Platinum-catalysed aerobic 1,2-aminooxygenation of alkenes†‡

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Platinum(π) salts in combination with copper salts and molecular oxygen catalyse an unprecedented intramolecular transfer of heteroatoms to alkenes to yield aminooxygenation products under sustainable conditions.

1,2-Difunctionalization of alkenes represents a powerful synthetic tool in the synthesis of organic building blocks. In particular, Sharpless devised seminal catalytic transformations based on osmium(VIII) catalysts for dihydroxylation¹ and aminohydroxylation.²

Recent efforts in the area of high oxidation state catalysis with noble metals have culminated in the development of palladiumcatalysed transformations that include diacetoxylation,³ aminoalkoxylation⁴ and diamination.⁵

These reactions share a common feature regarding the use of the strong oxidant iodosobenzene diacetate. While this reagent enables a rapid and reliable oxidation, it produces iodobenzene as an undesired by-product. We recently reported the first catalysis protocols for intramolecular diamination of unfunctionalised alkenes, which employed ureas and sulfamides as the respective nitrogen sources.^{5,6} This initial work employed high oxidation palladium and nickel catalyst states derived from iodosobenzene diacetate as a stoichiometric oxidant. In an attempt to devise alternative reoxidation conditions, we recently reported protocols with copper(II) halides as suitable oxidants for the case of palladium-catalysed 1,2-diamination reactions (Scheme 1).⁷

Still, these protocols call for the use of 2–3 equivalents of copper salts. Attempts to employ aerobic reaction conditions could not meet with success due to the requirement of basic reaction conditions in the initial step of aminopalladation.⁸

Here, we describe a new protocol for oxidative 1,2difunctionalisation of alkenes employing platinum catalysis⁹ under aerobic conditions. As aminoplatination represents a well-established process under neutral or even acidic conditions,¹⁰ we considered the application of platinum salts an attractive possibility for oxidation under base-free conditions. As outlined in Scheme 2, a simple combination of platinum

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dichloride and copper dibromide already promotes the oxidation of alkenyl urea **1a**. However, under these relatively harsh conditions the yield remains low due to significant amounts of decomposed starting material. Reducing the copper dibromide to a catalytic amount of 30 mol% leads to a significant increase in yield when benzoquinone is employed as terminal oxidant (Scheme 2, entry 2).

To our delight, experiments under aerobic conditions quickly led to the realization of suitable reaction conditions. A combination of 10 mol% PtCl₂, 30 mol% CuBr₂ and atmospheric dioxygen in dmso as the solvent provides an efficient catalyst system for the oxidation of **1a** (entry 5).

Apparently, copper bromide concentration is of key importance, as attempts to lower its amount further to 0.15 equivalents resulted in a significantly reduced rate (entry 6). Other copper salts, such as copper(II) chloride and acetate, had less efficient results.

Less than 10% conversion, with no formation of 2a, was obtained in the absence of the platinum catalyst. This observation confirms that the oxidation from 1a to 2a is indeed platinum-catalysed.

The outcome of this reaction is, however, unexpected, as the obtained product is not the expected cyclic urea, but rather its isomeric isourea. Obviously, under the given reaction conditions, the carbonyl oxygen displays a more pronounced nucleophilicity than the tosylamide nitrogen. This is not surprising given that the high nucleophilicity of the tosylamide in the related palladium reactions results from deprotonation at the outset of the reaction.⁵ Scheme 3 shows the results for eight different reactions of platinum-catalysed aerobic oxidation, demonstrating that the transformation from eqn (1) is general under the chosen reaction conditions of platinum catalysis. For this set of substrates, the reaction proceeded with complete chemoselectivity in favour of isourea formation. In particular, the efficient oxidation to six-membered bicyclic products 2a-f is without precedence in all currently available alkene oxidation protocols employing N-tosyl urea as the heteroatom source.^{5,7} Oxidation of **1b** displayed an interesting rate acceleration in the presence of carboxylic acids. More work is necessary to determine its basis, which was not found in other cases. In addition, complete chemoselectivity in favour of isourea formation¹¹ is noteworthy as



Scheme 1 Diamination of alkenes with copper bromide as reoxidant.

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Scheme 2 Platinum-catalysed oxidation of alkenes: optimization of the oxidant. BQ = 1,4-benzoquinone.

related pyrrolidine annelation reactions yield 2 : 1 mixtures of ureas and isoureas.¹² The isourea structure was established for compound **2h** by X-ray crystallography,¹³ and deduced for all other products **2** from the characteristic ¹³C carbon signal for CH_2O at 72–73 ppm and the typical carbonyl IR band at 1610–1614 cm⁻¹.



Scheme 3 Platinum-catalysed aerobic aminooxygenation of alkenes under concomitant piperidine annelation. ^a With 50 mol% tartaric acid as additive.



Scheme 4 Transformation of 2e into 4.

The isourea products may constitute interesting building blocks for further organic transformation. For example, acid-mediated cleavage of isourea **2e** led to clean isolation of the corresponding amino alcohol **3** in very good yield. Subsequent oxidative transformation under standard conditions¹⁴ gave rise to the piperidine-2-carboxylic acid, **4** (Scheme 4). This route provides convenient access to the motif of substituted piperidine-2-carboxylic acids. Its synthesis should be of interest in view of the recent successful application of proline and related derivatives in organocatalysis.

In order to understand the underlying features of this new aerobic catalysis, we chose compound **1d** for a competition study regarding the oxidation state of the involved platinum (atalyst. Since the oxidation potential of platinum(II) salts is rather low (0.74 V for $PtCl_6^{2-} + 2e^-/PtCl_4^{2-} + 2Cl^-]$,¹⁵ we reasoned that steady oxidation state of + Iv might be involved throughout the whole catalysis.¹⁶ However, a comparison of reactions using platinum dichloride and tetrachloride, respectively, as catalyst precursors revealed a significantly faster conversion in case of the former one (Fig. 1). After a total of 12 h, the reaction with the $PtCl_2$ catalyst precursor yielded 90% of **2d**, while the one from $PtCl_4$ led to only 55% yield. On the basis of this investigation, we favour a catalytic cycle involving Pt(II)/Pt(IV) catalysis.

We suggest the following catalytic cycle for the new transformation (Fig. 2). It starts from a Pt(II) complex, which, *via* a transient π -alkene complex of 1, undergoes intramolecular aminoplatination to A. This step has ample



Fig. 1 Monitored reaction progress for the oxidation of 1d to 2d in the presence of $PtCl_2$ and $PtCl_4$, respectively.



Fig. 2 Proposed catalytic cycle. X = Cl, Br.

precedence in platinum-catalysed hydroamination chemistry.¹⁰ Even under employed neutral conditions, protonolysis of **A** does not constitute a feasible pathway, as no hydroamination product was ever detected. Instead, rapid oxidation of the alkyl-platinum complex **A** to generate the corresponding platinum(IV) complex **B** may occur in the presence of copper bromide.^{17,19,20} This step characterises our present protocol as an oxidatively intercepted hydroamination pathway. Alkyl platinum(IV) catalyst state **B** undergoes intramolecular reductive elimination to generate the C–O bond. This step is reminiscent of related alkoxylation reactions at Pt(IV).^{17–19} Regeneration of the copper(II) oxidant is then accomplished under aerobic conditions in accordance with the established Wacker conditions.²⁰

In summary, we have developed a new catalytic approach in oxidative homogeneous platinum catalysis using aerobic conditions. The reaction employs catalytic amounts of copper(II) oxidant without any additives and represents a significant advance in oxidative 1,2-difunctionalisation of alkenes.

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