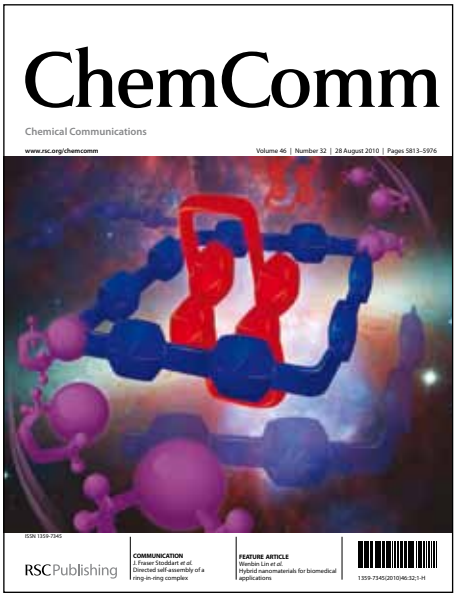
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Jeganmohan and K. Padala, *Chem. Commun.*, 2013, DOI: 10.1039/C3CC45350B.



This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

View Article Online
DOI: 10.1039/C3CC45350B

COMMUNICATION

Ruthenium-catalyzed oxidative *ortho*-benzoxylation of acetanilides with aromatic acids

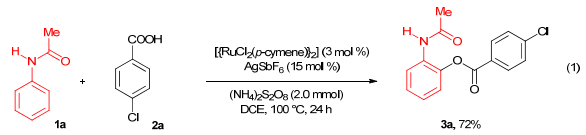
Kishor Padala and Masilamani Jeganmohan*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Substituted acetanilides reacted with aromatic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $(NH_4)_2S_2O_8$ in $ClCH_2CH_2Cl$ at 100 °C for 24 h yielding *ortho*-benzoxylated acetanilides in good to excellent yields in a highly regioselective manner via C-H bond activation.

The transition-metal-catalyzed chelation-assisted transformation of an unreactive *ortho* C-H bond of aromatics to C-C, C-X, C-N and C-O bonds via C-H bond activation is one of the efficient and highly atom-economical methods in organic synthesis.[1] Among them, C-O bond construction is quite difficult and less known in the literature. This is most probably due to high electronegativity of the element and also due to the metal-ligand bond strength.[2] Generally, substituted alcohols and carboxylic acids are widely used as a coupling partner (oxygen source) for the reaction.[3-5] In fact, coupling of carboxylic acids with aromatics is more challenging due to rapid complex formation of the carboxylic acids with the metals. To avoid the complex formation, carboxylate sources such as $PhI(OR)_2$, anhydride, acid halide, etc., have been used instead of the corresponding carboxylic acid.[4-5] Metal-catalyzed acetoxylation of heteroatom-substituted such as 2-pyridyl,[4a-c, h-i] oxime,[4d] carbonyl,[4e] amide[4e] and acetamide (NH-COMe)[4g] aromatics with various acetate sources have been well documented in the literature. Palladium- or ruthenium-catalyzed hydroxylation of heteroatom substituted such as acid,[5a] ketone,[5b] ester[5c] and amide[5d-e] aromatics in the presence of a TFA/TFAA combination has been reported recently in the literature. However, most of these transformations are limited to acetoxylation and hydroxylation of aromatics and there is no such report on benzoxylation of aromatics. In 2005, Sanford et al. reported benzoxylation of 2-phenylpyridines with benzoate iodonium salts in the presence of palladium catalyst.[6a] In 2009, Cheng's group demonstrated benzoxylation of 2-phenylpyridines with benzoic acids in the presence of rhodium catalyst.[6b] Subsequently, benzoxylation of 2-pheny pyridines with benzoyl chlorides and benzaldehydes has been reported in the presence of copper catalyst.[6c-d] Very recently, Shi's group reported *ortho*-benzoxylation of aromatic ketoximes with benzoic acids in the presence of palladium catalyst.[6e] Until, only benzoxylation of 2-phenylpyridines and aromatic ketoximes with benzoic acids is known in the literature.

Recently, a less expensive ruthenium complex has gained tremendous attention in heteroatom directed C-H bond activation of aromatics due to its remarkable reactivity and selectivity. Ruthenium-catalyzed *ortho* arylation, alkenylation, hydroxylation and amination of aromatics have been reported in the literature.[7-8] However, there is no report on *ortho*-benzoxylation of aromatics in the presence of ruthenium catalyst. Herein, we report for the first time an unprecedented oxidative *ortho*-benzoxylation of substituted acetanilides with benzoic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and $(NH_4)_2S_2O_8$ in a highly regioselective manner. The catalytic reaction was also compatible with acetic acid.

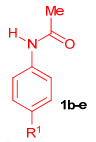
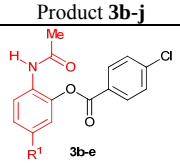
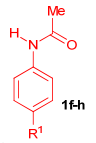
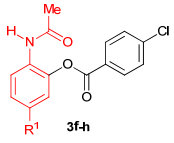
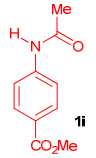
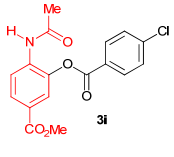
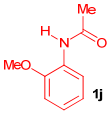
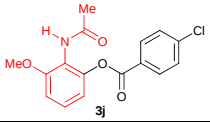


The reaction of acetanilide (**1a**) with 4-chlorobenzoic acid (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (15 mol %) and $(NH_4)_2S_2O_8$ (2.0 equiv) in 1,2-dichloroethane (DCE) at 100 °C for 24 h afforded *ortho*-benzoxylated acetanilide **3a** in 72% isolated yield (eq. 1). Initially, the reaction of **1a** and **2a** was tested with various oxidants (2.0 mmol) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] and $AgSbF_6$ in DCE at 100 °C for 24 h. Various oxidants such as Ag_2CO_3, AgOAc, Ag_2O, $Cu(OAc)_2$, CsOAc, KOAc, NaOAc, $K_2S_2O_8$, $PhI(OAc)_2$, $Na_2S_2O_8$ and oxone were examined. Among them, only silver salts such Ag_2CO_3, AgOAc and Ag_2O were active for the reaction, giving **3a** in 78%, 51% and 49% NMR yields, respectively. The yield of product **3a** was determined by the ^1H NMR integration method using mesitylene as an internal standard. Then, the catalytic reaction was tested with $(NH_4)_2S_2O_8$ oxidant to avoid the silver salt oxidant. Gratifyingly, product **3a** was observed in 80% NMR yield. Next, the catalytic reaction was tested with various solvents such as DCE, chlorobenzene, THF, DMSO, DMF, DME, 1,2-dioxane, toluene, benzene, MeOH, *tert*-BuOH and AcOH. Among them, DCE solvent was effective for the reaction, providing **3a** in 80% NMR yield. Chlorobenzene was partially effective for the reaction, affording **3a** in moderate 49% yield. Remaining solvents were totally inactive for the reaction. The reaction was tried with a catalytic amount of $AgBF_4$, AgOTf and KPF_6 instead of $AgSbF_6$ (15 mol %). AgOTf was slightly effective for the reaction, yielding **3a** in 42% yield. Remaining additives were not effective for the reaction. The control experiments clearly revealed that a catalytic amount of $AgSbF_6$ and ruthenium complex were crucial for the reaction.

The scope of *ortho*-benzoxylation of various substituted

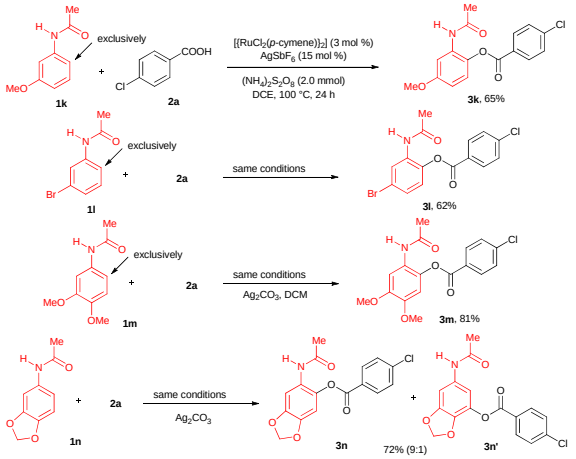
acetanilides **1** with 4-chlorobenzoic acid (**2a**) under the optimized reaction conditions was examined (Table 1). The reaction of 4-methoxy **1b** and 4-*n*-butoxy **1c** acetanilides with **2a** provided coupling products **3b** and **3c** in 72% and 75% yields, respectively (entries 1 and 2). Similarly, other electron-donating group substituted acetanilides such as 4-methyl **1d** and 4-*n*-butyl **1e** acetanilides yielded the corresponding coupling products **3d** and **3e** in 66% and 72% yields, respectively (entries 3 and 4). This result clearly revealed that more electron releasing substituents such as O-*n*Bu and *n*-Bu gave slightly better yields than a less electron releasing substituents such as OMe and Me. Halogen group substituted acetanilides were also compatible for the reaction. Thus, the reaction of 4-bromo **1f**, 4-chloro **1g** and 4-fluoro **1h** acetanilides with **2a** gave the corresponding *ortho*-benzoxylated acetanilides **3f-h** in 74%, 73% and 71% yields, respectively (entries 5-7). The catalytic reaction also worked effectively with electron-withdrawing group substituted acetanilide **1i**. The reaction of 4-methyl ester acetanilide (**1i**) with **2a** yielded product **3i** in 69% yield (entry 8). It is important to note that an ester is also a good directing group for the C-H bond activation reaction. However, in the reaction, the C-H bond activation takes place only ortho to the NHCOMe of the aromatic moiety. *ortho*-Methoxy acetanilide **1j** was also efficiently involved in the reaction with **2a**, providing coupling product **3j** in 67% yield (entry 9).

Table 1 The coupling of **1b-j** with 4-chlorobenzoic acid (**2a**)[a]

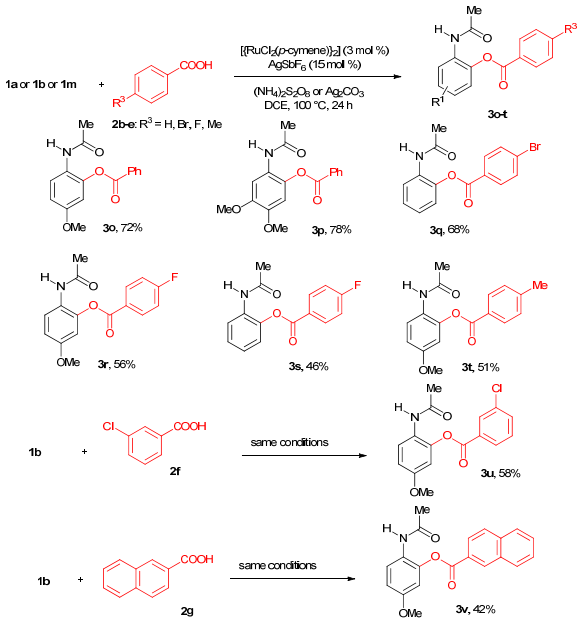
Entry	Acetanilides **1b-j**	Product **3b-j**	Yield (%)[b]
			
1	**1b**: R^1 = OMe	**3b**: R^1 = OMe	72
2	**1c**: R^1 = O-*n*Bu	**3c**: R^1 = O-*n*Bu	75
3	**1d**: R^1 = Me	**3d**: R^1 = Me	66
4	**1e**: R^1 = *n*-Bu	**3e**: R^1 = *n*-Bu	72
			
5	**1f**: R^1 = Br	**3f**: R^1 = Br	74
6	**1g**: R^1 = Cl	**3g**: R^1 = Cl	73
7	**1h**: R^1 = F	**3h**: R^1 = F	71
8			69
9			67

[a] All reactions were carried out using **1b-j** (1.20 mmol), **2a** (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (15 mol %) and $(NH_4)_2S_2O_8$ (2.0 mmol) in 1,2-dichloroethane at 100 °C for 24 h. [b]Isolated yield.

Next, the regioselectivity of unsymmetrical acetanilides **1k-n** with 4-chlorobenzoic acid (**2a**) was studied (Scheme 1). 3-Methoxy acetanilide (**1k**) underwent *ortho*-benzoxylation with **2a** selectively at a less hindered C-H bond under similar reaction conditions, affording **3k** in 65% yield. Likewise, 3-bromo acetanilide (**1l**) reacted with **2a** at a less hindered C-H bond, providing **3l** in 62% yield. Similarly, 3,4-dimethoxy acetanilide (**1m**) and 3,4-(methylenedioxy) acetanilide (**1n**) also underwent coupling with **2a** at a less hindered C-H bond, giving products **3m** and **3n** in 81% and 72% yields, respectively. However, in the reaction of **1n** with **2a**, the other regioisomer **3n'** was also observed in addition to **3n**. For the reaction of **1m** and **1n** with **2a**, Ag_2CO_3 (1.0 mmol) oxidant was used instead of $(NH_4)_2S_2O_8$ in CH_2Cl_2 solvent. Oxidant $(NH_4)_2S_2O_8$ was not effective for these reactions.



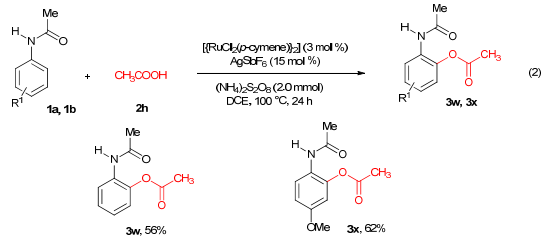
Scheme 1 Regioselective studies



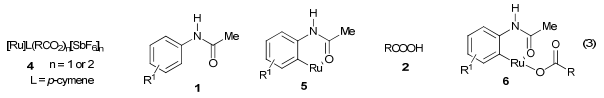
Scheme 2 Scope of the substituted benzoic acids **2**

This *ortho*-benzoxylation reaction was successfully extended with various aromatic acids **2** (Scheme 2). Benzoic acid (**2b**) reacted with **1b** or **1m** under similar reaction conditions to yield the corresponding coupling products **3o** and **3p** in 72% and 78% yields, respectively. In the reaction of **1m** with **2b**, Ag_2CO_3 oxidant was used. 4-Bromobenzoic acid (**2c**) reacted with **1a**,

giving coupling product **3q** in 68% yield. Electron deficient 4-fluorobenzoic acid (**2d**) and electron rich 4-methylbenzoic acid (**2e**) also efficiently participated in the reaction with **1a** or **1b**, providing coupling products **3r-t** in 56%, 46% and 51% yields, respectively. Next, the catalytic reaction was tested with *meta* substituted benzoic acid. The reaction of *meta*-chloro benzoic acid **2f** with **1b** gave coupling product **3u** in 58% yield. 2-Naphthoic acid (**2g**) also nicely participated in the reaction, yielding product **3v** in 42% yield. In fact, the catalytic reaction was also tested with 4-cyano, 4-nitro, 4-acetyl and 4-methoxybenzoic acids. However, in these reactions, no expected coupling products were observed. These results clearly showed that the catalytic reaction is highly sensitive to the type of the substituent present on the aromatic ring of the benzoic acids. Moderate electron releasing as well as electron withdrawing substituents such as Me, H, Br, Cl and F on the aromatic acids nicely participated in the reaction. But, strong electron donating as well as electron withdrawing substituents such as OMe, NO_2, CN and COMe on the aromatic acids were not suitable substrates for the reaction.



The catalytic reaction was also compatible with acetic acid (**2h**) (eq. 2). Treatment of acetanilide (**1a**) with acetic acid (**2h**) under the optimized reaction conditions gave *ortho*-acetoxylation product **3w** in 56% yield. Similarly, 4-methoxy acetanilide **1b** afforded *ortho*-acetoxylation product **3x** in 62% yield.



The catalytic reaction likely proceeds via removal of chloride ligand by Ag^+ salt from [{$RuCl_2$(*p*-cymene)}$_2$] complex followed by reaction with aromatic carboxylic acid **2**, giving cationic ruthenium carboxylate complex **4** (eq. 3). Coordination of the carbonyl oxygen of acetanilide **1** to the ruthenium cationic species **4** followed by *ortho*-metalation provides a six-membered ruthenacycle **5** and RCOOH.[9a] Coupling of carboxylic acid **2** into the ruthenacycle **5** affords an intermediate **6**. Reductive elimination of intermediate **6** gives the final product **3** and a Ru(0) species.[9b] Later, $(NH_4)_2S_2O_8$ oxidizes Ru(0) to an active Ru(II) carboxylate species **4** in the presence of carboxylic acid for the next catalytic cycle.

In conclusion, we have discussed a ruthenium-catalyzed benzoxylation of acetanilides with benzoic acids to provide *ortho*-benzoxylated acetanilides in good to moderate yields. The catalytic reaction was also compatible with acetic acid. Further extension of the C-H bond activation of other chelating group substituted aromatics and functionalization with other hetero nucleophiles (R-COOH, R-OH and R_2NH) and detailed mechanistic investigations are in progress.

We thank the Department of Science and Technology (DST) (SR/S1/OC-26/2011), India for the support of this research. K. P. thanks the Council of Scientific and Industrial Research (CSIR) for a fellowship.

View Article Online
DOI: 10.1039/C3CC45350B

Notes and references

[a] *Department of Chemistry, Indian Institute of Science Education and Research, Pune 411021, India; E-mail: mjeganmohan@iiserpune.ac.in*

† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectroscopic data. See DOI: 10.1039/b000000x/

1 Selected reviews: (*a*) Selected reviews: V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.* 2002, **102**, 1731; (*b*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.* 2010, **110**, 624. (*c*) T. W. Lyons and M. S. Sanford *Chem. Rev*. 2010, **110**, 1147. (*d*) F. Luo, C. Pan, J. Cheng, *Synlett* 2012, **23**, 357; (*e*) H. M. L. Davies, J. D. Bois and J.-Q. Yu, *Chem. Soc. Rev*. 2011, **40**, 1855; (*f*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev*. 2012, **41**, 3651; (*g*) B. Li and P. H. Dixneuf, *Chem. Soc. Rev*. 2013, **42**, 5744.

2 W. Li and P. Sun, *J. Org. Chem*. **2012**, *77*, 8362.

3 Selected C-O bond formation by alcohols: (*a*) L. V. Desai, H. A. Malik and M. S. Sanford, *Org. Lett*. 2006, **8**, 1141; (*b*) G. W. Wang and T. T. Yuan, *J. Org. Chem*. 2010, **75**, 476.

4 Selected acetoxylations: (*a*) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res*. 2012, **45**, 936; (*b*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.* 2004, **126**, 2300; (*c*) B. V. S. L. Reddy, R. Reddy and E. J. Corey, *Org. Lett.* 2006, **8**, 3391; (*d*) K. J. Stowers, A. Kubato and M. S. Sanford, *Chem. Sci.* 2012, **3**, 3192; (*e*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res*. 2012, **45**, 788; (*f*) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.* 2006, **128**, 6790; (*g*) G.-W. Wang, T.-T. Yuan and X.-L. Wu, *J. Org. Chem.* 2008, **73**, 4717; (*h*) S. J. Gu, C. Chen and W. Z. Chen, *J. Org. Chem.* 2009, **74**, 7203; (*i*) W. Wang, F. Luo, S. Zhang and J. Cheng, *J. Org. Chem.* 2010, **75**, 2415.

5 Selected hydroxylations: (*a*) Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.* 2009, **131**, 14654; (*b*) G. Shan, X. Yang, L. Ma and Y. Rao, *Angew. Chem., Int. Ed*. 2012, **51**, 13070; (*c*) Y. Yang, Y. Lin and Y. Rao, *Org. Lett*. 2012, **14**, 2874; (*d*) V. S. Thirunavukkarasu, J. Hubrich and L. Ackermann, *Org. Lett*. 2012, **14**, 4210; (*e*) F. Mo, L. J. Trzepkowski and G. Dong, *Angew. Chem., Int. Ed*. 2012, **51**, 13075.

6 (*a*) A. R. Dick, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.* 2005, **127**, 12790; (*b*) Z. S. Ye, W. H. Wang, F. Luo, S. H. Zhang and J. Cheng, *Org. Lett*. 2009, **11**, 3974; (*c*) W. H. Wang, F. Luo, S. H. Zhang and J. Cheng, *J. Org. Chem*. 2010, **75**, 2415; (*d*) W. H. Wang, C. D. Pan, F. Chen and J. Cheng, *Chem. Commun*. 2011, **47**, 3978; (*e*) C. L. Sun, J. Liu, Y. Wang, X. Zhou, B. J. Li and Z. J. Shi, *Synlett* 2011, 883.

7 Ruthenium reviews: (*a*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev*. 2012, **112**, 5879; (*b*) L. Ackermann, *Acc. Chem. Res*. 2013, DOI: 10.1021/ar3002798. Seleceted papers: (*c*) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Angew. Chem. Int. Ed*., 2010, **49**, 6629; (*d*) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Green Chem*. 2011, **13**, 3075; (*e*) B. Sundararaju, M. Achard, G. V. M. Sharma and C. Bruneau, *J. Am. Chem. Soc*., 2011, **133**, 10340; (*f*) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi and M. Miura, *Org. Lett*, 2012, **14**, 2058; (*g*) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed*., 2011, **50**, 6379; (*h*) K. Parthasarathy, N. Senthilkumar, J. Jayakumar and C.-H. Cheng, *Org. Lett*. 2012, **14**, 3478; (*i*). M. Ramu Yadav, R. K. Rit and A. K. Sahoo, *Org. Lett*. 2013, **15**, 1638.

8 (a) CG. Ravi Kiran and M. Jeganmohan, *Chem. Commun*., 2012, **48**, 2030; (*b*) M. C. Reddy and M. Jeganmohan, *Chem. Commun*., 2013, **49**, 481; (*c*) CG. Ravi Kiran, S. Pimparkar and M. Jeganmohan, *Chem. Commun*., 2013, **49**, 3146; (*d*) CG. Ravi Kiran, S. Pimparkar and M. Jeganmohan, *Chem. Commun*., 2013, **49**, 3703; (*e*) Reddy, M. C.; Jeganmohan, M. *Chem. Commun*., 2013, **49**, 6060.

9 (*a*) E. F. Flegeau, C. Bruneau, P. H. Dixneuf and A. Jutand, *J. Am. Chem. Soc*., 2011, **133**, 10161; (*b*) J. Racowski, A. R. Dick and M. S. Sanford, *J. Am. Chem. Soc*. 2009, **131**, 10974.