ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: A. B. Viveki, D. N. Garad, R. G. Gonnade and S. B. Mhaske, *Chem. Commun.*, 2020, DOI: 10.1039/C9CC09824K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC09824K

COMMUNICATION

para-Selective Copper-Catalyzed C(sp^2)–H Amidation/ Dimerization of Anilides *via a* Radical Pathway

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

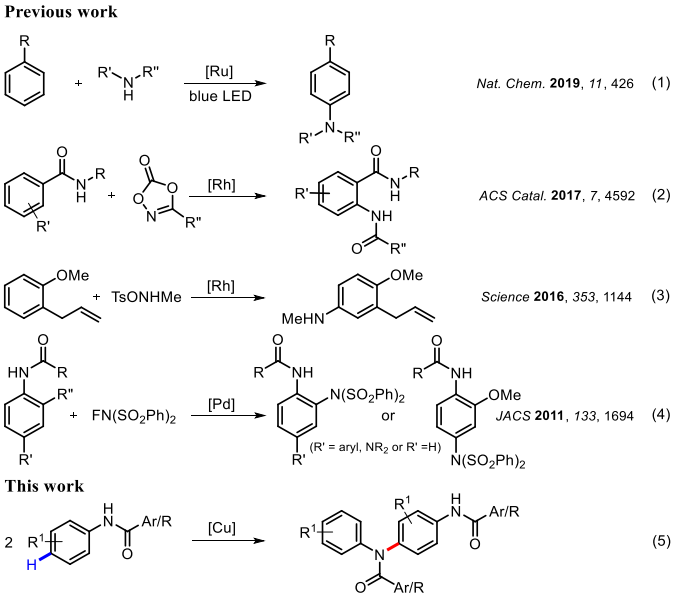
DOI: 10.1039/x0xx00000x

Amol B. Viveki,[†,‡] Dnyaneshwar N. Garad,[†,‡] Rajesh G. Gonnade[‡,§] and Santosh B. Mhaske[*,†,‡]

Copper-catalyzed amidation/dimerization of anilides via regioselective C(sp^2)–H functionalization is achieved. The *para*-selective amidation is accomplished on the anilide aromatic ring via a radical pathway leading to C–N bond formation in the presence of ammonium persulfate as a radical source/oxidant for the copper catalyst. The developed protocol tolerates a wide range of anilide substrates. The regioselectivity is confirmed by single-crystal X-ray.

Transition-metal-catalyzed C–H bond functionalization has emerged as a prominent synthetic tool in organic chemistry over the past few decades.[1] It avoids the need for prefunctionalization of substrates and offers straightforward access to the desired scaffold in high atom and step-economy. Regioselective C–H functionalization to furnish C–C and C–X (X = O, N, S, etc.) bond formation is generally achieved either by using a directing-group or steric/electronic factors. The functionalization of arenes *ortho* to the directing-groups can be realized easily since the metal can reach readily to the desired site. Whereas, selectively reaching *meta* or *para* position is difficult because of many other factors.[2] The pioneering work in the field of *meta* and *para*-selective C–H functionalization has been reported by Yu[3] and Maiti[4] groups respectively, employing molecular template to direct a metal catalyst to a specific position. Despite of the many advantages of template-assisted site-selective C–H functionalization over the traditional methods, sometimes the template is larger than the substrate and additional steps are required to install or remove them, which makes the process lengthy, tedious and economically unviable. Hence, the process wherein the functional group of the molecule itself acts as an inherent directing group is preferred over the earlier.[5] We have previously utilized amide as an inherent directing group for the functionalization of quinazolinones as well as acrylamides using ruthenium catalysis for alkenylation and cascade annulation respectively.[6]

Amide is one of the potential functional group as well as directing group, which has been utilized enormously in chelation controlled functionalization using transition-metal catalysis.[7] In continuation of our interest in developing new methods utilizing amide as an inherent directing group for the C–H activation, we were exploring the functionalization of anilide derivatives. Interestingly, during the course of our investigation, we observed self-dimerization of anilide under one of our Cu-catalyzed reaction condition. After careful observation and characterization of the obtained product, we have confirmed the C–N bond formation at the *para*-position to the nitrogen of the electron-rich anilide ring. Interestingly, literature survey revealed that Masui et al. observed dimerization of benzanilides during anodic oxidation,[8] however, metal-catalyzed *para*-selective amidation/ dimerization of anilides through C–N bond formation specifically on aniline aromatic ring as observed here is not



Scheme 1 Selected metal-catalyzed aminations and our work

[a] *Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411008, India*
[b] *Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India.*
[c] *Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India.*

† Electronic supplementary information (ESI) available. CCDC 1954354 and 1954355. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

reported until now. Nevertheless, $C(sp^2)$–H amidation/imidation/sulfonamidation or amination at *ortho*/*meta*/*para*-position of various functional/directing groups have been reported using transition-metal catalysis (Scheme 1, eq 1-4)[9] or transition metal-free methods.[10] Copper catalysts are the most desired transition-metal catalysts for this purpose as they are robust, cost-effective, and provide practical alternative over the other expensive transition-metal catalysts such as [Pd], [Ru], [Ir] etc.[9b,h,11] Hence, we aimed at optimizing the protocol using a copper catalyst. In this context, reported herein is a protocol for the *para*-selective amidation/dimerization of anilides using a copper catalyst and inexpensive ammonium persulfate (APS) as an oxidant/radical source (Scheme 1, eq 5).

The optimization of the protocol commenced with the modifications in the previously perceived condition. Selected modifications are presented in Table 1. Though several variations in oxidant, catalyst, reaction concentration, time and temperature were tried, the best yield achieved through optimization studies was 62% (Table 1, entry 9). However, 0.037 mmol of the starting material was recovered unchanged, and hence the actual yield based on the recovered starting material (brsm) was 77%. GC/GC-MS analysis of the crude reaction mixture, as well as purified product **2a**, confirms the formation of a single regioisomer. The *para* regioselectivity of **2a** was confirmed by X-ray crystallography (CCDC-1954354).

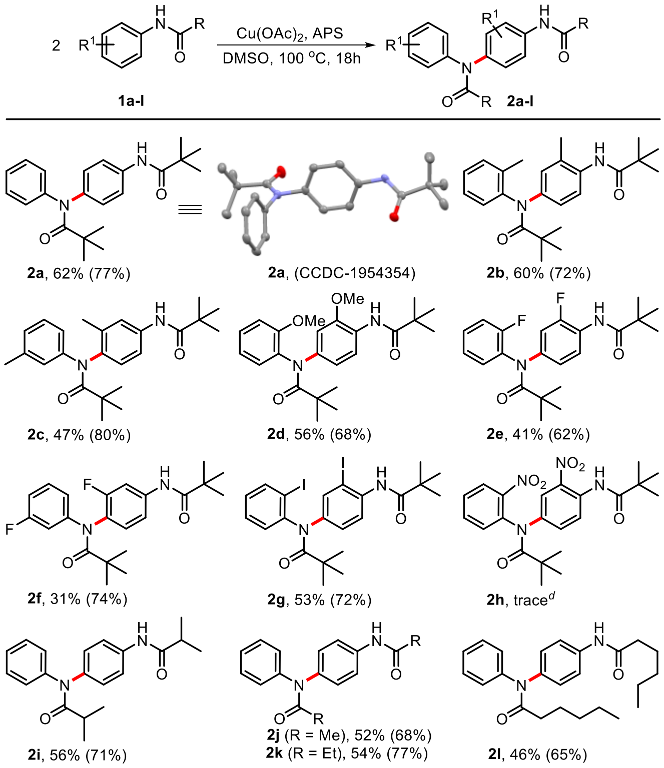
Table 1 Optimization of Reaction Conditions[a]

Obs. No.	Oxidant (equiv)	$Cu(OAc)_2$ (mol%)	Concen. (in M)	Yield[b] (%)
1	APS (1.5)	5	0.15	27
2	APS (1.0)	-	0.15	trace
3	-	5	0.15	NR
4	APS (2.0)	5	0.15	16
5	APS (1.0)	5	0.15	41
6	APS (0.75)	5	0.15	32
7	APS (1.0)	5	0.30	21
8	APS (1.0)	5	0.10	49
9	**APS (1.0)**	**10**	**0.10**	**62 (77)**[c]
10	$K_2S_2O_8$ (1.0)	10	0.10	46
11	$Na_2S_2O_8$ (1.0)	10	0.10	42
12	APS (1.0)/O_2	10	0.10	22
13	(*t*BuO)$_2$ (1.0)	10	0.10	NR
14[d]	APS (1.0)	10	0.10	40
15[e]	APS (1.0)	10	0.10	52

[a]Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2$, oxidant-ammonium persulfate (APS) in DMSO at 100 °C for 18h, [b]Isolated yield. [c]Yield in the parentheses is based on the recovered starting material. [d]Additive: AcOH (1 equiv), [e]Additive: NaOAc (1 equiv).

After optimizing the reaction condition, our next target was to generalize the scope of the developed protocol. The study began with the variation of substituents on the aromatic part of the anilide **1a**. The substrates with methyl substituent *ortho* or *meta* to anilide nitrogen furnished the corresponding products **2b** and **2c** respectively in good yields. Similarly, anilide with electron-donating methoxy group at the *ortho* position also worked smoothly to provide the expected compound **2d** in optimum yield. The fluoro substituted anilides resulted into the expected products **2e** and **2f** with comparatively lower yields. The *ortho*-substituted anilides (**1b**, **1e**) worked better than the corresponding *meta*-substituted anilides (**1c**, **1f**) probably because of the steric hindrance. Following the same trend, *iodo*-substituted anilide also provided the dimer **2g** in good yield. However, anilide with electron-withdrawing $–NO_2$ substituent failed to furnish the expected product **2h** under the optimized conditions. We reasoned that the amide group of the electron-deficient anilide fails to bind with the metal during the course of the reaction.

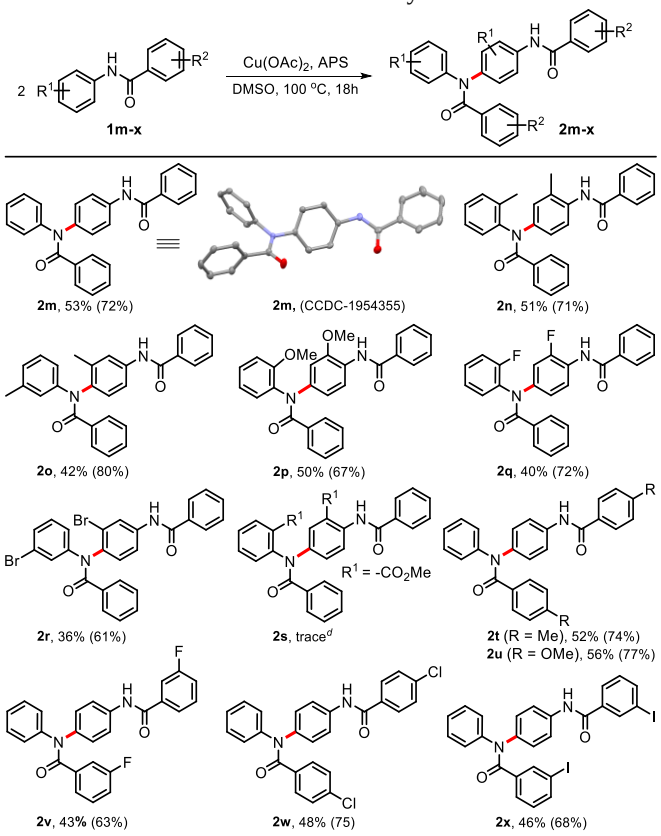
Table 2 Amidation/dimerization of *N*-arylalkylamide[a-c]



[a]Reaction conditions: **1a-l** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), APS (0.2 mmol), DMSO (0.1M) in a screw cap glass tube at 100 °C for 18 h. [b]Isolated yields. [c]Yields in parentheses are based on the recovered starting material. [d]Starting material recovered unchanged.

At this point, we decided to study the substrate scope by varying the aliphatic group of anilide **1a**. Accordingly, *N*-phenylisobutyramide was treated under the optimized reaction condition, which worked well leading to **2i**. *N*-phenylacetamide also resulted into the corresponding dimerized product **2j** in moderate yield. The reaction worked equally well with *N*-phenylpropionamide to obtain **2k**. However, the substrate *N*-phenylhexanamide having a long alkyl chain provided the corresponding dimer **2l** in relatively lower yield. Overall, the bulkiness of the aliphatic group had minimal effect on the yield. The regioselectivity of **2j** was confirmed by its synthesis from known amine (see SI).

Table 3 Amidation/dimerization of *N*-arylbenzamides[a-c]



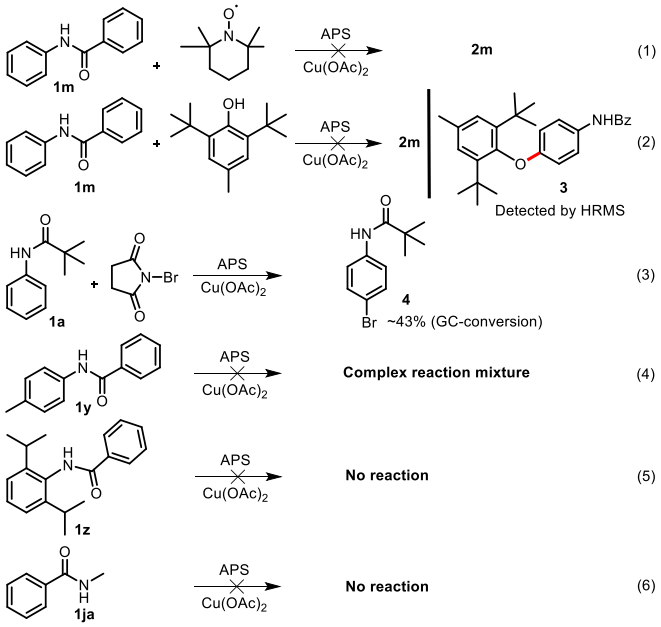
[a]Reaction conditions: **1m-x** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), APS (0.2 mmol), DMSO (0.1M) in a screw cap glass tube at 100 °C for 18 h. [b]Isolated yields. [c]Yields in parentheses are based on the recovered starting material. [d]Starting material recovered unchanged.

The successful completion of the substrate scope study of *N*-arylalkylamides prompted us to demonstrate the generality of the protocol with varyingly substituted *N*-arylbenzamides. The developed protocol was first applied on *N*-phenylbenzamide, and gratifyingly the product **2m** was obtained in a good yield. The regioselectivity of the product **2m** was also confirmed by single-crystal X-ray (CCDC-1954355). Initially, we studied the effect of substituents present on the electron-rich anilide aromatic ring. Two anilide substrates with electronically unbiased methyl substituent at *ortho* and *meta* position of the electron-rich aromatic ring worked well to provide **2n** and **2o**, respectively. The anilide substrate with electron-donating methoxy group furnished **2p** in moderate yield. The *ortho*-fluoro and *meta*-bromo-substituted anilides worked fine to provide the corresponding dimers **2q** and **2r**, respectively. However, as observed before, anilide having strong electron-withdrawing group failed to give the expected product **2s** under the developed protocol.

After the study of variation in the substituents present on the electron-rich aromatic ring of anilide, we targeted to study the effect of variation on electron-deficient aromatic ring of *N*-arylbenzamides. The substrate with methyl group at the *para*-position of the amide carbonyl did not affect the yield and **2t** was obtained in comparable yield with **2m**. Electron-donating methoxy group substituted anilide also worked well to furnish dimer **2u**. *meta*-Fluoro, *para*-chloro, and *meta*-iodo substituted anilides also worked fine to provide the corresponding desired products **2v**, **2w** and **2x** respectively in moderate yields.

Overall, the developed protocol is quite general and many substituents, except highly electron-withdrawing groups, are well tolerated. The protocol is highly selective for anilides. We neither observed cross-coupling products between anilides and aliphatic/aromatic amides/amines nor dimerization of other amides (see SI). Derivatives of the products **2a**-**2x** are commonly used in polymer/material chemistry,[12] and they would also be interesting precursors for the synthesis of the corresponding carbazoles or phenanthridinones via regioselective C–H activation strategy.

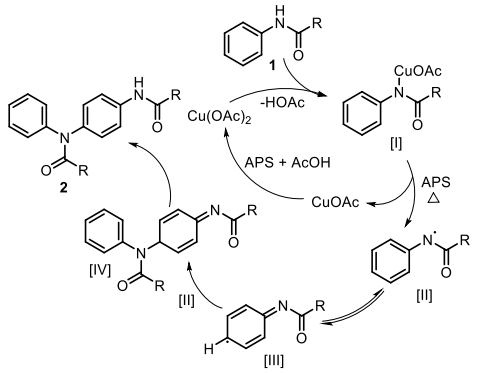
Few control experiments were performed for preliminary understanding of the mechanism of our protocol. The radical nature of the reaction was determined by performing the reaction of anilide **1m** under the standard reaction condition in the presence of radical scavengers such as TEMPO and BHT (Scheme 2, eq 1 and 2). Complete inhibition of reactions was observed in both cases. Interestingly, adduct **3** (Scheme 2, eq 2) was observed in HRMS of the crude reaction mixture, which confirms the radical pathway of the reaction. The formation of brominated product **4** instead of dimer **2a** in the presence of NBS also confirms the radical pathway (Scheme 2, eq 3). The reaction of anilide **1y** showed very less conversion and complex reaction mixture by TLC (Scheme 2, eq 4). The anilide substrate **1z** having bulky isopropyl substituent on both *ortho*-positions did not react under the standard reaction conditions



Scheme 2 Control Experiments

though the *para*-position was available for the reaction. This observation indicates that probably the approach of copper catalyst to the amide –NH is blocked due to the steric hindrance of isopropyl group leading to the failure of the reaction (Scheme 2, eq 5). We believe that the developed protocol works via a radical mechanism involving the formation of a *para*-quinone type of intermediate on aniline part of the anilide, which makes it highly regioselective. A

tentative proof for our hypothesis of *para*-quinone type intermediate was realized when the substrate **1ja** (a structural isomer of **1j**) lacking the aniline part of the aromatic ring was subjected to our protocol (Scheme 2, eq 6). The reaction did not work because *para*-quinone type intermediate is not possible on benzamide aromatic ring.



Scheme 3 Plausible Mechanism

Based on the literature survey,[9b,j,13] and the control experiments (Scheme 2), a plausible mechanism via a radical pathway has been depicted in Scheme 3. Anilide **1** first chelates with a copper catalyst to form complex [I], which converts to amidyl radical intermediate [II] in the presence of APS. The amidyl radical intermediate transforms to a stable *para*-quinone type imine radical intermediate [III]. A radical coupling between intermediates [II] and [III] provides the intermediate [IV], which on aromatization furnish the desired products **2**. The copper catalyst is again regenerated in the presence of the oxidant APS. The proposed mechanism provides important starting points for a detailed investigation of the mechanism.

In conclusion, we have developed a unique process for *para*-selective C–H functionalization leading to amidation /dimerization of anilide derivatives. The developed protocol is highly selective as the dimerization through C–N bond formation occurs specifically on aniline part of the anilide. Preliminary mechanistic investigation demonstrates that the reaction follows a radical pathway. A broad substrate scope has been demonstrated utilizing an inexpensive copper catalyst. The obtained products are potential precursors for the synthesis of bioactive heterocyclic scaffolds. Currently, we are exploring the protocol for C–H functionalization of anilide derivatives with other reacting partners leading to C–C as well as C–X bond formation.

A.B.V. thanks CSIR-New Delhi, and D.N.G. thanks UGC-New Delhi, for the research fellowship. S.B.M. gratefully acknowledges generous financial support from DST-SERB, New Delhi.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.,* 2019, **119**, 2192. (b) H. M. L. Davies and D. Morton, *J. Org. Chem.,* 2016, **81**, 343. (c) X. Chen, K. M. Engle, D.-H. Wang, and J.-Q. Yu, *Angew. Chem. Int. Ed.,* 2009*,* **48**, 5094.

2 (a) A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, *Angew. Chem. Int. Ed.,* 2019, **58**, 10820. (b) A. Dey, S. Maity, and D. Maiti, *Chem. Commun.,* 2016, **52**, 12398.

3 (a) M. Li, M. Shang, H. Xu, X. Wang, H.-X. Dai and J.-Q. Yu, *Org. Lett*., 2019, **21**, 540. (b) L. Wan, N. Dastbaravardeh, G. Li and J.-Q. Yu, *J. Am. Chem. Soc*., 2013, **135**, 18056. (c) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature,* 2012, **486**, 518.

4 (a) T. K. Achar, X. Zhang, R. Mondal, M. S. Shanavas, S. Maiti, S. Maity, N. Pal, R. S. Paton and D. Maiti, *Angew. Chem. Int. Ed*., 2019, ***58***, 10353. (b) U. Dutta, S. Maiti, S. Pimparkar, S. Maiti, L. R. Gahan, E. H. Krenske, D. W. Lupton and D. Maiti, *Chem. Sci*., 2019, **10**, 7426. (c) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, *J. Am. Chem. Soc.,* 2015, **137**, 11888.

5 (a) D. N. Garad, A. B. Viveki and S. B. Mhaske, *J. Org. Chem*., 2017, **82**, 6366. (b) L. Zheng and R. Hua, *Chem. Rec*., 2017, **17**, 1. (c) H. M.-F. Viart, A. Bachmann, W. Kayitare and R. Sarpong, *J. Am. Chem. Soc*., 2017, **139**, 1325.

6 (a) D. N. Garad and S. B. Mhaske, *J. Org. Chem***.,** 2019, **84**, 1863. (b) A. B. Viveki and S. B. Mhaske, *J. Org. Chem*., 2018, **83**, 8906.

7 (a) R. Das, G. S. Kumar and M. Kapur *Eur. J. Org. Chem*., 2017, *2017* (***37***), 5439. (b) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen and J.-Q. Yu, *Angew. Chem. Int. Ed*., 2016, **55**, 10578.

8 C. Ueda, H. Ohmori, K. Ueno, Y. Hamada, S. Tatsumi and M. Mausi, *Chem. Pharm. Bull.,* 1985, **33**, 1407.

9 (a) A. Ruffoni, F. Juliá, T. D. Svejstrup, A. J. McMillan, J. J. Douglas and D. Leonori, *Nature*, 2019, **11**, 426. (b) J. Xu, K. Du, J. Shen, C. Shen, K. Chai and P. Zhang, *ChemCatChem,* 2018, **17**, 2018. (c) G. N. Hermann and C. Bolm, *ACS Catal*., 2017, **7,** 4592. (d) J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li and N. Jiao, *Chem. Eur. J*., 2017, **23**, 563. (e) L. Legnani, G. P. Cerai and B. Morandi *ACS Catal*., 2016, **6**, 8162. (f) M. P. Paudyal, A. M. Adebesin, S. R. Burt, D. H. Ess, Z. Ma, L. Kürti and J. R. Falck, *Science*, *353*, 1144. (g) H. Kim, K. Shin and S. Chang, *J. Am. Chem. Soc*., 2014, **136**, 5904. (h) M. Shang, S. Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.,* 2014, **136**, 3354. (i) R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman and J. F. Hartwig, *J. Am. Chem. Soc*., 2013, **135**, 8480. (j) K. Sun, Y. Li, T. Xiong, J. Zhang and Q. Zhang, *J. Am. Chem. Soc*., 2011, **133**, 1694.

10 (a) Y. Zhao, B. Huang, C. Yang, B. Li, B, Gou and W. Xia, *ACS Catal*., 2017, **7**, 2446. (b) A. A. Kantak, S. Potavathri, R. A. Barham, K. M. Romano and B. DeBoef, *J. Am. Chem. Soc.,* 2011, **133**, 19960.

11 (a) M. Kumar, S. Verma, P. K. Mishra and A. K. Verma, *J. Org. Chem*., 2019, **84**, 8067. (b) J.-P. Wan and Y. Jing, *Beilstein J. Org. Chem.,* 2015, **11***,* 2209. (c) B. Berzina, I. Sokolovs and E. Suna, *ACS Catal*., 2015, **5**, 7008. (d) Q. Li, S.-Y. Zhang, G. He, Z. Ai, W. A. Nack and G. Chen, *Org. Lett*., 2014, **16**, 1764. (e) B. L. Tran, M. Driess and J. F. Hartwig, *J. Am. Chem. Soc*., 2014, **136**, 2555. (f) A. John and K. M. Nicholas, *J. Org. Chem*., 2011, **76**, 4158.

12 (a) L. Li, J. Ge, L. Wang, B. Guo and P. X. Ma, *J. Mater. Chem. B.,* 2014, **2**, 6119. (b) S. P. Surwade, S. R. Agnihotra, V. Dua, N. Manohar, S. Jain, S. Ammu and S. K. Manohar, *J. Am. Chem. Soc*., 2009, **131**, 12528. (c) K. Saito and T. Hirao, *Tetrahedron,* 2002, **58***,* 7491.

13 (a) D. Liang, Y. Li, S. Gao, R. Li, X. Li, B. Wang and H. Yang, *Green Chem*., 2017, **19**, 3344. (b) S. Liang, M. Bolte and G. Manolikakes, *Chem. Eur. J.,* 2017, **23**, 96. (c) P. Xiong, F. Xu, X.-Y., Qian, Y. Yohannes, J. Song, X. Lu, H.-C. Xu, *Chem. Eur. J.* 2016, **22**, 4379. (d) G. Brasche and S. L. Buchwald, *Angew. Chem., Int. Ed*., 2008, **47**, 1932.