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Metal controlled regioselectivity in the cyclometallation of 2-(1-naphthyl)-pyridine†

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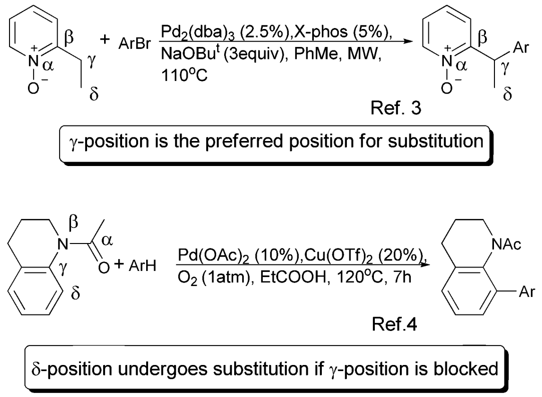
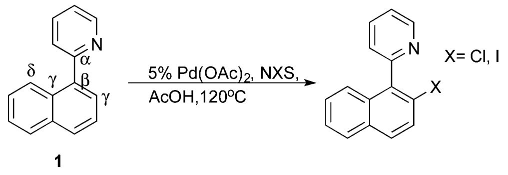
Cyclometallation of 2-(1-naphthyl)-pyridine is described. While cyclopalladation results in a five-membered metallacycle, cycloauration displays a completely orthogonal regioselectivity, resulting in the six-membered ring analogue. Bromination of the gold metallacycle results in the new C–H functionalisation product 2-(8-bromonaphth-1-yl)-pyridine.

The activation of unreactive C–H bonds remains a key challenge in the field of synthetic organic chemistry.[1] Discrimination between chemically similar C–H bonds is a particularly difficult task and only a few approaches have been successfully applied.[2] One successful way to differentiate bonds is directed C–H activation and then, typically, the position γ to the donor atom undergoes functionalisation,[3] but also the δ-position can be involved if the γ-position is blocked (as exemplified by an aliphatic system in Scheme 1).[4] The rationale behind this is that directed reactions normally proceed *via* the corresponding chelate, and in five-membered rings the sum of ideal bond angles is closer to the ideal angle sum of a polygon than it is in the corresponding four- or six-membered analogues. Thus, five-membered metallacycles are more easily formed. This is particularly true in the case of palladium, which is the metal most widely used in C–H activation reactions. However, there are only a few studies paying attention to the ring size selectivity of functionalisation in these types of reactions and it is still very difficult to control this selectivity.[5]

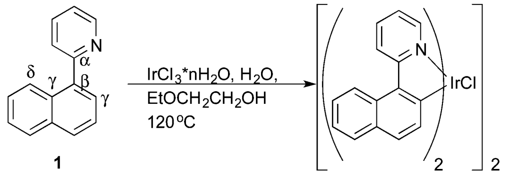


Scheme 1 Regioselectivity of the functionalisation.

2-(1-Naphthyl)-pyridine (**1**) is an interesting substrate for cyclometallation since it possesses two different, aromatic C–H bonds in close proximity to the directing nitrogen atom and while one of the substitution patterns can result in a formation of a five-membered metallacycle, the other one would lead to a six-membered metallacycle. Several metal-catalyzed directed substitutions of **1** were published[6] and with rare exceptions[6q] the γ-position is activated (an example of Pd-catalyzed halogenation published by Sanford[6a] is presented in Scheme 2); however, iridium compounds[7] remain the only examples of isolated 2-(1-naphthyl)-pyridine metallacycles (Scheme 3). In many cases the regioselectivity is not commented



Scheme 2 An example of C–H activation of 2-(1-naphthyl)-pyridine.



Scheme 3 Cycloiridation of 2-(1-naphthyl)-pyridine.

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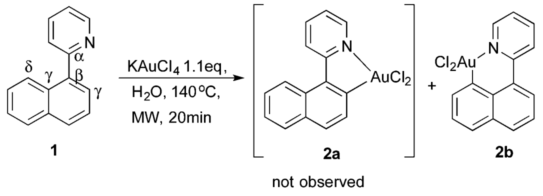


Scheme 4 Cycloauration of 2-(1-naphthyl)-pyridine.

on, and there is only one example of a gold-mediated reaction, which reports activation in the γ-position.[6y]

In the course of our studies on the catalytic and luminescent properties of Au(III) complexes we performed the reaction between **1** and potassium tetrachloroaurate.

To our surprise, the substitution occurred at the non-functionalised aromatic fragment resulting in the formation of the six-membered metallacycle **2b** (Scheme 4). The gCOSY NMR spectrum showed three chains of J_3-coupled protons, with 4, 3 and 3 in each respectively, indicating that the γ-position of the substituted naphthalene ring remained untouched and that the gold atom is bound to the other aromatic ring. The structure was unambiguously confirmed using X-ray crystallography. The crystal structure reveals an almost un-distorted square-planar arrangement around the Au atom, showing that the six-membered ring does not induce any strain in the primary coordination sphere. However, the steric requirements of the six-membered ring lead to a highly puckered molecule with an almost 40° dihedral angle between the exocyclic C–C and the C–Au bonds (Au1–C15–C7–C6) of the naphthalene system. As expected, the Au–Cl bond *trans* to carbon is substantially longer (*ca.* 0.12 Å) than *trans* to nitrogen. The molecular structure together with selected bond angles and distance are given in Fig. 1.

The probable explanation for this unusual regioselectivity is that the δ-position is located within the unsubstituted aromatic ring, which is more electron-rich than the other aromatic ring, bearing a weakly electron-withdrawing pyridine substituent bound to a Lewis-acidic metal atom. A DFT calculation of the possible N–$AuCl_3$ non-metalated intermediate was performed

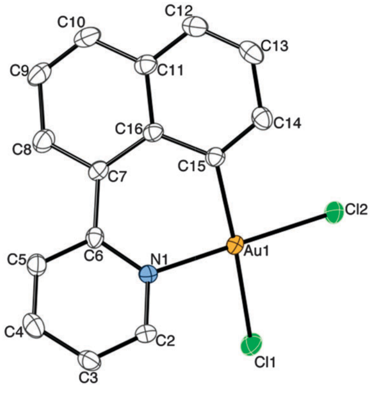


Fig. 1 Molecular structure of **2b** at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (°) with estimated standard deviations: C15–Au1 2.024(3); N1–Au1 2.024(3); Cl1–Au1 2.3963(9); Cl2–Au1 2.2771(9); Cl2–Au1–Cl1 89.76; Cl1–Au1–N1 90.89; N1–Au1–C15 88.68; C15–Au–Cl2 90.95; Au1–C15–C7–C6 39.68.

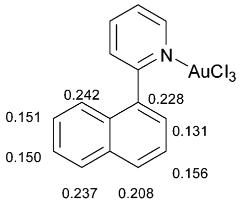
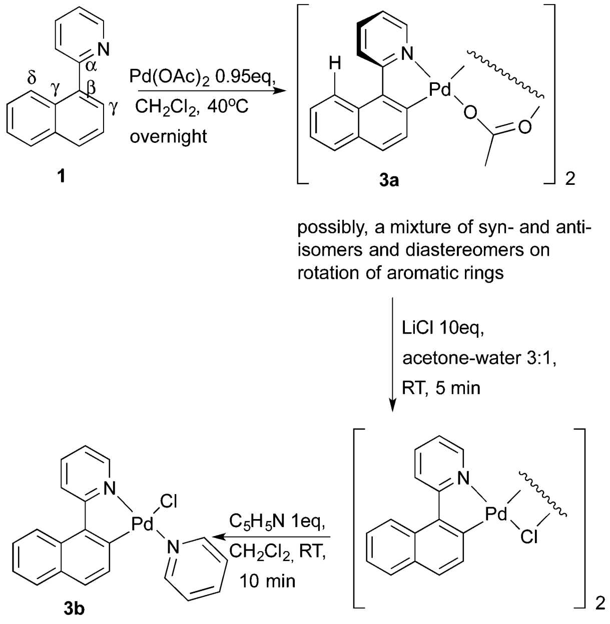


Fig. 2 Highest coefficients of input into HOMO by atomic p_x orbitals.

(see ESI† for full details). Indeed, the calculations show that the modulus of the HOMO coefficient at the δ-position is 0.242 for the p_x orbital, and thus significantly higher than the value for γ-position, which is 0.131 (Fig. 2).

In light of this unexpected regioselectivity compared to previous results (*cf.* Schemes 2 and 3), we decided to re-investigate the regioselectivity for palladium which is the most common metal used for catalytic C–H activation. Therefore, we performed a cyclopalladation of the substrate using $Pd(OAc)_2$ as a suitable reagent. Although the cyclometallation is straightforward, the characterisation and purification of the product appeared to be troublesome, probably due to the formation of a diastereomeric mixture of acetate-bridged dimers. Simple ligand exchange with chloride and pyridine afforded a monomeric compound, **3b** (Scheme 5) which was characterised by means of ^{1}H, gCOSY and gTOCSY NMR spectroscopy. In this case the gCOSY spectrum showed a pattern of 4, 2 and 4 ^{1}H nuclei in the 2-(1-naphthyl)-pyridine system pointing to formation of the expected five-membered ring. Again, the structure was unambiguously confirmed using X-ray crystallography and the molecular structure is given in Fig. 3. For crystal data and collection and refinement details for compounds **2b** and **3b**, see Table S1 in the ESI.† Evidently, the cyclopalladation results in the formation of a five-membered ring in agreement with the results of the directed halogenation



Scheme 5 Cyclopalladation of 2-(1-naphthyl)-pyridine.

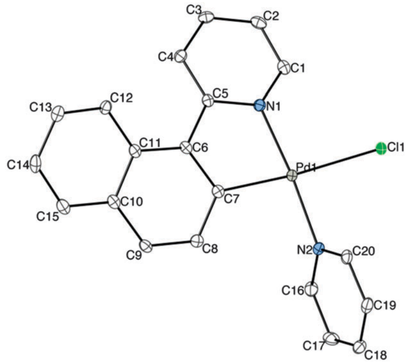
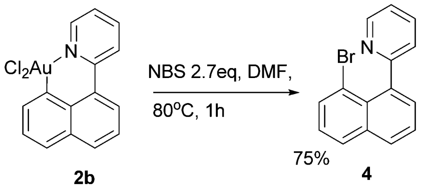


Fig. 3 Molecular structure of **3b** at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (°) with estimated standard deviations: Pd1–C7 1.992(3); Pd1–N1 2.017(2); Pd1–N2 2.037(2); Pd1–Cl1 2.4204(7); Cl1–Pd1–N2 88.95; N2–Pd1–C7 94.53; N1–Pd1–C7 81.03; N1–Pd1–Cl1 95.57; C5–C6–C7–Pd1 16.29.



2b **4**

Scheme 6 Bromination of **2b**.

by Sanford and coworkers.[6a] The palladium atom displays a distorted square planar coordination geometry where the ligand bite angle forces the C–Pd–N angle to be 81°. On the other hand the five-membered ring makes the ligand almost co-planar with the coordination plane. The angle between the coordination plane and the plane through the atoms in metallacycle (except the metal) is 10.8° in **3b** compared to 44.1° in the substantially more puckered **2b**.

The completely orthogonal metal-dictated regioselectivity of the cyclometallation opens up for development of catalytic reactions giving isomeric products based on a choice of the metal catalyst. In the case of palladium further functionalisation of the cyclometallated complex is clearly possible and we sought to find further transformations of **2b** leading to demetallation and functional group installment in the δ-position. Overall, compound **2b** was found to be kinetically inert and poorly soluble in most of the common organic solvents, but, gratifyingly, it was successfully brominated by *N*-bromosuccinimide in DMF forming 2-(8-bromonaphth-1-yl)-pyridine (**4**), which is isomeric to the halogenated products obtained through palladium catalysis (Scheme 6). Unfortunately, our attempts to devise a catalytic protocol based on this reaction failed due to the competing non-catalysed bromination of the naphthalene ring by NBS.

In conclusion we have found that cyclometalation of the 2-(1-naphthyl)-pyridine with gold and palladium precursors proceeds with completely different regioselectivities. The gold metallacycle can be brominated leading to a product which is isomeric to the product of the similar palladium-catalysed functionalisation. 2-(1-Naphthyl)-pyridine can be used as a model compound for studying steric and electronic requirements of different metallating agents and we are currently pursuing investigations to understand and further exploit these metal-dictated reactivity patterns in catalysis.

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