ChemComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx
DOI: 10.1039/x0xx00000x

www.rsc.org/

Nickel-Catalysed Alkylation of C(sp^3)-H Bond with Alcohols: Direct Access to Functionalised *N*-Heteroaromatics

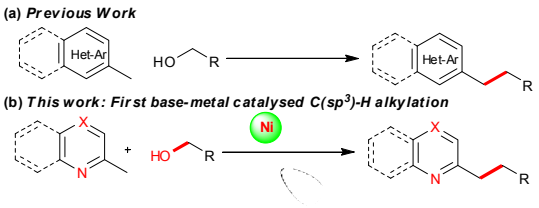
Mari Vellakkaran,‡ Jagadish Das,‡ Sourajit Bera, and Debasis Banerjee*

The first base-metal catalysed coupling of primary alcohols with methyl-*N*-heteroaromatics is reported. Use of an earth abundant and nonprecious $NiBr_2$/L1 system enables to access a series of C(sp^3)-alkylated *N*-heteroaromatics. Mechanistic studies established the participation of hydrogen-borrowing strategy for α-alkylation.

Transition metal-catalysed alkylation of C(sp^3)-H bond for construction of carbon-chain elongated products constitutes a fundamental challenge in organic synthesis. Due to high C(sp^3)-H bond dissociation energy, often an efficient and selective functionalisation of alkyl chain represents a key issue in catalysis. Therefore, since last decade significant efforts have been directed involving C-H bond activation using alkyl halides,[1] directing group assisted functionalisation of C(sp^3)-H bond with olefins,[2] reductive alkylation including nucleophilic substitutions as well as α-alkylation of ketone enolates and related studies were documented.[3-4]

N-Heteroaromatics and their derivatives are important targets in medicines, pharmaceuticals, material chemistry and significantly used as intermediates in natural products and ligands in catalysis.[5] Thus, functionalisation of C(sp^3)-H bond in methylazaarenes provides direct access to chain-elongated *N*-heteroaromatics with valuable applications. However, such transformations often limited with pre-functionalised alkyl halides, carbonates or esters and often required harsh reaction conditions involving generation of stoichiometric equivalents of waste.[6] Therefore, development of environmentally benign, sustainable and atom-economic alkylation technology for C(sp^3)-H bond in *N*-heteroaromatics is still a demand goal.[7]

Notably, direct application of highly abundant and renewable alcohols would be a promising alternative to the above process.[6b] Nevertheless, currently, metal-catalysed borrowing hydrogen (HB) approach has been identified as an elegant tool to construct C-X (X = C, N etc.) bonds.[8] In this direction, only handful examples are known based on precious metal-catalysts (Ir-, Ru-, and Pt) for such C(sp^3)-H bond functionalisation in *N*-heteroaromatics using alcohol as coupling partner. Notable breakthrough by Kempe,[9a] on well-defined Ir-catalysed alkylation of *N*-heteroaromatics is worth mentioning. Later, Obora and co-workers reported functionalisation of 2-methyl heteroarenes using Ir-catalyst.[9b] Recently, Ru-catalysed ligand free alkylation as well as Pt-supported heterogeneous catalysts has also been developed for alkylation of methyl *N*-hetero aromatics using alcohols following HB approach (Scheme 1a).[9c,d]



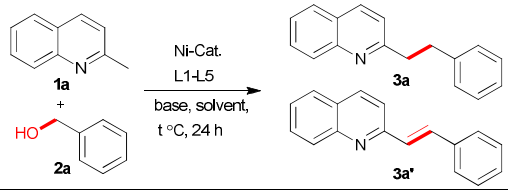
Department of Chemistry, Laboratory of Catalysis and Organic Synthesis, Indian Institute of Technology Roorkee, Roorkee-247667, Uttarakhand, India.
E-mail: dbane.fcy@iitr.ac.in
‡ These authors contributed equally to this work

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

View Article Online
DOI: 10.1039/C8CC06370B

were examined with the model reaction of quinaldine **1a** and benzyl alcohol **2a** (Table 1, entries 1-5). Gratifyingly, we observed 70% isolated yield of α-alkylated product **3a**, when, a combination of 10 mol % $NiBr_2$, 20 mol % 1,10-phenthroline **L1** in combination with 0.25 mmol of *t*-BuOK at 130 °C in toluene were used (entry 2).

Table 1: Optimisation of the reaction conditions[a]



entry	catalyst (mol %)	ligand (mol %)	base	conv (%) 3a	3a'
1	$NiCl_2$ (10)	**L1** (20)	*t*-BuOK	53	47
2	$NiBr_2$ (10)	**L1** (20)	*t*-BuOK	73 (70)[b]	25
3	$Ni(acac)_2$ (10)	**L1** (20)	*t*-BuOK	30	34
4	$NiCl_2$(DME) (10)	**L1** (20)	*t*-BuOK	13	48
5	$Ni(cod)_2$ (10)	**L1** (20)	*t*-BuOK	8	22
6	**$NiBr_2$ (10)**	**L1 (50)**	***t*-BuOK**	**100 (96)**[b]	**0**
7[c]	**$NiBr_2$ (10)**	**L1 (50)**	***t*-BuOK**	**100 (97)**[b]	**0**
8	$NiBr_2$ (2.5)	**L1** (12.5)	*t*-BuOK	8	36
9	$NiBr_2$ (5.0)	**L1** (25)	*t*-BuOK	13	18
10	-	-	*t*-BuOK	0	0
11	$NiBr_2$ (10)	**L1** (50)	-	0	0

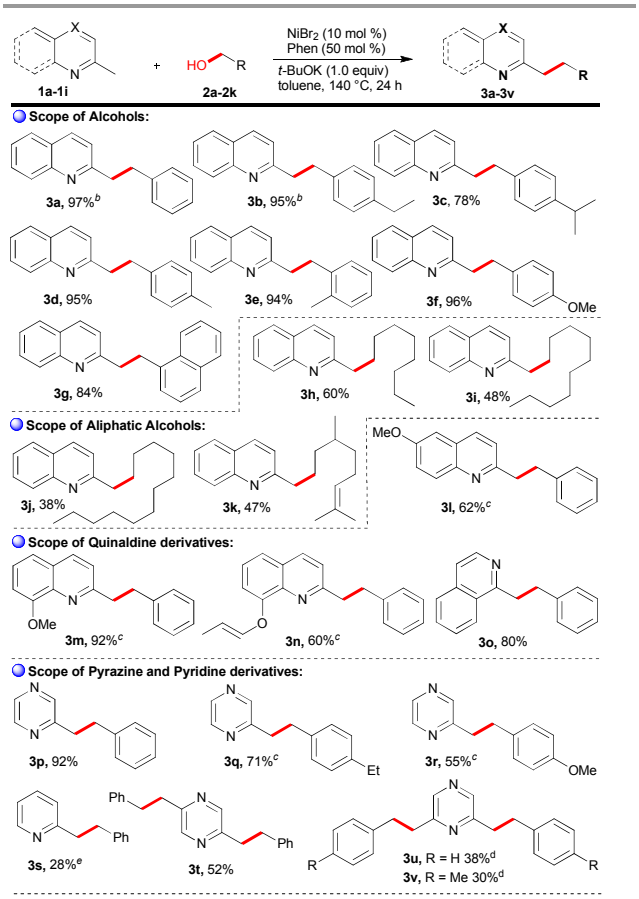
Reaction conditions: [a]Unless otherwise specified, quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (10 mol %), phen (X mol %), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schenk tube under nitrogen atmosphere, 130 °C oil bath, 24 h reaction time. [b]Isolated yield (average of two run). [c]140 °C oil bath, 24 h reaction time. **L1** = 1,10-phenanthroline. **L2** = 2,9-dimethyl 1,10-phenanthroline. **L3** = bipyridine. **L4** = 4,4'- dimethylbipyridine. **L5** = 2,2'-biquinoline.

Further, application of a variety of nitrogen ligands **L2-L5** did not result any product **3a**, instead we observed up to 47% conversion of α-olefinated product **3a'** using GC-MS analysis (SI, Table S2). This results evident the significant role of ligands to achieve higher product yields. At this point, we envisioned that, ligands might be playing a crucial role for hydrogenation of the inadequate amount of α-olefinated product **3a'** present in the reaction mixture. Therefore, we examined the role of additional ligands and to our delight, almost quantitative yield of product **3a** was observed with 99% selectivity (entries 6-7 and SI Table S6). Next, application of different bases, solvents as well as control experiments resulted only moderate product yield (SI, Table S3-S6). As expected, product yield suppress significantly when, a lower catalyst/ligand combination was employed (entries 8-9). Control experiments in absence of catalyst, ligand and base shows their potential role as individual catalytic component (Table 1, entries 10-11 and SI Table S1-S6).

After having identified the optimum conditions, nickel-catalysed functionalisation of $C(sp^3)$-H bond of 2-methyl quinoline was performed using a series of electronically different benzyl alcohols (Table 2). Pleasingly, irrespective of the electronic nature, almost quantitative yields of C_2-alkylated *N*-heteroaromatics **3b**-**3d** were obtained (Table 2). Quantitative product yield of **3e** was achieved when sterically hindered 2-methyl benzyl alcohol was used. To our delight, 4-methoxybenzyl alcohol as well as 1-naphthalenemethanol furnished the desired alkylated product with excellent isolated yield, 84-96% respectively (Table 2, **3f** and **3g**).

Gratifyingly, more challenging long chain C8-C12 renewable alkyl alcohols, efficiently participated in $C(sp^3)$-H bond functionalisation with **1a** under standard conditions and resulted chain-elongated C_2-alkylated *N*-heteroaromatics in up to 60% yield **3h**-**3j**. To our delight, renewable terpenoid intermediate citronellol could be employed for the α-alkylation and afford 47% isolated yield of **3k.** It is noteworthy to mention that, this chemo-selective transformation of unsaturated alcohol represents a rare instance under Ni-catalysis.[10-11] To our delight, we witnessed an excellent reactivity profile of various alkyl and benzyl alcohols using inexpensive nickel-catalysts.

Table 2: Ni-catalysed α-alkylation of methyl *N*-heteroaromatics[a]

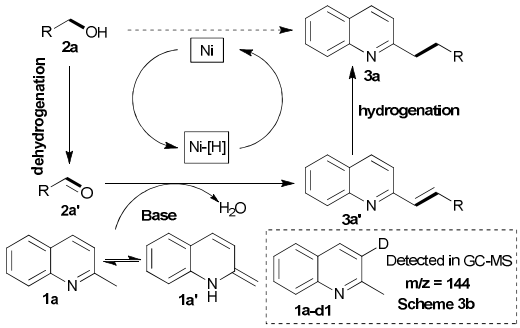


Reaction conditions: [a]Quinaldine **1** (0.25 mmol), alcohol **2** (0.50 mmol), $NiBr_2$ (10 mol %), phen (50 mol %), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schenk tube under nitrogen atmosphere, 140 °C oil bath, 24 h reaction time. [b]130 °C, 24 h. [c]*t*-BuOK (0.375 mmol) was used. [d]**1** (0.25 mmol), alcohol **2** (1.0 mmol), $NiBr_2$ (20 mol%), phen (100 mol%), *t*-BuOK (0.50 mmol) were used. [e]GC-MS conversion.

Next, functionalisation of $C(sp^3)$-H bond of various methyl *N*-heteroaromatics using benzyl alcohols were demonstrated

View Article Online
DOI: 10.1039/C8CC06370B

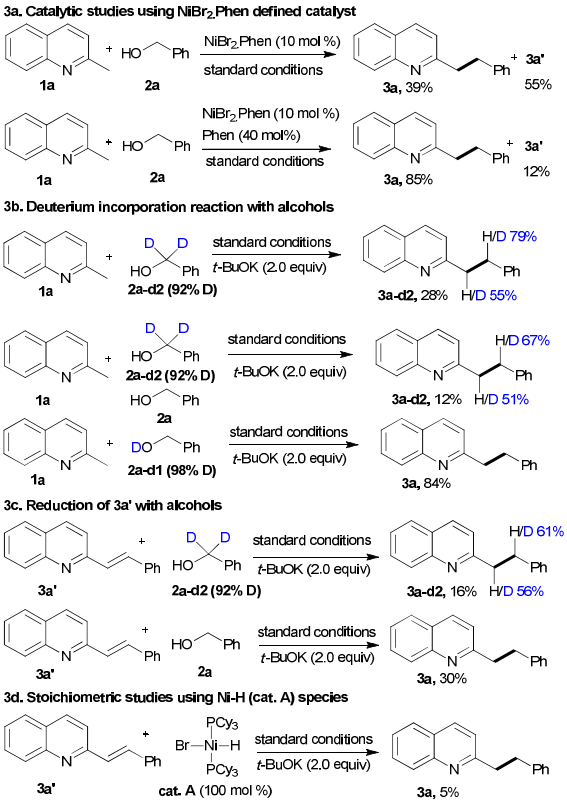
under standard conditions (Table 2). For instance, 2-methyl quinoline substituted with methoxy or alkoxy groups at different position of the aryl ring (C_6 or C_8 position) furnished the desired products **3l**-**3n** in up to 60-92% isolated yield (Table 2). Importantly, 2-methyl isoquinoline also participated in the α-alkylation process and efficiently transformed into the excellent product yield (Table 2, **3o**). Further, scope of the alcohols alkylation were directed using C_2-alkylated pyrazines, moderate to excellent isolated yield of **3p**-**3r** were obtained (Table 2). Notably, reaction with 2-methyl pyridine was sluggish under the optimised conditions and observed diminished product yield of **3s**. The catalytic protocol could be applied for the synthesis of symmetric pyrazine derivatives. Gratifyingly, when 2,5-dimethyl as well as 2,6-dimethyl pyrazine were employed with benzyl alcohols, moderate yield of bis-alkylated pyrazines **3t**-**3v** were obtained (Table 2). Notably, the catalytic protocol is tolerant to nitrogen heterocycles (pyridine, pyrazine, quinolines etc.), allylic ethers, including alkene and alkoxy moieties. Remarkable transformations in the presence of reducible groups, such as, terminal alkene evident the synthetic potential of the established protocol.



Scheme 2: Proposed mechanism for C_2-alkylated *N*-heteroaromatics with alcohols

Next, we studied the preliminary mechanistic insight for such C(sp^3)-H bond functionalisation of methyl *N*-heteroaromatics using Ni-catalyst. To date, there is no such mechanistic study is reported for α-alkylation of C_2-alkylated *N*-heteroaromatics with primary alcohols. During the progress of the reaction we realised that, such Ni-catalysed α-alkylation, consisting of multi-step process, such as, dehydrogenation of alcohol **2a** to aldehyde **2a'**, where transient Ni-H species is generated (Scheme 2). Thereafter, base mediated isomerisation of **1a** to **1a'** followed by reaction with aldehyde **2a'** resulted the α-olefinated product **3a'**. At this point, hydrogenation of **3a'** by Ni-H species resulted the desired product **3a**. However, we realised that, nitrogen ligands plays a key role to achieve selective hydrogenation of **3a'** (Scheme 2).

Further, to confirm the participation of **1a'**, deuterium labeling experiments using **2a**-**d2** (92% D), resulted **1a**-**d1** and detected using GC-MS analysis of the crude reaction mixture (Schemes 2 and 3b). Next, to understand the participation of key Ni-intermediate species, $NiBr_2$.Phen was prepared,[12] and independently employed in catalytic (10 mol %) amount in the model reaction. Under optimised conditions, **3a** was obtained in 39% yield along with 55% conversion to **3a'** (Scheme 3a). However, when using 40% **L1** with $NiBr_2$.Phen, 85% yield of **3a** was obtained. These experimental results provide evidences for the role of excess ligand in the hydrogenation step (Scheme 3a).



Scheme 3: Preliminary mechanistic studies.

Additionally, we made an attempt to prepare the Ni-H species of $NiBr_2$.Phen and was not successful (SI, Scheme S7, i).[13] At that point, when, electron rich tri-cyclohexyl phosphine was used, defined complex $(Cy)_3PNiBr_2$ and the Ni-hydride species $(Cy)_3PNiBrH$, were readily prepared,[12] and employed in stoichiometric equiv. with α-olefinated product **3a'** under standard conditions. Pleasingly, **3a** was detected in the GC-MS analysis of the crude reaction mixture (Scheme 3d and SI, Scheme S7, ii). These experimental outcomes are in strong agreement with the participation of Ni-H species for C(sp^3)-H bond functionalisation of methyl *N*-heteroaromatics.

Further, we performed a series of deuterium-labeling experiments for α-alkylation process (Scheme 3, 3b-3c). Initially, α-olefinated product **3a'** was employed with **2a** and **2a-d2** (92% D) under standard conditions, and resulted **3a** and **3a-d2** were obtained in moderate yields and exhibited 56% and 61% incorporation of deuterium in α-and β-position of **3a-d2** (Scheme 3c and SI Scheme S3). Afterward, α-alkylation of **1a** with **2a-d1** (98% D) was performed, ^{1}H-NMR and GC-MS analysis detected the formation of **3a-d2** along with deuterium incorporation at variable ratio in α-and β-position (Scheme 3b and SI Scheme S1). In addition, a crossover experiment using 1:1 mixture of **2a** and **2a-d2** under

View Article Online
DOI: 10.1039/C8CC06370B

standard conditions of Table 2, afford the formation of H/D-scrambled product **3a-d2** (Scheme 3b and SI Scheme S2).[14] These deuterium labelling experiments strongly support the micro-reversible transformation for the alkylation process under nickel-catalysis and the formation of H/D-scrambled products provide evidences for the participation of the hydrogen borrowing strategy. [12,14] Notably, when the reaction of **1a** was performed with benzyl alcohol **2a-d1,** we did not observe any deuterated labeling product and only, **3a** was obtained in 84% yield, suggests that, hydrogen in hydroxyl group, does not participate in the hydrogen shuffling involving Ni-H species (Scheme 3b). Further, we studied the progress of the alkylation reaction and monitored using gas-chromatography over time (SI, Scheme S5). The reaction was interrupted after five hour and the reaction profile indicating the formation of intermediate **3a'** in faster rate, whereas, hydrogenation to **3a** are quite slow. These kinetic experiments revealed the crucial role of excess ligand and another equivalent of alcohol to achieve higher product yield. Finally, to determine the rate and order of the reaction, we performed two sets of kinetic studies (SI, Scheme S6). First order kinetics with respect to quinaldine **1a** was observed for α-alkylation of *N*-heteroaromatics considering a steady state approximation for benzyl alcohol.

In conclusion, we reported the first Ni-catalysed functionalisation of $C(sp^3)$-H bond of methyl N-heteroaromatics using primary alcohols. Easily available, inexpensive Ni-catalyst and 1,10-phenthroline ligand enables the long chain C_2-alkylated *N*-heteroaromatics in up to quantitative yields. The catalytic system allow the transformations in the presence of reducible functional moieties, such as, allylic ether and alkenes including unsaturated alcohols. Initial mechanistic studies strongly support the participation Ni-H species and bifunctional nature of the Ni-catalyst. A series of deuterium labeling experiments revealed the involvement of the H/D exchange during the progress of the reaction.

Conflicts of interest

There are no conflicts to declare.

The authors thank DAE-BRNS, India (Young Scientist Research Award to D. B., 37(2)/20/33/2016-BRNS) and IIT Roorkee (SMILE-32). M. V. Thank SERB-NPDF (SERB-PDF/2017/002784), India for a fellowship. J. D. and S. B. thank IIT-R and INSPIRE (DST) for financial support.

Notes and references

1 For selected examples, see: (a) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965; (b) S. Y. Zhang, G. He, W. A. Nack, Y. S. Zhao, Q. Li and G. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 2124; (c) J. Pedroni, M. Boghi, T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 9064; (d) Z. Y. Zhu, J. He, X. C. Wang and J. Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 13194.

2 For selected examples, see: (a) F. Y. Mo and G. B. Dong, *Science*, 2014, **345**, 68; (b) J. L. Jeffrey, J. A. Terrett and D. W. C. MacMillan, *Science*, 2015, **349**, 1532; (c) B. Li, C. Darcel and P. H. Dixneuf, *Chem. Commun.*, 2014, **50**, 5970.

3 For selected examples, see: (a) K. Yuan, F. Jiang, Z. Sahli, M. Achard, T. Roisnel and C. Bruneau, *Angew. Chem., Int. Ed.*, 2012, **51**, 8876; (b) B. Sundararaju, M. Achard, G. V. Sharma and C. Bruneau, *J. Am. Chem. Soc.*, 2011, **133**, 10340; (c) B. Sundararaju, Z. Tang, M. Achard, G. V. M. Sharma, L. Toupet and C. Bruneau, *Adv. Synth. Catal.*, 2010, **352**, 3141; (d) F. Jiang, M. Achard and C. Bruneau, *Chem.-Eur. J.*, 2015, **21**, 14319; (e) Z. Sahli, B. Sundararaju, M. Achard and C. Bruneau, *Green Chem.*, 2013, **15**, 775.

4 For selected examples, see: (a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu and F. Zanardi, *Chem. Rev.*, 2011, **111**, 3076; (b) C. Palomo, M. Oiarbide and J. M. Garcia, *Chem. Soc. Rev.*, 2004, **33**, 65.

5 (a) L. C. Campeau and K. Fagnou, *Chem. Soc. Rev.*, 2007, **36**, 1058; (b) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.

6 (a) B. M. Trost, *Science*, 1991, **254**, 147; (b) K. Barta and P. C. Ford, *Acc. Chem. Res.*, 2014, **47**, 1503.

7 (a) E. Pasquinet, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron*, 1998, **54**, 8771; (b) B. M. Trost and D. A. Thaisrivongs, *J. Am. Chem. Soc.*, 2008, **130**, 14092; (c) B. M. Trost and D. A. Thaisrivongs, *J. Am. Chem. Soc.*, 2009, **131**, 12056; (d) B. M. Trost, D. A. Thaisrivongs and J. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 12439.

8 (a) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (b) G. Guillena, D. J. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (c) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635; (d) S. Bähn, I. Sebastian, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem.*, 2011, **3**, 1853; (e) J. Moran, M. J. Krische, *Pure Appl. Chem.*, 2012, **84**, 1729.

9 (a) B. Blank and R. Kempe, *J. Am. Chem. Soc.*, 2010, **132**, 924; (b) Y. Obora, S. Ogawa and N. Yamamoto, *J. Org. Chem.*, 2012, **77**, 9429; (c) C. Chaudhari, S. M. A. H. Siddiki and K. Shimizu, *Tetrahedron Letters*, 2013, **54**, 6490; (d) T. Feng, H. Li, D. Young and J. Lang, *J. Org. Chem.*, 2017, **82**, 4113. For recent selected examples, see: (a) Z. Tan, H. Jiang and M. Zhang, *Chem. Commun*., 2016, **52**, 9359; (b) C.-S. Wang, T. Roisnel, P. H. Dixneuf, and J.-F. Soulé, *Org. Lett.*, 2017, **19**, 6720; (c) M. Xiao, D. Ren, L. Xu, S.-S. Li, L. Yu, and J. Xiao, *Org. Lett.*, 2017, **19**, 5724; (d) Y. Fukumoto, M. Hirano, N. Matsubara, and N. Chatani, *J. Org. Chem.*, 2017, **82**, 13649.

10 (a) R. M. Bullock, *Catalysis Without Precious Metals*, Eds.: Wiley-VCH, Weinheim, 2010; (b) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, **48**, 886; (c) G. Zhang, T. Irrgang, T. Dietel, F. Kallmeier, and R. Kempe, Angew. Chem. Int. Ed. 2018, **57**, 9131; (d) M. K. Barman, S. Waiba, B. Maji, Angew. Chem. Int. Ed. 2018, **57**, 9126.

11 For selected reviews, see: (a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature*, 2014, **509**, 299; (b) A. Valentine and P. Ananikov, *ACS Catal.*, 2015, **5**, 1964; (c) J. E. Dander and N. K. Garg, *ACS Catal.*, 2017, **7**, 1413 and references cited therein; (d) F. Alonso, P. Riente and M. Yus, *Acc. Chem. Res.*, 2011, **44**, 379.

12 (a) M. Vellakkaran, K. Singh and D. Banerjee, *ACS Catal.*, 2017, **7**, 8152; (b) J. Das and D. Banerjee, *J. Org. Chem.*, 2018, **83**, 3378; (c) K. Singh, M. Vellakkaran and D. Banerjee, *Green Chem.*, 2018, **20**, 2250.

13 S. Chakraborty, P. E. Piszel, W. W. Brennessel and W. D. Jones, *Organometallics*, 2015, **34**, 5203.

14 M. H. S. A. Hamid, C. L. Allen, G.W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watsom and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766.