ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Dai, S. Yu, Y. Shao, R. Li, Z. Chen, N. Lv and J. Chen, *Chem. Commun.*, 2021, DOI: 10.1039/D0CC07547G.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/D0CC07547G

Journal Name

COMMUNICATION

Palladium-catalyzed C-H activation of simple arenes and cascade reaction with nitriles: access to 2,4,5-trisubstituted oxazoles

Ling Dai,[a] Shuling Yu,[a] Yinlin Shao,[a] Renhao Li,[b] Zhongyan Chen,[a] Ningning Lv*[a] and Jiuxi Chen*[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

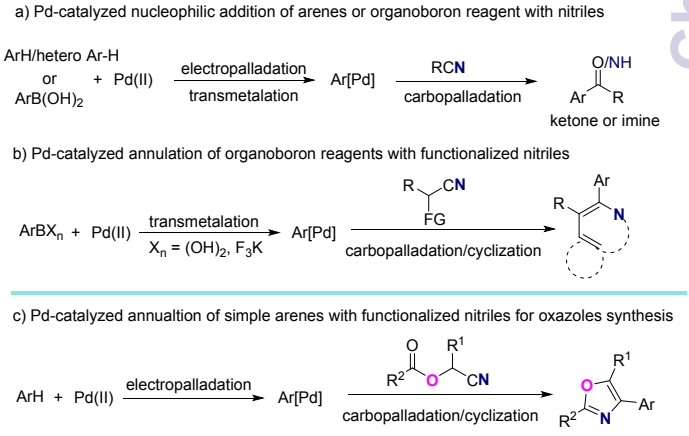
An efficient and straightforward protocol for the assembly of pharmaceutically and biologically valuable oxazole skeleton is achieved for the first time from readily available simple arenes and functionalized aliphatic nitriles. This transformation involves palladium-catalyzed C-H activation, carbopalladation and tandem annulation sequence in one pot. Notably, the reaction proceeds efficiently under redox-neutral conditions, and exhibits high atom-economy. Deuterium-labeling experiments suggested that C-H bond cleavage of the simple arenes might be the rate-determining step.

Nitrile is a highly privileged skeleton that has found widely applications in synthetic chemistry and pharmaceutical fileds.[1] In the pioneering work, Larock exploited the nucleophilic addition strategy of arylpalladium species to the cyano group, giving the corresponding ketones and imines (Scheme 1, eq a).[2] Afterwards, transition-metal-catalyzed functionalization of nitriles reacting with various coupling partners[3-8] has aroused much attention owing to its efficency. However, most of examples exclusively deliver simple ketones, rendering the waste of nitrogen atom and lowering the complexity of the target molecules.

Over the past few decades, cascade cyclization reactions have become a powerful protocol for the synthesis of complicated heterocycles and carbocycles through the introduction of multiple functional groups on the substrates. By the employment of this methodology, functionalized nitriles have been successfully transformed into a range of high-valued nitrogen-containing heterocyclic compounds (Scheme 1, eq b).[9] Among them, our group has realized the construction of practical utility *N*-heterocycle frameworks, including isoquinolines, isoquinolones, quinazolines, pyrroles, pyridines, dibenzo[*c,e*]azepines and benzofuro[2,3-*c*]pyridines etc.[10] Nevertheless, such reactions are still confined to using preactivated organoboron reagent as the coupling partner, leading to multistep synthetic procedures and undesirable waste.

From the synthetic and environmental perspective, the use of inert C-H bond instead of prefunctionalized arene building blocks represents the most straightforward route of formation organometallic species. There have recently been several examples of electron-rich heteroarenes reacting with nitriles to produce heterocycles.[11] To the best of our knowledge, the example of simple arenes reacting with functionalized nitriles has still remained rare, owing to the low electron density of simple arenes.[12] Stimulated by our ongoing efforts and interests in the nitrile chemistry, we herein reported the first example of synthesis trisubstituted oxazoles through palladium-catalyzed direct C-H activation of simple arenes, followed by carbopalladation and tandem cyclization with functionalized nitriles (Scheme 1, eq c). This transformation features excellent reactivity and high atom-economy. Additionally, this conversion could be easily scaled-up with excellent yield. Deuterium-labeling experiments suggested that C-H activation process might be the rate-determining step. It should be noted that 2,4,5-trisubstituted oxazoles is an important class of five-membered nitrogen/oxygen-containing heterocyclic framework that occur in a broad library of natural products and synthetic bioactive molecules.[13]

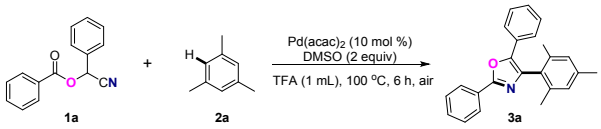
Scheme 1 Nucleophilic addition of arylpalladium species with nitriles.



[a] College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, China E-mail: ningninglv@wzu.edu.cn; jiuxichen@wzu.edu.cn.
[b] School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou 325035, P. R. China

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of reaction conditions[a]



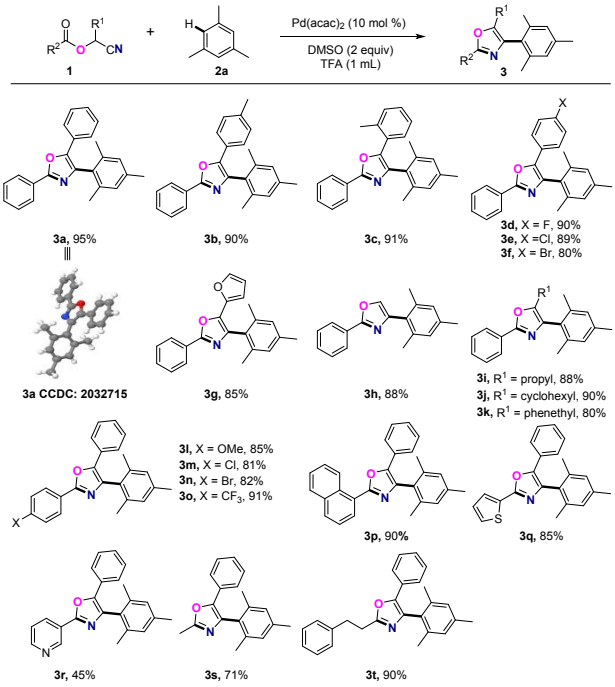
entry	deviation from"standard conditions"	yield(%)[b]
1	none	95
2	no $Pd(acac)_2$	nr
3	mesitylene as solvent without TFA	trace
4	$Pd(TFA)_2$ instead of $Pd(acac)_2$	78
5	$Pd(OAc)_2$ instead of $Pd(acac)_2$	72
6	no DMSO	25
7	0.2 equiv. DMSO was used	82
8	0.5 equiv. DMSO was used	88
9	1 equiv. DMSO was used	91
10	DMF instead of DMSO	85
11[c]	2,2'-bipyridine instead of DMSO	40
12[c]	1,10-phenanthroline instead of DMSO	60

[a]Conditions: **1a** (0.3 mmol), **2a** (7 equiv), Pd-catalyst (10 mol %), DMSO (2 equiv), TFA (1 mL), 100 °C, 6 h, air. [b]Isolated yield. [c]20 mol % ligand was used.

We commenced our investigations by screening the reaction conditions of the model reaction of cyano(phenyl)methyl benzoate **1a** with mesitylene **2a** (Table 1). Optimal conditions were obtained by using catalyst derived from $Pd(acac)_2$ and additive DMSO in solution of TFA at 100 °C for 6 h, generating target oxazole **3a** in 95% yield (Table 1, entry 1). Control experiments indicated that Pd-catalyst and TFA were essential to this transformation (Table 1, entries 2-3). Using $Pd(TFA)_2$ or $Pd(OAc)_2$ instead of $Pd(acac)_2$, the decreased yield of product **3a** was observed (Table 1, entries 4-5). It was found that DMSO, which is known to be a unique ligand in many Pd(II) transformations,[2,14] has a significant effect on this transformation. The addition of 0.2 equiv DMSO into the reaction, the yield was drastically increased to 82%. Subsequently, the yield was increased by margin when DMSO was increased to 2 equivalents (Table 1, entries 6-9). Additionally, DMSO showed better reactivity than other ligands, including DMF, 2,2'-bipyridine and phenanthroline. (Table 1, entries 10-12). Further screening revealed that the optimal dosage of the simple arene is 7 equivalents (see the ESI† for details, Table S1)

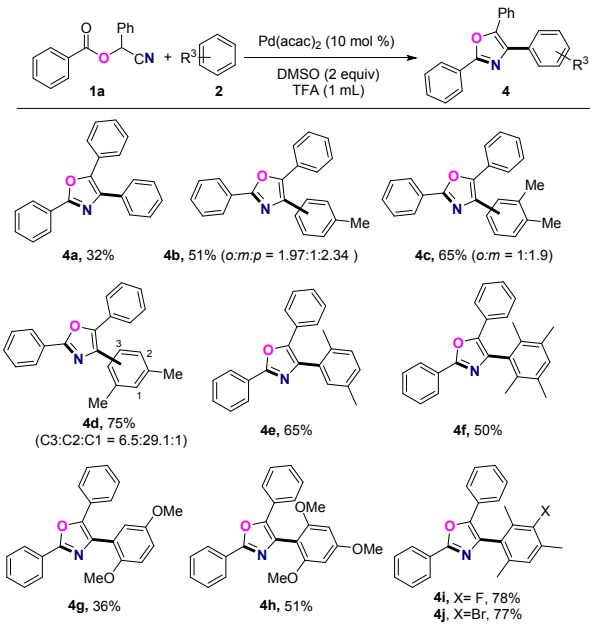
With the optimal reaction conditions in hand, the generality by varying the substituents on the cyanomethyl carboxylates was demonstrated in Table 2. In general, this transformation exhibits a broad substrate scope. Substrates of *para*-tolyl and *ortho*-tolyl attached to α-position of the cyano group give the corresponding oxazoles in 90% and 91% yield, respectively (**3b**-**3c**), suggesting that the steric hindrance has a negligible impact on the reaction. Halogen substituents attached to the benzene ring of α-position of the cyano group could be tolerated well, affording the target products in excellent yields (**3d**-**3f**), which allows the as-prepared oxazoles for late-stage elaborations. Substrates with diverse R^1 substituents, such as furyl, hydrogen atom, propyl, cyclohexyl and phenethyl groups, are also amenable to this transformation and exhibit excellent reactivity (**3g**-**3k**). In addition, the cyano(phenyl)methyl benzoates with -OMe, -Cl, -Br and -CF_3 groups on the aryl ring participate in this transformation smoothly, giving the desired products **3l**-**3o** in 81-91% yields. Notably, this methodology could be successfully extended to heterocyclic-substituted substrates, leading to the corresponding oxazole products (**3p**-**3r**). With respect to alkyl-substituted substrates, the reaction underwent smoothly to give the 2-alkylsubstituted oxazoles in good yields (**3s-3t**). The exact structure of **3a** was identified by X-ray diffraction.[15]

Table 2 Scope of functionalized nitriles[a]



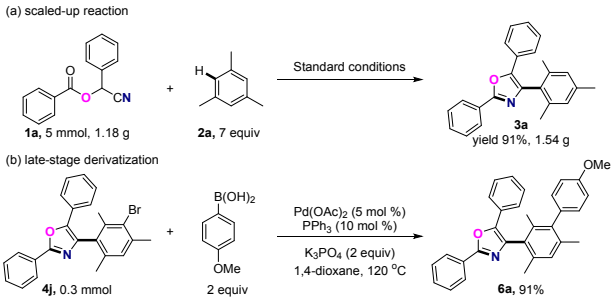
[a]Conditions: **1** (0.3 mmol), **2a** (7 equiv), $Pd(acac)_2$ (10 mol %), DMSO (2 equiv), TFA (1 mL), 100 °C, 6 h, air. [b]Isolated yield.

Table 3 Scope of simple arenes[a]



[a]Conditions: **1a** (0.3 mmol), **2** (7 equiv), $Pd(acac)_2$ (10 mol %), DMSO (2 equiv), TFA (1 mL), 100 °C, 6 h, air. [b]Isolated yield. [c]The value given in parentheses denotes the relative ratio of regioisomers detected by GC-MS.

Scheme 2 Synthetic applications

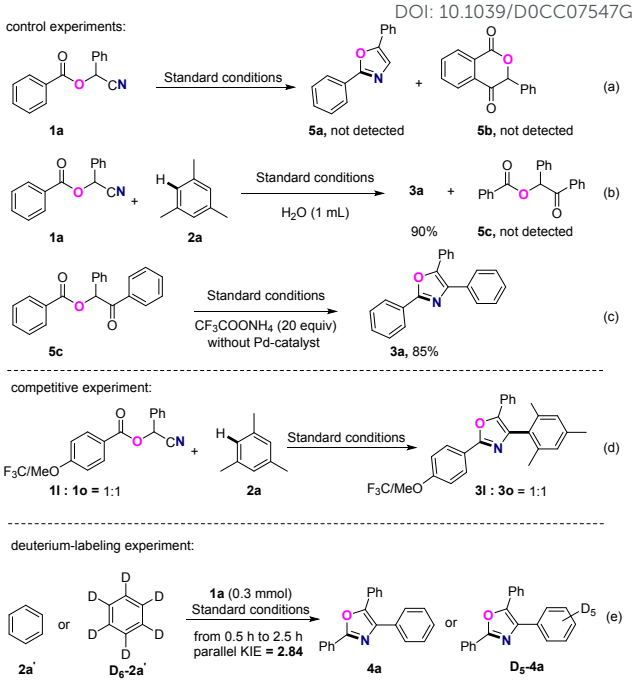


After examining the compatibility of the various cyanomethyl carboxylates, we next investigated the substrate scope of simple arenes (Table 3). It should be noted that the reaction system displayed good tolerance toward bare benzene substrate (**4a**), indicating that large steric effect of the simple arene is not essential to this conversion. Toluene, *o*-xylene and *m*-xylene substrates, each of which possesses two or three potential reaction sites, generated the corresponding mixtures of oxazoles in good yields (**4b-4d**). With respect to *p*-xylene and 1,2,4,5-tetramethylbenzene, the reaction proceeded well to provide the desired products in 65% and 50% yield, respectively (**4e-4f**). Methoxyl-substituted benzenes were also compatible in this reaction to produce the target products (**4g-4h**). The transformation was further extended to 2-fluoro-1,3,5-trimethylbenzene and 2-bromo-1,3,5-trimethylbenzene, delivering the target oxazoles in excellent yields (**4i-4j**). However, no reaction occurred with respect to the electron-deficient arenes, such as benzonitrile, (trifluoromethyl)benzene, methyl benzoate and pentafluorobenzene, owing to the key arylpalladium species was formed via the electrophilic palladation between the palladium catalyst with the simple arenes.

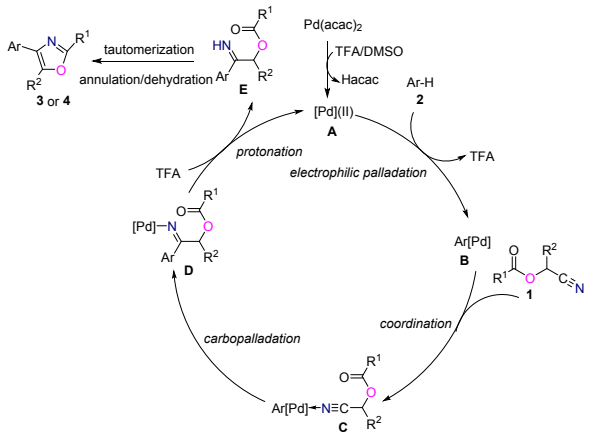
Gratifyingly, this transformation could be easily scaled-up to 5 mmol scale, producing the target oxazloe **3a** in 91% yield (Scheme 2, eq a). Moreover, the as-prepared oxazole **4j** could be further transformed into more complicated molecules through cross-coupling reaction (Scheme 2, eq b). These results further highlight the robustness and practical potential of this protocol.

Preliminary experiments were performed under standard conditions for the better understanding of the reaction mechanism as depicted in Scheme 3. First, the reaction was carried out in the absence of simple arenes, the corresponding cyclized products 2,5-diphenyloxazole (**5a**) and 3-phenylisochromane-1,4-dione (**5b**) were not detected. These results implicated that this transformation was initiated by the carbopalladation between the arylpalladium species with nitrile substrate. The arylpalladium species was generated from the electropalladation of palladium catalyst with the simple arenes (Scheme 3, eq a). When the model reaction of **1a** with **2a** was treated with 1 mL water, no 2-oxo-1,2-diphenylethyl benzoate (**5c**) was obtained, indicating that the ketimine intermediate is more prone to undergo domino cyclization reaction compared with the hydrolysis process (Scheme 3, eq b). In addition, we synthesized the compound **5c** according to the literature,[16] then the target oxazole **3a** was obtained when it reacted with 20 equiv ammonium trifluoroacetate in the absence of palladium catalyst, further underscoring the ketimine was the indeed intermediate of this transformation (Scheme 3, eq c). An intermolecular competition experiment of **1l** and **1o** with mesitylene **2a** was performed (Scheme 3, eq d), and the result revealed that the electronic effect of the benzene ring of the benzoate had little impact on this conversion. Subsequently, the parallel kinetic isotope reactions of **2a**′ or **D_6-2a**′ with **1a** were conducted from 0.5 h to 2.5 h separately (Scheme 3, eq e, see the

Scheme 3 Mechanistic investigations



Scheme 4 Proposed reaction mechanism



ESI† for details). Then, the primary kinetic isotope effect of 2.84 was observed, revealing that the C-H activation process might be the rate determining step.[17]

On basis of the aforementioned experiment results and previous reports,[2,18] we propose a plausible mechanism for the synthesis of trisubstituted oxazole as demonstrated in Scheme 4. Initially, an activated palladium catalyst **A** is formed from $Pd(acac)_2$ catalyst in the presence of TFA and DMSO.[2,14] The subsequent electropalladation between the species **A** and the simple arene **2** furnishes the key arylpalladium species **B**,[2,18] followed by coordination with the nitrile substrate gives the intermediate **C**. The carbopalladation of species **C** generates imine-Pd complex **D**, which undergoes protonation process to form the ketimine intermediate **E** and release the activated palladium catalyst **A** to fulfil the catalytic cycle. Subsequently, the tautomerization/nucleophilic addition/dehydration of complex **E** deliver the target oxazole products.

In summary, we have developed a new route to construct diverse 2,4,5-trisubstituted oxazoles via palladium-catalysed domino

reaction of readily accessible simple arenes with cyanomethyl carboxylates. The transformation involves the direct cleavage of inert C-H bond and formation of multiple bonds in one pot under redox-neutral reaction condition. Moreover, this synthetic strategy is distinguished by its excellent reactivity (up to 95% yield) and high atom efficiency. Notably, this protocol is of practical utility could be easily scaled-up reaction and for late-stage derivatization. Further investigations on exploiting efficient pathway to access more privileged heterocycles are underway in our laboratory.

We thank the National Natural Science Foundation of China (No. 21572162), the Natural Science Foundation of Zhejiang Province (No. LY20B020015 and Q21B050002) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 *(a)* V. Y. Kukushkin and A. J. L. Pombeiro, *Chem. Rev.,* 2002, **102,** 1771−1802; *(b)* D. Enders and J. P. Shilvock, *Chem. Soc. Rev.,* 2000, **29,** 359−373; For selected examples, see: *(c)* K. Tokmic, B. J. Jackson, A. Salazar, T. J. Woods and A. R. Fout, *J. Am. Chem. Soc.,* 2017, **139,** 13554−13561; *(d)* J. B. Geri and N. K. Szymczak, *J. Am. Chem. Soc.,* 2015, **137,** 12808−12814; *(e)* A. Mukherjee, D. Srimani, S. Chakraborty, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.,* 2015, **137,** 8888−8891.

2 *(a)* C. Zhou and R. C. Larock, *J. Am. Chem. Soc.,* 2004, **126,** 2302−2303; *(b)* C. Zhou and R. C. Larock, *J. Org. Chem.,* 2006, **71,** 3551−3558.

3 *(a)* R. C. Larock, Q. Tian and A. A. Pletnev, *J. Am. Chem. Soc.,* 1999, **121,** 3238−3239; *(b)* A. A. Pletnev, Q. Tian and R. C. Larock, *J. Org. Chem.,* 2002, **67,** 9276−9287.

4 *(a)* K. Ueura, T. Satoh and M. Miura, *Org. Lett.,* 2005, **7,** 2229−2231; *(b)* B. Zha and X. Lu, *Tetrahedron Lett.,* 2006, **47,** 6765−6768; *(c)* H. Shimizu and M. Murakami, *Chem. Commun.,* **2007,** 2855−2857; *(d)* Y.-C. Wong, K. Parthasarathy and C.-H. Cheng, *Org. Lett.,* 2010, **12,** 1736−1739; *(e)* G. Tsui, Q. Glenadel, C. Lau and M. Lautens, *Org. Lett.,* 2011, **13,** 208−211.

5 J. Lindh, P. Sjberg and M. Larhed, *Angew. Chem., Int. Ed.*,2010, **49,** 7733−7737.

6 K. Cheng, G. Wang, M. Meng and C. Qi, *Org. Chem. Front.,* 2017, **4,** 398−403.

7 *(a)* J. Liu, X. Zhou, H. Rao, F. Xiao, C. Li and G. Deng, *Chem. – Eur. J.,* 2011, **17,** 7996−7999; *(b)* M. Behrends, J. Sämarker, P. Sjöberg and M. Larhed, *ACS Catal.,* 2011, **1,** 1455−1459; *(c)* T. Miao and G. Wang, *Chem. Commun.,* 2011, **47,** 9501−9503.

8 *(a)* J. Sheng, Y. Wang, X. Su, R. He and C. Chen, *Angew. Chem., Int. Ed.,* 2017, **56,** 4824−4828; *(b)* X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou and M. Li, *Chem. Commun.,* 2013, **49,** 6752−6754; *(c)* X. Pang, C. Chen, X. Su, M. Li and L. Wen, *Org. Lett.,* 2014, **16,** 6228−6231.

9 *(a)* H. Yu, L. Xiao, X. Yang and L. Shao, *Chem. Commun.,* 2017, **53,** 9745−9748; *(b)* M. Yousuf and S. Adhikari, *Org. Lett.,* 2017, **19,** 2214−2217; *(c)* H. Song, N. Cheng, L. She, Y. Wu and W. Liao, *RSC Adv.,* 2019, **9,** 29424−29428.

10 *(a)* L. Qi, K. Hu, S. Yu, J. Zhu, T. Cheng, X. Wang, J. Chen and H. Wu, *Org. Lett.,* 2017, **19,** 218−221; *(b)* K. Hu, Q. Zhen, J. Gong, T. Cheng, L. Qi, Y. Shao and J. Chen, *Org. Lett.,* 2018, **20,** 3083−3087; *(c)* X. Yao, Y. Shao, M. Hu, Y. Xia, T. Cheng and J. Chen, *Org. Lett.,* 2019, **21,** 7697−7701; *(d)* W. Xiong, K. Hu, Y. Lei, Q. Zhen, Z. Zhao, Y. Shao, R. Li, Y. Zhang and J. Chen, *Org. Lett.,* 2020, **22,** 1239−1243; *(e)* L. Chen, J. Gong, Y. Zhang, Y. Shao, Z. Chen, R. Li and J. Chen, *Org. Lett.*,2020, **22,** 6943−6947; *(f)* X. Yao, Y. Shao, M. Hu, M. Zhang, S. Li, Y. Xia, T. Cheng and J. Chen, *Adv. Synth. Catal.,* 2019, **361,** 4707−4713; *(g)* L. Dai, S. Yu, W. Xiong, Z. Chen, T. Xu, Y. Shao and J. Chen, *Adv. Synth. Catal.,* 2020, **362,** 1893−1898; *(h)* S. Yu, L. Dai, Y. Shao, R. Li, Z. Chen, N. Lv and J. Chen, *Org. Chem. Front.,* 2020, **7,** 3439−3445.

11 *(a)* D. Zhang, H. Song, N. Cheng and W.-W. Liao, *Org. Lett.*,2019, **21,** 2745−2749; *(b)* W. Xiong, Z. Chen, Y. Shao, R. Li, K. Hu and J. Chen, *Org. Chem. Front.,* 2020, **7,** 756−762; *(c)* L. Zhao and W.-W. Liao, *Org. Chem. Front.,* 2018, **5,** 801−805; *(d)* T-T. Wang, D. Zhang and W.-W. Liao, *Chem. Commun.,* 2018, **54,** 2048−2051; *(e)* T.-S. Jiang and G.-W. Wang, *Org. Lett.,* 2013, **15,** 788−791; *(f)* T.-S. Jiang and G.-W. Wang, *Adv. Synth. Catal*., 2014, **356,** 369–373; *(g)* Y. Ma, J. You and F. Song, *Chem. Eur. J.,* 2013, **19,** 1189–1193; *(h)* J. Rydfjord, B. Skillinghaug, P. Brandt, L. R. Odell and M. Larhed, *Org. Lett.,* 2017, **19,** 4066-4069.

12 *(a)* B. Zhou, Y. Hu and C. Wang, *Angew. Chem. Int. Ed.,* 2015, **54,** 13659−13663; *(b)* H. Takaya, M. Ito and S. Murahashi, *J. Am. Chem. Soc.,* 2009, **131,** 10824–10825.

13 For selected cases, see: *(a)* P. A. Searle and T. F. Molinski, *J. Am. Chem. Soc.,* 1995, **117,** 8126−8131; *(b)* O. Banzragchgarav, T. Murata, G. Odontuya, B. Buyankhishig, K. Suganuma, B.-O. Davaapurev, N. Inoue, J. Batkhuu and K. Sasaki, *J. Nat. Prod.,* 2016, **79,** 2933−2940; *(c)* B. Clapham, A. J. Richards, M. L. Wood and A. J. Sutherland, *Tetrahedron Lett.,* 1997, **38,** 9061−9064; *(d)* P. A. Todd and R. N. Brogden, *Drugs,* 1986, **32,** 291−312; *(e)* F. Akutsu, M. Inoki, K. Sunouchi, Y. Sugama, Y. Kasashima, K. Naruchi and M. Miura, *Polymer.,* 1998, **39,** 1637−10641.

14 *(a)* D. Tanaka, S. P. Romeril and A. G. Myers, *J. Am. Chem. Soc.,* 2005, **127,** 10323−10333; *(b)* R. I. McDonald and S. S. Stahl, *Angew. Chem., Int. Ed.,* 2010, **49,** 5529−5532; *(c)* Z. Lu and S. S. Stahl, *Org. Lett.,* 2012, **14,** 1234−1237; *(d)* C. Engelin, T. Jensen, S. Rodriguez-Rodriguez and P. Fristrup, *ACS Catal.,* 2013, **3,** 294−302; *(e)* K. J. Fraunhoffer, D. A. Bachovchin and M. C. White, Org. Lett., 2005, **7,** 223−226; *(f)* M. S. Chen, N. Prabagaran, N. A. Labenz and M. C. White, J. Am. Chem. Soc., 2005, **127,** 6970−6971.

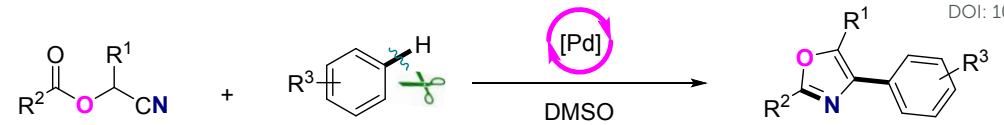
15 The structures of compounds **3a** was determined by X-ray crystallography (see the Supporting Information for full details). CCDC **2032715** (**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

16 Y.-J. Kim, N. Y. Kim and C.-H. Cheon, *Org. Lett.,* 2014, **16,** 2514−2517.

17 *(a)* E. M. Simmons and J. F. Hartwig, *Angew. Chem. Int. Ed.,* 2012, **51,** 3066−3072; *(b)* X. Wu, J. Fan, C. Fu and S. Ma, *Chem. Sci.,* 2019, **10,** 6316−6321; *(c)* N. Lv, Y. Liu, C. Xiong, Z. Liu and Y. Zhang, *Org. Lett.,* 2017, **19,** 4640−4643; *(d)* E. F. Flegeau, C. Bruneau, P. H. Dixneuf and A. Jutand, *J. Am. Chem. Soc.,* 2011, **133,** 10161−10170; *(e)* C. S. Yi and S. Y. Yun, *J. Am. Chem. Soc.,* 2005, **127,** 17000−17006.

18 *(a)* D. R.Stuart and K. Fagnou, *Science.,* 2007, **316,** 1172-1175; *(b)* Y. Wei and W. Su, *J. Am. Chem. Soc.,* 2010, **132,** 16377−16379; *(c)* J. A. Ashenhurst, *Chem. Soc. Rev.,* 2010, **39,** 540–548; *(d)* S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.,* 2011, **40,** 5068–5083.

View Article Online
DOI: 10.1039/D0CC07547G



R^1 = Aryl, heteroaryl, alkyl, H
R^2 = Aryl, heteroaryl, alkyl

up to 95% yield
30 examples

● high atom-economy ● redox-neutral reaction conditions ● good functional group tolerance

An efficient and straightforward protocol for the assembly of pharmaceutically and biologically valuable oxazole skeleton is achieved for the first time through palladium-catalyzed C-H activation, carbopalladation and tandem annulation sequence from readily available simple arenes and functionalized aliphatic nitriles.