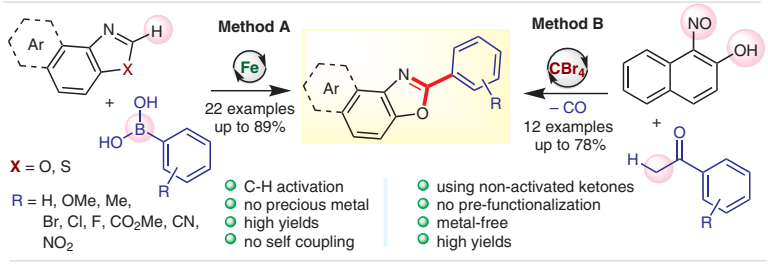
Synlett N. Vodnala et al. Letter

Facile Protocols towards C2-Arylated Benzoxazoles using Fe(III)-Catalyzed C(sp^2-H) Functionalization and Metal-Free Domino Approach

Nagaraju Vodnala[a]
Raghuram Gujjarappa[a]
Arup K. Kabi[a]
Mohan Kumar[a]
Uwe Beifuss[b]
Chandi C. Malakar*[a]

[a] Department of Chemistry, National Institute of Technology Manipur, Langol, Imphal 795004, Manipur, India
cmalakar@nitmanipur.ac.in
[b] Institut für Chemie, Universität Hohenheim, Garbenstr. 30, 70599 Stuttgart, Germany



Received: 14.03.2018
Accepted after revision: 22.03.2018
Published online: 16.05.2018
DOI: 10.1055/s-0037-1609718; Art ID: st-2018-v0047-l

Abstract Considering their growing attention in the field of medicinal chemistry and drug-discovery research, the facile and convenient approaches towards the preparation of 2-aryl benzoxazole derivatives have been described. The transformation is accomplished by using Fe(III)-catalyzed C–H activation of benzoxazoles with boronic acids to obtain a wide range of C2-arylated benzoxazoles in high yields. The developed method excludes the formation of self-coupling compounds as side products. On the other hand, the synthesis of the products is also achieved via a metal-free domino protocol by the reaction between 1-nitroso-2-naphthol and acetophenones using catalytic amounts of CBr_4 in the presence of Cs_2CO_3 as base. The devised tandem method avoids the use of pre-activated α-haloketones as substrates. Due to their immense impact in marketed drugs and molecules under clinical trial, the described method can be a powerful tool for their synthesis which restricts the use of precious metals as catalyst.

Key words benzoxazoles, Fe(III)-catalysis, C-arylation, C–H Activation, domino reaction

Within the azole family, the benzoxazole core structures have gained remarkable attention in the field of medicinal chemistry and drug discovery research due to their unique biological and pharmacological profiles.[1]

A broad range of natural as well as non-natural benzoxazole scaffolds are the key moieties of valuable medicinally active molecules including marketed drugs and compounds under clinical trial.[2,3] Among the benzoxazole containing natural and non-natural compounds, the important molecule includes AJI9561, pseudopteroxazole, salviamine B, isosalviamine E, UK-1, antibiotic A-33853, NSC-693638, salvianen, neosalvianen, nataxazole (antitumor agent), JTP-426427 and flunoxaprofen (anti-inflammatory drug).[2,3]

Selected examples of bioactive compounds containing benzoxazole moieties are depicted in Figure 1.[2,3] These core structures have also been investigated as topoisomerase II inhibitors, PTP-1B inhibitors, cathepsin inhibitors and lysophosphatidic acid acyltransferase-β inhibitors.[3]

Additionally, a number of functionalized benzoxazoles are recognized to act as the inhibitors of fatty acid amide hydrolase, cysteine protease inhibitors, and channel-activating protease inhibitors.[3] Apart from their immense medicinal use, these core structures are extensively used as important building blocks and intermediates in organic synthesis, and play a crucial role in the field of material science towards the discovery of novel fluorescent materials.[4] Therefore, during the recent years a tremendous growth has been witnessed on the improvement of the existing synthetic protocols towards C2-arylated benzoxazole scaffolds.[5–18] Among the traditionally used methods, the most commonly attempted approaches namely rely on: (a) metal-catalyzed carbonylative coupling of aryl halides with benzoxazoles,[5] (b) metal-catalyzed acylation which can be achieved by the deprotonation of benzoxazoles,[6] (c) decarboxylative coupling between benzoxazoles and α-carboxylic acids using transition metal salt as catalyst,[7] (d) direct arylation of benzoxazoles using metal-catalyzed coupling reaction with pre-activated aromatic compounds.[8] Recently the Cu-catalyzed reaction towards the preparation of C2-arylated benzoxazoles gained noteworthy attention and has remained one of the most attractive routes.[9]

Additionally, among the surrogate commonly used methods the reaction between 2-aminophenols and aldehydes or a broad range of carboxylic acid derivatives have been investigated in great details.[10] Apart from the discussed methods, recent literature witnessed several useful transformations for the synthesis of C2-arylated benzoxazole scaffolds.[1,11] A summary of previously reported procedures towards the preparation of 2-aryl benzoxazoles is

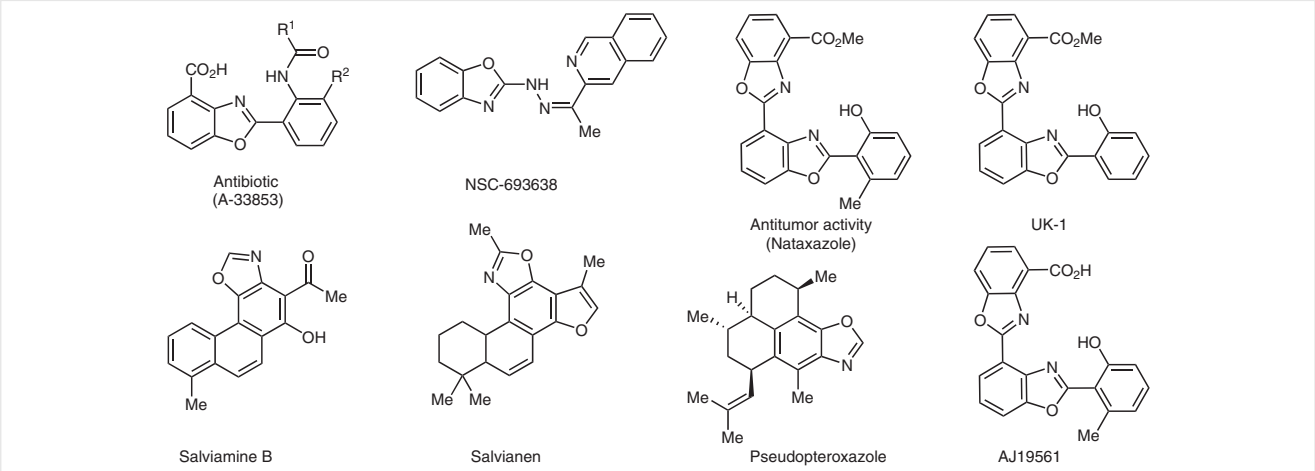
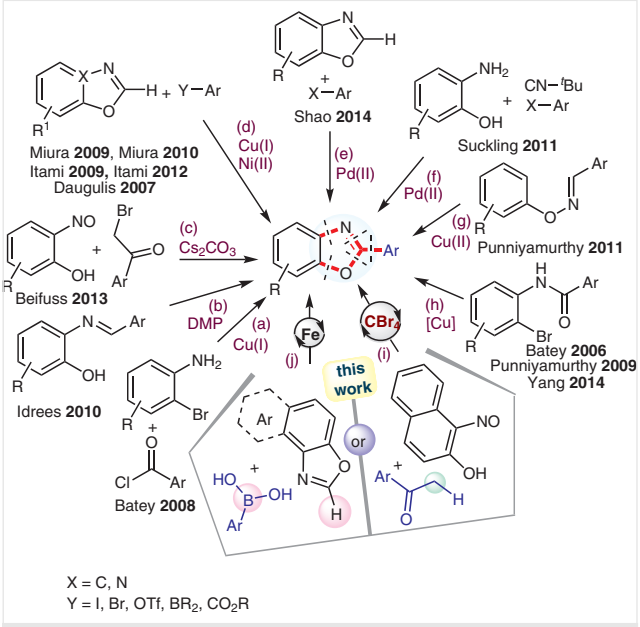


Figure 1 Selected natural products and drug molecules containing benzoxazole moieties

presented in Scheme 1. Batey and co-workers introduced a versatile one-pot domino acylation annulation approach of 2-bromoanilines with acyl chlorides in the presence of Cu(I) as catalyst for the syntheses of 2-aryl benzoxazoles (Scheme 1a).[9d] The similar transformation has been also achieved by several research groups under Cu-catalyzed intramolecular domino cyclization reaction using the *ortho*-haloanilides as substrates to obtain the products (Scheme 1h).[9b,f,g] The metal-free approaches for the syntheses of 2-aryl benzoxazoles have been achieved by the intramolecular cyclization of phenolic azomethines at ambient temperature using Dess–Martin periodinane (DMP) as oxidant (Scheme 1b)[9h] and by the reaction between *ortho*-hydroxynitroso aromatics and α-bromoketones using Cs_2CO_3 as base (Scheme 1c)[11b,c] Additionally, C–H functionalization of benzoxazoles using activated arenes in the presence of transition metals such as Cu, Ni, Pd proved to be an effective route for the syntheses of desired scaffolds (Scheme 1d,e).[8i,13,16] Suckling and co-workers reported an efficient method towards 2-aryl benzoxazoles by the reaction between 2-aminophenols, isocyanides and aryl halides. The reaction proceeds via isocyanide insertion in the presence of Pd catalyst to deliver the desired products (Scheme 1f).[16e]

Recently, Punniyamurthy has described an alternative approach towards the same scaffold by Cu-catalyzed conversion of bisaryloxime ethers to 2-arylbenzoxazoles that involves a cascade C–H functionalization and C–N/C–O bond formation under oxygen atmosphere (Scheme 1g).[16f] Nevertheless, the associated limitations with previous methods such as the use of precious metals as catalyst, harsh reaction conditions and sensitive, and prefunctionalized starting materials have not been studied extensively. Therefore, the development of an efficient approach towards C2-arylated benzoxazoles using cheap metal as catalyst and from non-activated substrates is highly desired.



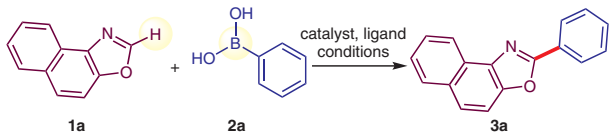
Scheme 1 Protocols for the syntheses of C2-functionalized of benzoxazoles

On the other hand, recently the nitroso compounds were rarely investigated as starting materials for the syntheses of 2-substituted naphthoxazoles under transition-metal-free reaction conditions.[11b,c] In these reports, the reaction between nitrosophenols and 2-bromoacetophenones were realized using Cs_2CO_3 as base under reflux conditions to obtain the desired products in high yields (Scheme 1c). However, apart from the use of sensitive nitroso compounds as substrates, the developed methods rely on the use of pre-activated α-bromoketones that could be prepared from the reaction between acetophenones and suitable brominating agents.[19] Albeit, the described ap-

proaches are shown to be general in terms of good functional groups compatibility with high isolated yield of the products, their further application suffer from the limited commercial access to the corresponding nitroso derivatives and tedious protocols for the preparation of both α-bromoketones, and nitroso derivatives. Hence, we report two distinct protocols for the convenient preparation of 2-aryl benzoxazoles (Scheme 1i and 1j). The developed methods are based on (i) a Fe(III)-catalyzed C2-arylation of benzoxazoles using C–H functionalization approach, and (ii) using the domino reaction between 1-nitroso-2-naphthol and non-activated ketones in the presence of catalytic CBr_4 and Cs_2CO_3 as base.

In order to screen the optimized conditions for the Fe-catalyzed reactions, the model substrate naphthoxazole (**1a**) was reacted with phenylboronic acid (**2a**) in the presence of Cu salt as catalyst using N,N-bidentate ligands and Cs_2CO_3 as base (Table 1, entries 1–3). Interestingly, it was observed that the reactions using Cu(II) salts as catalyst afforded slightly better yields of the desired product **3a** (Table 1, entries 1 and 2). Next, a reaction between naphthoxazole (**1a**) and phenylboronic acid (**2a**) has been examined using $Pd(OAc)_2$ as catalyst in the presence of Davephos as ligand which resulted in the formation of product **3a** in 73% yield under the influence of Na_2CO_3 as base and 1,4-dioxane as solvent (Table 1, entry 4). However, a lower yield of the product **3a** was obtained when the same transformation was aimed using catalytic $NiCl_2$ in the presence of P(*o*-Tol)$_3$ as ligand (Table 1, entry 5). Further the conversion of **1a** and **2a** into product **3a** was realized under a set of reaction conditions using Fe salts as catalysts (Table 1, entries 6–11). It was found that the product **3a** was isolated in high yields when the reactions were carried out in the presence of both Fe(II) and Fe(III) salts as catalysts. The Fe-catalyzed reactions were performed using suitable dichloroalkane as oxidant in the presence of ligands and base. After having surveyed the literature for the best oxidants for Fe-catalyzed reactions,[20e] 1,2-dichloroisobutane (DCIB) was employed as the efficient oxidant for the reaction between substrates **1a** and **2a** in order to access the product **3a** in high yields.

Table 1 Screening of the Reaction Conditions towards Catalytic C–H Functionalization of **1a** with **2a**[a]



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

Entry	Catalyst, ligand	Reagents and Conditions	Yield (%) **3a**[b]
1	$CuCl_2$ (5 mol%), TMEDA (20 mol%)	Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 20 h	39[c]
2	$Cu(OAc)_2$ (5 mol%), TMEDA (20 mol%)	Cs_2CO_3 (1.5 equiv), DMSO, 110 °C, 20 h	42[c]
3	CuI (5 mol%), 1,10-phen (15 mol%)	Cs_2CO_3 (1.5 equiv), DMSO, 100 °C, 16 h	35
4	$Pd(OAc)_2$ (5 mol%), DavePhos (10 mol%)	Na_2CO_3 (1.5 equiv), 1,4-dioxane, 120 °C, 16 h	73
5	$NiCl_2$ (5 mol%), P(*o*-Tol)$_3$ (10 mol%)	Cs_2CO_3 (1.5 equiv), 1,4-dioxane, 100 °C, 16 h	33
6	$FeBr_2$ (5 mol%), TMEDA (20 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 20 h	78
7	$FeBr_2$ (5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 20 h	83
8	$FeCl_3$ (5 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 20 h	57
9	$FeCl_3$ (5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 16 h	85
10	$FeCl_3$ (5 mol%), TMEDA (20 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 16 h	75
11	$Fe(acac)_3$ (5 mol%), TMEDA (20 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 20 h	72
12	$FeCl_3$ (5 mol%), 1,10-phen (10 mol%)	Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 20 h	25
13	$FeCl_3$ (5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), DMF, 100 °C, 20 h	11[d]
14	$FeCl_3$ (2.5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMF, 100 °C, 16 h	59
15	$FeCl_3$ (5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), NMP, 100 °C, 16 h	81
16	$FeCl_3$ (5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), DMSO, 100 °C, 16 h	63
17	$FeCl_3$ (5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), MeCN, 100 °C, 16 h	27
18	$FeCl_3$ (5 mol%), 1,10-phen (10 mol%)	DCIB (1.3 equiv), Cs_2CO_3 (1.5 equiv), THF, 100 °C, 16 h	43

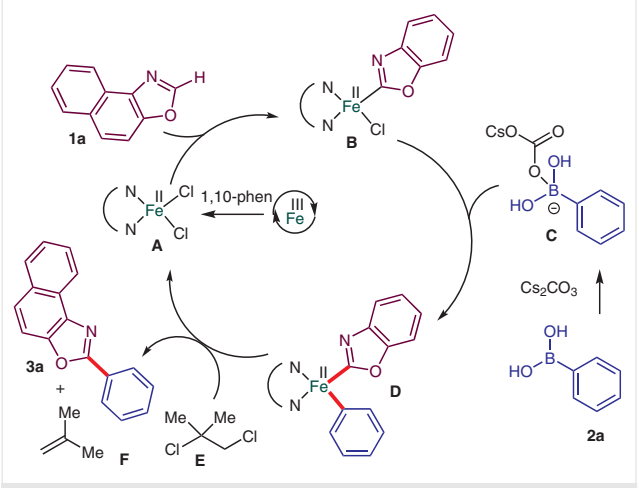
[a] Unless otherwise mentioned, the reactions were performed using **1a** (1.0 mmol) and **2a** (1.0 mmol) in solvent (2 mL) under nitrogen atmosphere.
[b] Isolated yields.
[c] Reactions were performed under air.
[d] Compound **1a** (45%) was recovered.

Among the ligands investigated 1,10-phenanthroline showed the highest efficacy for the formation of product **3a** in the presence of Cs_2CO_3 (Table 1, entries 6–11). After having the successful screening of the preliminary conditions (Table 1, entries 1–11) it was observed that the high yield of the product **3a** was obtained when the reactions were performed in the presence of both catalytic Fe and Pd salts. However, due to the recent awareness on developing Fe-catalyzed synthetic transformations,[20] the screened Fe(III)-catalyzed reaction was investigated under various reaction parameters such as influence of oxidant, base, catalyst loading, ligands, solvents, reaction temperature and time (Table 1, entries 12–18 and in SI). Further optimization of the conditions revealed that the formation of the product **3a** was dramatically reduced when the reaction was performed in the absence of both oxidant and base as well as with decreased amounts of catalyst loading (Table 1, entries 12–14). Additionally, among the solvents tested DMF showed maximum efficiency for the formation of product **3a** (Table 1, entries 9, 15–18). A detailed optimization study (Table 1 and in SI) showed that the highest yield of the product **3a** was obtained when the reaction between **1a** and **2a** was performed in the presence of 5 mol% of $FeCl_3$ as catalyst and 10 mol% of 1,10-phenanthroline as ligand using 1.3 equivalents of DCIB as oxidant, and 1.5 equivalents of Cs_2CO_3 as base in anhydrous DMF as solvent at 100 °C for 16 hours (Table 1, entry 9). These reaction parameters are considered as optimal conditions to investigate the further scope of the developed reaction towards the synthesis of C2-arylated benzoxazoles (Method A).

Having the optimized conditions in hand, next the synthesis of a broad spectrum of C2-arylated benzoxazoles **3a–v** was attempted (Table 2). It is described that the arylboronic acids **2a–o** can be reacted successfully with benzoxazoles **1a–e** and benzothiazole **1f** under the optimized reaction conditions. The monosubstituted arylboronic acids containing methoxy and methyl residue as electron-donating groups, as well as bromo, chloro, fluoro, ester, cyano, and nitro groups as electron-withdrawing substituents were well tolerated under the developed reaction conditions to furnish the products **3**. It is noteworthy to mention that the high yields (84–88%) of the C2-arylated products **3** were observed with the arylboronic acids having electron-donating groups; however, in the case of arylboronic acids having electron-withdrawing groups the yield of the C2-arylated products **3** remains relatively low (from 55–79%). Moreover, it has been shown that the disubstituted arylboronic acids containing both electron-donating and electron-withdrawing groups can be utilized efficiently for the described Fe(III)-catalyzed C2-arylation of benzoxazoles **1a–c** and the corresponding products **3g**, **3o** and **3r** were isolated in 73%, 83% and 67% yields, respectively. The scope of the C–H functionalization has also been extended using naphthylboronic acid **2l** to obtain the corresponding C2-arylated product **3l** in 62% yield. Moreover, C2-aryl benzothiazoles **3u**,**v** were obtained in 74% and 71% yield, respectively when benzothiazole **1f** was reacted with boronic acids **2e** and **2k**. Therefore, it has been described that the substrate scope of the devised Fe(III)-catalyzed protocol remains general as a broad spectrum of arylboronic acids containing diverse functionality can be well tolerated under the reaction conditions.

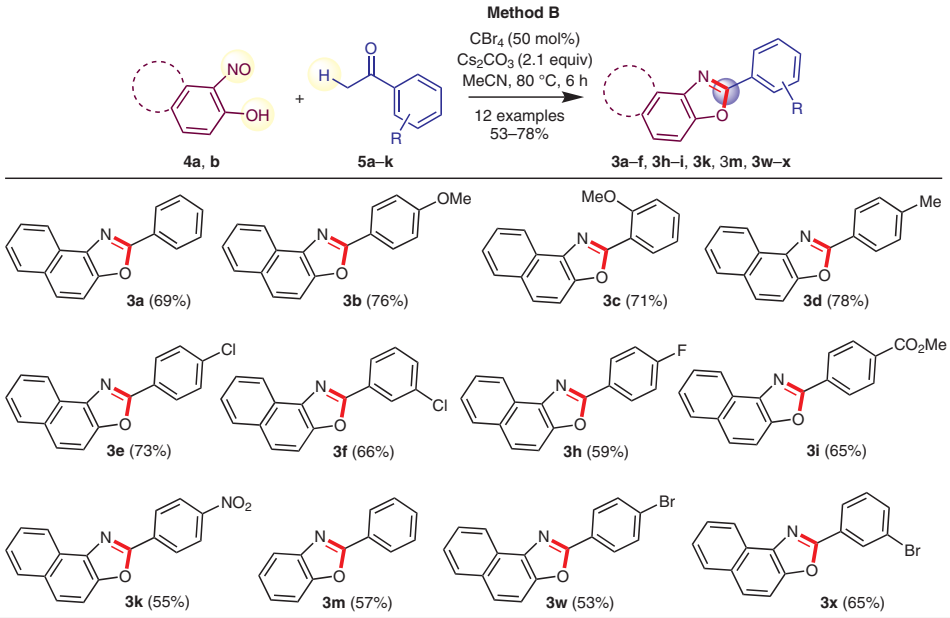
Based on the literature evidence,[20e] a plausible mechanistic proposal for the Fe-catalyzed reaction between naphthoxazole **1a** and phenylboronic acid **2a** is depicted in Scheme 2. It is believed that a reversible coordination of the pyridyl groups delivers the active catalytic iron species **A** that may lead to the formation of the iron species **B** via irreversible metalation of the C–H bond of heteroaromatic **1a** with elimination of HCl.

Next, the transmetalation of iron species **B** with boronate intermediate **C** may generate the diaryl iron species **D** which upon reaction with DCIB **E** leads to the formation of the desired coupling product **3a**, isobutene **F** and regenerates the active catalytic species **A**.



Scheme 2 Plausible mechanism for the Fe(III)-catalyzed C2-arylation of benzoxazoles

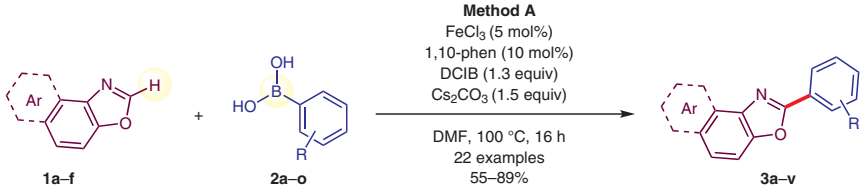
After the successful development of Fe(III)-catalyzed C–H functionalization of benzoxazoles **1** with arylboronic acids **2** (Method A), we diverted our attention towards the syntheses of 2-aryl benzoxazoles using nitroso derivatives and the modification of substrate used in the previous reports.[11b–c] In the previous reports, the 2-aryl benzoxazoles **3** were furnished by the reaction between 1-nitroso-2-naphthol and 2-bromoacetophenones using Cs_2CO_3 as base and the desired products **3** were obtained via the loss of a carbon monoxide molecule from the α-bromoketones. To avoid the use of preactivated α-bromoketones, here we have attempted to revise the previous method using acetophenones as easily available substrates. In this regard, the reaction between 1-nitroso-2-naphthol (**4a**) and acetophenone (**5a**) has been carried out in the presence of 50 mol%



Scheme 3 Synthesis of 2-aryl naphthoxazoles using 1-nitroso-2-naphthol **4** and acetophenones **5** as substrate

of CBr_4 and 2.1 equivalents of Cs_2CO_3 as base in MeCN as solvent at 80 °C for six hours to obtain the desired product **3a** in 69% yield (Scheme 3). However, the same transformation failed to deliver the product **3a**, when 1.1 equivalents of NBS or 1.1 equivalents of I_2 were realized as halogenating agents under the identical conditions (in SI). After the detailed optimization of the conditions (in SI) for the reaction between **4a** and **5a**, it was found that the maximum yield of **3a** was afforded when 1 mmol of **4a** was reacted with 1 mmol of **5a** using 50 mol% of CBr_4 and 2.1 equivalents of Cs_2CO_3 in MeCN at 80 °C for six hours. Therefore, these conditions are considered as the optimal conditions (Method B). Then, the scope of the developed reaction was explored using a number of acetophenone derivatives **5** containing both electron-donating and electron-withdrawing groups (Scheme 3). It was found that the substituted acetophenones with methoxy and methyl groups on aromatic ring were well tolerated under the reaction conditions (Method B) to deliver the products **3b–d** in good yields (71–78%). On the other hand, the bromo, chloro, fluoro, ester and nitro-substituted acetophenones furnished the corresponding products **3e**,**f**,**h**,**i**,**k**,**w**,**x** in yields ranging from 53–73%. Additionally, the product 2-phenylbenzoxazole **3m** was obtained in 57% yield when the reaction between 2-nitrosophenol **4b** and acetophenone (**5a**) was carried out under the standard conditions.

Table 2 Scope of the Fe(III)-Catalyzed C–H Functionalization Approach for the Synthesis of C2-Arylated Benzoxazoles **3a–v**[a,b]



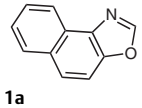
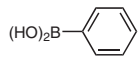
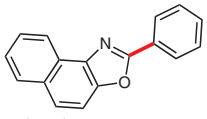
Entry	1	2	3, Yield (%)[b]
1	 **1a**	 **2a**	 **3a** (85%)

Table 2 (continued)

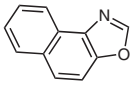
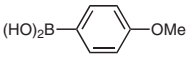
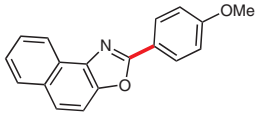
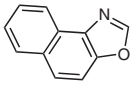
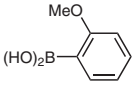
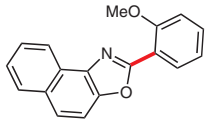
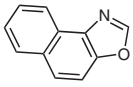
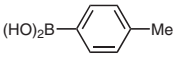
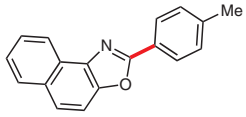
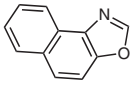
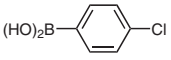
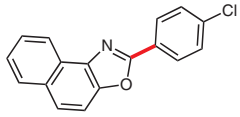
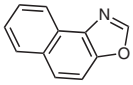
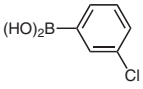
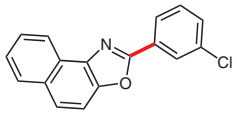
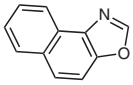
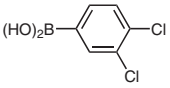
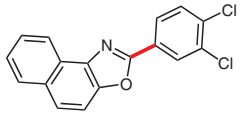
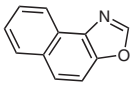
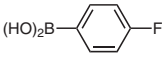
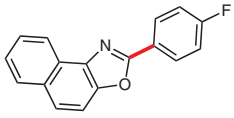
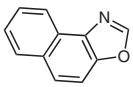
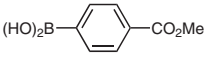
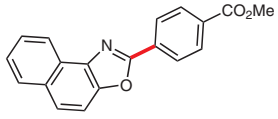
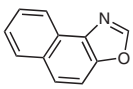
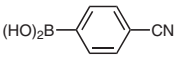
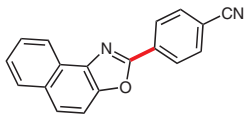
Entry	1	2	3, Yield (%)[b]
2	 **1a**	 **2b**	 **3b** (88%)
3	 **1a**	 **2c**	 **3c** (84%)
4	 **1a**	 **2d**	 **3d** (86%)
5	 **1a**	 **2e**	 **3e** (79%)
6	 **1a**	 **2f**	 **3f** (71%)
7	 **1a**	 **2g**	 **3g** (73%)
8	 **1a**	 **2h**	 **3h** (65%)
9	 **1a**	 **2i**	 **3i** (76%)
10	 **1a**	 **2j**	 **3j** (64%)

Table 2 (continued)

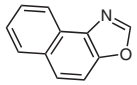
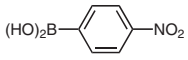
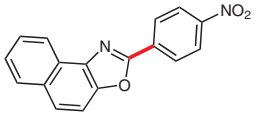
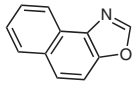
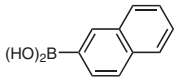
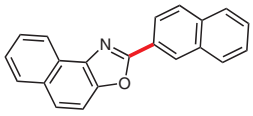
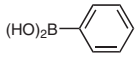
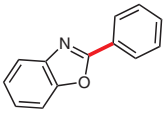
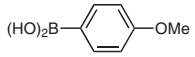
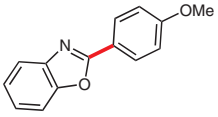
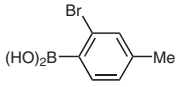
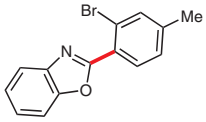
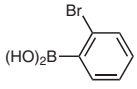
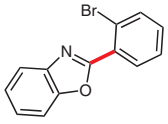
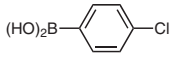
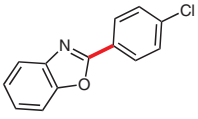
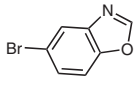
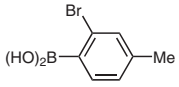
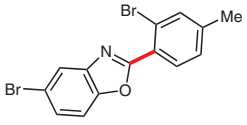
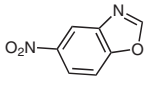
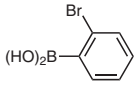
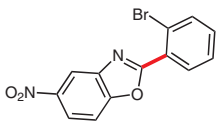
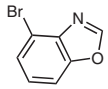
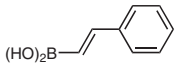
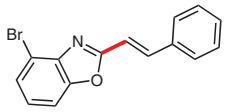
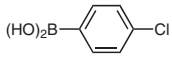
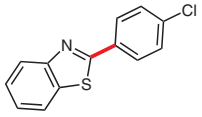
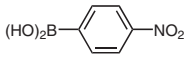
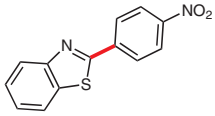
Entry	1	2	3, Yield (%)[b]
11	 **1a**	 **2k**	 **3k** (55%)
12	 **1b**	 **2l**	 **3l** (62%)
13	 **1b**	 **2a**	 **3m** (89%)
14	 **1b**	 **2b**	 **3n** (87%)
15	 **1b**	 **2m**	 **3o** (83%)
16	 **1b**	 **2n**	 **3p** (66%)
17	 **1b**	 **2e**	 **3q** (74%)
18	 **1c**	 **2m**	 **3r** (67%)
19	 **1d**	 **2n**	 **3s** (69%)

Table 2 (continued)

Entry	1	2	3, Yield (%)[b]
20	 **1e**	 **2o**	 **3t** (63%)
21	 **1f**	 **2e**	 **3u** (74%)
22	 **1f**	 **2k**	 **3v** (71%)

[a] Reactions were performed using **1a–f** (1.0 mmol) and **2a–o** (1.0 mmol) in anhyd DMF (2 mL) under a nitrogen atmosphere.
[b] Isolated yields.

In conclusion, two facile and convenient protocols for the syntheses of C2-aryl benzoxazoles are described.[21,22] Notably, the present methods avoid the use of precious metal as catalyst and pre-activated halogenated compounds as substrates. The reaction proceeds via Fe(III)-catalyzed C–H activation approach with high yields of C2-aryl benzoxazoles and restricts the formation of self-coupling compounds as side products. On the other hand, an efficient domino approach has been devised using nitroso aromatics and non-activated ketones as substrates. Using these developed methods a broad spectrum of substrate scope was investigated to synthesize 2-aryl benzoxazoles in high yields.

Funding Information

CCM acknowledges the Science and Engineering Research Board (SERB), New Delhi and NIT Manipur for the financial support in the form of a research grant (ECR/2016/000337).

Acknowledgment

We acknowledge Mr. M. Wolf (Institut für Chemie, Universität Hohenheim) and the central instrumentation facilities at the Indian Institute of Technology, Guwahati for recording NMR and Mass spectra. We sincerely thank Prof. T. Punniyamurthy, V. Satheesh and R. Bag from the Department of Chemistry, Indian Institute of Technology, Guwahati for sample analysis and research support. DK, NV, RG and AKK are grateful to the Ministry of Human Resource Development (MHRD), New Delhi for fellowship support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609718.

References and Notes

(1) (a) Demmer, C. S.; Bunch, L. *Eur. J. Med. Chem.* **2015**, *97*, 778. (b) Gautam, M. K.; Sonal; Sharma, N. K.; Priyanka; Jha, K. K. *Int. J. Chem. Tech. Res.* **2012**, *4*, 640. (c) Hartner, F. W. Jr. *Oxazoles: In Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, **1996**, 261–318. (d) Johnson, S. M.; Connelly, S.; Wilson, I. A.; Kelly, J. W. *J. Med. Chem.* **2008**, *51*, 260. (e) Razavi, H.; Palaninathan, S. K.; Powers, E. T.; Wiseman, R. L.; Purkey, H. E.; Mohamedmohaideen, N. N.; Deechongkit, S.; Chiang, K. P.; Dendle, M. T. A.; Sacchettini, J. C.; Kelly, J. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 2758. (f) Kumar, R. V. *Asian J. Chem.* **2004**, *16*, 1241. (g) Boyd, G. V. *In Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Schaumann, E., Ed.; Thieme: Stuttgart, **2002**, 481. (h) Doepp, H.; Doepp, D. In *Houben-Weyl Methoden der Organischen Chemie*; Schaumann, E., Ed.; Thieme: Stuttgart, **1993**, 1020.

(2) (a) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143. (b) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995. (c) Rodríguezam Reodrgueonlez, E. *Org. Lett.* **1999**, *3*, 527. (d) Ueki, M.; Ueno, K.; Miyadoh, S.; Abe, K.; Shibata, K.; Taniguchi, M.; Oi, S. *J. Antibiot.* **1993**, *46*, 1089. (e) Sato, S.; Kajiura, T.; Noguchi, M.; Takehana, K.; Kobayashi, T.; Tsuji, T. *J. Antibiot.* **2001**, *54*, 102. (f) Lin, F.-W.; Damu, A. G.; Wu, T.-S. *J. Nat. Prod.* **2006**, *69*, 93. (g) Don, M.-J.; Shen, C.-C.; Lin, Y.-L.; Syu, W.-J.; Ding, Y.-H.; Sun, C.-M. *J. Nat. Prod.* **2005**, *68*, 1066.

(3) (a) Tully, D. C.; Liu, H.; Alper, P. B.; Chatterjee, A. K.; Epple, R.; Roberts, M. J.; Williams, J. A.; Nguyen, K. T.; Woodmansee, D. H.; Tumanut, C.; Li, J.; Spraggon, G.; Chang, J.; Tuntland, T.; Harris, J. L.; Karanewsky, D. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1975. (b) McGrath, M. E.; Sprengeler, P. A.; Hill, C. M.; Martichonok,

V.; Cheung, H.; Somoza, J. R.; Palmer, J. T.; Janc, J. W. *Biochemistry* **2003**, *42*, 15018. (c) Reynolds, M. B.; DeLuca, M. R.; Kerwin, S. M. *Bioorg. Chem.* **1999**, *27*, 326. (d) Kumar, A.; Ahmad, P.; Maurya, R. A.; Singh, A. B.; Srivastava, A. K. *Eur. J. Med. Chem.* **2009**, *44*, 109. (e) Gong, B.; Hong, F.; Kohm, C.; Bonham, L.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455. (f) Yoshida, S.; Shiokawa, S.; Kawano, K.; Ito, T.; Murakami, H.; Suzuki, H.; Sato, Y. *J. Med. Chem.* **2005**, *48*, 7075. (g) Sato, Y.; Yamada, M.; Yoshida, S.; Soneda, T.; Ishikawa, M.; Nizato, T.; Suzuki, K.; Konno, F. *J. Med. Chem.* **1998**, *41*, 3015. (h) Leventhal, L.; Brandt, M. R.; Cummons, T. A.; Piesla, M. J.; Rogers, K. E.; Harris, H. A. *Eur. J. Pharmacol.* **2006**, *553*, 146. (i) Manas, E. S.; Unwalla, R. J.; Xu, Z. B.; Malamas, M. S.; Miller, C. P.; Harris, H. A.; Hsiao, C.; Akopian, T.; Hum, W.-T.; Malakian, K.; Wolfrom, S.; Bapat, A.; Bhat, R. A.; Stahl, M. L.; Somers, W. S.; Alvarez, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15106. (j) Malamas, M. S.; Manas, E. S.; McDevitt, R. E.; Gunawan, I.; Xu, Z. B.; Collini, M. D.; Miller, C. P.; Dinh, T.; Henderson, R. A.; Keith, J. C. Jr.; Harris, H. A. *J. Med. Chem.* **2004**, *47*, 5021. (k) Sun, L.-Q.; Chen, J.; Bruce, M.; Deskus, J. A.; Epperson, J. R.; Takaki, K.; Johnson, G.; Iben, L.; Mahle, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3799.

(4) (a) Ooyama, Y.; Kagawa, Y.; Fukuoka, H.; Ito, G.; Harima, Y. *Eur. J. Org. Chem.* **2009**, 5321. (b) Ooyama, Y.; Egawa, H.; Yoshida, K. *Eur. J. Org. Chem.* **2008**, 5239. (c) Ooyama, Y.; Kagawa, Y.; Harima, Y. *Eur. J. Org. Chem.* **2007**, 3613. (d) Ohshima, A.; Momotake, A.; Nagahata, R.; Arai, T. *J. Phys. Chem. A* **2005**, *109*, 9731. (e) Mayer Dumas Cheresse, F. *Chem. Commun.* **2005**, 345. (f) Taki, M.; Wolford, J. L.; O'Halloran, T. V. *J. Am. Chem. Soc.* **2004**, *126*, 712. (g) Seo, J.; Kim, S.; Park, S. Y. *J. Am. Chem. Soc.* **2004**, *126*, 11154.

(5) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 7316.

(6) (a) Boger, D. L.; Miyauchi, H.; Hedrick, M. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1517. (b) Boger, D. L.; Sato, H.; Lerner, A. E.; Hedrick, M. P.; Fecik, R. A.; Miyauchi, H.; Wilkie, G. D.; Austin, B. J.; Patricelli, M. P.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5044. (c) Chen, J.; Li, C.-M.; Wang, J.; Ahn, S.; Wang, Z.; Lu, Y.; Dalton, J. T.; Miller, D. D.; Li, W. *Bioorg. Med. Chem.* **2011**, *19*, 4782. (d) Harn, N. K.; Gramer, C. J.; Anderson, B. A. *Tetrahedron Lett.* **1995**, *36*, 9453.

(7) (a) Sharma, S.; Khan, I. A.; Saxena, A. K. *Adv. Synth. Catal.* **2013**, *355*, 673. (b) Yang, K.; Zhang, C.; Wang, P.; Zhang, Y.; Ge, H. *Chem.-Eur. J.* **2014**, *20*, 7241.

(8) (a) Richardson, C.; Rewcastle, G. W.; Hoyer, D.; Denny, W. A. *J. Org. Chem.* **2005**, *70*, 7436. (b) Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino, R. J.; Pangborn, J. J. *Org. Process Res. Dev.* **2003**, *7*, 696. (c) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *6*, 979. (d) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583. (e) Kosugi, M.; Koshiba, M.; Atoh, A.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677. (f) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 201. (g) Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169. (h) Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008**, *49*, 1598. (i) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.

(9) (a) Barbero, N.; Carril, M.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2007**, *63*, 10425. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Ueda, S.; Nagasawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6411. (d) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452. (e) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (f) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (g) Yang, D.; Zhu, X.; Wei, W.; Jiang, M.; Zhang, N.; Ren, D.; You, J.; Wang, H. *Synlett* **2014**, *25*, 729. (h) Bose, D. S.; Idrees, M. *Synthesis* **2010**, 398.

(10) (a) Fan, X.; He, Y.; Zhang, X.; Guo, S.; Wang, Y. *Tetrahedron* **2011**, *67*, 6369. (b) Cui, L.; He, Y.; Fan, X. *Chin. J. Chem.* **2012**, *30*, 992. (c) Seijas, J. V.; Zquez-Tato, M. P.; Carballido-Reboredo, M. R.; Crecente-Campo, J. *Synlett* **2007**, 313. (d) Isomura, Y.; Ito, N.; Homma, H.; Abe, T.; Kubo, K. *Chem. Pharm. Bull.* **1983**, *31*, 3168. (e) Terashima, M.; Ishii, M. *Synthesis* **1982**, 484. (f) Hegedus, L. S.; Odle, R. R.; Winton, P. M.; Weider, P. R. *J. Org. Chem.* **1982**, *47*, 2607. (g) Holan, G.; Evans, J. J.; Linton, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1200. (h) Jackson, P. F.; Morgan, K. J.; Turner, A. M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1582. (i) Kanaoka, Y.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1970**, *18*, 587. (j) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427. (k) Bywater, W. G.; Coleman, W. R.; Kamm, O.; Merrit, H. H. *J. Am. Chem. Soc.* **1945**, *67*, 905. (l) Reddy, M. B. M.; Nizam, A.; Pasha, M. A. *Synth. Commun.* **2011**, *41*, 1838. (m) Li, H.; Wei, K.; Wu, Y.-J. *Chin.J. Chem.* **2007**, *25*, 1704. (n) Osma, A.-M.; Bassiouni, I. *J. Org. Chem.* **1962**, *27*, 558. (o) Stephens, F. F. *Nature (London)* **1949**, *164*, 243.

(11) (a) Kumar, R. V. *Asian J. Chem.* **2004**, *16*, 1241. (b) Aljaar, N.; Malakar, C. C.; Conrad, J.; Frey, W.; Beifuss, U. *J. Org. Chem.* **2013**, *78*, 154. (c) Aljaar, N.; Malakar, C. C.; Conrad, J.; Beifuss, U. *J. Org. Chem.* **2015**, *80*, 10829.

(12) Correa, A.; Fiser, B.; Gómez-Bengoa, E. *Chem. Commun.* **2015**, *51*, 13365.

(13) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169.

(14) Wang, J.; Hou, J.-T.; Wen, J.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2011**, *47*, 3652.

(15) Wen, J.; Qin, S.; Ma, L.-F.; Dong, L.; Zhang, J.; Liu, S.-S.; Duan, Y.-S.; Chen, S.-Y.; Hu, C.-W.; Yu, X.-Q. *Org. Lett.* **2010**, *12*, 2694.

(16) (a) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *ChemCatChem.* **2010**, *2*, 1403. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (c) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (d) Shen, X.-B.; Zhang, Y.; Chen, W.-X.; Xiao, Z.-K.; Hu, T.-T.; Shao, L. X. *Org. Lett.* **2014**, *16*, 1984. (e) Boissarie, P. J.; Hamilton, Z. E.; Lang, S.; Murphy, J. A.; Suckling, C. J. *Org. Lett.* **2011**, *13*, 6184. (f) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194.

(17) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.

(18) For recent reviews, see: (a) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (b) Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343. (c) Kazzouli, S. E.; Koubachi, J.; Brahmi, N. E.; Guillaumet, G. *RSC Adv.* **2015**, *5*, 15292. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

(19) (a) Xu, H.; Wu, X.; Ding, Y.; Peng, C.; Peng, X. *Asian J. Chem.* **2015**, *27*, 3185. (b) Das, B.; Venkateswarlu, K.; Mahender, G.; Mahender, I. *Tetrahedron Lett.* **2005**, *46*, 3041.

(20) (a) Ilies, L.; Matsumoto, A.; Kobayashi, M.; Yoshikai, N.; Nakamura, E. *Synlett* **2012**, *23*, 2381. (b) Adak, L.; Yoshikai, N. *Tetrahedron* **2012**, *68*, 5167. (c) Wong, M. Y.; Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2015**, *17*, 442. (d) Matsubara, T.; Ilies, L.; Nakamura, E. *Chem. -Asian J.* **2016**, *11*, 380. (e) Shang, R.; Ilies, L.; Nakamura, E. *Chem. Rev.* **2017**, *117*, 9086.

(21) **General Experimental Procedure for the Synthesis of Products 3a–v**:

Method A: A-10 mL pressure tube was charged with a mixture of **1a–f** (1.0 mmol), **2a–o** (1.0 mmol), $FeCl_3$ (0.05 mmol, 8.1 mg), 1,10-phenanthroline (0.1 mmol, 18 mg), DCIB (1.3 mmol, 165 mg), Cs_2CO_3 (1.5 mmol 487 mg), and DMF (2 mL). The pressure

tube was then sealed and heated at 100 °C for 16 h. After completion of the reaction, the mixture was diluted with hot EtOAc (50 mL) and H_2O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (2 × 50 mL) and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography over silica gel using hexane–EtOAc (10:1) as an eluent to obtain the desired products **3a–v**.

Method B: In an oven-dried 100-mL round-bottomed flask **4a–b** (1.0 mmol), **5a–k** (1.0 mmol), CBr_4(0.5 mmol, 165 mg), Cs_2CO_3 (2.1 mmol, 682 mg) and 10 mL MeCN (10 mL) were added successively and the reaction mixture was heated for 6 h at 80 °C under nitrogen atmosphere. The reaction mixture was allowed to cool to r.t. and then the solvent was removed under vacuum. The crude product was purified by using column chromatography over silica gel using hexane–EtOAc (10:1) as an eluent to get the products **3a–f**, **3h**, **3i**, **3k**, **3m**, **3w**, **3x** as yellow crystalline solids.

(22) **Characterization Data for 2-Phenylnaptho[1,2-d]oxazole (3a)**: yield: 85%, 208 mg (Method A) and 69%, 169 mg (Method B). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.49 (m, 5 H, 8-H, 9-H, 10-H, 11-H, 12-H), 7.69 [dd, ^3J (1-H, 2-H) = 7.0 Hz, ^3J (2-H, 3-H) = 8.0 Hz, ^3J (3-H, 4-H) = 8.1 Hz, ^3J (2-H, 3-H), 2 H, 2-H, 3-H], 7.89 [d, ^3J (3-H, 4-H) = 7.0 Hz, 1 H, 4-H], 8.23–8.29 [m, ^3J (5-H, 6-H)= 8.9 Hz, 2 H, 5-H, 6-H], 8.52 [d, ^3J (1-H, 2-H) = 8.0 Hz, 1 H, 1-H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.8 (C-6), 115.5 (C-14), 121.2 (C-1), 123.4 (C-15), 124.3 (C-2), 124.9 (C-3), 125.9 (C-4), 126.2 (C-8, C-12), 127.5 (C-10), 127.8 (C-9, C-11), 130.0 (C-5), 130.1 (C-19), 136.5(C-16), 147.0 (C-17), 161.2 (C-18).
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{12}NO$: 246.0918; found: 246.0914.