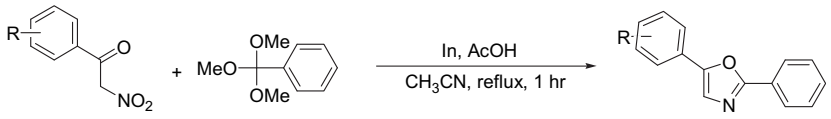


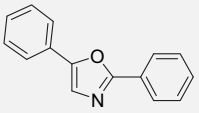
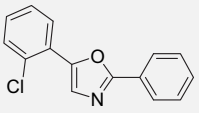
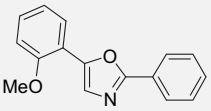
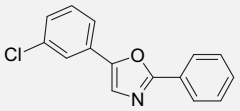
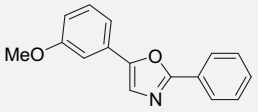
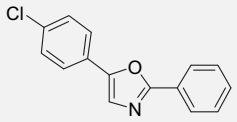
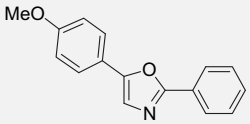
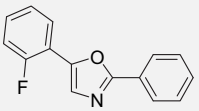
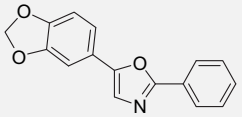
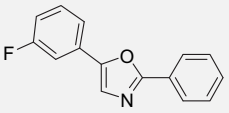
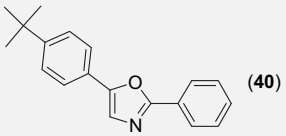
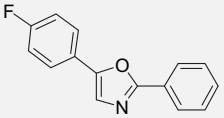
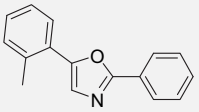
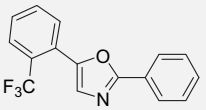
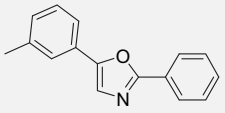
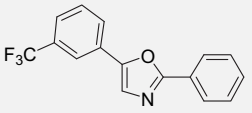
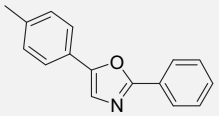
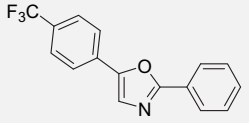
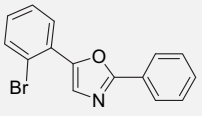
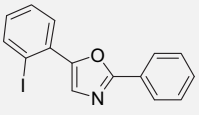
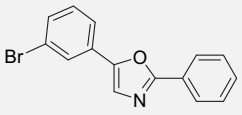
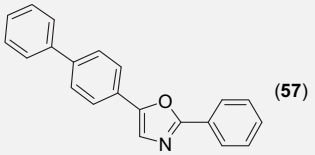
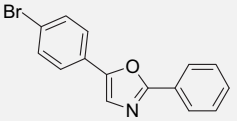
Scheme 2.



Scheme 1.

Table 3
Indium/acetic acid-triggered reductive heterocyclizations of various 2-nitro-1-phenylethanones (1 mmol) to trimethyl orthobenzoate (4 equiv) in the presence of indium (4 equiv) and acetic acid (10 equiv) in acetonitrile (15 mL) at reflux for 1 h



Entry	Substrate	Product	Yield[a] (%)	Entry	Substrate	Product	Yield[a] (%)
1	H	 (**35**)	60	13	2-Cl	 (**47**)	63[b]
2	2-OCH_3	 (**36**)	53	14	3-Cl	 (**48**)	68
3	3-OCH_3	 (**37**)	55	15	4-Cl	 (**49**)	68
4	4-OCH_3	 (**38**)	47	16	2-F	 (**50**)	75[b]
5	3,4-OCH_2O	 (**39**)	46	17	3-F	 (**51**)	70
6	4-*t*-buytl	 (**40**)	53	18	4-F	 (**52**)	66
7	2-CH_3	 (**41**)	66	19	2-CF_3	 (**53**)	73
8	3-CH_3	 (**42**)	59	20	3-CF_3	 (**54**)	67
9	4-CH_3	 (**43**)	55	21	4-CF_3	 (**55**)	66
10	2-Br	 (**44**)	72[b,c]	22	2-I	 (**56**)	45[d]
11	3-Br	 (**45**)	67	23	4-Ph	 (**57**)	59
12	4-Br	 (**46**)	64[c]				

[a] Isolated yield.
[b] After 1 N aq HCl work-up, the concentrated organic layer was added to MeOH/10 M aq NaOH solution (10 mL/3 mL), stirred for 0.5 h at room temperature for the methyl benzoate removal that overlapped with the product on TLC, and extracted with CH_2Cl_2/satd aq NH_4Cl.
[c] Debrominated 2,5-diphenyloxazole trace was detected on GC–MS.
[d] Deiodinated 2,5-diphenyloxazole was observed on GC–MS (GC yield ~5%).

trimethyl orthobenzoate is still worth investigating as the syntheses of biologically active 2,5-diaryl-substituted oxazole alkaloids, such as texaline, texamine, and balsoxin have recently been getting more interest.[9]

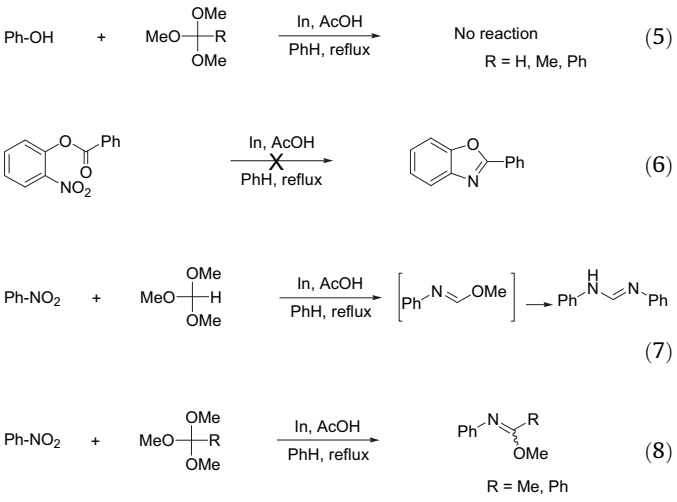
Thus, to develop the 2,5-diaryl-substituted oxazole synthesis, various 1-aryl-2-nitroethanone precursors were prepared by the two-step synthesis starting from the corresponding acid chloride as shown in Scheme 2. The overall yield of the two-step synthesis was 50–79%.

After the starting 1-aryl-2-nitroethanone substrates were prepared, indium-mediated intermolecular coupling-based oxazole syntheses were examined. The results are summarized in Table 3. Most of the reactions worked fairly well and produced the desired 2,5-aryl-substituted oxazoles in yields ranging from 45 to 75%. As shown in Table 3, reactions performed with differently substituted 1-aryl-2-nitroethanone derivatives seemed to be unaffected by substitution on the phenyl group. Neither electron-donating nor electron-withdrawing groups showed any great influence on product yield, similar to the benzoxazole synthesis. However, it is worth noting that some of the bromo- (entries 10 and 12) or iodo- (entry 22) substituted substrates produced a dehalogenated product that served as strong evidence of the involvement of radical or radical anion species in the reaction.

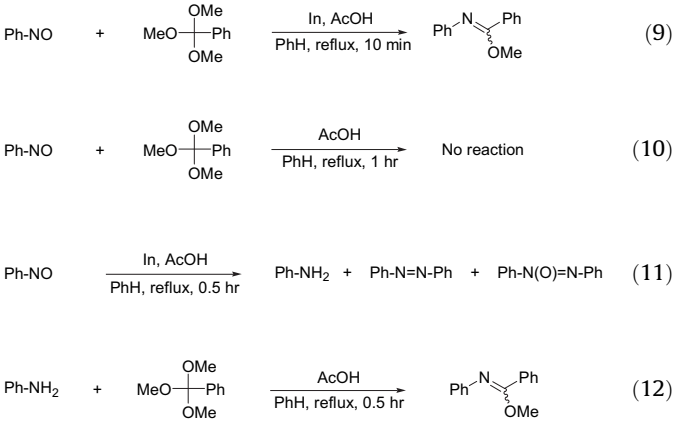
2.3. Mechanistic considerations

2.3.1. Intermediacy. To elucidate the possible intermediate, several control reactions were attempted in order to determine the possibility of coupling between the orthoester and the nitrogen intermediate that forms in situ from the reduction of the nitro group. There were two possibilities for the intermediate formation: one was the reaction of the phenol group with orthoesters to form an ester-like intermediate that may cyclize with the reduced nitrogen intermediate, and the other was that a reduced nitro group first produces an intermediate, which is then followed by cyclization with the neighboring hydroxyl group. Thus, the coupling reactions of phenol with orthoesters and reductive coupling reactions of nitrobenzene with orthoesters in the presence of indium and AcOH were independently examined, which may provide a clue for the identification of the prior intermediate stage. The various coupling reactions of phenol with orthoesters failed to elicit a reaction in any condition (Eq. 5). In addition, pre-prepared 2′-nitrophenyloxy benzoate did not proceed to cyclization in our reductive condition (Eq. 6). Therefore, the possibility of an initial in situ ester formation and a follow-up reductive cyclization to the benzoxazole ring could be eliminated.

In contrast, reductive coupling reactions of nitrobenzene with orthoesters in the presence of indium and AcOH exhibited interesting results. The reaction of nitrobenzene (1 mmol) with trimethyl orthoformate (**1**, 4 equiv) in the presence of AcOH (10 equiv)/indium (4 equiv) in benzene (5 mL) at reflux transformed into *N*,*N*′-diphenylformamidine with a trace amount of imidate, as identified by GC–MS (Eq. 7), within 0.5 h. Meanwhile, the reactions of nitrobenzene (1 mmol)/indium (4 equiv) with trimethyl orthoacetate (**2**, 4 equiv) or trimethyl orthobenzoate (**3**, 4 equiv) in benzene (5 mL) at reflux produced mostly methyl imidate (Eq. 8) within 0.5 h. The formation of *N*,*N*′-diphenylformamidine shown in Eq. 7 is believed to have arisen from *N*-phenylformimidate and aniline, which are formed in situ during the reductive reaction of nitrobenzene and trimethyl orthoformate. Roberts et al. reported the *N*-phenylformimidate formation from the reactions of aniline hydrochloride with a large excess of trimethyl orthoformate.[10] They also observed the formation of *N*,*N*′-diphenylformamidine. Thus, imidate could be an actual intermediate for our reductive one-pot cyclization of 2-nitrophenols and orthoesters to the benzoxazole ring formation.

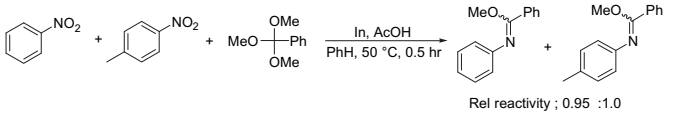


As imidate formation during the reductive coupling reactions of 2-nitrophenols with orthoesters was expected from the reaction of nitroso intermediate and orthoesters, several control experiments with nitrosobenzene were examined to confirm the reaction intermediacy. As we expected, reactions of nitrosobenzene (1 mmol) with trimethyl orthobenzoate (**3**, 4 equiv) in the presence of AcOH (10 equiv)/indium (4 equiv) in benzene (5 mL) at reflux produced the desired imidate quantitatively within 10 min (Eq. 9). In the absence of indium, no reaction was observed (Eq. 10). The reaction of nitrosobenzene in the presence of indium (4 equiv)/AcOH (10 equiv) in the absence of trimethyl orthobenzoate (**3**) at benzene reflux for 0.5 h produced mixtures of aniline, azobenzene, and azoxybenzene (approximately ~3/2/1 by GC analysis, Eq. 11). It was certain that the nitroso anion was involved in the imidate formation. However, it was difficult to distinguish whether the orthoester coupled with the nitroso anion species or if the aniline intermediate produced the imidate intermediate as aniline coupled with trimethyl orthobenzoate as readily as with nitrosobenzene within 0.5 h under the same conditions (Eq. 12).

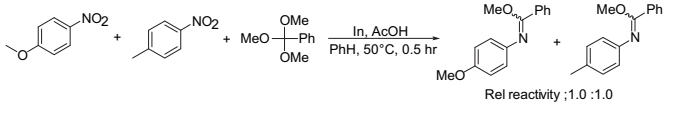


2.3.2. Relative reactivity. As the reductive coupling step could be a key step for the reaction rate, the influence of the substituent on the reductive coupling step was studied. To evaluate the reactivity difference in the reductive coupling step of the nitro group, several competition reactions were examined. Competition reactions for the relative reactivities of the substituted nitrobenzenes for the reduction step examined [substrates (0.5 mmol for each)/trimethyl orthobenzoate (4 equiv)/indium (4 equiv)/AcOH (10 equiv) in benzene (5 mL) at 50 °C for 0.5 h] revealed about the

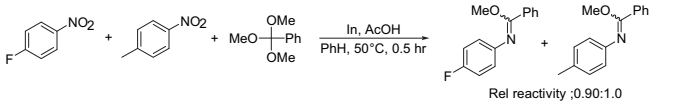
same relative reactivity regardless of the substituent, that is, there was little effect from the electron-donating (methoxy or methyl) group or the electron-withdrawing group (fluoro) (Eqs. 13–15). Thus, based on the competition experiments, it was concluded that there should be no significant reactivity differences in the reductive coupling step in our cyclization reaction. As all of the reactions had similar reaction completion times, the cyclization step also seemed to be unaffected by the electronic effects of the substituent.



(13)

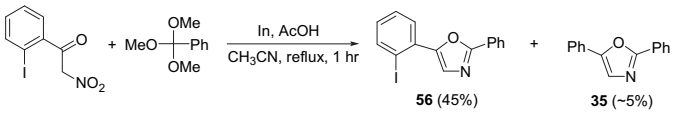


(14)



(15)

2.3.3. Evidences of radical anion/radical species. As mentioned earlier, bromo- (Table 2, entries 19–21 and Table 3, entries 10 and 12) and iodo- (Table 3, entry 22 and Eq. 16) substituted substrates exhibit a dehalogenated product as a trace (bromo-derivatives) or a minor (iodo-derivative). Those derivatives are possible by-products when the radical or radical anion species were involved during the reaction path.[11] Without doubt, indium-mediated single-electron transfer (SET) processes were involved during the cyclization reaction. As nitroarenes or 1-aryl-2-nitroethanones can easily accept an electron from the indium, the radical anion species formation would trigger the initial reductive reaction, and the consecutive proton and electron transfer processes may easily produce a nitroso intermediate.

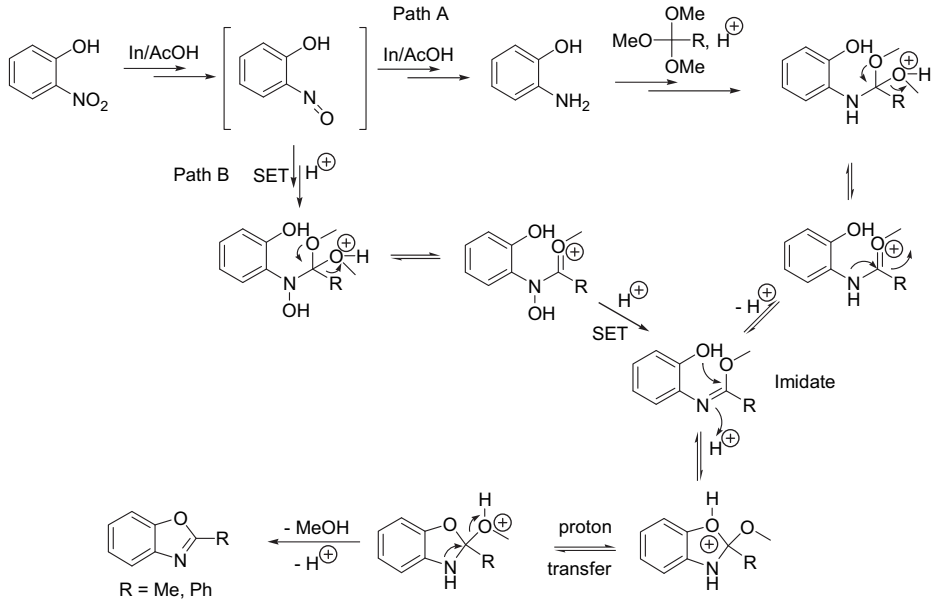


(16)

2.3.4. Plausible mechanism. Based on various experiments, a plausible mechanism is proposed in Scheme 3. By the consequent electron transfers and proton transfers, the nitro group could first transform into a nitroso intermediate. The nitroso intermediate may be transformed into the aniline species via electron transfer and proton transfer processes, if the proton transfer reactions are highly favorable (path A in Scheme 3), and then it can react further to the imidate intermediate. Another possibility is the coupling reaction of the nitroso radical anion with the orthoester to form the imidate intermediate, as shown in path B in Scheme 3. After the imidate intermediate is formed by either path A or B, an acid-assisted attack by the hydroxyl group toward the neighboring imidate group followed by the loss of MeOH due to the aromatization driving forces would produce the benzoxazole ring. A similar reaction path is also expected for the oxazole ring formation from 1-aryl-2-nitroethanone derivatives.

3. Conclusion

In conclusion, we have described a simple and efficient method for a one-pot reduction-triggered heterocyclization toward benzoxazoles or oxazoles. In the presence of indium/AcOH in benzene at reflux, 2-nitrophenols and R–C(OMe)$_3$ (R=H, Me, Ph) produced corresponding benzoxazoles within an hour with excellent yield. Similarly, 1-aryl-2-nitroethanones and Ph–C(OMe)$_3$ in the presence of indium/AcOH in acetonitrile transformed into the corresponding oxazoles with good yield. Our findings may serve as a foundation for the development of a new synthetic path toward valuable benzoxazole and oxazole derivatives.



Scheme 3.

4. Experimental section

4.1. General considerations

Most of the chemical reagents were purchased from Aldrich and, in most cases, were used without further purification. Solvents were purchased and dried using the standard method. ^{1}H NMR spectra were recorded on a 400 MHz Jeol instrument, and ^{13}C NMR spectra were recorded on a 100 MHz Jeol instrument. Chemical shifts were reported in parts per million relative to the residual solvent as an internal standard. HRMS spectra were recorded on a JEOL JMS-DX 303 mass spectrometer, and GC–MS spectra were recorded on an Agilent 6890 N GC connected with an Agilent 5975 mass selective detector. Infrared (IR) spectra were recorded using MB104 FTIR (ABB Bomem Inc.). Melting points were determined on an electrothermal apparatus and were uncorrected. All the major products were isolated by flash column chromatography on silica gel (230–400 mesh ATSM, purchased from Merck) with eluents of mixed solvents (ethyl acetate and hexane).

4.2. General procedure for the indium-mediated reductive reaction of 2-nitrophenols with trimethyl orthoesters to benzoxazoles

2-Nitrophenol derivative (1 mmol) was added to a mixture of indium powder (459 mg, 4.0 mmol) and acetic acid (0.572 mL, 10 mmol) in benzene (2 mL), and then trimethyl orthoester (4.0 mmol) in benzene (3 mL) was added. The reaction mixture was stirred at reflux under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was diluted with CH_2Cl_2 (30 mL), filtered through Celite, poured into satd aq NH_4Cl solution (30 mL), and then extracted with CH_2Cl_2 (30 mL×3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v=10/90) through a silica gel column to give the corresponding benzoxazoles. Some of the reaction mixture (refer to Table 2) was additionally treated to remove the methyl benzoate that overlapped with the product on TLC and column chromatography after the routine work-up process, i.e., the concentrated organic layer was added in MeOH/10 M aq NaOH solution (8 mL/2 mL), stirred for 0.5 h at room temperature, and extracted with satd aq NH_4Cl/CH_2Cl_2. The structures of the benzoxazoles were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and GC–MS, and were mostly known compounds.[12]

*4.2.1. Benzoxazole (**5**)*[12a]. Yield 69%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.82–7.78 (m, 1H), 7.61–7.57 (m, 1H), 7.41–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 149.9, 140.0, 125.5, 124.5, 120.6, 110.9; IR (KBr) 3110, 1450, 1235 cm^{-1}; GC–MS *m*/*z* (rel intensity) 119 (M^+, 100), 91 (48), 63 (28).

*4.2.2. 2-Methylbenzoxazole (**6**)*[12b]. Yield 92%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.47; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (m, 1H), 7.47–7.45 (m, 1H), 7.30–7.27 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.9, 141.5, 124.4, 124.0, 119.4, 110.1, 14.5; IR (KBr) 3058, 2931, 1456, 1242 cm^{-1}; GC–MS *m*/*z* (rel intensity) 133 (M^+, 100), 104 (19), 78 (14), 63 (19).

*4.2.3. 2-Phenylbenzoxazole (**7**)*[12c]. Yield 97%. White solid, mp 110–111 °C; TLC (30% ethyl acetate/hexane) R_f 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.25 (m, 2H), 7.80–7.77 (m, 1H), 7.60–7.56 (m, 1H), 7.54–7.52 (m, 3H), 7.37–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 150.7, 142.1, 131.5, 128.9, 127.6, 127.2, 125.1, 124.5, 120.0, 110.6; IR (KBr) 3060, 1450, 1244 cm^{-1}; GC–MS *m*/*z* (rel intensity) 195 (M^+, 100), 92 (21), 77 (7), 63 (11).

*4.2.4. 5-Methoxybenzoxazole (**8**)*[12d]. Yield 83%. White solid, mp 49–52 °C; TLC (30% ethyl acetate/hexane) R_f 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.47 (d, 1H, *J*=8.9 Hz), 7.27 (d, 1H, *J*=2.6 Hz), 7.00 (dd, 1H, *J*=8.9, 2.6 Hz), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 153.2, 144.6, 140.9, 114.5, 111.0, 103.1, 55.9; IR (KBr) 3126, 3012, 2979, 2939, 1480, 1282 cm^{-1}; GC–MS *m*/*z* (rel intensity) 149 (M^+, 100), 134 (61), 119 (6), 107 (28), 91 (3), 79 (28), 63 (6), 51 (11).

*4.2.5. 5-Methoxy-2-methylbenzoxazole (**9**)*[12e]. Yield 96%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 1H, *J*=9.2 Hz), 7.14 (d, 1H, *J*=2.8 Hz), 6.88 (dd, 1H, *J*=9.2, 2.8 Hz), 3.84 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 157.0, 145.5, 142.3, 112.6, 110.2, 102.6, 55.8, 14.5; IR (KBr) 3072, 3005, 2941, 2835, 1440, 1286 cm^{-1}; GC–MS *m*/*z* (rel intensity) 163 (M^+, 100), 148 (77), 107 (37), 79 (23), 63 (5), 51 (8).

*4.2.6. 5-Methoxy-2-phenylbenzoxazole (**10**)*[12d]. Yield 97%. White solid, mp 81–84 °C; TLC (30% ethyl acetate/hexane) R_f 0.53; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24–8.21 (m, 2H), 7.52–7.51 (m, 3H), 7.46 (d, 1H, *J*=8.8 Hz), 7.26 (d, 1H, *J*=2.4 Hz), 6.96 (dd, 1H, *J*=8.8, 2.4 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 157.4, 145.4, 142.9, 131.4, 128.9, 127.5, 127.3, 113.7, 110.7, 102.9, 55.9; IR (KBr) 3066, 3009, 2979, 2939, 2828, 1477, 1279 cm^{-1}; GC–MS *m*/*z* (rel intensity) 225 (M^+, 100), 210 (68), 182 (4), 107 (19), 79 (18), 63 (4), 51 (9).

*4.2.7. 6-Methoxybenzoxazole (**11**)*[12f]. Yield 87%. White solid, mp 52–54 °C; TLC (30% ethyl acetate/hexane) R_f 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.66 (d, 1H, *J*=8.8 Hz), 7.09 (d, 1H, *J*=2.3 Hz), 6.99 (dd, 1H, *J*=8.8, 2.3 Hz), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 151.5, 150.9, 133.7, 120.5, 113.1, 95.4, 55.9; IR (KBr) 3123, 3063, 2838, 1436, 1286 cm^{-1}; GC–MS *m*/*z* (rel intensity) 149 (M^+, 100), 134 (59), 119 (5), 106 (35), 91 (5), 80 (12), 63 (7), 51 (11).

*4.2.8. 6-Methoxy-2-methylbenzoxazole (**12**)*[12e]. Yield 98%. White solid, mp 60–61 °C; TLC (30% ethyl acetate/hexane) R_f 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1H, *J*=8.7 Hz), 7.01 (d, 1H, *J*=2.3 Hz), 6.91 (dd, 1H, *J*=8.7, 2.3 Hz), 3.85 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 157.7, 151.7, 135.2, 119.3, 111.9, 95.3, 55.9, 14.4; IR (KBr) 3073, 2979, 2955, 2845, 1488, 1291 cm^{-1}; GC–MS *m*/*z* (rel intensity) 163 (M^+, 100), 148 (96), 120 (13), 106 (28), 79 (13), 51 (14).

*4.2.9. 6-Methoxy-2-phenylbenzoxazole (**13**)*[12g]. Yield 98%. White solid, mp 66–69 °C; TLC (30% ethyl acetate/hexane) R_f 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21–8.19 (m, 2H), 7.65 (d, 1H, *J*=8.7 Hz), 7.51–7.49 (m, 3H), 7.11 (d, 1H, *J*=2.4 Hz), 6.97 (dd, 1H, *J*=8.7, 2.4 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.3, 151.6, 135.9, 131.0, 128.9, 127.4, 127.2, 120.0, 112.8, 95.4, 55.9; IR (KBr) 3069, 2999, 2935, 2835, 1453, 1269 cm^{-1}; GC–MS *m*/*z* (rel intensity) 225 (M^+, 100), 210 (85), 182 (17), 154 (5), 105 (8), 79 (11), 63 (4), 51 (7).

*4.2.10. 4-Methylbenzoxazole (**14**)*[12h]. Yield 71%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.41 (d, 1H, *J*=7.6 Hz), 7.29 (t, 1H, *J*=7.6 Hz), 7.17 (d, 1H, *J*=7.6 Hz), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 149.7, 139.2, 130.9, 125.2, 125.0, 108.2, 16.4; IR (KBr) 3099, 2928, 1460, 1242 cm^{-1}; GC–MS *m*/*z* (rel intensity) 133 (M^+, 100), 104 (25), 78 (40), 63 (5), 51 (17).

*4.2.11. 2,4-Dimethylbenzoxazole (**15**)*[12b]. Yield 88%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.53; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 1H, *J*=8.0 Hz), 7.18 (t, 1H, *J*=8.0 Hz), 7.09 (d, 1H, *J*=8.0 Hz), 2.62 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 150.6,

140.5, 129.6, 124.6, 124.0, 107.4, 16.4, 14.4; IR (KBr) 3062, 2924, 2854, 1419, 1242 cm^{-1}; GC–MS *m*/*z* (rel intensity) 147 (M^+, 100), 132 (7), 118 (12), 106 (17), 78 (34), 51 (8).

*4.2.12. 4-Methyl-2-phenylbenzoxazole (**16**)*[12i]. Yield 96%. White solid, mp 94–97 °C; TLC (30% ethyl acetate/hexane) R_f 0.67; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29–8.26 (m, 2H), 7.54–7.51 (m, 3H), 7.42 (dd, 1H, *J*=8.0, 0.8 Hz), 7.26 (t, 1H, *J*=8.0 Hz), 7.16 (dd, 1H, *J*=8.0, 0.8 Hz), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 150.5, 141.4, 131.2, 130.6, 128.8, 127.6, 127.4, 125.0, 124.7, 107.8, 16.6; IR (KBr) 3061, 2955, 2918, 1443, 1237 cm^{-1}; GC–MS *m*/*z* (rel intensity) 209 (M^+, 100), 180 (13), 105 (8), 78 (15), 51 (5).

*4.2.13. 5-Methylbenzoxazole (**17**)*[12h]. Yield 73%. White solid, mp 49–51 °C; TLC (30% ethyl acetate/hexane) R_f 0.53; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.58 (s, 1H), 7.46 (d, 1H, *J*=8.3 Hz), 7.20 (d, 1H, *J*=8.3 Hz), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 148.2, 140.2, 134.4, 126.7, 120.4, 110.3, 21.4; IR (KBr) 3103, 2925, 2865, 1480, 1259 cm^{-1}; GC–MS *m*/*z* (rel intensity) 133 (M^+, 100), 104 (19), 78 (33), 63 (5), 51 (15).

*4.2.14. 2,5-Dimethylbenzoxazole (**18**)*[12j]. Yield 89%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.43; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.33 (d, 1H, *J*=8.2 Hz), 7.09 (d, 1H, *J*=8.2 Hz), 2.60 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 149.2, 141.7, 133.8, 125.4, 119.3, 109.5, 21.4, 14.5; IR (KBr) 3032, 2922, 2861, 1483, 1262 cm^{-1}; GC–MS *m*/*z* (rel intensity) 147 (M^+, 100), 132 (8), 118 (8), 106 (21), 78 (39), 51 (10).

*4.2.15. 5-Methyl-2-phenylbenzoxazole (**19**)*[12k]. Yield 98%. White solid, mp 112–114 °C; TLC (30% ethyl acetate/hexane) R_f 0.68; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26–8.21 (m, 2H), 7.55 (m, 1H, *J*=1.0 Hz), 7.52–7.49 (m, 3H), 7.45 (d, 1H, *J*=8.3 Hz), 7.15 (dd, 1H, *J*=8.3, 1.0 Hz), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 149.0, 142.3, 134.3, 131.3, 128.8, 127.5, 127.3, 126.2, 119.9, 109.9, 21.5; IR (KBr) 3058, 2920, 2860, 1442, 1264 cm^{-1}; GC–MS *m*/*z* (rel intensity) 209 (M^+, 100), 180 (7), 105 (7), 78 (15), 51 (4).

*4.2.16. 6-Methylbenzoxazole (**20**)*[12l]. Yield 77%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.43; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.66 (d, 1H, *J*=8.0 Hz), 7.38 (s, 1H), 7.19 (d, 1H, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 150.2, 137.8, 136.0, 125.8, 119.8, 111.0, 21.7; IR (KBr) 3110, 3036, 2922, 2861, 1433, 1255 cm^{-1}; GC–MS *m*/*z* (rel intensity) 133 (M^+, 100), 104 (21), 78 (35), 63 (5), 51 (11).

*4.2.17. 2,6-Dimethylbenzoxazole (**21**)*[12b]. Yield 95%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.45; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 1H, *J*=8.2 Hz), 7.27 (s, 1H), 7.10 (d, 1H, *J*=8.2 Hz), 2.60 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 151.2, 139.2, 134.6, 125.1, 118.6, 110.3, 21.6, 14.4; IR (KBr) 3032, 2925, 2865, 1436, 1242 cm^{-1}; GC–MS *m*/*z* (rel intensity) 147 (M^+, 100), 132 (8), 118 (11), 106 (19), 91 (4), 78 (43), 63 (6), 51 (15).

*4.2.18. 6-Methyl-2-phenylbenzoxazole (**22**)*[12k]. Yield 98%. White solid, mp 99–102 °C; TLC (30% ethyl acetate/hexane) R_f 0.66; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24–8.21 (m, 2H), 7.64 (d, 1H, *J*=8.0 Hz), 7.51–7.49 (m, 3H), 7.36 (s, 1H), 7.16 (d, 1H, *J*=8.0 Hz), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 151.0, 140.0, 135.5, 131.2, 128.8, 127.4, 127.3, 125.8, 119.3, 110.7, 21.8; IR (KBr) 3056, 2918, 2858, 1447, 1244 cm^{-1}; GC–MS *m*/*z* (rel intensity) 209 (M^+, 100), 180 (11), 105 (9), 78 (15), 51 (5).

*4.2.19. 5-Bromobenzoxazole (**23**)*[12g]. Yield 81%. White solid, mp 40–42 °C; TLC (30% ethyl acetate/hexane) R_f 0.41; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.94 (s, 1H), 7.52 (d, 1H, *J*=8.5 Hz), 7.48 (d, 1H, *J*=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 149.0, 141.6, 128.8, 123.6, 117.4, 112.2; IR (KBr) 3093, 1447, 1262 cm^{-1}; GC–MS *m*/*z* (rel intensity) 196 (M^+, 100), 168 (25), 141 (7), 90 (8), 63 (38).

*4.2.20. 5-Bromo-2-methylbenzoxazole (**24**)*[12n]. Yield 94%. White solid, mp 67–69 °C; TLC (30% ethyl acetate/hexane) R_f 0.52; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1H, *J*=1.8 Hz), 7.42 (d, 1H, *J*=8.6 Hz), 7.40 (dd, 1H, *J*=8.6, 1.8 Hz), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 150.0, 143.1, 127.5, 122.5, 116.8, 111.4, 14.5; IR (KBr) 3093, 3059, 2922, 1453, 1262 cm^{-1}; GC–MS *m*/*z* (rel intensity) 210 (M^+, 100), 182 (3), 169 (6), 141 (9), 132 (10), 104 (25), 91 (7), 63 (29).

*4.2.21. 5-Bromo-2-phenylbenzoxazole (**25**)*[12o]. Yield 98%. White solid, mp 117–118 °C; TLC (30% ethyl acetate/hexane) R_f 0.72; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24–8.21 (m, 2H), 7.89 (dd, 1H, *J*=1.6, 0.8 Hz), 7.57–7.49 (m, 3H), 7.47–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.7, 143.7, 131.9, 129.0, 128.1, 127.8, 126.6, 123.0, 117.3, 111.8; IR (KBr) 3089, 3063, 1444, 1257 cm^{-1}; GC–MS *m*/*z* (rel intensity) 272 (M^+, 100), 246 (8), 194 (5), 166 (5), 91 (4), 77 (6), 63 (15).

*4.2.22. 5-Chlorobenzoxazole (**26**)*[12h]. Yield 81%. White solid, mp 41–44 °C; TLC (30% ethyl acetate/hexane) R_f 0.50; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.79 (d, 1H, *J*=1.9 Hz), 7.53 (d, 1H, *J*=8.7 Hz), 7.39 (dd, 1H, *J*=8.7, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 148.6, 141.2, 130.2, 126.1, 120.6, 111.7; IR (KBr) 3110, 3009, 1457, 1262 cm^{-1}; GC–MS *m*/*z* (rel intensity) 153 (M^+, 100), 125 (33), 98 (12), 63 (25).

*4.2.23. 5-Chloro-2-methylbenzoxazole (**27**)*[12j]. Yield 87%. White solid, mp 61–64 °C; TLC (30% ethyl acetate/hexane) R_f 0.52; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 1H, *J*=2.0 Hz), 7.39 (d, 1H, *J*=8.6 Hz), 7.28 (dd, 1H, *J*=8.6, 2.0 Hz), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 149.7, 142.7, 129.6, 124.7, 119.5, 110.9, 14.5; IR (KBr) 3093, 3059, 2925, 1457, 1259 cm^{-1}; GC–MS *m*/*z* (rel intensity) 167 (M^+, 100), 139 (4), 126 (6), 104 (25), 63 (21).

*4.2.24. 5-Chloro-2-phenylbenzoxazole (**28**)*[12d]. Yield 95%. White solid, mp 110–113 °C; TLC (30% ethyl acetate/hexane) R_f 0.68; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24–8.22 (m, 2H), 7.74 (d, 1H, *J*=2.0 Hz), 7.58–7.52 (m, 3H), 7.51 (d, 1H, *J*=8.6 Hz), 7.33 (dd, 1H, *J*=8.6, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 149.3, 143.3, 131.9, 130.0, 129.0, 127.7, 126.7, 125.4, 120.0, 111.3; IR (KBr) 3096, 3066, 3026, 1443, 1262 cm^{-1}; GC–MS *m*/*z* (rel intensity) 229 (M^+, 100), 201 (11), 166 (5), 126 (5), 98 (6), 77 (7), 63 (14).

*4.2.25. 5-Fluorobenzoxazole (**29**)*[12p]. Yield 50%. White solid, mp 43–45 °C; TLC (30% ethyl acetate/hexane) R_f 0.54; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.55 (dd, 1H, *J*=8.8, 4.4 Hz), 7.49 (dd, 1H, *J*=8.4, 2.4 Hz), 7.17 (td, 1H, *J*=8.8, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (d), 154.1, 146.3 (d), 141.0 (d), 113.6 (d), 111.3 (d), 107.1 (d); IR (KBr) 3096, 3002, 1480, 1268 cm^{-1}; GC–MS *m*/*z* (rel intensity) 137 (M^+, 100), 109 (38), 82 (33), 63 (9), 56 (4).

*4.2.26. 5-Fluoro-2-methylbenzoxazole (**30**)*[12j]. Yield 70%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.48; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 1H, *J*=8.8, 4.0 Hz), 7.34 (dd, 1H, *J*=8.4, 2.4 Hz), 7.05 (td, 1H, *J*=8.8, 2.4 Hz), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 161.0 (d), 147.3 (d), 142.4 (d), 112.1 (d), 110.4 (d), 106.1 (d), 14.6; IR (KBr) 3076, 2928, 2858, 1477, 1279 cm^{-1}; GC–MS *m*/*z* (rel intensity) 151 (M^+, 100), 122 (18), 110 (6), 96 (19), 82 (28), 63 (7).

*4.2.27. 5-Fluoro-2-phenylbenzoxazole (**31**)*[4e]. Yield 92%. White solid, mp 117–119 °C; TLC (30% ethyl acetate/hexane) R_f 0.69; ^1H NMR (400 MHz, $CDCl_3$) δ .23–8.21 (m, 2H), 7.56–7.51 (m, 3H), 7.50 (ddd, 1H, *J*=8.0, 4.4, 0.4 Hz), 7.45 (ddd, 1H, *J*=8.4, 2.4, 0.4 Hz), 7.09 (ddd, 1H, *J*=9.2, 8.8, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7,

161.3 (d), 147.0 (d), 143.0 (d), 131.8, 128.9, 127.6, 126.8, 112.8 (d), 110.8 (d), 106.5 (d); IR (KBr) 3110, 3073, 3046, 1436, 1272 cm^{-1}; GC–MS *m*/*z* (rel intensity) 213 (M^+, 100), 185 (20), 110 (5), 82 (14), 63 (5).

*4.2.28. 6-Fluorobenzoxazole (**32**)*[12p]. Yield 53%. White solid, mp 53–54 °C; TLC (30% ethyl acetate/hexane) R_f 0.52; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.75 (dd, 1H, *J*=8.8, 5.2 Hz), 7.33 (dd, 1H, *J*=8.0, 2.4 Hz), 7.16 (ddd, 1H, *J*=9.2, 8.8, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d), 153.0 (d), 150.0 (d), 136.3 (d), 121.0 (d), 112.9 (d), 99.0 (d); IR (KBr) 3103, 3016, 1487, 1286 cm^{-1}; GC–MS *m*/*z* (rel intensity) 137 (M^+, 100), 109 (42), 82 (28), 63 (7).

*4.2.29. 6-Fluoro-2-methylbenzoxazole (**33**)*[12j]. Yield 84%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.42; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, 1H, *J*=8.8, 4.8 Hz), 7.20 (dd, 1H, *J*=8.0, 2.4 Hz), 7.06 (ddd, 1H, *J*=9.6, 8.8, 2.4 Hz), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (d), 161.4 (d), 150.9 (d), 137.8 (d), 119.6 (d), 112.0 (d), 98.4 (d), 14.4; IR (KBr) 3075, 2934, 2857, 1477, 1286 cm^{-1}; GC–MS *m*/*z* (rel intensity) 151 (M^+, 100), 122 (23), 96 (25), 82 (19), 63 (8).

*4.2.30. 6-Fluoro-2-phenylbenzoxazole (**34**)*[12c]. Yield 94%. White solid, mp 111–112 °C; TLC (30% ethyl acetate/hexane) R_f 061; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24–8.20 (m, 2H), 7.71 (dd, 1H, *J*=8.8, 4.8 Hz), 7.56–7.49 (m, 3H), 7.32 (dd, 1H, *J*=8.0, 2.4 Hz), 7.13 (ddd, 1H, *J*=9.6, 8.8, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d), 161.9 (d), 150.8 (d), 138.4 (d), 131.6, 128.9, 127.5, 126.9, 120.3 (d), 112.6 (d), 98.8 (d); IR (KBr) 3066, 1477, 1255 cm^{-1}; GC–MS *m*/*z* (rel intensity) 213 (M^+, 100), 185 (18), 110 (7), 82 (9), 63 (5).

5. General procedure for the indium-mediated reductive reaction of the 2-nitro-1-phenylethanones trimethyl orthoalkylates to oxazoles

5.1. Preparation of the 2-nitro-1-phenylethanones starting from acyl chlorides

5.1.1. Step 1. Imidazole (6.0 mmol) and triethylamine (6.0 mmol) were dissolved in dry CH_2Cl_2 (25 mL), and acyl chloride (5 mmol) was slowly added to the stirred solution. The mixture was stirred for 0.5 h at room temperature. The mixture was filtered, and the solution was rapidly washed with cold water (150 mL×3). The organic phase was dried with $MgSO_4$, filtered, and concentrated, yielding the crude *N*-acylimidazoles. The crude *N*-acylimidazoles were used for the synthesis of 2-nitro-1-phenylethanones without further purification.

5.1.2. Step 2. A mixture of the nitromethane (5.0 mmol) and sodium hydride (11 mmol) in DMSO (25 mL) was stirred for 0.5 h, while the temperature was maintained at 10 °C. The crude *N*-acylimidazole (5.0 mmol) in DMSO (25 mL) was added dropwise to the resulting solution, and the mixture was stirred for 30 min at 10 °C and then at room temperature for 12 h. The mixture was diluted with ethyl acetate (150 mL), poured into 1 N HCl (150 mL), and then extracted with ethyl acetate (150 mL×3). The combined organic extracts were washed with cold water (150 mL×3), dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with dichloromethane/hexane (v/v=50/50) through a silica gel column to give the corresponding 2-nitro-1-phenylethanones, which were used as starting substrates for the oxazole synthesis.

5.2. Indium-mediated reductive reaction of 2-nitro-1-phenylethanones with trimethyl orthoesters to 2,5-diaryloxazoles

2-Nitro-1-phenylethanone derivative (1 mmol) was added to a mixture of indium powder (459 mg, 4.0 mmol) and acetic acid (0.566 mL, 10 mmol) in acetonitrile (10 mL), and then trimethyl orthoester (4.0 mmol) in acetonitrile (5 mL) was added. The reaction mixture was stirred at reflux under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was diluted with CH_2Cl_2 (30 mL), filtered through Celite, poured into 1 N HCl solution (30 mL), and then extracted with CH_2Cl_2 (30 mL×3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v=2/98) through a silica gel column to give the corresponding 2,5-diaryloxazoles. Some of the reaction mixture (refer to Table 3) was additionally treated to remove the methyl benzoate that overlapped with the product on TLC and column chromatography after the routine work-up process, i.e., the concentrated mixture was added to MeOH/10 M aq NaOH solution (10 mL/3 mL), stirred for 0.5 h at room temperature, and extracted with satd aq NH_4Cl/CH_2Cl_2 again. The structures of the 2,5-diaryloxazoles were characterized by ^1H NMR, ^{13}C NMR, FTIR, and GC–MS for known compounds.[13] Elemental analysis or HRMS data were additionally obtained for the unknown compounds.

*5.2.1. 2,5-Diphenyloxazole (**35**)*[13a]. Yield 60%. White solid, mp 75–77 °C; TLC (30% ethyl acetate/hexane) R_f 0.50; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.09 (m, 2H), 7.73 (dd, 2H, *J*=8.4, 1.2 Hz), 7.50–7.42 (m, 6H), 7.35–7.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 151.3, 130.3, 128.9, 128.8, 128.4, 128.0, 127.5, 126.3, 124.2, 123.5; IR (KBr) 3063, 3039, 1481, 1133 cm^{-1}; GC–MS *m*/*z* (rel intensity) 221 (M^+, 100), 193 (13), 165 (48), 116 (10), 89 (18), 77 (15), 63 (11), 51 (10).

*5.2.2. 5-(2-Methoxyphenyl)-2-phenyloxazole (**36**)*[13b]. Yield 53%. White solid, mp 129–131 °C; TLC (30% ethyl acetate/hexane) R_f 0.50; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, 2H, *J*=8.4, 2.0 Hz), 7.90 (dd, 1H, *J*=7.6, 1.6 Hz), 7.65 (s, 1H), 7.50–7.44 (m, 3H), 7.32 (ddd, 1H, *J*=8.4, 7.6, 1.6 Hz), 7.09 (td, 1H, *J*=7.6, 1.2 Hz), 7.00 (dd, 1H, *J*=8.4, 1.2 Hz), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 155.7, 147.8, 130.1, 129.0, 128.7, 127.6, 127.6, 126.3, 125.8, 120.8, 117.3, 110.9, 55.4; IR (KBr) 3151, 3069, 3009, 2965, 2841, 1495, 1130 cm^{-1}; GC–MS *m*/*z* (rel intensity) 251 (M^+, 100), 208 (8), 195 (18), 167 (6), 133 (28), 118 (10), 105 (21), 89 (11), 77 (24), 63 (5), 51 (5).

*5.2.3. 5-(3-Methoxyphenyl)-2-phenyloxazole (**37**).* Yield 55%. White solid, mp 97–98 °C; TLC (30% ethyl acetate/hexane) R_f 0.53; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.09 (m, 2H), 7.50–7.45 (m, 3H), 7.43 (s, 1H), 7.37 (t, 1H, *J*=7.6 Hz), 7.32 (dt, 1H, *J*=7.6, 1.2 Hz), 7.25 (dd, 1H, *J*=2.4, 1.2 Hz), 6.70 (ddd, 1H, *J*=7.6, 2.4, 1.2 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 160.0, 151.1, 130.3, 130.0, 129.2, 128.8, 127.4, 126.2, 123.7, 116.7, 113.9, 109.7, 55.3; IR (KBr) 3095, 2995, 2954, 2832, 1483, 1131 cm^{-1}; GC–MS *m*/*z* (rel intensity) 251 (M^+, 100), 208 (11), 195 (9), 181 (20), 165 (13), 153 (9), 116 (9), 89 (11), 77 (14), 63 (6), 51 (5). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.48; H, 5.35; N, 5.60.

*5.2.4. 5-(4-Methoxyphenyl)-2-phenyloxazole (**38**)*[13c]. Yield 47%. White solid, mp 88–89 °C; TLC (30% ethyl acetate/hexane) R_f 0.41; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, 2H, *J*=8.0, 1.6 Hz), 7.66–7.63 (m, 2H), 7.49–7.42 (m, 3H), 7.32 (s, 1H), 6.98–6.95 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 159.8, 151.3, 130.1, 128.8, 127.6, 126.1, 125.7, 121.9, 120.9, 114.4, 55.3; IR (KBr) 3042, 3016, 2965, 2835, 1503, 1175 cm^{-1}; GC–MS *m*/*z* (rel intensity) 251 (M^+, 100), 236 (29), 196 (12), 181 (12), 153 (6), 112 (6), 77 (18).

*5.2.5. 5-Benzo[1,3]dioxol-5-yl-2-phenyloxazole (**39**)*[9a]. Yield 46%. White solid, mp 144–146 °C; TLC (30% ethyl acetate/hexane) R_f 0.57; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, 2H, *J*=8.0, 2.0 Hz), 7.49–7.42 (m, 3H), 7.30 (s, 1H), 7.24 (dd, 1H, *J*=8.0, 1.6 Hz), 7.17 (d, 1H, *J*=1.6 Hz), 6.88 (d, 1H, *J*=8.0 Hz), 6.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.1, 148.2, 147.9, 130.2, 128.8, 127.5, 126.1, 122.4,

122.2, 118.3, 108.8, 104.8, 101.4; IR (KBr) 3113, 3009, 2922, 1483, 1105 cm^{-1}; GC–MS *m*/*z* (rel intensity) 265 (M^+, 100), 237 (9), 180 (14), 152 (28), 133 (5), 119 (6), 105 (5), 89 (5), 76 (8), 63 (5).

*5.2.6. 5-[4-(1,1-Dimethylethyl)phenyl]-2-phenyloxazole (**40**)*[13d]. Yield 53%. Colorless liquid; TLC (30% ethyl acetate/hexane) R_f 0.58; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.10 (m, 2H), 7.67 (d, 2H, *J*=8.3 Hz), 7.50–7.44 (m, 5H), 7.40 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 151.7, 151.4, 130.2, 128.8, 127.5, 126.2, 125.8, 125.2, 124.0, 122.9, 34.7, 31.2; IR (KBr) 3123, 3083, 2953, 2868, 1487, 1133 cm^{-1}; GC–MS *m*/*z* (rel intensity) 277 (M^+, 59), 262 (100), 234 (15), 131 (8), 117 (12), 103 (7).

*5.2.7. 5-(2-Methylphenyl)-2-phenyloxazole (**41**)*[9b]. Yield 66%. White solid, mp 72–74 °C; TLC (30% ethyl acetate/hexane) R_f 0.54; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.10 (m, 2H), 7.79 (d, 1H, *J*=7.2 Hz), 7.51–7.46 (m, 3H), 7.35 (s, 1H), 7.33–7.25 (m, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 150.7, 134.9, 131.2, 130.3, 128.8, 128.4, 127.5, 127.3, 126.8, 126.3, 126.2, 126.2, 21.9; IR (KBr) 3163, 3066, 2952, 2858, 1486, 1151 cm^{-1}; GC–MS *m*/*z* (rel intensity) 235 (M^+, 100), 206 (10), 179 (20), 165 (7), 131 (10), 104 (15), 89 (10), 77 (11).

*5.2.8. 5-(3-Methylphenyl)-2-phenyloxazole (**42**)*[13e]. Yield 59%. White solid, mp 120–121 °C; TLC (30% ethyl acetate/hexane) R_f 0.53; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, 2H, *J*=7.7, 1.8 Hz), 7.53–7.42 (m, 5H), 7.42 (s, 1H), 7.34 (t, 1H, *J*=7.6 Hz), 7.16 (d, 1H, *J*=7.6 Hz), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 151.4, 138.6, 130.2, 129.2, 128.8, 128.8, 127.9, 127.5, 126.2, 124.8, 123.3, 121.4, 21.4; IR (KBr) 3103, 3056, 2952, 2915, 1487, 1131 cm^{-1}; GC–MS *m*/*z* (rel intensity) 235 (M^+, 100), 207 (11), 179 (16), 165 (40), 116 (8), 103 (8), 89 (11), 77 (8), 63 (5).

*5.2.9. 5-(4-Methylphenyl)-2-phenyloxazole (**43**)*[9b]. Yield 55%. White solid, mp 85–86 °C; TLC (30% ethyl acetate/hexane) R_f 0.59; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, 2H, *J*=7.9, 1.6 Hz), 7.62 (d, 2H, *J*=8.0 Hz), 7.50–7.44 (m, 3H), 7.39 (s, 1H), 7.25 (d, 2H, *J*=8.0 Hz), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 151.5, 138.5, 130.2, 129.6, 128.8, 127.6, 126.2, 125.3, 124.2, 122.8, 21.3; IR (KBr) 3126, 3026, 2989, 2955, 1476, 1133 cm^{-1}; GC–MS *m*/*z* (rel intensity) 235 (M^+, 100), 207 (11), 179 (12), 165 (42), 116 (5), 103 (6), 91 (9), 77 (6), 63 (5).

*5.2.10. 5-(2-Bromophenyl)-2-phenyloxazole (**44**).* Yield 72%. White solid, mp 70–72 °C; TLC (30% ethyl acetate/hexane) R_f 0.69; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.10 (m, 2H), 7.95 (s, 1H), 7.86 (dd, 1H, *J*=8.0, 1.6 Hz), 7.69 (dd, 1H, *J*=8.0, 1.2 Hz), 7.51–7.46 (m, 3H), 7.43 (ddd, 1H, *J*=8.0, 7.6, 1.2 Hz), 7.20 (ddd, 1H, *J*=8.0, 7.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 148.7, 134.2, 130.5, 129.2, 128.8, 128.4, 128.1, 128.1, 127.5, 127.2, 126.4, 119.9; IR (KBr) 3167, 3066, 1471, 1142 cm^{-1}; GC–MS *m*/*z* (rel intensity) 298 (M^+, 85), 192 (7), 165 (100), 116 (11), 89 (31), 77 (11), 63 (9), 51 (5). Anal. Calcd for $C_{15}H_{10}BrNO$: C, 59.52; H, 3.57; N, 4.57. Found: C, 60.02; H, 3.36; N, 4.67.

*5.2.11. 5-(3-Bromophenyl)-2-phenyloxazole (**45**).* Yield 67%. White solid, mp 116–117 °C; TLC (30% ethyl acetate/hexane) R_f 0.57; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.08 (m, 2H), 7.86 (t, 1H, *J*=1.6 Hz), 7.64 (ddd, 1H, *J*=8.0, 1.6, 1.2 Hz), 7.52–7.44 (m, 5H), 7.32 (t, 1H, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 149.7, 131.2, 130.6, 130.4, 129.9, 128.8, 127.1, 127.0, 126.4, 124.4, 123.1, 122.6; IR (KBr) 3105, 3056, 1486, 1139 cm^{-1}; GC–MS *m*/*z* (rel intensity) 298 (M^+, 100), 192 (9), 165 (57), 116 (17), 89 (29), 76 (8), 63 (11). Anal. Calcd for $C_{15}H_{10}BrNO$: C, 59.52; H, 3.57; N, 4.67. Found: C, 60.01; H, 3.37; N, 4.63.

*5.2.12. 5-(4-Bromophenyl)-2-phenyloxazole (**46**)*[13c]. Yield 64%. White solid, mp 110–112 °C; TLC (30% ethyl acetate/hexane) R_f 0.50; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.08 (m, 2H), 7.59 (br s, 2H), 7.57 (br s, 2H), 7.50–7.46 (m, 3H), 7.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 150.3, 132.1, 130.5, 128.8, 127.3, 126.9, 126.3, 125.6, 124.0, 122.3; IR (KBr) 3120, 3039, 1477, 1135 cm^{-1}; GC–MS *m*/*z* (rel intensity) 298 (M^+, 100), 270 (5), 243 (8), 192 (8), 165 (61), 154 (6), 116 (11), 89 (28), 77 (5), 63 (9).

*5.2.13. 5-(2-Chlorophenyl)-2-phenyloxazole (**47**)*[13e]. Yield 63%. White solid, mp 79–80 °C; TLC (30% ethyl acetate/hexane) R_f 0.61; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.11 (m, 2H), 7.92 (dd, 1H, *J*=8.0, 1.6 Hz), 7.88 (s, 1H), 7.51–7.47 (m, 4H), 7.39 (td, 1H, *J*=8.0, 1.2 Hz), 7.28 (ddd, 1H, *J*=8.0, 7.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 147.8, 130.7, 130.5, 128.9, 128.8, 128.4, 128.4, 127.6, 127.2, 127.0, 126.8, 126.4; IR (KBr) 3173, 3076, 3039, 1487, 1144 cm^{-1}; GC–MS *m*/*z* (rel intensity) 255 (M^+, 100), 227 (8), 200 (11), 165 (85), 139 (6), 116 (13), 89 (28), 77 (7), 63 (9), 51 (5).

*5.2.14. 5-(3-Chlorophenyl)-2-phenyloxazole (**48**)*[13f]. Yield 68%. White solid, mp 119–120 °C; TLC (30% ethyl acetate/hexane) R_f 0.54; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.09 (m, 2H), 7.70 (t, 1H, *J*=1.2 Hz), 7.59 (ddd, 1H, *J*=8.0, 2.0, 1.2 Hz), 7.51–7.46 (m, 4H), 7.38 (t, 1H, *J*=8.0 Hz), 7.31 (ddd, 1H, *J*=8.0, 2.0, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 149.8, 135.0, 130.6, 130.2, 129.6, 128.8, 128.3, 127.1, 126.4, 124.4, 124.1, 122.2; IR (KBr) 3107, 3059, 3032, 1487, 1141 cm^{-1}; GC–MS *m*/*z* (rel intensity) 255 (M^+, 100), 227 (8), 192 (9), 165 (52), 116 (15), 89 (24), 75 (7), 63 (8).

*5.2.15. 5-(4-Chlorophenyl)-2-phenyloxazole (**49**)*[13c]. Yield 68%. White solid, mp 110–111 °C; TLC (30% ethyl acetate/hexane) R_f 0.52; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.08 (m, 2H), 7.65–7.62 (m, 2H), 7.51–7.45 (m, 3H), 7.44–7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 150.2, 134.1, 130.5, 129.2, 128.8, 127.2, 126.5, 126.3, 125.4, 123.8; IR (KBr) 3123, 3059, 1481, 1132 cm^{-1}; GC–MS *m*/*z* (rel intensity) 255 (M^+, 100), 227 (8), 200 (11), 165 (56), 116 (9), 89 (21), 75 (5), 63 (8).

*5.2.16. 5-(2-Fluorophenyl)-2-phenyloxazole (**50**).* Yield 75%. White solid, mp 103–104 °C; TLC (30% ethyl acetate/hexane) R_f 0.63; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.11 (m, 2H), 7.88 (td, 1H, *J*=7.6, 1.6 Hz), 7.59 (d, 1H, *J*=4.0 Hz), 7.51–7.45 (m, 3H), 7.33–7.23 (m, 2H), 7.19 (ddd, 1H, *J*=11.2, 7.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.1 (d), 145.6 (d), 130.5, 129.4 (d), 128.8, 127.8 (d), 127.3, 126.4, 126.0 (d), 124.5 (d), 116.6 (d), 116.1 (d); IR (KBr) 3079, 3066, 3042, 1487, 1138 cm^{-1}; GC–MS *m*/*z* (rel intensity) 239 (M^+, 100), 211 (13), 183 (74), 123 (7), 107 (14), 89 (16), 75 (6), 63 (9), 51 (5); HRMS (EI) calcd for $C_{15}H_{10}FNO$ 239.0746, found 239.0741.

*5.2.17. 5-(3-Fluorophenyl)-2-phenyloxazole (**51**).* Yield 70%. White solid, mp 88–90 °C; TLC (30% ethyl acetate/hexane) R_f 0.57; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.08 (m, 2H), 7.51–7.45 (m, 5H), 7.05 (tdd, 1H, *J*=9.2, 2.4, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3 (d), 161.5, 150.1 (d), 130.6, 130.6 (d), 130.0 (d), 128.8, 127.2, 126.3, 124.4, 119.8 (d), 115.3 (d), 111.2 (d); IR (KBr) 3105, 3079, 3059, 1489, 1196 cm^{-1}; GC–MS *m*/*z* (rel intensity) 239 (M^+, 100), 211 (15), 183 (62), 116 (19), 89 (17), 75 (5), 63 (17); HRMS (EI) calcd for $C_{15}H_{10}FNO$ 239.0746, found 239.0743.

*5.2.18. 5-(4-Fluorophenyl)-2-phenyloxazole (**52**).* Yield 66%. White solid, mp 101–103 °C; TLC (30% ethyl acetate/hexane) R_f 0.53; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.07 (m, 2H), 7.72–7.67 (m, 2H), 7.51–7.45 (m, 3H), 7.38 (s, 1H), 7.17–7.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d), 161.1, 150.4, 130.4, 128.8, 127.4, 126.3, 126.1 (d), 124.4 (d), 123.1, 116.2 (d); IR (KBr) 3130, 3063, 3042, 1503, 1131 cm^{-1}; GC–MS *m*/*z* (rel intensity) 239 (M^+, 100), 211 (19), 183 (59), 123 (5), 107 (11), 95 (11), 75 (4), 63 (5); HRMS (EI) calcd for $C_{15}H_{10}FNO$ 239.0746, found 239.0746.

*5.2.19. 5-(2-Trifluoromethylphenyl)-2-phenyloxazole (**53**).* Yield 73%. White solid, mp 46–47 °C; TLC (30% ethyl acetate/hexane) R_f 0.61; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14–8.09 (m, 2H), 7.82 (d,

2H, J=8.0 Hz), 7.65 (t, 1H, J=8.0 Hz), 7.51–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 147.9, 132.0, 130.6, 129.6, 128.8, 128.6, 127.9 (q), 127.7 (q), 127.2 (q), 127.1, 126.9 (q), 126.4, 126.4; IR (KBr) 3187, 3063, 1490, 1125 cm^{-1}; GC–MS m/z (rel intensity) 289 (M^+, 100), 233 (32), 214 (23), 158 (5), 145 (9), 116 (19), 89 (11), 63 (5); HRMS (EI) calcd for $C_{16}H_{10}F_3NO$ 289.0714, found 289.0714.

*5.2.20. 5-(3-Trifluoromethylphenyl)-2-phenyloxazole (**54**).* Yield 67%. White solid, mp 132–133 °C; TLC (30% ethyl acetate/hexane) R_f 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.10 (m, 2H), 7.95 (br s, 1H), 7.88 (d, 1H, J=6.8 Hz), 7.60–7.46 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 149.8, 132.1 (q), 131.1, 129.5, 128.9, 128.8, 127.9 (q), 127.2, 127.1, 126.4, 124.9 (q), 124.7, 120.9 (q); IR (KBr) 3123, 3066, 1488, 1125 cm^{-1}; GC–MS m/z (rel intensity) 289 (M^+, 100), 270 (6), 261 (7), 233 (6), 165 (28), 145 (9), 116 (11), 89 (10); HRMS (EI) calcd for $C_{16}H_{10}F_3NO$ 289.0714, found 289.0713.

*5.2.21. 5-(4-Trifluoromethylphenyl)-2-phenyloxazole (**55**)*[13g]. Yield 66%. White solid, mp 113–115 °C; TLC (30% ethyl acetate/hexane) R_f 0.64; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.10 (m, 2H), 7.83 (d, 2H, J=8.3 Hz), 7.71 (d, 2H, J=8.3 Hz), 7.55 (s, 1H), 7.54–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.8, 131.2, 130.7, 130.6 (q), 128.9, 128.0 (q), 127.1, 126.5, 126.0 (q), 125.2, 124.2; IR (KBr) 3120, 3049, 1476, 1108 cm^{-1}; GC–MS m/z (rel intensity) 289 (M^+, 100), 261 (8), 233 (8), 165 (25), 145 (9), 116 (10), 89 (9).

*5.2.22. 5-(2-Iodophenyl)-2-phenyloxazole (**56**).* Yield 45%. White solid, mp 104–106 °C; TLC (30% ethyl acetate/hexane) R_f 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.11 (m, 2H), 8.01 (d, 1H, J=8.0 Hz), 7.86 (s, 1H), 7.71 (dd, 1H, J=8.0, 1.2 Hz), 7.51–7.42 (m, 4H), 7.06 (td, 1H, J=8.0, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 150.7, 141.0, 132.7, 130.5, 129.7, 129.2, 128.8, 128.2, 127.3, 127.2, 126.4, 94.1; IR (KBr) 3156, 3066, 1467, 1141 cm^{-1}; GC–MS m/z (rel intensity) 347 (M^+, 100), 192 (8), 165 (47), 89 (24), 77 (9), 63 (7). Anal. Calcd for $C_{15}H_{10}INO$: C, 51.90; H, 2.90; N, 4.03. Found: C, 51.92; H, 2.87; N, 4.04.

*5.2.23. 5-Biphenyl-4-yl-2-phenyloxazole (**57**)*[13a]. Yield 59%. White solid, mp 165–166 °C; TLC (30% ethyl acetate/hexane) R_f 0.66; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 2H, J=6.8 Hz), 7.79 (d, 2H, J=8.4 Hz), 7.68 (d, 2H, J=8.4 Hz), 7.63 (d, 2H, J=7.6 Hz), 7.51–7.44 (m, 6H), 7.38 (t, 1H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 151.0, 141.1, 140.2, 130.3, 128.9, 128.8, 127.6, 127.5, 127.4, 126.9, 126.9, 126.3, 124.6, 123.6; IR (KBr) 3130, 3066, 3032, 1484, 1140 cm^{-1}; GC–MS m/z (rel intensity) 297 (M^+, 100), 269 (10), 241 (36), 165 (19), 152 (13), 134 (8).

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References and notes

1. (a) Boyd, G. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Potts, K. T., Eds.; Pergamon: New York, NY, 1984; Vol. 6, pp 177–223; (b) Hartner, F. W., Jr. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Shinkai, S., Eds.; Pergamon: New York, NY, 1996; Vol. 3, pp 261–318.
2. (a) DeLuca, M. R.; Kerwin, S. M. *Tetrahedron Lett.* **1997**, *38*, 199–202; (b) Reynolds, M. B.; DeLuca, M. R.; Kerwin, S. M. *Bioorg. Chem.* **1999**, *27*, 326–337; (c) Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. *Bioorg. Med. Chem.* **2002**, *10*, 3997–4004; (d) Wang, B. B.; Maghami, N.; Goodlin, V. L.; Smith, P. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3221–3226; (e) Huang, S.-T.; Hsei, I.-J.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14*, 6106–6119; (f) McKee, M. L.; Kerwin, S. M. *Bioorg. Med. Chem.* **2008**, *16*, 1775–1783.
3. (a) Turchi, I. J. In *The Chemistry of Heterocyclic Compounds: A Series of Monographs, Oxazoles*; Turchi, I. J., Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons: New York, NY, 1986; Vol. 45, pp 1–342; (b) Palmer, D. C.; Venkatraman, S. In *The Chemistry of Heterocyclic Compounds: A Series of Monographs, Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A*; Taylor, E. C., Wipf, P., Weissberger, A., Eds.; John Wiley & Sons: Hoboken, NJ, 2003; Vol. 60, pp 1–390.
4. (a) Chang, J. C.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951–954; (b) Lee, J. C.; Choi, H. J.; Lee, Y. C. *Tetrahedron Lett.* **2003**, *44*, 123–125; (c) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712–2713; (d) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391–4394; (e) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802–1808; (f) Kidwai, M.; Bansal, V.; Saxena, A.; Aerry, S.; Mozumdar, S. *Tetrahedron Lett.* **2006**, *47*, 8049–8053.
5. (a) Yamamoto, H.; Oshima, K. *Main Group Metals in Organic Synthesis*; Wiley-VCH: Weinheim, 2004; Vol. 1, Chapter 8, pp 323–386; (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley-Interscience: New York, NY, 1997; (c) Li, C. J. *Tetrahedron* **1996**, *52*, 5643–5668; (d) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633–655; (e) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959–1982; (f) Kumar, S.; Pervinder, K.; Vijay, K. *Curr. Org. Chem.* **2005**, *9*, 1205–1235.
6. (a) Kim, B. H.; Jin, Y.; Jun, Y. M.; Han, R.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2000**, *41*, 2137–2140; (b) Kim, B. H.; Cheong, J. W.; Han, R.; Jun, Y. M.; Baik, W.; Lee, B. M. *Synth. Commun.* **2001**, *31*, 3577–3586; (c) Kim, B. H.; Han, R.; Piao, F.; Jun, Y. M.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2003**, *47*, 77–79; (d) Han, R.; Choi, S. H.; Son, K. I.; Jun, Y. M.; Lee, B. M. *Synth. Commun.* **2005**, *35*, 1725–1733; (e) Kim, B. H.; Han, R.; Kim, J. S.; Jun, Y. M.; Baik, W.; Lee, B. M. *Heterocycles* **2004**, *62*, 41–54; (f) Han, R.; Chen, S.; Lee, S. J.; Qi, F.; Wu, X.; Kim, B. H. *Heterocycles* **2006**, *68*, 1675–1684; (g) Han, R.; Son, K. I.; Ahn, G. H.; Jun, Y. M.; Lee, B. M.; Park, Y.; Kim, B. H. *Tetrahedron Lett.* **2006**, *47*, 7295–7299; (h) Ahn, G. H.; Lee, J. J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Org. Biomol. Chem.* **2007**, *5*, 2472–2485; (i) Kim, J. S.; Han, J. H.; Lee, J. J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Tetrahedron Lett.* **2008**, *49*, 3733–3738.
7. Lee, S. J.; Lee, J. J.; Kim, C.-H.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Tetrahedron Lett.* **2009**, *50*, 484–487.
8. (a) Villemin, D.; Hammadi, M.; Martin, B. *Synth. Commun.* **1996**, *26*, 2895–2899; (b) Wang, L.; Sheng, J.; Tian, H.; Qian, C. *Synth. Commun.* **2004**, *34*, 4265–4272; (c) Heravi, M. M.; Montazeri, N.; Rahmizadeh, M.; Bakavoli, M.; Ghassemzadehb, M. *J. Chem. Res., Synop.* **2000**, 584–585; (d) Zhang, Z.-H.; Li, J.-J.; Gao, Y.-Z.; Liu, Y.-H. *J. Heterocycl. Chem.* **2007**, *44*, 1509–1512; (e) Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Catal. Commun.* **2007**, *8*, 1126–1131; (f) Zhang, Z.-H.; Li, T.-S.; Li, J.-J. *Monatsh. Chem.* **2007**, *138*, 89–94.
9. (a) Giddens, A. C.; Boshoff, H. I. M.; Franzblau, S. G.; Barry, C. E.; Copp, B. R. *Tetrahedron Lett.* **2005**, *46*, 7355–7357; (b) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, 1241–1243; (c) Besselievre, F.; Mahuteau-Betzer, F.; Grierson, D. S.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278–3280.
10. Roberts, R. M.; Higgins, T. D., Jr.; Noyes, P. R. *J. Am. Chem. Soc.* **1955**, *77*, 3801–3805.
11. Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford: New York, NY, 2003; Chapter 8.
12. (a) Lomov, D. A.; Yutilov, Y. M.; Smolyar, N. N. *Russ. J. Org. Chem.* **2006**, *42*, 241–242; (b) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 6646–6647; (c) Marsden, S. P.; McGonagle, A. E.; McKeever-Abbas, B. *Org. Lett.* **2008**, *10*, 2665–2667; (d) Sanchez, R. S.; Zhuravlev, F. A. *J. Am. Chem. Soc.* **2007**, *129*, 5824–5825; (e) Nishioka, H.; Ohmori, Y.; Iba, Y.; Tsuda, E.; Harayama, T. *Heterocycles* **2004**, *64*, 193–198; (f) Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Hajos, Z. G.; Shriver, D. A.; Scott, C. K. *J. Med. Chem.* **1988**, *31*, 1778–1785; (g) El-Sheikh, M. I.; Marks, A.; Biehl, E. R. *J. Org. Chem.* **1981**, *46*, 3256–3259; (h) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Monatsh. Chem.* **2007**, *138*, 663–667; (i) Pottorf, R. S.; Chadha, N. K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. R. *Tetrahedron Lett.* **2003**, *44*, 175–178; (j) Said, N. PCT Int. Appl. 2008, 59; CAN 148: 428491; (k) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452–3459; (l) Iyengar, R. R.; Lynch, J. K.; Mulhern, M. M.; Judd, A. S.; Freeman, J. C.; Gao, J.; Souers, A. J.; Zhao, G.; Wodka, D.; Falls, H. D.; Brodjian, S.; Dayton, B. D.; Reilly, R. M.; Swanson, S.; Su, Z.; Martin, R. L.; Leitza, S. T.; Houseman, K. A.; Diaz, G.; Collins, C. A.; Sham, H. L.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 874–878; (m) Kunz, K. R.; Taylor, E. W.; Hutton, H. M.; Blackburn, B. J. *Org. Prep. Proced. Int.* **1990**, *22*, 613–618; (n) Gershon, H.; Clarke, D. D.; Gershon, M. *Monatsh. Chem.* **1993**, *124*, 367–379; (o) Sunder, S.; Peet, N. P. *J. Heterocycl. Chem.* **1979**, *16*, 33–37; (p) Dawood, K. M.; Higashiya, S.; Hou, Y.; Fuchigami, T. *J. Fluorine Chem.* **1999**, *93*, 159–164.
13. (a) Keni, M.; Tepe, J. J. *J. Org. Chem.* **2005**, *70*, 4211–4213; (b) Jacobsen, N. W.; Philippides, A. *Aust. J. Chem.* **1985**, *38*, 1335–1338; (c) Pulici, M.; Quartieri, F.; Felder, E. R. *J. Comb. Chem.* **2005**, *7*, 463–473; (d) Krasovitskii, B. M.; Lysova, I. V.; Afana-Siadi, L. S. *Zh. Vses. Khim. Ova.* **1983**, *28*, 706–707; (e) Fukushima, K.; Ibata, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3469–3481; (f) Ibata, T.; Fukushima, K. *Chem. Lett.* **1992**, *21*, 2197–2200; (g) Vachal, P.; Toth, L. M. *Tetrahedron Lett.* **2004**, *45*, 7157–7161.