Ruthenium-catalysed dehydrogenative C–H borylation of arenes with pinacolborane

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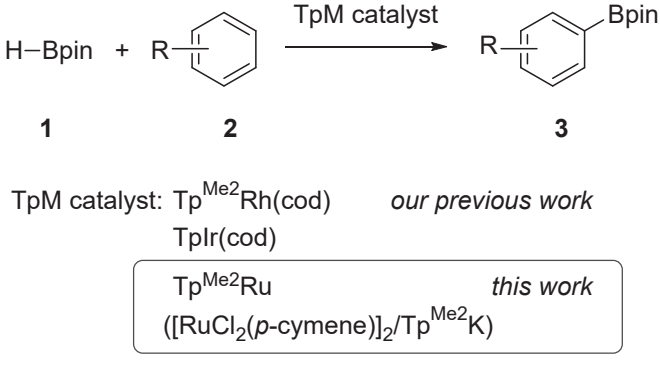
A ruthenium complex prepared *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and $Tp^{Me_2}K$ [Tp^{Me_2} = hydrotris(3,5-dimethylpyrazolyl)borate] is efficient for aromatic C–H borylation with pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Arenes were borylated at more electron-rich positions. DFT calculations and kinetic isotope effect experiments suggest that the catalytic cycle should involve an electrophilic aromatic substitution with a borenium cation.

Keywords: C–H bond activation, ruthenium catalyst, borane, tris(pyrazolyl)borate ligand

Since the versatility of organoboronates in modern organic chemistry has made them attractive targets for synthesis, there has been considerable interest in the development of transition metal-catalysed C–B bond-forming reactions.[1] From an environmental and economic point of view, the direct borylation of ubiquitous C–H bonds of aromatic hydrocarbons should be an ultimate goal in this area.[2–5] Numerous catalyst systems, most of which were Rh(I) and Ir(I) complexes, have been proposed for utilisation in the C–H borylation of arenes with pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane, HBpin, **1**) or bis(pinacolato)diboron as a boron source. Meanwhile, we have reported that TpIr(cod) [Tp = hydrotris(pyrazolyl)borate] and Tp^{Me_2}Rh(cod) [Tp^{Me_2} = hydrotris(3,5-dimethylpyrazolyl)borate] showed high catalytic activities in the borylation of aromatic C–H bonds of arenes using **1**.[6,7] During the course of further investigation of the aromatic C–H borylation, we found a novel, efficient catalyst system based upon Tp derivatives. In this paper, we wish to report the C–H borylation of arenes **2** with **1** catalysed by a ruthenium complex prepared *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and $Tp^{Me_2}K$ (Scheme 1).

Despite the enthusiastic reports on C–H borylations, examples of such transformations using ruthenium catalysts are rare. The $[Cp^*RuCl_2]_2$-catalysed C–H borylation of alkanes with bis(pinacolato)diboron has been reported.[8] However, neither **1** nor benzene was the suitable substrate under these conditions. The ruthenium-catalysed C–H borylation of indoles with **1** has been achieved; however, no example of simple benzene derivatives has been described.[9] Very recently, both Nolan[10] and our group[11] demonstrated that the ruthenium-catalysed C–H borylation of 2-arylpyridines took place at ortho-positions of the benzene ring.



Scheme 1 Aromatic C–H borylation using pinacolborane.

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Results and discussion

In order to optimise reaction parameters, benzene (R = H, **2a**) was used as a substrate for the dehydrogenative C–H borylation. The results are summarised in Table 1. Treatment of **1** with **2a** (20 equiv.) in the presence of 1.5 mol% of $[RuCl_2(p\text{-cymene})]_2$ (3 mol% of Ru) and 3 mol% of $Tp^{Me_2}K$ was found to lead to the corresponding phenylboronate **3a** in 82% yield (entry 1). The use of an excess amount of **2a** completely suppressed the formation of diborylated products. The Tp^{Me_2} ligand was essential for this reaction (entry 2); however, employing TpK or BpK [Bp = dihydrobis(pyrazolyl)borate] provided poor yields of **3a** (entries 3 and 4). $[RuCl_2(benzene)]_2$ was also used as a catalyst precursor (entry 5). The use of $[OsCl_2(p\text{-cymene})]_2$ instead of $[RuCl_2(p\text{-cymene})]_2$ afforded a moderate result (entry 6). As expected from the previous report, Cp*Ru catalyst systems did not promote the borylation of **2a** (entries 7 and 8).[8] In contrast to the previous results by Hartwig's group, the use of bis(pinacolato)diboron instead of **1** resulted no reaction (entry 9).[8] Furthermore, the related reaction of octane with **1** under the present conditions did not afford dehydrogenative borylation products.

The results obtained with representative arenes **2**, giving the corresponding arylboronates **3** similarly as above, are listed in Table 2. The yields and product ratios were determined by GC analysis of crude reaction mixtures. In most cases, substituents on the aromatic ring disturbed C–B bond formation at the *ortho*-positions probably due to the steric effect. Indeed, on one hand, disubstituted arenes **2b** and **2c** were borylated regioselectively for steric reasons (entries 1 and 2). However, the small fluorine substituent of **2d** was tolerated (entry 3). On the other hand, the reaction of monosubstituted arenes **2e–2g**

Table 1 Optimisation of Ru-catalysed borylation of **2a**[a]

Entry	Catalyst	Yield/%[b]
1[c]	$[RuCl_2(p\text{-cymene})]_2$/ $Tp^{Me_2}K$	82
2	$[RuCl_2(p\text{-cymene})]_2$	8
3[c]	$[RuCl_2(p\text{-cymene})]_2$/TpK	25
4[c]	$[RuCl_2(p\text{-cymene})]_2$/BpK	17
5[c]	$[RuCl_2(benzene)]_2$/ $Tp^{Me_2}K$	78
6[c]	$[OsCl_2(p\text{-cymene})]_2$/ $Tp^{Me_2}K$	49
7	$[Cp^*RuCl]_4$	0
8	$[Cp^*RuCl_2]_2$	0
9[c,d]	$[RuCl_2(p\text{-cymene})]_2$/ $Tp^{Me_2}K$	0

[a]Reaction conditions: **1** (0.25 mmol), **2a** (5 mmol), Ru catalyst (3 mol% Ru atom), 120 °C, 16 h.

[b]GLC yields are based on **1**.

[c]Additional Tp ligands (7.5 μmol) were used.

[d]Bis(pinacolato)diboron (0.125 mmol) was used instead of **1**.

Table 2 Ru-catalysed borylation of representative arenes **2** with **1**[a]

Entry	Arene **2**	Product **3**	Yield/%[b]
1	**2b** [R = 1,3-$(CF_3)_2$]	**3b** [R = 3,5-$(CF_3)_2$]	58
2	**2c** (R = 1,2-Me_2)	**3c** (R = 3,4-Me_2)	77
3	**2d** (R = 1,4-F_2)	**3d** (R = 2,5-F_2)	71
4	**2e** (R = OMe)	**3e** (R = OMe) *o*:*m*:*p* = 2:38:60[b]	59
5	**2f** (R = Me)	**3f** (R = Me) *o*:*m*:*p* = 0:53:47[b]	90
6	**2g** (R = CF_3)	**3g** (R = CF_3) *o*:*m*:*p* = 0:74:26[b]	98

[a]Reaction conditions: **1** (0.25 mmol), **2** (5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.8 μmol), $Tp^{Me_2}K$ (7.5 μmol), 120 °C, 16 h.

[b]Yields and isomer ratios were determined by GC analysis.

resulted in a mixture of *meta*- and *para*-regioisomers (entries 4–6); however, only a trace amount of *ortho*-isomer was also observed in the borylation of **2g** (entry 4). While the most common catalysts, including Tp complexes of Rh and Ir, are known to afford statistical mixtures of *meta*- and *para*-isomers in the borylation of monosubstituted arenes,[6] the present isomeric distributions obviously differed from statistical ratios. The borylation of **2g** gave a 4:1 ratio of *meta*- to *para*-isomers (entry 6), whereas the reaction of **2e** favoured the *para*-isomer (entry 4). The borylation of **2f** gave a 1:1 ratio, indicating that the *para*-position was preferentially borylated over the *meta*-position (entry 5). Thus, there is apparently a tendency for the site-selectivity to increase at more electron-rich positions. It is noteworthy that the electronic characteristics of the substituent on **2** affected the isomeric ratios.

To gain mechanistic insights into this ruthenium-catalysed C–H borylation, we conducted preliminary kinetic isotope effect (KIE) experiments with deuterated benzene. As shown below in Scheme 2, an intermolecular k_H/k_D of 0.74 was obtained from the competition reaction of an equimolar amount of benzene (**2a**) and benzene-d_6. Furthermore, the reaction of benzene-1,3,5-d_3 exhibited an intramolecular k_H/k_D of 0.86. The deuterium kinetic isotope effects of less than 1.0 would suggest that an electrophilic aromatic substitution pathway is involved in this reaction.[12,13]

An outline of a proposed mechanism is illustrated in Fig. 1. When a mixture of $[RuCl_2(p\text{-cymene})]_2$ and $Tp^{Me_2}K$ was treated with pinacolborane (**1**), ^1H NMR showed a new singlet at –10.2 ppm (see ESI, Fig. S1). As this singlet could be attributed to a ruthenium hydride complex, the proposed pathway first involves the formation of a tris(pyrazolyl)borate-hydride complex of ruthenium(II) $Tp^{Me_2}Ru(H)L_n$.[14–16]

The following process was computationally addressed by density functional theory (DFT) calculations. We have adopted the reaction of benzene (**2a**) with HBeg (1,3,2-dioxaborolane) as a model reaction, and the Tp^{Me_2} ligand was replaced by Tp in the computed structures. The energy profile for this reaction sequence is presented in Fig. 2. The first step is the coordination of HBeg to the ruthenium centre of ruthenium hydride **4** forming a σ-borane ruthenium complex **5**. Subsequently, one of the pyrazole rings of the Tp ligand would split the B–H bond into a ruthenium hydride as well as a nitrogen-stabilised borenium ion, respectively, to form a ruthenium dihydride **6**. After the coordination of **2a**, the electrophilic aromatic substitution of the borenium moiety takes place through an arenium ion intermediate **8** to give a ruthenium hydride complex **9** which

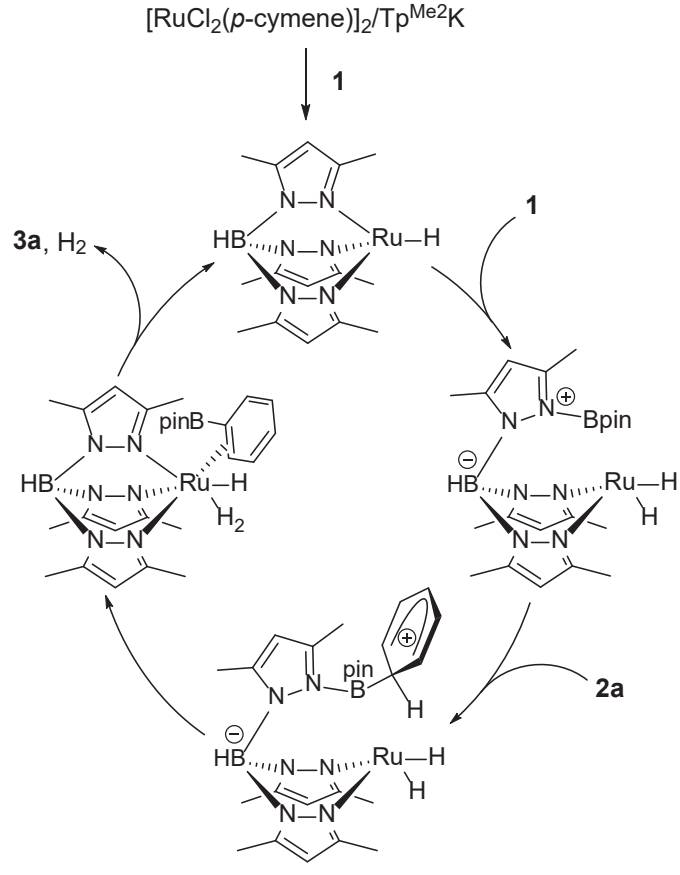
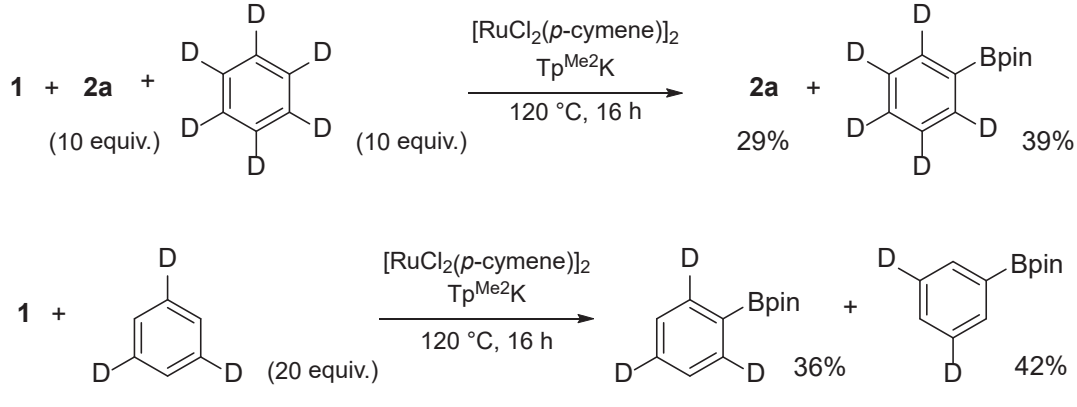


Fig. 1 Outline of a proposed mechanism.



Scheme 2 KIE experiments.

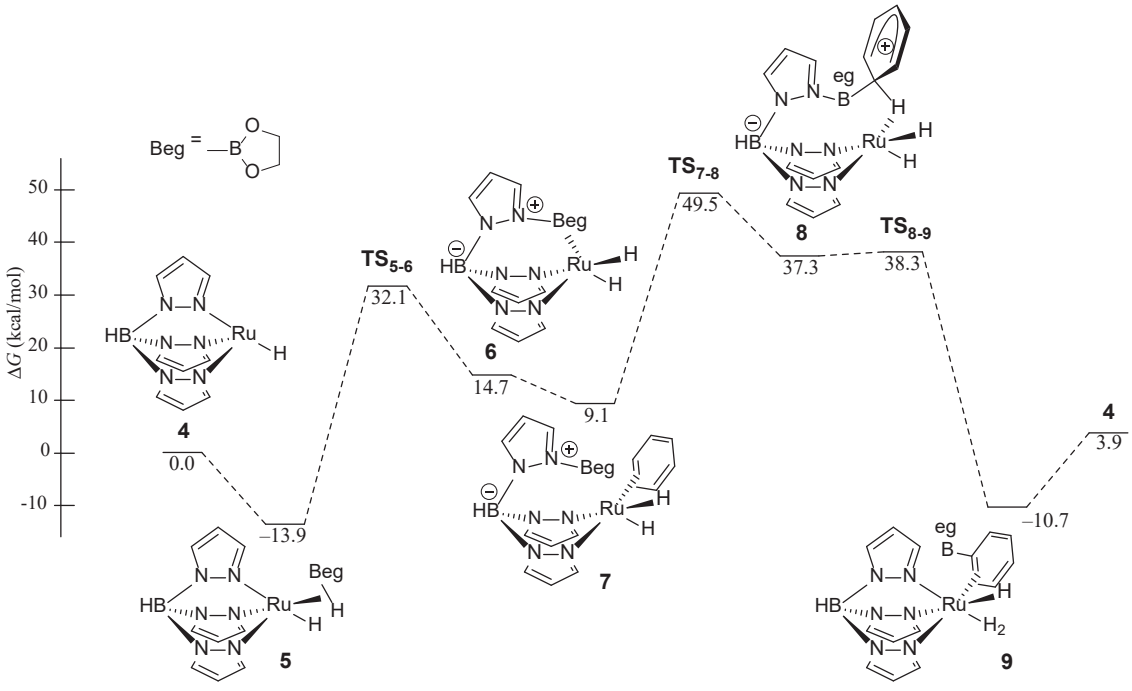


Fig. 2 Reaction pathway with calculated relative free energies (kcal mol^{-1}).

contains a coordinated **3a**. Finally, the elimination of the product **3a** and H_2 from **9** regenerates **4**.

As shown in Fig. 2, the transition state for the electrophilic attack of the borenium moiety $\mathbf{TS_{7-8}}$ is the highest point on the free energy profile of the catalytic cycle. The electrophilic aromatic substitution involving the carbon's hybridisation change from sp^2 to sp^3 would be in agreement with the inverse secondary isotope effect as shown in Scheme 2.[12,13] Furthermore, we believe that the electrophilic attack step, $\mathbf{7 \rightarrow TS_{7-8}}$, should greatly contribute to determining the product selectivity.

Conclusions

In conclusion, we have demonstrated that the ruthenium complex prepared *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and $Tp^{Me_2}K$ catalysed the C–H borylation of arenes **2** with pinacolborane (**1**). Theoretical calculations support that the catalytic cycle involves a borenium cation equivalent. The calculations as well as KIE experiments suggest that the electrophilic attack of the borenium ion on the aromatic carbon is the rate-determining step of the catalytic cycle. Further studies are currently underway to obtain detailed mechanistic insights.

Experimental

General information

All experiments were carried out under a nitrogen atmosphere using oven-dried (120 °C) glassware. NMR spectra were recorded on a JEOL JNM-A500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz). GLC analyses were carried out with a Shimadzu GC-14B instrument equipped with a glass column (OV-17 on Chromosorb W, 2 m) and with a capillary column (DB-1, 0.53 mm I.D., 30 m). GLC yields were determined using suitable hydrocarbons as internal standards. GC–MS analyses were performed on a Shimadzu GC/MS QP-5000 spectrometer at an ionisation potential of 70 eV.

4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (**1**; Aldrich) and all arenes **2a**–**g** (TCI) were purchased from commercial sources and purified by distillation before use. $[RuCl_2(p\text{-cymene})]_2$ (Kanto Chemical Co., Inc.) and $Tp^{Me_2}K$ (TCI) were purchased and used as received.

Ru-catalysed borylation of arenes; general procedure

$[RuCl_2(p\text{-cymene})]_2$ (2.3 mg, 3.8 μmol) and $Tp^{Me_2}K$ (2.5 mg, 7.5 μmol) were placed in a resealable Schlenk tube. The tube was evacuated, backfilled with dinitrogen and then charged with the arene **2** (5 mmol). After stirring the mixture at room temperature for 1 h, pinacolborane (**1**; 36 μL, 0.25 mmol) was added. The reaction mixture was then stirred at 120 °C for 16 h. After the reaction, the mixture was analysed by GC and GC–MS. The volatile material was removed *in vacuo*, and the residue was purified by Kugelrohr distillation.

4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (**3a**):[6] yield 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 12H), 7.37 (t, J = 7.2 Hz, 2H), 7.46 (tt, J = 7.4, 1.5 Hz, 1H), 7.81 (dd, J = 7.7, 1.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.86, 83.75, 127.69, 131.23, 134.72.

2-[3,5-bis(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3b**):[6] yield 58%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 12H), 7.94 (s, 1H), 8.23 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.84, 84.84, 123.49 (q, J = 33.3 Hz), 124.7 (br s), 130.89 (q, J = 247.3 Hz), 134.64 (br s).

2-(3,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3c**):[6] yield 77%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 12H), 2.27 (s, 3H), 2.27 (s, 3H), 7.15 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.44, 19.99, 24.54, 24.81, 83.55, 129.13, 132.37, 135.90, 140.11.

2-(2,5-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3d**):[6] yield 71%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 12H), 6.98 (br s, 1H), 7.10 (br s, 1H), 7.39 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.77, 84.21, 116.54 (dd, J = 8.3 and 26.9 Hz), 119.69 (dd, J = 9.3 and 24.8 Hz), 122.22 (dd, J = 9.3 and 22.8 Hz), 158.84 (d, J = 242.1 Hz), 162.92 (d, J = 247.3 Hz).

3e: the above procedure afforded an inseparable mixture of *o*-, *m*-, and *p*-**3e**. By comparing with the retention time of a prepared authentic mixture of **3e** (isomer mixture, *o*:*m*:*p* = 4:63:33),[6] the product distribution was determined by GC analysis of the crude product.

3f: the above procedure afforded an inseparable mixture of *m*- and *p*-**3f**. By comparing with the retention time of a prepared authentic mixture of **3f** (isomer mixture, *m*:*p* = 62:38),[6] the product distribution was determined by GC analysis of the crude product.

3g: the above procedure afforded an inseparable mixture of *m*- and *p*-**3g**. By comparing with the retention time of a prepared authentic mixture of **3g** (isomer mixture, *m*:*p* = 70:30),[6] the product distribution was determined by GC analysis of the crude product.

Computational methods

All calculations were performed using Gaussian 03 and 09 program suite.[17] Geometries were fully optimised at the PBE0[18,19]/def2-SVP[20] level. Frequency calculations were performed at this level of theory to identify the optimised stationary points (minima or transition states) and to estimate thermodynamic corrections at 298 K and 1 atm. The electronic energies were then improved by M06[21]/def2-TZVPP[20] single-point calculations, which took the solvent effects of benzene into account by using the SMD solvation model.[22] Gibbs energies in solution were obtained by adding the gas-phase Gibbs energy corrections of the solute (the PBE0/def2-SVP level) to the single-point energies (the M06/def2-TZVPP level).

Electronic Supplementary Information

Figure S1, copies of ^{1}H NMR and GLC chromatographs, and optimised geometries of computed species, are available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

Received 22 February 2016; accepted 7 April 2016
Paper 1603934 doi: 10.3184/174751916X14639973714726
Published online: 9 June 2016

References

1 D.G. Hall, *Boronic Acids. Preparation, Applications in Organic Synthesis and Medicine*, ed. D.G. Hall, Wiley-VCH, Weinheim, 2005.
2 I.A.I. Mkhalid, J.H. Barnard, T.B. Marder, J.M. Murphy and J.F. Hartwig, *Chem. Rev.*, 2010, **110**, 890.
3 J.F. Hartwig, *Chem. Soc. Rev.*, 2011, **40**, 1992.
4 J.F. Hartwig, *Acc. Chem. Res.*, 2012, **45**, 864.
5 A. Ros, R. Fernandez and J.M. Lassaletta, *Chem. Soc. Rev.*, 2014, **43**, 3229.
6 M. Murata, H. Odajima, S. Watanabe and Y. Masuda, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 1980.
7 Abbreviations for hydrotris(pyrazolyl)borate ligands follow the accepted nomenclature. See: S. Trofimenko, *Scorpionates: The Coordination Chemistry of Polypyrazolylborate Ligand*, Imperial College Press, London, 1999.
8 J.M. Murphy, J.D. Lawrence, K. Kawamura, C. Incarvito and J.F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 13684.
9 T. Stahl, K. Muther, Y. Ohki, K. Tatsumi and M. Oestreich, *J. Am. Chem. Soc.*, 2013, **135**, 10978.
10 J.A. Fernández-Salas, S. Manzini, L. Piola, A.M.Z. Slawin and S.P. Nolan, *Chem. Commun.*, 2014, **50**, 6782.
11 S. Okada, T. Namikoshi, S. Watanabe and M. Murata, *ChemCatChem*, 2015, **7**, 1531.
12 G.A. Olah, S.J. Kuhn and S.H. Flood, *J. Am. Chem. Soc.*, 1961, **83**, 4571.
13 R. Nakane, O. Kurihara and A. Takematsu, *J. Org. Chem.*, 1971, **36**, 2753.
14 N.W. Alcock, I.D. Burns, K.S. Claire and A.F. Hill, *Inorg. Chem.*, 1992, **31**, 2906.
15 F.A. Jalón, A. Otero and A. Rodríguez, *J. Chem. Soc., Dalton Trans.*, 1995, 1629.
16 W.-C. Chan, C.-P. Lau, Y.-Z. Chen, Y.-Q. Fang, S.-M. Ng and G. Jia, *Organometallics*, 1997, **16**, 34.
17 M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, *et al.*, Gaussian, Inc., Wallingford CT, 2009.
18 J.P. Perdew, K. Burke and M. Ernzerhof, *Phys. Rev. Lett.*, 1996, **77**, 3865.
19 C. Adamo and V. Barone, *J. Chem. Phys.*, 1999, **110**, 6158.
20 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297.
21 Y. Zhao and D.G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215.
22 A.V. Marenich, C.J. Cramer and D.G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378.