



Cite this: *Dalton Trans.*, 2016, **45**, 525

Received 16th October 2015,  
Accepted 13th November 2015

DOI: 10.1039/c5dt04068j

[www.rsc.org/dalton](http://www.rsc.org/dalton)

## Regioselectivity in C–H activation: reagent control in cyclometallation of 2-(1-naphthyl)-pyridine†

Mikhail Kondrashov, David Provost and Ola F. Wendt\*

2-(1-Naphthyl)-pyridine (**1**) possesses  $sp^2$  C–H bonds in both the  $\gamma$ - and  $\delta$ -positions and is therefore a suitable substrate for studying the cyclometallation selectivity with different reagents and conditions. Such selectivity studies are reported. Based on deuterium-exchange experiments it is concluded that cycloruthenation with  $\text{RuCl}_2(p\text{-cymene})$  dimer is reversible with kinetic and thermodynamic preference for  $\gamma$ -substitution. Electrophilic cycloborylation, on the other hand, shows unusual  $\delta$ -substitution. The previously published cyclopalladation and cycloauration of the substrate was studied in detail and was shown to be irreversible; they proceed under kinetic control and give  $\gamma$ - and  $\delta$ -substitution for palladium and gold, respectively.

## Introduction

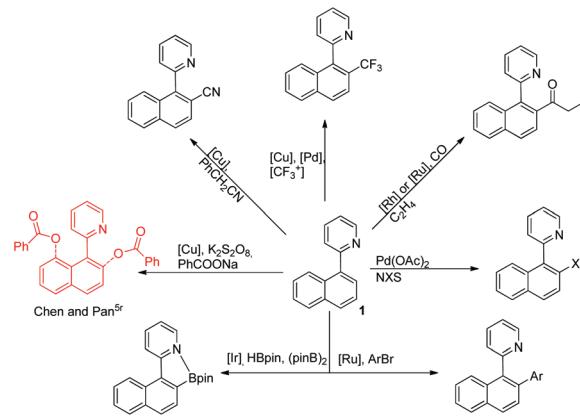
Although major advances in the area of C–H activation have been made in the last decades, selectivity remains a critical issue. Ligand-directed C–H activation has been a successful approach towards selectivity and here, typically, the position  $\gamma$  to the directing atom is ultimately functionalised,<sup>1</sup> since five-membered metallacycles are normally preferred, especially for palladium. This is also the selectivity found in the majority of *ortho*-metallation reactions of aromatic substrates, where it is dictated by the geometric accessibility. However, certain procedures allowing other selectivities are known. To override the  $\gamma$ -selectivity, the most common approach is to make the  $\gamma$ -position of the substrate hindered<sup>2</sup> or unavailable for substitution,<sup>3</sup> and only in a few cases an inherent, preferential substitution of the  $\beta$ -position has been observed.<sup>4</sup>

One of the substrates used in the screening of novel catalytic protocols, 2-(1-naphthyl)-pyridine (**1**), possesses  $sp^2$  C–H bonds in both the  $\gamma$ - and  $\delta$ -positions. This is unusual, and **1** is therefore an excellent substrate to use as a model for investigating the regioselectivity ligand-directed C–H activation with different reagents and conditions. As expected, ligand-directed substitution reactions performed with **1** almost always resulted in  $\gamma$ -substitutions,<sup>5</sup> the only exception being the work by Pan and Chen and co-workers<sup>5r</sup> in which the selectivity remains

unclear, since different substitution patterns are reported in the main article and the supporting information, *cf.* Scheme 1.

In a recent study we could show that **1** can be cyclometallated with palladium or gold precursors and while cyclopalladation occurred at the expected  $\gamma$ -position (as previously indicated in catalysis),<sup>5a</sup> the cycloauration took place with exclusive  $\delta$ -selectivity and the so formed gold complex could be functionalised with *N*-bromo succinimide, *cf.* Scheme 2.<sup>6</sup>

This unusual orthogonal regioselectivity could open up for development of catalytic reactions giving isomeric products based on a choice of the metal catalyst. Therefore, we decided to investigate the reactivity of **1** further, and here we report its reactivity with other standard cyclometallating agents, *viz.* ruthenium and boron precursors, and we also report further

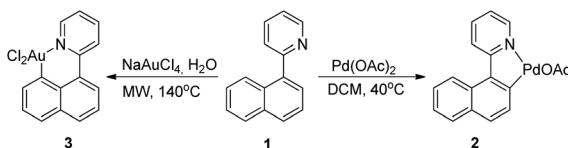


**Scheme 1** Selected examples of metal-catalysed substitutions of 2-(1-naphthyl)-pyridine.

Centre for Analysis and Synthesis, Department of Chemistry, Lund University, P. O. Box 124, S-221 00 Lund, Sweden. E-mail: [Ola.Wendt@chem.lu.se](mailto:Ola.Wendt@chem.lu.se)

† Electronic supplementary information (ESI) available: X-ray data in cif format. CCDC 1404269 and 1404270. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5dt04068j





**Scheme 2** Cyclometallation of **1** with Au and Pd precursors.

studies with all reagents to unravel kinetic and thermodynamic preferences for the different reactivities.

## Experimental section

## General

All manipulations were conducted under ambient conditions, unless noted. Solvents and chemicals were purchased from commercial suppliers and used as received. Compounds **1** and **3** were synthesised according to the literature.<sup>6a</sup> NMR spectra were acquired on a Bruker Avance 400 FT-NMR spectrometer ( $^1\text{H}$ : 400.1 MHz) or a Varian Unity INOVA 500 spectrometer ( $^1\text{H}$ : 499.76 MHz). Residual solvent peaks were used as an internal reference. Elemental analyses were performed by H. Kolbe Microanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Microwave experiments were performed on Biotage Initiator 2.5 microwave synthesiser with automatic power adjustment using “high absorption” setting.

**Synthesis of ruthenacycle ( $C^N$ )Ru(*p*-cymene)Cl (4).** Compound 4 was synthesised using a modification of the procedure for the corresponding phenylpyridine complex.<sup>7</sup> To a solution of 1 (131  $\mu$ mol, 27 mg, 1 equiv.) and KOAc (357  $\mu$ mol, 35 mg, 2.7 equiv.) in 2 ml of methanol [ $RuCl_2(p$ -cymene)]<sub>2</sub> (65  $\mu$ mol, 40 mg, 0.5 equiv.) was added. The mixture was kept in an ultra-sonication bath at room temperature for 30 min, and then heated in a screw-cap vial at 70 °C for 30 min, decanted and kept on a rotary evaporator until the volume decreased 4 times. Then, the vial was kept at -18 °C for 12 h. The solution was decanted and the precipitate was washed with cold ether and dried in vacuum. This yielded 35 mg (56%) of yellow orange-crystals, which were directly suitable for X-ray diffraction. The compound undergoes decomposition on silica, in contact with air and slowly decomposes in inert conditions and therefore failed to give a satisfactory microanalysis. The NMR spectrum shows the presence of minute amounts of unidentified aliphatic impurities.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.36 (d, *J* = 6.7 Hz, 1H), 8.34 (vt, *J* = 8.2 Hz, 2H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.71 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.47 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.33 (ddd, *J* = 7.9, 6.8, 1.1 Hz, 1H), 7.05 (ddd, *J* = 7.2, 5.7, 1.3 Hz, 1H), 5.58 (dd, *J* = 11.1, 6.0 Hz, 2H), 5.27 (d, *J* = 6.0 Hz, 1H), 5.04 (d, *J* = 4.9 Hz, 1H), 2.40 (hept, *J* = 7.0 Hz, 1H), 2.07 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 188.0, 165.3, 155.4, 138.4, 136.9, 136.5, 132.1, 131.1, 129.6, 128.4, 126.4, 123.2, 123.1, 121.9, 120.2, 101.6, 101.5, 91.6, 89.8,

84.9, 82.3, 31.0, 22.6, 22.0, 19.0. HR-MS ES<sup>+</sup> (H<sub>2</sub>O-CH<sub>3</sub>CN): 440.0951, calculated for C<sub>25</sub>H<sub>24</sub>NRu ([M - Cl]<sup>+</sup>) 440.0952.

**Deuteration of 1.** A solution of 2-(1-naphthyl)-pyridine (**1**) (141  $\mu$ mol, 29.1 mg, 1 equiv.) in dichloromethane was added to a J. Young NMR tube. The solvent was removed under reduced pressure followed by addition of  $\text{CD}_3\text{COOD}$  (2.82 mmol, 180 mg, 20 equiv.), 0.5 mL of  $\text{CD}_3\text{CN}$  and  $[\text{RuCl}_2(p\text{-cymene})]_2$  (14.1  $\mu$ mol, 8.5 mg, 0.1 equiv.). The mixture was heated and the reaction was followed by  $^1\text{H}$  NMR spectroscopy. After 1 h at 70 °C, the intensity of the multiplet at 7.70–7.45 ppm (overlapping multiplet, which includes the resonance of the  $\gamma$ -position) had decreased by 78% and the resonance at 7.90–7.80 ( $\delta$ -position) by 15% relative to the resonance at 8.92–8.81. After heating at 150 °C for 1 h, the intensities of both multiplets had decreased by 84%. Without the ruthenium compound there was no change in the spectrum under the same conditions.

Compound **1-d2** was isolated in the following way: the reaction mixture above was partitioned between 5% HCl and dichloromethane. The aqueous phase was separated and neutralised with aqueous potassium carbonate and extracted with diethyl ether. The new organic phase was dried over potassium carbonate and evaporated. This yielded 26 mg (90%) of a colourless oil. Alternatively, the deuteration can be performed with lower loading of ruthenium catalyst (0.05 equiv.) and at lower temperature (80 °C) if the heating is extended to 3 days. A higher percent of deuteration can be achieved if the isolated product is subjected to the same procedure again.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.81 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.92 (dd, *J* = 7.9, 2.0 Hz, 2H), 7.83 (td, *J* = 7.7, 1.8 Hz, 1H), 7.65–7.44 (m, 4H), 7.34 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H). ESI-MS *m/z* 208 ([M + H])<sup>+</sup>.

**Deuterium exchange in the synthesis of 3 and 3-d.** Compound 3 was synthesised from compound 1 according to a literature procedure (Method B).<sup>6a</sup> When the reaction was reproduced in D<sub>2</sub>O at 140 °C or 160 °C, the isolated product was identical to the product of the reaction in H<sub>2</sub>O. When 1-d2 was subjected to the same procedure in H<sub>2</sub>O, the intensity of the resonance at 8.67 ppm in the product NMR was decreased by 90%.

**Kinetic isotope effect of cycloauration.** Compounds **1** and **1-d2** were mixed as ether solutions. The relative ratio between **1** and **1-d2** was calculated from the relative intensities of  $[\text{M} + \text{H}]^+$  peaks (206 and 208  $m/z$  respectively) in an ESI-MS spectrum and adjusted to be equivalent.<sup>8</sup> The solvent was removed under vacuum and 14.0 mg (68  $\mu\text{mol}$ , 2.3 eq.) were placed in a microwave vial followed by water (4 ml) and sodium tetrachloroaurate dihydrate (11.8 mg, 30  $\mu\text{mol}$ , 1 eq.). The mixture was sonicated for 10 min and heated under MW irradiation at 140 °C for 1 h. The precipitated product was centrifuged, washed with water, cold acetonitrile and ether and dried to yield 3.1 mg (22%) of yellow powder. The relative content of **3** and **3-d** was measured from the intensity of the  $^1\text{H}$  NMR resonance at 8.67 ppm and found to be 0.6. The result was confirmed by the comparison of intensities of MS  $[\text{M} + \text{Na}]^+$  (495 and 496  $m/z$  respectively) peaks, relative to those of pure **3** and **3-d**.

**Synthesis of boracycle ( $C^NBF_2$  (6).** Crude compound 5 was synthesised using a modification of the procedure for the corresponding phenylpyridine compound.<sup>9</sup> To a solution of **1** (1.64 mmol, 252 mg, 1 equiv.) and i-Pr<sub>2</sub>NEt (1.64 mmol, 204 mg, 1 equiv.) in dry dichloromethane BBr<sub>3</sub> (4.92 mmol, 4.92 mL, 1 M solution in dichloromethane, 3 equiv.) was added at -10 °C. The mixture became orange and was allowed to warm to room temperature and then stirred for 24 h. The mixture was quenched with a saturated, aqueous solution of K<sub>2</sub>CO<sub>3</sub> and was stirred overnight. The phases were separated, the aqueous phase was washed twice with dichloromethane and the organic phase was washed once with water and once with brine. The organic phase was dried with MgSO<sub>4</sub> and evaporated to yield 504 mg of a brown oil. The crude compound 5 was taken up in a 1:1 mixture of MeOH/HFAQ (48%), and the mixture was stirred for 30 minutes. Water and dichloromethane were added, followed by aqueous potassium carbonate. The layers were separated and the organic phase was washed with 10% HCl to eliminate the byproduct **1**. Drying over MgSO<sub>4</sub> and filtering through a short plug of silica yielded 303 mg (73%) of product as a white powder after evaporation of the solvent. X-ray quality crystals were obtained by vapour-exchange crystallisation using dichloromethane as a solvent and pentane as a counter-solvent.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.06 (dd, *J* = 6.0, 1.7 Hz, 1H), 8.47 (d, *J* = 8.5 Hz, 1H), 8.32 (dd, *J* = 7.5, 1.0 Hz, 1H), 8.20–8.13 (m, 2H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.91 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.71 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.64–7.53 (m, 2H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  152.4, 143.2 (br.t.,  $J$  = 3.5 Hz), 141.6, 134.3, 132.8, 131.6, 130.9, 128.2, 127.7, 125.7, 125.0, 124.8, 123.3, 122.2. Elemental analysis, calcd for C<sub>15</sub>H<sub>10</sub>BF<sub>2</sub>N: C, 71.19; H, 3.98; N, 5.54; found: C, 71.27; H, 3.93; N, 5.49

**Synthesis of 2-(8-d-naphth-1-yl)-pyridine (1- $\delta$ d).** To a solution of **6** (6.0 mg) in CH<sub>3</sub>COOD 0.5 mL of DCl 20%/D<sub>2</sub>O was added. The mixture was heated to 100 °C for 15 minutes. The completion of the reaction was checked by TLC (pet. ether: EtOAc 9 : 1). The mixture was quenched with 3 M NaOH and extracted with 3 × 5 mL of DCM. The organic phase was dried over K<sub>2</sub>CO<sub>3</sub> and evaporated to result in 4.5 mg (93%) of colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.80 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.92 (d, *J* = 7.2 Hz 2H), 7.83 (td, *J* = 7.7, 1.8 Hz, 1H), 7.67–7.43 (m, 5H), 7.34 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H).

## Crystallography

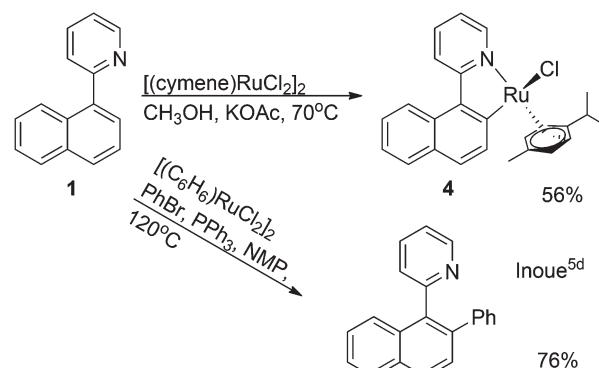
XRD-quality crystals of compounds were obtained as described above for **4** and **6**. Intensity data were collected with an Oxford Diffraction Excalibur 3 system, using  $\omega$ -scans and Mo K $\alpha$  ( $\lambda = 0.71073 \text{ \AA}$ ) radiation.<sup>10</sup> The data were extracted and integrated using CrysAlis RED.<sup>11</sup> The structures were solved by direct methods and refined by full-matrix least-squares calculations on  $F^2$  using SHELXL<sup>12</sup> and SIR-92.<sup>13</sup> Molecular graphics were generated using Diamond 3.2i.<sup>14</sup> CCDC deposition numbers are 1404269 for **4** and 1404270 for **6**.

## Results and discussion

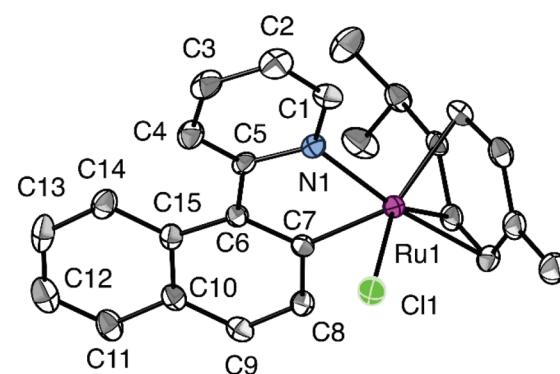
## Selectivity in cycloruthenation

Ruthenium metallacycle **4** was synthesised by cyclometallation of **1** with ruthenium(*p*-cymene) dichloride dimer as shown in Scheme 3. The  $^1\text{H}$  COSY NMR spectrum indicates the presence of three chains of neighbouring  $^1\text{H}$  resonances, containing **4**, **4** and **2** resonances each. From this we concluded that the structure of the compound contained a five-membered ring, meaning that the  $\gamma$ -position was functionalised, which is in agreement with previous results from Inoue and co-workers,<sup>5d</sup> where ruthenium-catalysed arylation takes place in the  $\gamma$ -position.

The structure was unambiguously assigned with the help of X-ray crystallography, *cf.* Fig. 1. The structure contains moderate distortions: the exocyclic C-C bond and the C-H bond in the *peri*-position are found to have a dihedral angle (C5-C6-C14-H14) of 14°, which is almost coplanar compared to the 40° observed for similar positions in auracycle 3.<sup>6a</sup> The ruthe-



**Scheme 3** Isolation of metallacycle 4 – a possible intermediate in the catalytic arylation published by Inoue<sup>5d</sup>



**Fig. 1** Molecular structure of **4** at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond and torsion angles (°) with estimated standard deviations: Ru1–N1 2.088(3), Ru1–C7 2.051(3), C7–Ru1–N1 76.6(1), C5–C6–C7–Ru1 6.2, C5–C6–C14–H14 14.3

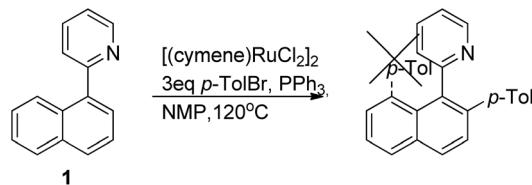
nium atom is tilted away from the naphthalene ring, creating a dihedral angle C5–C6–C7–Ru1 of  $6^\circ$ , which is less than the corresponding angle in palladacycle 2.<sup>6a</sup> The ruthenium atom has a distorted octahedral geometry with a C7–Ru1–N1 angle of  $77^\circ$ , which is substantially lower than expected for an octahedron, but in good agreement with what is found in the square-planar complexes with Au and Pd.

It should be noted that the catalytic reaction published by Inoue and co-workers proceeds under different conditions and they proposed cyclometallation to take place at a Ru(IV) metal centre. In our view, the present results suggest that cyclometallation can also proceed at a Ru(II) centre, and a compound similar to 4 could be an intermediate in the reaction published by Inoue, if oxidation takes place after the cyclometallation, contrary to the original proposal. (Scheme 3).<sup>5d</sup>

A similar ruthenacycle with a 2-(1-naphthyl)-pyridine ligand was previously synthesised by Wright and co-workers,<sup>5ab</sup> but it was made *via* transmetallation from an organomercury compound, rather than in a direct cyclometallation (Scheme 4).

In order to gain some mechanistic insight we decided to run a deuterium exchange experiment using catalytic amounts of the ruthenium salt (Scheme 5). Compound 1 was dissolved in acetonitrile-*d*3 and heated in a J. Young tube with an excess of acetic acid-*d*4 and 10 mol% of ruthenium(*p*-cymene) dichloride dimer. Following the disappearance of certain  $^1\text{H}$  resonances we were able to detect the reaction progress. The deuterium exchange is superstoichiometric indicating that the cycloruthenation process is reversible and catalytic in Ru, which is in agreement with previous mechanistic studies by Dixneuf and Jutand.<sup>17</sup> At  $70^\circ\text{C}$  the deuterium exchange occurs in both  $\gamma$ - and  $\delta$ -positions, but  $\gamma$ -deuteration is significantly faster, as shown by a *ca.* 5-fold excess of deuterium in the  $\gamma$ -position after 1 h. At elevated temperatures or prolonged reaction times the  $\delta$ -position can be fully deuterated as well. Thus, the  $\gamma$ -position is both kinetically and thermodynamically preferred.

Interestingly, the substitution ambiguity does not present itself in the arylation reaction. Repeating the reaction published by Inoue and co-workers,<sup>5d</sup> we did not observe any dis-



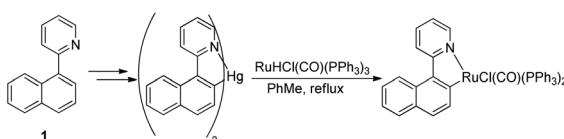
Scheme 6 Attempted bis-arylation of 1.

ubstituted product even at elevated temperatures in the presence of excess of the arylating agent. A probable explanation for this difference between deuterium exchange and the arylation process is that the substitution in the  $\gamma$ -position creates a rotational restriction for the pyridine ring, thus blocking the potential  $\delta$ -cyclometallation (Scheme 6).

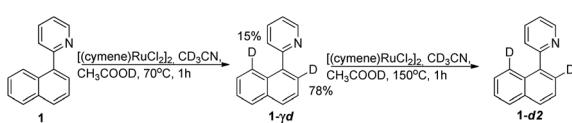
### Selectivity in cycloborylation

We were also interested in comparing the selectivity in reactions with transition metals to that of main-group cyclosubstitution reagents. As a test reaction electrophilic cycloborylation with boron tribromide was chosen, a reaction which was previously performed on similar 2-aryl-pyridine substrates by Murakami and co-workers.<sup>9</sup> The direct product of the cycloborylation decomposes on a silica gel column, but after an anion exchange with HF, a more stable difluoride could be purified and isolated in good yield (Scheme 7). The COSY spectrum and the X-ray crystallographic study show that the product contains a six-membered ring, and that, hence, the substitution proceeds with  $\delta$ -selectivity. The molecular structure is shown in Fig. 2. The cycloborylation presumably proceeds *via* a highly electrophilic boreonium cation,<sup>15</sup> and, under kinetic control, the nucleophilicity of the different positions determine the selectivity. Hence, the observed selectivity is in agreement with our previous assumption<sup>6a</sup> that the  $\delta$ -position, belonging to the less substituted ring is significantly more nucleophilic.

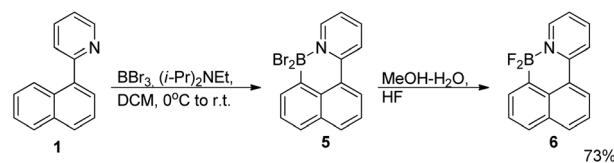
It is important to note that the geometric requirements for the tetrahedrally substituted boron atom are different compared to the square-planar  $d^8$ -metal complexes. In the six-membered ring the angles around the atom of boron are negligibly different from the expected  $109^\circ$  and the whole structure is almost flat with a dihedral angle between exocyclic C–C and C–B bonds of  $5^\circ$ . It would therefore seem that for boron, six-membered cycle is not only kinetically preferred, but also thermodynamically more stable.



Scheme 4 Synthesis of ruthenacycle by Wright.<sup>5ab</sup>

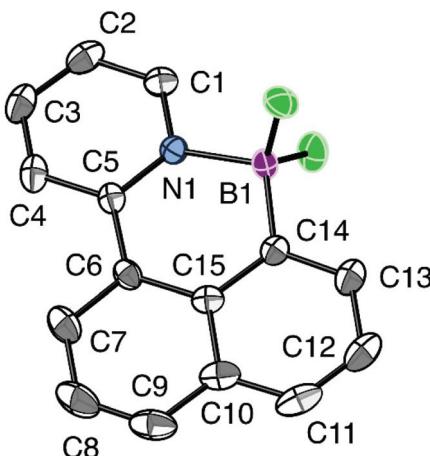


Scheme 5 Ru-catalysed deuterium exchange in 1.



Scheme 7 Synthesis of the boracycle 6.





**Fig. 2** Molecular structure of **6** at the 30% probability level. Selected bond lengths (Å) and bond and torsion angles (°) with estimated standard deviations: B1–N1 1.604(2), B1–C14 1.576(2), N1–B1–C14 110.3(1), B1–C14–C6–C5 4.7, C5–N1–B1–C14 12.3.

Interestingly, the selectivity of this direct cycloborylation is also orthogonal to the published iridium,<sup>5g</sup> rhodium<sup>5ac</sup> and palladium-catalysed<sup>5z</sup> and transition metal-free<sup>5z</sup> borylations (Scheme 8).

Acidic hydrolysis of this compound in deuterated acid afforded a  $\delta$ -monodeuterated 2-(1-naphthyl)-pyridine, isomeric to the product of the low temperature ruthenium-catalysed deuterium exchange (Scheme 9).

Unfortunately, our attempts to employ **6** in further electrophilic substitutions failed. While **6** was unreactive in electrophilic bromination and transmetallation to palladium precursors, the Cu-catalysed iodination, which was previously published<sup>16</sup> for the similar 2-(phenyl)-pyridine dibromobora-



**Scheme 10** Attempts of electrophilic substitutions of **6**.

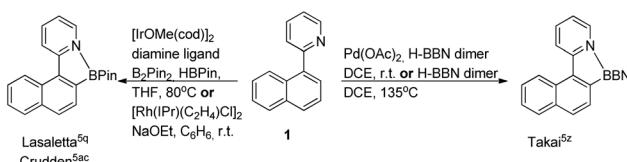
cycles unfortunately resulted in predominant formation of free **1**, cf. Scheme 10.

### Deuterium labelling studies for gold and palladium

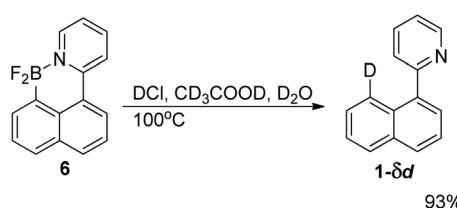
To gain more insight in the cycloauration and -palladation reactions we performed some labelling studies for these reactions. Heating **1** with catalytic amounts of palladium acetate in the presence of acetic acid-**d4** showed no H-D exchange, which indicates that the cyclopalladation process is irreversible and proceeds under kinetic control, which is in agreement with previous studies by Dixneuf and Jutand (Scheme 11).<sup>17</sup>

Unfortunately, a similar experiment could not be performed for the cycloauration procedure, since both **1** and **3** have very poor solubility in water, which is the reaction solvent in this case. Instead we performed a stoichiometric reaction in D<sub>2</sub>O. The product formed showed no sign of deuteration in the  $\gamma$ -position. Similarly, when we used a bis-deuterated starting material **1-d2** and performed the reaction in H<sub>2</sub>O, the  $\gamma$ -position remained completely deuterated. This is somewhat surprising since it is known that the cycloauration in the  $\gamma$ -position is possible at these conditions for very similar substrates.<sup>18</sup> Thus, for cycloauration the reaction proceeds irreversibly under kinetic control with the  $\delta$ -position kinetically favourable (Scheme 12).

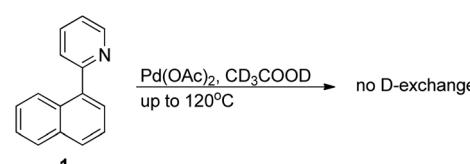
While the mechanisms of the majority of cyclometallations,<sup>19</sup> including cyclopalladation and cycloruthenation,<sup>17</sup> have been studied to some extent, little is known about the mechanism of cycloauration. In order to shine more light on this mechanism we decided to also study the kinetic isotope effect for this reaction. Hence, we decided to run a reaction between 1 equivalent of sodium tetrachloroaurate, and 1.1 equivalent of each **1** and **1-d2**. The observed ratio of the deuterated and non-deuterated metallacyclic products was 40 : 60, indicating a k.i.e. of 1.5, cf. Scheme 13. This observed value is potentially lower than the real value since the concentration of the non-deuterated starting material is dropping faster than the concentration of the non-deuterated starting material.



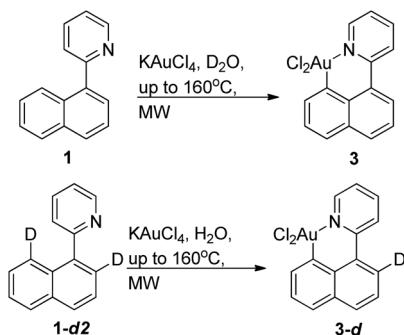
**Scheme 8** Published,<sup>5g,z,ac</sup> protocols for the synthesis of five-membered boracycles of **1**.



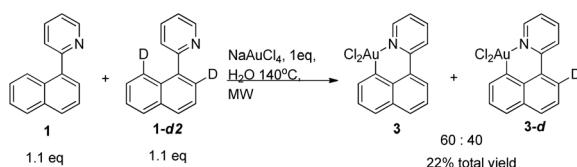
**Scheme 9** Acid-catalysed hydrolysis of **6**.



**Scheme 11** Attempted deuterium-exchange in **1** in the presence of palladium acetate.



**Scheme 12** Attempt of deuterium-exchange during the synthesis of auracycle 3.



**Scheme 13** Kinetic isotope effect of the cycloauration.

However, we believe that this effect has very little significance since the total conversion in C–H activation at this conditions is very low. Assuming an electrophilic aromatic substitution-type mechanism, we can conclude that the value is somewhat higher than what is found for standard electrophiles,<sup>20</sup> but significantly lower than the value for electrophilic mercuration<sup>21</sup> where C–H bond cleavage is proposed to be rate-determining.

## Conclusions

In summary we have studied the regioselectivity of directed aromatic substitution of 2-(1-naphthyl)-pyridine and shown that the choice of metal precursor dictates the reactivity. Thus, palladium gives an irreversible  $\gamma$ -selective cyclometallation, on one hand, whereas gold gives an irreversible  $\delta$ -selective cyclo-metallation. Hence, it is clear that both positions can be kinetically preferred. Cycloruthenation, on the other hand, is reversible and the  $\gamma$ -position is both kinetically and, as expected, thermodynamically preferred. Electrophilic cycloboration, finally, also resulted in formation of a  $\delta$ -substituted product. The probable origin of the observed regioselectivity for gold and boron is the higher nucleophilicity of the unsubstituted naphthalene ring, which leads to its higher reactivity towards the electrophilic metal centres. Simultaneously, the cyclopalladation and cycloruthenation proceed *via* a CMD-type mechanism,<sup>22</sup> which poses less restrictions on the nucleophilicity of the reactive carbon atom. Accordingly, the relative thermodynamic stability of five-membered rings is relevant for the case of ruthenium, since cycloruthenation proceeds under equilibrium conditions. These results show the possibility of

controlling the selectivity in ligand-directed C–H activation reactions forming a variety of substituted products in a selective manner. Accordingly, 2-(1-naphthyl)-pyridine can be used as a model compound to study the properties and preferences of different new catalytic systems.

## Acknowledgements

Financial support from the Swedish Research Council, the Knut and Alice Wallenberg Foundation and the Royal Physiographic Society in Lund is gratefully acknowledged.

## References

- For example see: L. X. Campeau, D. J. Schipper and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 3266.
- B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391.
- For example see: B.-J. Li, S.-L. Tian, Z. Fang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1115.
- A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129.
- (a) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Tetrahedron*, 2006, **62**, 11483; (b) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama and T. Tanabe, *J. Am. Chem. Soc.*, 2009, **131**, 11310; (c) N. Chatani, Y. Ie, F. Kakiuchi and S. Murai, *J. Org. Chem.*, 1997, **62**, 2604; (d) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano and Y. Inoue, *Org. Lett.*, 2001, **3**, 2579; (e) X. Jia, D. Yang, S. Zhang and J. Cheng, *Org. Lett.*, 2009, **11**, 4716; (f) G. Zhang, G. Lv, C. Pan, J. Cheng and F. Chen, *Synlett*, 2011, 2991; (g) S. Oi, S. Fukita and Y. Inoue, *Chem. Commun.*, 1998, **22**, 2439; (h) C. Xu and Q. Shen, *Org. Lett.*, 2014, **16**, 2046; (i) P. Patel and S. Chang, *Org. Lett.*, 2014, **16**, 3328; (j) Q. Wu, C. Du, Y. Huang, X. Liu, Z. Long, F. Song and J. You, *Chem. Sci.*, 2015, **6**, 288; (k) C.-Z. Luo, P. Gandeepan, J. Jayakumar, K. Parthasarathy, Y.-W. Chang and C.-H. Cheng, *Chem. – Eur. J.*, 2013, **19**, 14181; (l) M. Chaitanya, D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2013, **15**, 4960; (m) J. Qi, L. Huang, Z. Wang and H. Jiang, *Org. Biomol. Chem.*, 2013, **11**, 8009; (n) K. Cheng, B. Yao, J. Zhao and Y. Zhang, *Org. Lett.*, 2008, **10**, 5309; (o) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648; (p) W.-N. Sit, C.-W. Chan and W.-Y. Yu, *Molecules*, 2013, **18**, 4403; (q) A. Ros, B. Estepa, R. Lopez-Rodriguez, E. Alvarez, R. Fernandez and J. M. Lassaletta, *Angew. Chem., Int. Ed.*, 2011, **50**, 11724; (r) L. Li, P. Yu, J. Cheng, F. Chen and C. Pan, *Chem. Lett.*, 2012, **41**, 600; (s) J. Jin, Q. Wen, P. Lu and Y. Wang, *Chem. Commun.*, 2012, **48**, 9933; (t) R.-J. Tang, C.-P. Luo, L. Yang and C.-J. Li, *Adv. Synth. Catal.*, 2013, **355**, 869; (u) M. Iwasaki, M. Iyanaga, Y. Tsuchiya, Y. Nishimura, W. Li, Z. Li and Y. Nishihara, *Chem. – Eur. J.*, 2014, **20**, 2459; (v) Q. Xiao, X. Meng, M. Kanai and Y. Kuninobu, *Angew. Chem., Int.*



*Ed.*, 2014, **53**, 3168; (w) J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272; (x) J. A. Fernandez-Salas, S. Manzini, L. Piola, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.*, 2014, **50**, 6782; (y) S. A. Denisov, Y. Cudre, P. Verwilst, G. Jonusauskas, M. Marin-Suarez, J. F. Fernandez-Sanchez, E. Baranoff and N. D. McClenaghan, *Inorg. Chem.*, 2014, **53**, 2677; (z) Y. Kuninobu, T. Iwanaga, T. Omura and K. Takai, *Angew. Chem., Int. Ed.*, 2013, **52**, 4431; (aa) Z.-H. Guan, Z.-H. Ren, Y.-M. Liang, S. M. Spinella, S. Yu and X. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 729; (ab) A. M. Clark, C. E. F. Rickard, W. R. Roper and L. J. Wright, *J. Organomet. Chem.*, 2000, **598**, 262; (ac) E. C. Keske, B. D. Moore, O. V. Zenkina, R. Wang, G. Schatte and C. M. Cradden, *Chem. Commun.*, 2014, **50**, 9883.

6 (a) M. Kondrashov, S. Raman and O. F. Wendt, *Chem. Commun.*, 2015, **51**, 911; (b) For related halofunctionalisations of organometallic intermediates, see for example: T. Wang, S. Shi, M. Rudolph and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2014, **356**, 2337.

7 B. Li, T. Roisnel, C. Darcel and P. H. Dixneuf, *Dalton Trans.*, 2012, **41**, 10934.

8 The compound **1-d**<sub>2</sub> contains approximately 7% of mono-deuterated analogue. The residual <sup>1</sup>H is equivalently distributed between two positions. Overall this contamination has a negligible effect on the calculated k.i.e. value.

9 N. Ishida, T. Moriya, T. Goya and M. Murakami, *J. Org. Chem.*, 2010, **75**, 8709.

10 *Crysaliis CCD*, Oxford Diffraction Ltd., Abingdon, Oxfordshire, UK, 2005.

11 H. Putz and K. Brandenburg, *Crystal Impact – GbR*, Kreuzherrenstr. 102, 53227 Bonn, Germany.

12 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112.

13 A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla and M. Polidori, *J. Appl. Crystallogr.*, 1994, **27**, 435.

14 *Crysaliis RED*, Oxford Diffraction Ltd, Abingdon, Oxfordshire, UK, 2005.

15 A borenium cation was the proposed intermediate in the original publication by Murakami,<sup>9</sup> but also directly observed in a similar non-directed borylation in the following article: A. Del Gross, P. J. Singleton, C. A. Muryn and M. J. Ingleson, *Angew. Chem., Int. Ed.*, 2011, **50**, 2102.

16 L. Niu, H. Yang, D. Yang and H. Fu, *Adv. Synth. Catal.*, 2012, **354**, 2211.

17 I. Fabre, N. von Wolff, G. Le Duc, E. F. Flegeau, C. Bruneau, P. H. Dixneuf and A. Jutand, *Chem. – Eur. J.*, 2013, **19**, 7595.

18 A. P. Shaw, M. Tilset, R. H. Heyn and S. J. Jakobsen, *Coord. Chem.*, 2011, **64**, 38.

19 For example see reviews: (a) Y. Boutadla, D. L. Davies, S. A. Macgregor and A. I. Poblador-Bahamonde, *Dalton Trans.*, 2009, 5820; (b) D. Balcells, E. Clot and O. Eisenstein, *Chem. Rev.*, 2010, **110**, 749.

20 E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito California, 2006, p. 608, ISBN 978-1-891389-31-3.

21 A. J. Kresge and J. F. Brennan, *Proc. Chem. Soc.*, 1963, 215.

22 For the role of carboxylate ligands enabling the CMD mechanism of cyclometallation see, for example, L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315.

