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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 metalacycle 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. Discrimination between chemically similar C–H bonds is a particularly difficult task and only a few approaches have been successfully applied. One successful way to differentiate bonds is directed C–H activation and then, typically, the position γ to the donor atom undergoes functionalisation, but also the δ-position can be involved if the γ-position is blocked (as exemplified by an aliphatic system in Scheme 1). 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 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.

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 and with rare exceptions the γ-position is activated (an example of Pd-catalyzed halogenation published by Sanford is presented in Scheme 2); however, iridium compounds remain the only examples of isolated 2-(1-naphthyl)-pyridine metallacycles (Scheme 3). In many cases the regioselectivity is not commented on, and there is only one example of a gold-mediated reaction, which reports activation in the γ-position.

In the course of our studies on the catalytic and luminescent properties of Au(III) complexes we performed the reaction between 1 and potassium tetrachloraurate. To our surprise, the substitution occurred at the non-
Figure 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–Au1–Cl2 90.95; Au1–C15–C7–C6 39.68.

Figure 2. Highest coefficients of input into HOMO by atomic px orbitals.

Functionalised aromatic fragment resulting in the formation of the six-membered metalacycle 2b (Scheme 4). The gCOSY NMR spectrum showed three chains of J3-coupled protons, with 4, 3 and 3 in each respectively, indicating that the β-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 Figure 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-AuCl3 non-metallated intermediate was performed (see SI for full details). Indeed, the calculations show that the modulus of the HOMO coefficient at the δ-position is 0.242 for the px orbital, and thus significantly higher than the value for γ-position, which is 0.131 (Figure 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 1H, gCOSY and gTOCSY NMR spectroscopy. In this case the gCOSY spectrum showed a pattern of 4, 2 and 4 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 Figure 3. For crystal data and collection and refinement details for compounds 2b and 3b, see Table S1 in the ESL. Evidently, the cyclopalladation results in the formation of a five-membered

Figure 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.
ring in agreement with the results of the directed halogenation by Sanford and coworkers.\(^6\) 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 \(2b\) compared to 44.1° in the substantially more puckered \(2b\).

The completely orthogonal metal-directed 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 \(\delta\)-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 \(N\)-bromo-succinimide in DMF forming 2-(8-bromonaphthyl)-pyridine (4), which is isomeric to the halogen products obtained through palladium catalysis (Scheme 6). Unfortunately, our attempts to devise a catalytic bromination protocol based on this reaction failed due to the competing non-catalysed bromination of the naphthalene ring by NBS.

**Conclusions**

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 metatllating agents and we are currently pursuing investigations to understand and further exploit these metal dictated reactivity patterns in catalysis.

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**Notes and references**

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