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EDGE ARTICLE

"Push effect" of sulfur coordination: promoting the breaking of C(sp^2)–I bond by pincer thioimido-Pd(II) complexes†

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Aryl–iodo bond cleavage by pincer thioimido-Pd(II) complex was demonstrated by *in situ* IR and X-ray analysis. Stoichiometric reactions indicated the crucial role of substrate sulfur coordination to the Pd centre. Possible mechanisms were proposed and catalytic reaction was developed.

Exploration of the reaction of Pd(II) species with electrophiles such as organic halides and application of such species in a catalytic version is an important innovation in Pd chemistry. It could provide opportunities for enabling a Pd(II)–Pd(IV) catalytic cycle. Compared with the well-established Pd(0)–Pd(II) chemistry,[1] the reaction of Pd(II) species with electrophiles is thriving[2–10] and still challenging. C–X bonds were reported to be able to be activated by Pd(II) species under certain conditions.[11–15] Catalytic reactions in which Pd(IV) intermediacy were established or speculated to be involved mainly function in two modes: utilization of strong oxidants[16–20] or interaction of electrophiles with C–Pd(II) species in which the carbon is a very strong electron donor.[21–25] Besides, the existence of Pd(IV) species in pincer-Pd catalytic systems is often proposed because tridentate pincer ligands could provide the metal centre a robust chelating environment with tunable electronic factors.[26–28] For example, Milstein *et al.* pioneered in tentatively excluding a classical Pd(0) cycle in a PCP-type Pd(II) complex catalyzed Heck reactions.[29] Also, our group recently identified a pincer thioimido-Pd(II) ate complex as the active catalyst to react with aryl iodides in Negishi coupling.[30,31]

Nature employs sulfur ligands to tune the electronic properties of metal centres in metalloproteins. For example, in heme-containing oxygenase P450, proximal cysteine ligand serves as a strong electron donor to promote the formation of high-valent iron-oxo species.[32,33] Theoretically, readily available thiourea or thioamide type ligands with one H on the N of the backbone could play an analogous role as thiocarbonyl or mercapto type donors (Scheme 1), and the sulfur coordination could potentially facilitate the formation of high-valent metal intermediates under appropriate conditions. Herein we report our recent work on sulfur coordination promoted breaking of aryl–iodo bonds by pincer thiomido Pd(II) species under mild conditions.

Pd(II) species such as $Pd(OAc)_2$, $PdCl_2(MeCN)_2$ and $PdCl_2(PPh_3)_2$ *etc.* are prone to be reduced to Pd(0) species by organometallic reagents. Contrarily, tetrameric pincer thioimido Pd(II) complex **1** (Scheme 2) exhibited good stability towards reductants such as organozinc reagents since it was prepared from the reaction of alkylzinc reagents with a pincer thioamide Pd(II) precursor.[30,31] Thus, **1** might serve as a good model for the investigation of the reaction of Pd(II) species with electrophiles. However, no reaction occurred when **1** was treated with ethyl 2-iodobenzoate and 4-iodoanisole from 0 to 80 °C.

Inspired by the "push effect" of the axial thiolate ligand in P450, we designed a substrate incorporating a sulfur containing ligand and an aryl–iodo group in one molecule to probe the reactivity of Pd(II) center towards electrophiles in our pincer thioimido system (**2a** in Scheme 2). We envisioned that the donation of the sulfur ligand would possibly push the Pd(II) centre to react with the aryl–iodo bond.

Stoichiometric reaction of **1** and **2a** was monitored by *in situ* IR. Upon addition of **2a** into THF solution of **1** at room temperature, disappearance of **1** was observed within 30 s (red line in Fig. 1) with concomitant formation of a new species (black line in Fig. 1). No further transformation was detected within 1 h under the reaction conditions. The process was confirmed by ^1H NMR in CD_2Cl_2 to be dissociation of **1** by the thiourea part of **2a** with the aryl–iodo part remaining intact (Scheme 2). The dissociation process was further corroborated by the reaction of **1** with 1-butyl-3-phenylthiourea **2b** and 1,2-diphenylthiourea **2c**,

Scheme 1 Thiourea or thioamide as tunable mercapto ligands.

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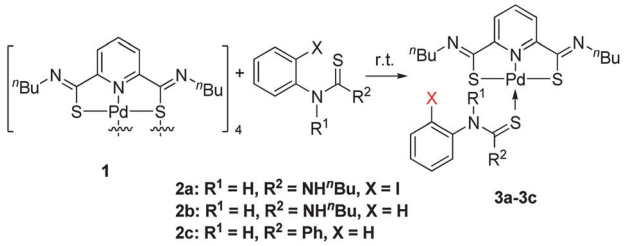


Scheme 2 Dissociation of tetramer **1** by thiourea ligands **2a–2c**.

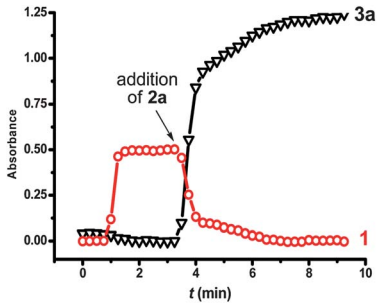
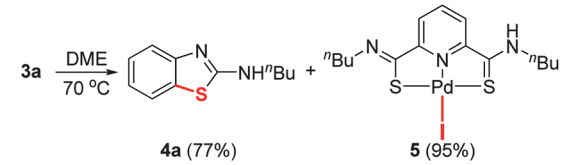


Fig. 1 Kinetic profile of the reaction of **1** and **2a**.

and the coordination mode was clarified by a single-crystal structure of complex **3c** prepared from **1** and **2c** (Fig. 2).

Upon heating at 70 °C for 2 h without any additive, **3a** was transformed into thiazole **4a** and a precipitate (Scheme 3), which was crystallized and clarified by X-ray analysis to be Pd(II) complex **5** (Fig. 3). Noticeably, the reaction could also be finished at room temperature after three days. Overall, the aryl–iodo bond was successfully cleaved with concomitant formation of a C–S bond and the iodo group was transferred to the Pd(II) center.

Coordination of the sulfur ligand facilitated the process (Scheme 3) as expected, yet whether the thiourea form or the mercapto form (Scheme 1) played the key role was not explicit. Thus, *N*-(2-iodophenyl)ethanethioamide **2d** and *N*-(2-iodophenyl)-*N*-methyl-ethanethioamide **2e** were prepared as controls to **2a**. In stoichiometric reaction of **2d** with **1**, the dissociation process at room temperature was similar to that of **2a**. Upon heating at 70 °C for 3 h, 80% of thioazole **4d** and 87% of complex **5** were obtained as expected. However, when **1** was treated with



Scheme 3 Transformation of **3a** into **4a** and complex **5**.

1 equiv. of **2e**, a dissociation process was observed, but no further transformation was detected after heating at 70 °C for 3 h (Scheme 4). The results indicated that H on the N of the backbone was crucial for the C–I bond breaking and that the mercapto form facilitated the reaction of Pd(II) with C–I bond.

It is known that transformation from **2a** to **4a** could proceed in the presence of both Cu-catalysts and bases.[34,35] Base alone could also promote the reaction under heating conditions through an S_NAr mechanism,[36,37] or by photoinduced cyclization through an S_{RN1} mechanism.[38,39]

However, the transformation from **3a** to **4a** (Scheme 3) could proceed without any additive at room temperature (heating only facilitating the process). The Pd(II)-centre could act as a Lewis acid, but not as a base. This ruled out the S_NAr and S_{RN1} pathways mentioned above. Considering that complex **1** was unlikely to be reduced to Pd(0) under the reaction conditions, three possible pathways could be proposed for the transformation: (1) Pd(II)–Pd(IV) cycle; (2) Pd(II)–Pd(III) cycle; and (3) σ-bond metathesis. Scheme 5 lists the possible key intermediates of these pathways.

3a could tautomerize to mercapto form **3a–1** (Scheme 5). Three thiolates as strong electron donating ligands would render a more electron-rich Pd(II) centre, which could possibly undergo oxidative addition with C–I bond to afford Pd(IV) intermediate **3a–II**. Successive reductive elimination would generate **4a** and the Pd(II) state.

Ritter *et al.* recently reported direct observation of Pd(III) species from reaction of Pd(II) with oxidant $PhICl_2$ or $PhI(OAc)_2$.[40,41] Analogously, the electron-rich Pd(II) centre of **3a–I** could transfer an electron to aryl iodide in an intramolecular manner, and result in a Pd(III) intermediate and an aromatic anion radical species **3a–III**.[42] Nucleophilic replacement of iodo group by the axial sulfur would lead to the formation **4a**, and the rebound of the iodide would yield complex **5**.[42,43]

Attempts to detect intermediates failed possibly due to the high reactivity of any intermediate that might be involved,[44] and

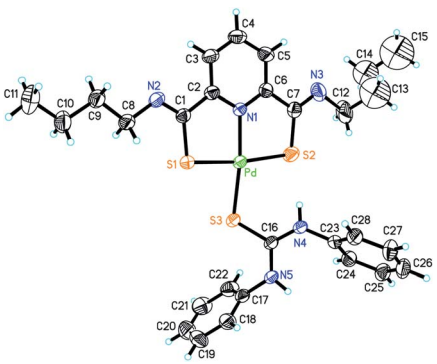


Fig. 2 The single-crystal structure of complex **3c**.

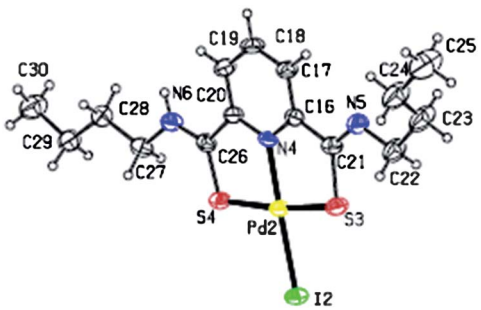
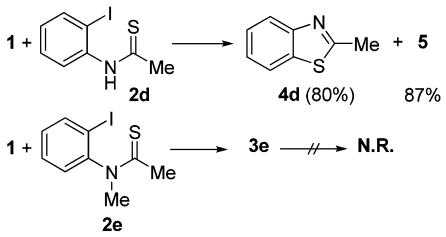
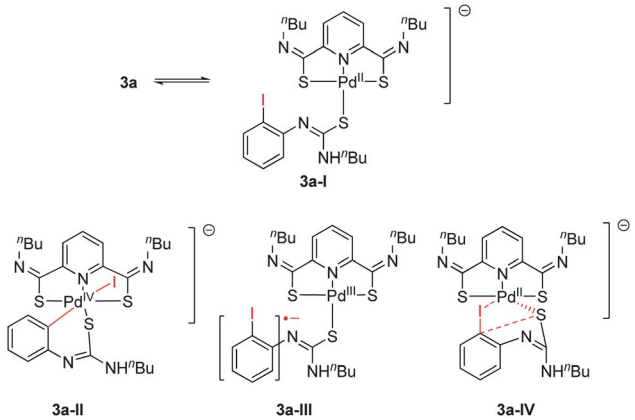


Fig. 3 The single-crystal structure of complex **5**.



Scheme 4 Stoichiometric reactions of **1** with **2d** and **2e**, respectively.

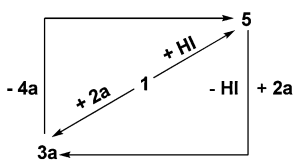


Scheme 5 Possible intermediates in the transformation of **3a** to **4a** and **5**.

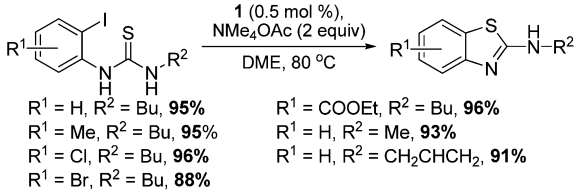
as yet we do not have clear evidence to differentiate between the three reaction pathways. However, it is important to point out that all of the three possible pathways involve breaking of a C(sp^2)–I bond by a Pd(II)-species under very mild conditions.

The reaction of **1** and 4 equiv. of **2a** in DME without any additive was also completed after heating at 80 °C for 8 h. The catalytic process indicated a transformation from **5** to **3a** under the reaction conditions. This hypothesis was supported by the complete conversion of **2a** to **4a** by 1 equiv. of **5** prepared *in situ* from tetramer **1** with HI (aq) in THF (Scheme 6). The slowness of the reaction was possibly due to the precipitate of complex **5** as an off-cycle species. Thus, base should be good for enhancing the efficiency of the catalytic reaction by trapping the HI generated in the reaction system and accelerating the transformation from **5** to **3a**.

Therefore, the catalytic reaction was tried with 0.5 mmol of **2a**,[34,35,45] 0.5 mol% of **1** and 2 equiv. of NMe_4OAc in DME at 80 °C. The reaction proceeded smoothly and furnished 95% of **4a** after 10 h (Scheme 7). Since both the reactant thiourea and product thiazole are good ligands for Pd, the catalytic efficiency was satisfactory, and could be reasonably explained since substrate coordination was necessary to initiate rather than inhibit the reaction. The substrate scope of the reaction was



Scheme 6 The reversibility between complex **3a** and **5**.



Scheme 7 Pincer-Pd(II) complex **1** catalyzed formation of thiazoles.

explored by variation of either the R^1 or R^2 group, and the reaction was demonstrated to be compatible with both electron donating and withdrawing groups on the aromatic part, and even aryl bromo group was well tolerated. The yields were from good to excellent (Scheme 7).

Conclusions

We have achieved sulfur coordination promoted cleavage of aryl–iodo bonds by a Pd(II) centre under mild conditions. Stoichiometric reaction under neutral conditions without additives indicated direct interaction of the aryl–iodo bond with the Pd(II) center. The reaction was also successfully applied in a catalytic version. Further investigation to elucidate the mechanism is ongoing in our laboratory and will be reported in due course.

Acknowledgements

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44 If the reaction goes through a Pd(II)–Pd(IV) pathway, oxidative addition is possibly the rate-limiting step, so no accumulation of Pd(IV) species resulting from oxidative addition should be expected. If the reaction undergoes the Pd(II)–Pd(III) pathway, due to the coordination, the single-eletron transfer is within the molecule, and radical trap experiments might not work: when TEMPO was added as an additive the reaction still occurred smoothly. If the reaction goes through a σ-bond metathesis course, the concerted process is unlikely to be detected by a physical method.
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