ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, **51**, 12807

Received 12th May 2015,
Accepted 6th July 2015

DOI: 10.1039/c5cc03951g

www.rsc.org/chemcomm

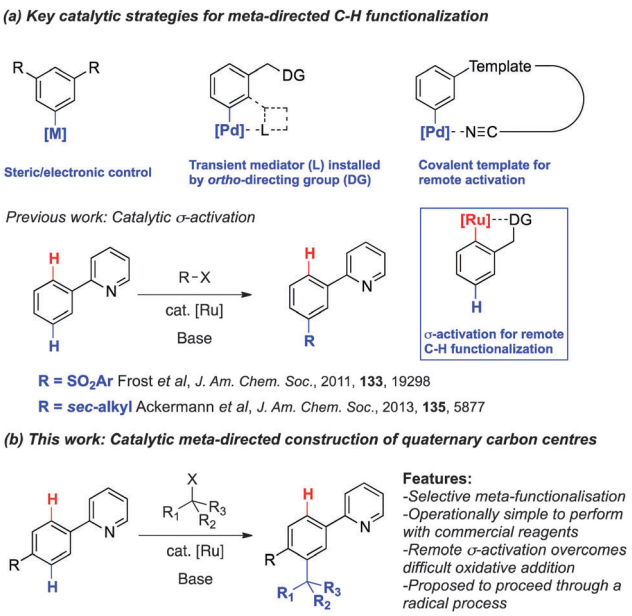
Catalytic *meta*-selective C–H functionalization to construct quaternary carbon centres†

Andrew J. Paterson,[a] Sahra St John-Campbell,[b] Mary F. Mahon,[b] Neil J. Press[c] and Christopher G. Frost*[ab]

A catalytic *meta*-selective C–H functionalization of 2-phenylpyridines using a range of tertiary halides is described. The protocol is simple to perform and uses commercially available reagents to construct challenging quaternary carbon centres in a regioselective manner. Preliminary studies suggest the C–H functionalization proceeds through a radical process directed *via* a remote σ-activation.

The transition-metal catalyzed cleavage and functionalization of inert C–H bonds is evolving into a fundamental methodology for the design of atom economical approaches to useful organic molecules.[1] While the direct functionalization at the *ortho* position of aromatic compounds by chelation assisted C–H bond cleavage has become well established in recent years, developing reactions with complementary regioselectivity continues to challenge contemporary catalytic methodology.[2] In this context, examples of *meta* selective catalytic C–H functionalization have been reported offering diversity in molecular design through alternative reaction strategies (Scheme 1a). These include substrate controlled systems,[3] transient mediators such as a carboxylic acid[4] or norbornene[5] and covalent template strategies for remote activation.[6] We first reported a novel catalytic σ-activation protocol for C–H functionalization that allows the *meta* sulfonation of 2-phenylpyridines *via* cyclometalated ruthenium intermediates.[7] Interestingly, the catalytic σ-activation strategy proved effective for *meta*-alkylations with secondary alkyl halides[8] whilst acyl halides and primary alkyl halides afford only the *ortho*-functionalized products consistent with a mechanism involving oxidative addition of the organohalide.[9]

Here we report a new catalytic *meta*-selective C–H functionalization of 2-phenylpyridines to construct quaternary carbon centres (Scheme 1b). The transition-metal catalyzed coupling of tertiary alkyl halides and aromatic C–H bonds is an especially challenging reaction due to the difficult oxidative addition of a metal complex into a bulky C–X bond.[10] We hypothesized that a catalytic σ-activation strategy would therefore be amenable to establishing quaternary carbon centres by avoiding a general oxidative addition pathway.



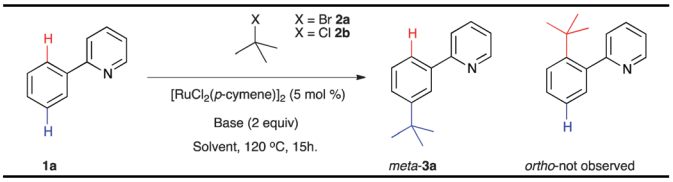
Scheme 1 Catalytic *meta*-directed C–H functionalization.

In preliminary experiments, 2-phenylpyridine **1a** was treated under conditions analogous to those developed in our *meta*-sulfonation reaction: $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) K_2CO_3 (2 equiv.), *t*-BuBr **2a** (3 equiv.) using MeCN as the solvent.[7] Unfortunately no coupled products were formed under these conditions however the desired *meta*-substituted product was observed in 12% conversion when the reaction solvent was changed to 1,4-dioxane (Table 1, entries 1 and 2). By simply changing the base from K_2CO_3 to various acetate salts, a significant increase in conversion was

[a] *Centre for Sustainable Chemical Technologies, University of Bath, Bath, BA2 7AY, UK*
[b] *Department of Chemistry, University of Bath, Bath, BA2 7AY, UK. E-mail: c.g.frost@bath.ac.uk; Fax: +44 (0)1225 386231; Tel: +44 (0)1225 386142*
[c] *Novartis Institutes for BioMedical Research, Novartis Campus, Fabrikstrasse, 22, CH-4056, Basel, Switzerland*

† Electronic supplementary information (ESI) available: Full experimental details. CCDC 1064109. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc03951g

Table 1 Optimization of catalytic *meta* tertiary alkylation



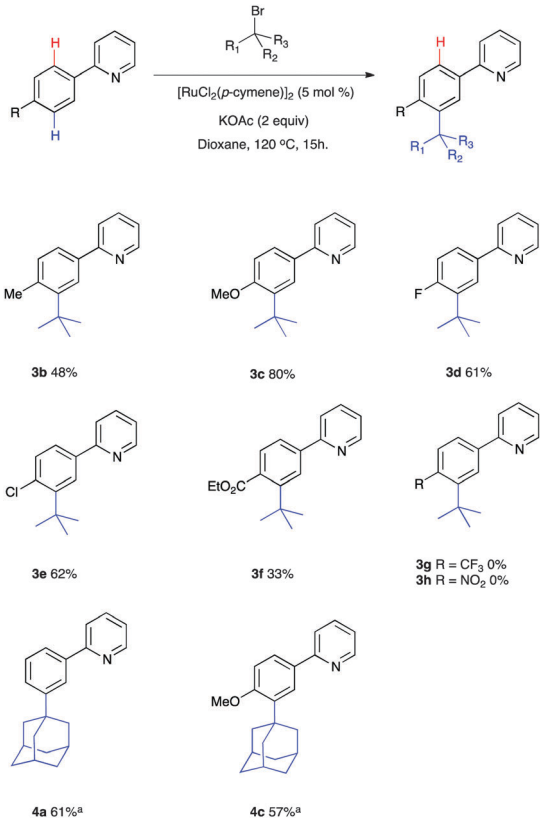
Entry	*t*-Bu-X	Base	Solvent	Conversion[a] (%)
1	**2a**	K_2CO_3	MeCN	0
2	**2a**	K_2CO_3	1,4-Dioxane	12
3	**2a**	KOAc	Neat	69
4	**2a**	KOAc	2-Me-THF	68
5	**2a**	KOAc	2-Butanone	61
6	**2a**	KOAc	1,4-Dioxane	74
7[b]	**2a**	K_2CO_3	1,4-Dioxane	60
8	**2a**	NaOAc	1,4-Dioxane	31
9	**2a**	CsOAc	1,4-Dioxane	64
10	**2a**	Bu_4NOAc	1,4-Dioxane	13
11[c]	**2a**	KOAc	1,4-Dioxane	0
12[d]	**2a**	KOAc	1,4-Dioxane	25
13[e]	**2a**	KOAc	1,4-Dioxane	50
14[f]	**2a**	KOAc	1,4-Dioxane	72
15	**2b**	KOAc	1,4-Dioxane	20
16	**2b**	K_2CO_3	1,4-Dioxane	27
17	**2b**	KOAc (0.5 equiv.) K_2CO_3 (1.5 equiv.)	1,4-Dioxane	63
18[b]	**2b**	K_2CO_3	1,4-Dioxane	62

[a] Conversion of **1a** to **3a** by ^{1}H NMR. [b] With 30 mol% MesCOOH. [c] Without $[RuCl_2(p\text{-cymene})]_2$. [d] Reaction in air. [e] $[RuCl_2(p\text{-cymene})]_2$ (1 mol%). [f] Reaction time 4 h.

observed with KOAc proving the most effective (entry 6). In the absence of ruthenium complex, no product was observed (entry 11). This catalytic system was found to perform well in a range of solvents as well as under solvent free conditions and was completed in as little as 4 hours (entry 14). When *t*-BuCl **2b** was used as the coupling reagent, a significant drop in conversion was observed, however by using a combination of K_2CO_3 and KOAc, the reaction performed competitively (entry 17).

With optimized catalytic systems in hand, we then investigated how reaction conversions were affected when substituents at the 4-position of the aryl ring were varied (Scheme 2). It was found that electron donating substituents favoured the reaction whereas strongly electron withdrawing groups shut the reaction down entirely. The reaction was tolerant of halogen and ester substituents which is useful for further synthetic transformations. The reactions led to the sole formation of the mono substituted *meta* products with no decomposition or by-products observed although quantitative separation by conventional methods was not always possible (see ESI† for full analysis). Intriguingly, 1-bromoadamantane was found to be an effective coupling partner and product **4c** was characterised by X-ray analysis confirming the regioselective *meta* substitution (Fig. 1).[11] Our procedure also effectively coupled a range of tertiary alkyl chlorides, reagents which are readily available and generally considered to be less reactive (Scheme 3). In these examples, it was found that the incorporation of longer alkyl chain lengths maintained high conversions and enabled better separation of the products by normal phase flash chromatography.

In addition to the alkyl halide reagents outlined in Schemes 2 and 3, tertiary α-bromo ester **2c** was effectively coupled, generating



Scheme 2 Catalytic *meta* functionalization using tertiary alkyl bromides. Numbers quoted are direct conversions to product by ^{1}H NMR. [a] Using KOAc (0.5 equiv.) and K_2CO_3 (1.5 equiv.).

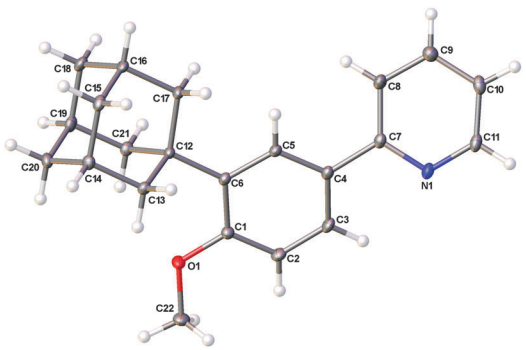
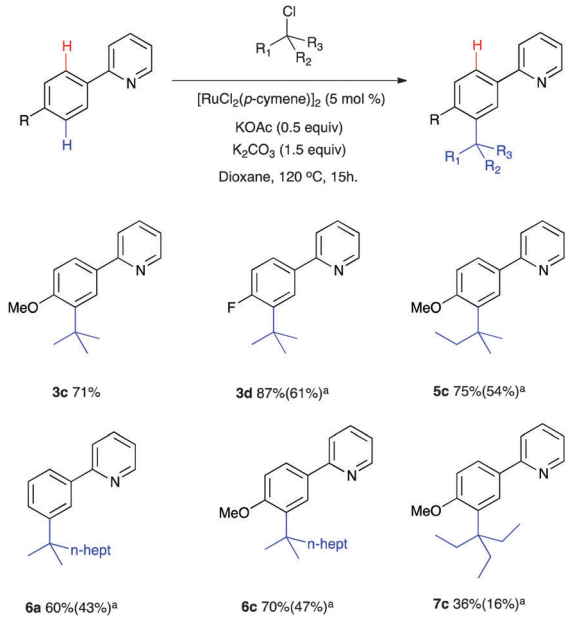


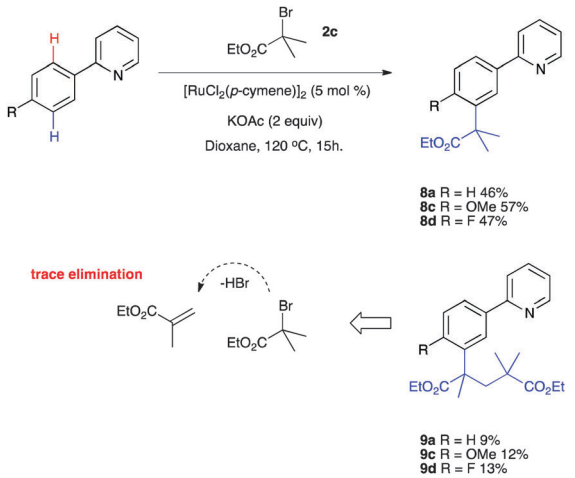
Fig. 1 The asymmetric unit in the crystal structure of **4c**. Ellipsoids are illustrated at 30% probability.

meta-substituted products **8a**, **8c** and **8d**, compounds with a useful functional handle, in reasonable isolated yields (Scheme 4). This result provided key insight into the reaction mechanism and strongly suggested a radical type pathway, rather an S_EAr type mechanism previously proposed in our *meta*-sulfonation reaction.[7]

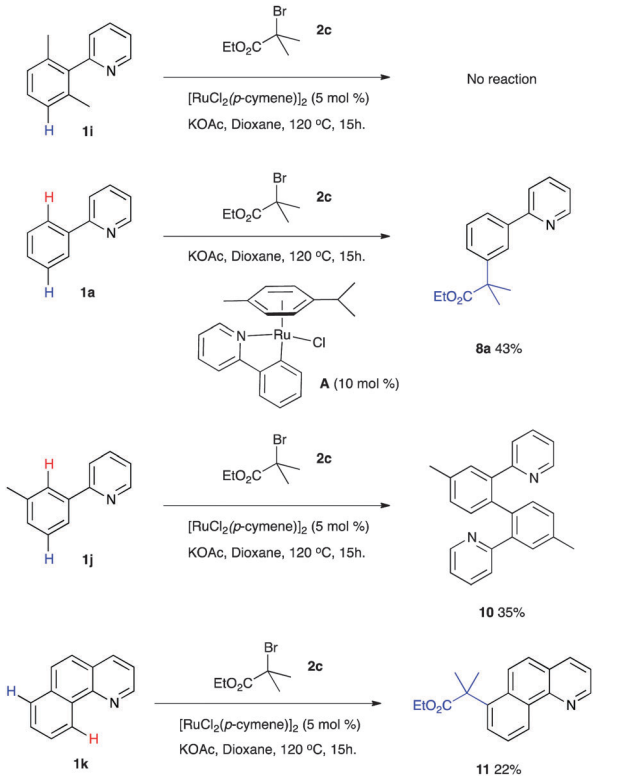
Heterolytic cleavage of the C–X bond of **2c** in an S_N1-type manner would result in a strongly disfavoured carbocation residing alpha to an electron withdrawing ester. It is therefore unlikely that reaction with the aromatic substrate would occur in this fashion. The possibility of S_N2 type reactivity can also be effectively ruled out given the steric effects of the tertiary alkyl



Scheme 3 Catalytic *meta* functionalization using alkyl chloride reagents. Numbers quoted are direct conversions to product by ^{1}H NMR. [a] Numbers in brackets indicate isolated yields.



Scheme 4 Catalytic *meta* functionalization with α-bromo ester **2c**. Numbers quoted are isolated yields.



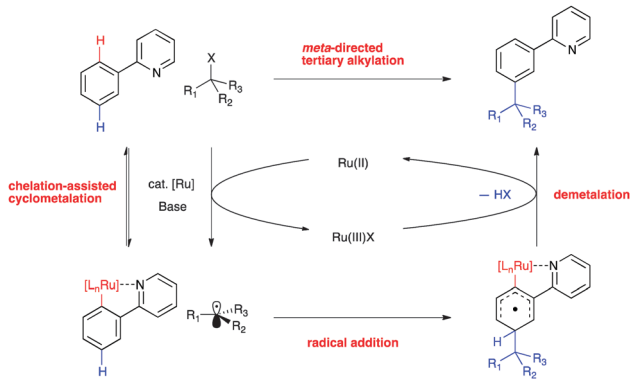
Scheme 5 Mechanistic investigation. Numbers quoted are isolated yields.

halides used. The generation of tertiary alkyl radicals has however been widely reported with a range of transition metal catalysts and shown to be effective in the substitution of aromatics, heteroaromatics and olefins.[12]

In contrast to the reactions with simple alkyl-halides outlined in Schemes 2 and 3 which led to the sole formation of one product, reaction with **2c** generated additional by-products. Compounds **9a**, **9c** and **9d** were isolated along with spectroscopic evidence of trace higher oligomers which is consistent with a radical conjugate polymerisation pathway. We hypothesise that a tertiary carbon-centered radical species can add onto elimination products formed under the reaction conditions, which can in turn propagate onto a cyclometalated (σ-activated) substrate molecule to afford the observed by-products. Furthermore, the addition of radical scavenger TEMPO proved detrimental to the reaction with no desired product observed when stoichiometric quantities were used (see ESI†).

Further mechanistic work was conducted to provide additional insight into the interesting *meta* selectivity displayed by this reaction (Scheme 5). It has previously been proposed that initial ruthenium insertion into an *ortho* C–H bond to generate a cyclometalated complex is key to this type of reactivity.[7,8] In support of this, reaction of the *ortho*, *ortho* dimethyl substrate **1i** resulted in no conversion to the desired *meta* substituted product. The importance of ruthenium σ-activation is also highlighted with the successful *meta*-selective reaction using pre-formed complex **A.** No *meta*-substituted product was observed when substrate **1j** bearing a methyl group at the 3-position of the aromatic ring was used. Instead, the only product isolated was dimer **10** suggesting a competing reductive elimination of two coordinated substrate molecules when the site *para* to the C–Ru bond is blocked.[13] Conformationally locked benzoquinoline **1j** was however effectively alkylated generating **10** as the only isolated product.

Together these results suggest that substitution occurs preferentially at a position *para* to the C–Ru bond formed following cyclometalation. Interestingly, analogous reactivity has also recently been reported in a stoichiometric process on iridium complexes.[14] In light of this work we now propose the following mechanism (Scheme 6). Initial *ortho* C–H insertion generates a cyclometalated complex, a process shown to be reversible and aided by carboxylate ligands.[15] Substitution at the position *para* to the newly installed C–Ru bond then most likely occurs *via* a radical process whereby single-electron transfer (SET) from a



Scheme 6 Proposed catalytic cycle.

ruthenium(II) species can generate a tertiary alkyl radical and the corresponding ruthenium(III)X species. The carbon-centered radical then adds to the aromatic ring to generate a cyclohexadienyl radical intermediate. Rearomatisation could occur *via* single-electron oxidation and deprotonation to regenerate a ruthenium(II) complex and furnish the *meta* alkylated product after proto-demetalation.

In summary, we have developed a novel *meta* selective catalytic C–H functionalisation of 2-phenylpyridine substrates for the installation of quaternary carbon centres. The procedure is operationally simple and was found to couple a useful range of tertiary alkyl bromides and more challenging tertiary alkyl chlorides. Mechanistic studies indicate that site selective radical addition occurs at the position *para* to the C–Ru bond formed following cyclometalation to afford products with net *meta* substitution. More detailed mechanistic studies are underway to determine the precise nature of the organometallic species and redox processes involved.

We are grateful to the University of Bath, EPSRC DTC in Sustainable Chemical Technologies and Novartis for funding. We acknowledge the valuable assistance of Dr Anneke Lubben (Mass Spectrometry, University of Bath), Dr John Lowe and Dr Catherine Lyall (NMR Spectroscopy, University of Bath).

Notes and references

1 For selected reviews, see: (*a*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (*b*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (*c*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*d*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*e*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*f*) *Topics in Current Chemistry: C–H Activation*, ed. J.-Q. Yu and Z. Shi, Springer, Berlin Heidelberg, 1st edn, 2010.

2 (*a*) F. Julia-Hernandez, M. Simonetti and I. Larrosa, *Angew. Chem., Int. Ed.*, 2013, **52**, 11458; (*b*) J. Yang, *Org. Biomol. Chem.*, 2015, **13**, 1930.

3 (*a*) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 463; (*b*) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593. For an excellent review of of non-chelate-assisted C–H activation, see: (*c*) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 10236.

4 (*a*) J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109; (*b*) S. Mochida, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 5776; (*c*) J. Cornella, M. Righi and I. Larrosa, *Angew. Chem., Int. Ed.*, 2011, **50**, 9429.

5 (*a*) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519**, 334; (*b*) Z. Dong, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 5887.

6 For selected examples, see: (*a*) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518; (*b*) H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 7567; (*c*) L. Wan, N. Dastbaravardeh, G. Li and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 18056; (*d*) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 10807; (*e*) R.-Y. Tang, G. Li and J.-Q. Yu, *Nature*, 2014, **507**, 215.

7 (*a*) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298; (*b*) W. R. Reynolds, P. M. Liu, G. Kociok-Köhn and C. G. Frost, *Synlett*, 2013, 2687.

8 N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877.

9 (*a*) P. M. Liu and C. G. Frost, *Org. Lett.*, 2013, **15**, 5862; (*b*) L. Ackermann, N. Hofmann and R. Vicente, *Org. Lett.*, 2011, **13**, 1875.

10 For selected reviews, see: (*a*) J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591; (*b*) P. G. Cozzi, R. Hilgraf and N. Zimmermann, *Eur. J. Org. Chem.*, 2007, 5969; (*c*) O. Riant and J. Hannedouche, *Org. Biomol. Chem.*, 2007, **5**, 873; (*d*) Y. Tu and B. Wang, *Acc. Chem. Res.*, 2011, **44**, 1207; (*e*) A. Y. Hong and B. M. Stoltz, *Eur. J. Org. Chem.*, 2013, 2745; (*f*) T. Nishikata and S. Ishikawa, *Synlett*, 2015, 716.

11 CCDC 1064109.

12 For selected examples, see: (*a*) C. Liu, D. Liu, W. Zhang, L. Zhou and A. Lei, *Org. Lett.*, 2013, **15**, 6166; (*b*) X. Wu, J. W. T. See, K. Xu, H. Hirao, J. Roger, J.-C. Hierso and J. S. Zhou, *Angew. Chem., Int. Ed.*, 2014, **53**, 13573; (*c*) T. Nishikata, Y. Noda, R. Fujimoto and T. Sakashita, *J. Am. Chem. Soc.*, 2013, **135**, 16372.

13 This pathway is also favoured on steric grounds when substrate bearing a methyl group at the 2-position of the aromatic ring was used (see ESI†).

14 J. J. Devery III, J. J. Douglas, J. D. Nguyen, K. P. Cole, R. A. Flowers II and C. R. J. Stephenson, *Chem. Sci.*, 2015, **6**, 537.

15 (*a*) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf and A. Jutand, *J. Am. Chem. Soc.*, 2011, **133**, 10161; (*b*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315.

