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The Natural Product Lepidiline A as an N-Heterocyclic Carbene Ligand Precursor in Complexes of the Type [Ir(cod)(NHC)PPh₃]X: Synthesis, Characterisation, and Application in Hydrogen Isotope Exchange Catalysis

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Abstract: A range of iridium(I) complexes of the type [Ir(cod)(NHC)PPh₃]X are reported, where the N-heterocyclic carbene (NHC) is derived from the naturally-occurring imidazolium salt, Lepidiline A (1,3-dibenzyl-4,5-dimethylimidazolium chloride). A range of complexes were prepared, with a number of NHC ligands and counter-ions, and various steric and electronic parameters of these complexes were evaluated. The activity of the [Ir(cod)(NHC)PPh₃]X complexes in hydrogen isotope exchange reactions was then studied, and compared to established iridium(I) complexes.

Keywords: iridium; N-heterocyclic carbene; hydrogen isotope exchange; deuterium

1. Introduction

Isotopically labelled compounds are of importance in a range of scientific disciplines. In particular, the isotopes of hydrogen, deuterium, and tritium find application in several key areas. Within the physical sciences, deuterated compounds are routinely used in the elucidation of reaction mechanisms [1]. In the life sciences, deuterated and tritiated compounds are used to determine the pharmacokinetic properties of bioactive molecules [2–4]. More recently, active pharmaceutical ingredients themselves have begun to feature deuterium, exploiting the effect of relative C-H/C-D bond strengths to deliver drug molecules with improved metabolic profiles [5,6].

Amongst the synthetic methods available for incorporation of deuterium or tritium into a molecule, hydrogen isotope exchange (HIE) stands out due to its simplicity and generality [7–9]. A particularly powerful variant of this process is directed HIE, whereby a Lewis basic group within the molecule directs a metal catalyst to an adjacent site, and a subsequent C-H activation results in a metallocyclic intermediate which facilitates HIE at this adjacent position (Scheme 1).

![Scheme 1. Directed hydrogen isotope exchange.](gid00001)
Iridium(I) complexes are amongst the most effective metal catalysts for directed HIE [10] and, in recent years, we have introduced a suite of highly active Ir(I) catalysts bearing a combination of bulky phosphine and N-heterocyclic carbene ligands (Figure 1). These catalysts are compatible with a broad variety of directing groups, enabling HIE on a wide range of substrates [11–18].

Figure 1. Iridium(I) N-heterocyclic carbene (NHC)/phosphine complexes for directed hydrogen isotope exchange.

These benchmark complexes 1–2 feature three distinct phosphine ligands. However, our early studies [11,12], which focused on identifying the most effective catalyst system, evaluated a broader range of phosphines based on their steric and electronic properties. In contrast, although we have optimised the NHC ligand for some specific HIE use cases [19,20], there remains scope for a more systematic study of the steric and electronic parameters of this ligand component. The natural product Lepidiline A 3·HCl is an imidazolium chloride salt, featuring two N-benzyl substituents, and methyl groups at the heterocycle’s 4- and 5-positions [21] (Figure 2). We envisaged that this naturally-occurring imidazolium salt could serve as a vehicle to begin to explore the effect of steric and electronic changes in the NHC on the activity of our Ir(I) NHC/phosphine catalysts [22].

Figure 2. Naturally-occurring imidazolium salt Lepidiline A 3·HCl.

Herein we report a study of the complexes 1a, 6a, and 7, of the type [Ir(cod)(NHC)PPh3)]PF6 (cod = 1,5-cyclooctadiene), where the NHC ligand is IMes 4, IBn 5, or IBnMe 3, derived from Lepidiline A 3·HCl (Figure 3). These complexes are then used to explore the effect of steric and electronic variance within the NHC through comparison of (a) N-benzyl vs. N-mesityl substituents; and (b) 4,5-H2 vs. 4,5-Me2 substitution, on the reactivity in HIE processes. The effect of the counter on the activity of the IBnMe complexes is also investigated.

Figure 3. Iridium(I) complexes with varying NHC ligands to probe their steric and electronic influence.

2. Results and Discussion

To initiate our studies, we set out to prepare quantities of the desired [Ir(cod)(NHC)PPh3)]PF6 complexes 1a, 6a and 7. Complex 1a was prepared by a modification of previously reported conditions [11,23]. The IBn-containing complex 7 was prepared [23] by using an analogous procedure from the previously reported complex [Ir(cod)(IBn)Cl] [24]. Lastly, the imidazolium chloride salt 3·HCl, representing the natural product Lepidiline A, was targeted to deliver complex 6a.
2.1. Synthesis of Lepidiline A

Surprisingly, to our knowledge, no preparation of this naturally-occurring material has yet been reported. Our synthetic route is summarised in Scheme 2. Chlorination of the commercially available hydroxymethyl imidazolium salt 8 in neat thionyl chloride was easily achieved in excellent yield on a multi-gram scale to deliver 9. Reduction and basification of 9 yielded the free 4,5-dimethylimidazole 10 with good levels of efficiency. Subsequently, double-alkylation of 10 under basic conditions could be achieved using benzyl chloride to give Lepidiline A 3·HCl with good effectiveness, or with benzyl bromide to give 3·HBr in excellent yield. Imidazolium bromide 3·HBr could then undergo salt metathesis to very efficiently afford 3·HPF₆ and 3·HBArF.

![Scheme 2. Synthesis of Lepidiline A and counter-ion analogues.](image)

Following the successful preparation of Lepidiline A 3·HCl and a range of its counterion derivatives, X-ray quality crystals of 3·HCl were grown and the structure solved to reveal a molecular footprint in direct agreement with the spectroscopic data and the reported natural product structure. The crystal structure was found to be a solvate containing one molecule of water per cation (Figure 4, left). The same cationic motif was found in the X-ray structure of 3·HPF₆. This latter structure has two crystallographically independent salt units per asymmetric unit (Z’ = 2). Both cations in this structure adopt anti conformations of the benzyl rings with respect to the heteroaromatic ring (Figure 4, right). This is in contrast to the syn conformation found for 3·HCl and in the Ir complexes described below.

![Figure 4. Structures of Lepidiline A (left) and its PF₆ derivative (right) as determined by single crystal diffraction. Atoms are shown as 50% probability ellipsoids. H atoms, disorder in the solvent, and anion of 3·HCl and the second independent cation-anion pair of 3·HPF₆ have been omitted for clarity.](image)
2.2. Preparation of Iridium Complexes Based on Lepidiline A 3

With a range of imidazolium salt precursors in hand, formation of the corresponding iridium complexes was investigated. Based on work by Wang and Lin [25], and Liu et al. [26], the [(cod)Ir(NHC)Cl] complexes can be prepared via a transmetallation procedure from the corresponding silver bis-carbene complex. Employing the bromide salt 3-HBr, mixing with silver(I) oxide and sodium iodide in dichloromethane gave silver complex 11 in high yield (Scheme 3). This intermediate could be taken forward into a transmetallation procedure with [(cod)IrCl]2 13 to provide the desired chloro-carbene complex 12 in excellent yield following a short reaction time. Alternatively, it was also found that isolation of 11 could be circumvented via direct addition of [(cod)IrCl]2 13 following in situ formation of the silver complex 11, delivering 12 in a further improved overall yield. With this high-yielding method in place, X-ray quality crystals of 12 were grown, confirming the proposed structure (Figure 5).

Scheme 3. Preparation of iridium complex 12.

With quantities of the NHC chloride complex 12 secured, treatment with triphenylphosphine, followed by silver hexafluorophosphate, delivered target NHC-phosphine complex 6a in a good 75% yield (Table 1, entry 1). In order to probe the effects of varying the counter-ion in these novel complexes, derivatives 6b–6d were also prepared in an analogous manner and with excellent isolated yields (Table 1, entries 2–4).
Table 1. Preparation of [(cod)Ir(IBnMe)PPh3]X complexes 6a–6d.

| Entry | Complex   | X      | Yield |
|-------|-----------|--------|-------|
| 1     | 6a        | PF6    | 75    |
| 2     | 6b        | BF4    | 87    |
| 3     | 6c        | SbF6   | 81    |
| 4     | 6d        | OTf    | 88    |

We have previously shown that iridium NHC/phosphine complexes bearing a BArF (tetrakis [3,5-bis(trifluoromethyl)phenyl]borate) counter-ion have a broader solvent applicability than the corresponding PF6 complexes [13]. Based on this, BArF-containing complex 6e was prepared in a one-pot procedure from [(cod)IrCl]2 13 in a good 82% yield (Scheme 4). Complexes 6a–6e were all characterized by X-ray crystallography [23].

Scheme 4. One-pot synthesis of BArF counter-ion catalyst 6e.

2.3. Steric and Electronic Characterisation of the Iridium NHC/Phosphine Complexes

Having successfully prepared a range of Ir complexes containing the Lepidiline A-derived NHC 3, attention now turned to evaluating this novel ligand sphere versus the alternative ligand sets in PPh3/IMes complex 1a and PPh3/IBn complex 7. The electronic properties of ligands in a specific complex are often characterised by carbonylation of the complex, whereby the νCCO stretching frequency reports on the electron-donating nature of the other ligands on the metal [27]. Recent work on Ir(I) dicarbonyl complexes has revealed that the configuration of the carbonyl ligands, though preferentially cis, is dictated by the ligand size, with larger combinations driving a trans dicarbonyl arrangement [28]. This structural fluidity limits the use of electronic parameters derived from such complexes [28]. However, the synthesis and X-ray characterisation of the carbonylated analogues of our NHC/phosphine complexes could instead be used to indicate a steric threshold—the ligand size at which Ir(I) carbonyl complexes switch from a cis- to a trans-configuration, and this could be correlated with the well-known steric parameter, percentage buried volume, %Vbur [29] of the ligands.

Accordingly, we investigated the carbonylation of complexes 1a, 6a, and 7 (Scheme 5). Direct exposure of complexes 6a and 7 to an atmosphere of CO resulted in complexes 14 and 15, where both the NHC/phosphine pair and the two CO ligands are each cis-orientated, as shown by the X-ray crystal structures [23]. The combined ligand %Vbur values (Σ(%Vbur)) were similar for both complexes, as determined by density functional theory (DFT) calculations (Table 2) [23]. As perhaps expected, the enhanced bulk of the NHC ligand in 1a resulted in a complex, 16, with a trans-arrangement of the NHC/P pair and of the two CO ligands, indicating the size and geometry of this complex to be quite distinct from the IBn and IBnMe analogues 14 and 15. Based on these parameters, there is little
steric difference evident on moving from the IBn to the IBnMe ligand, with the latter appearing to be a very slightly bulkier system, based on the %Vbur values.

![Scheme 5. Preparation of iridium carbonyl complexes 14–16.]

**Table 2. Properties of Ir-carbonyl complexes 14–16.**

| Entry | Complex | N-Substituent | R  | Yield | %Vbur (PPh₃) | %Vbur (NHC) | Σ (%Vbur) | θ (°) |
|-------|---------|---------------|----|-------|--------------|-------------|-----------|-------|
| 1     | 14      | Bn            | H  | 49%   | 26.9         | 28.9        | 55.8      | 93.2  |
| 2     | 15      | Bn            | Me | 50%   | 27.0         | 29.2        | 56.2      | 92.6  |
| 3     | 16      | Mes           | H  | 68%   | 27.9         | 32.6        | 60.5      | 160.0 |

1 θ represents the angle OC-Ir-CO. 2 Representative %Vbur values are calculated from DFT-optimized [(NHC)(PPh₃)(Ir(H)₂(DCM)₂)]⁺ complex cations. Full details are presented in the SI. 3 Carbonyl complex 15 crystallized with two different conformations.

Although these dicarbonyl complexes permitted only a steric, and not electronic, evaluation, literature examples of Ir(I) chloro-carbonyl complexes have demonstrated that the combined influence of various ligand partnerships on the metal’s π-donating ability can be measured via IR spectroscopy, based on the carbonyl stretching frequency, ν_CO [26,30]. Furthermore, the effect of the ligands on the σ-donating nature of the complex can be measured by ¹H nuclear magnetic resonance (NMR) spectroscopic evaluation of the corresponding dihydride complexes [31]. The electronic characteristics of the IMes, IBn, and IBnMe ligands in our complexes were thus explored by preparing the chloro-carbonyl complexes, 17–19 (Table 3). Additionally, from the NHC/PPh₃ complexes, in situ generation of the dihydride complexes 20–22, in CD₃CN [23], provided insight into the σ-donating properties (Table 3). Based on both electronic parameters, the IBnMe/PPh₃ combination was found to be slightly more electron-rich than IBn/PPh₃, and more significantly less electron-rich than IMes/PPh₃.
2.4. Evaluation of Iridium Complex Catalytic Activity in HIE

We next chose to focus on the relationship between the IBn/PPh3 and IBnMe/PPh3 complex pair in terms of catalyst activity in HIE reactions. The two precatalysts 6a and 7 were compared via kinetic analysis of the simple reference labelling reaction with acetophenone 23 (Table 4). Catalyst 6a, derived from Lepidiline A, was clearly faster reacting, displaying a pseudo first order rate constant, $k_{\text{obs}}(6a) = 0.0224 \text{ s}^{-1}$, versus $k_{\text{obs}}(7) = 0.0145 \text{ s}^{-1}$ for IBn/PPh3 catalyst 7 [23].

Table 4. Evaluation of complexes 6a and 7 in a benchmark HIE reaction.

| Entry | Complex | NHC   | $k_{\text{obs}}$ |
|-------|---------|-------|-----------------|
| 1     | 6a      | IBnMe | 0.0224 s$^{-1}$ |
| 2     | 7       | IBn   | 0.0145 s$^{-1}$ |

This result was supported by DFT modelling of the turnover-limiting [12] C-H activation step (24→26, Scheme 6). Based on our electronic characterization of these complexes, the greater reactivity of catalyst 6a over 7 can be rationalised on the basis of an increased $\pi$-donating ability of the Ir centre, and not on any appreciable steric difference between the two catalysts 6a and 7.
Scheme 6. Computational evaluation of the C-H activation process with catalyst 6a vs. 7.

The variation in reactivity between the IBnMe/PPh3 ligand sphere in 6a and IMes/PPh3 in 1a was most interestingly drawn out in studying the counterion dependence on catalyst reactivity (Table 5). Even at a relatively high and unoptimised catalyst loading of 5 mol%, larger and more weakly coordinating substrates 23, 27, and 28 perform relatively poorly when catalyst 6d, bearing the OTf counter-ion, is used in the HIE reaction. Alternatively, the more strongly binding substrate, 29, is relatively unaffected, and the order of reactivity generally reflects that previously observed when evaluating counter-ion effects with the IMes/PPh3 combination [13]. Presumably, the smaller size of the IBnMe/PPh3 system suffers from competitive coordination of the triflate to the metal centre [32]. Most curiously, the catalyst series 6 is ineffective at labelling the weakly coordinating substrate, nitrobenzene 30, whereas the flagship IMes/PPh3 system 1a labels to ~95% D under similar conditions [11]. This may be due to differences in available intermolecular (for example π-π) interactions of the substrate to the different catalyst systems upon binding. Nonetheless, such effects have the potential to be exploited favourably to induce directing group chemoselectivity in labelling multifunctional molecules.
Table 5. Evaluation of counter-ion effects in IBnMe/PPh₃ complexes 6.

| Entry | Substrate   | %D  | %D  | %D  | %D  | %D  | %D  |
|-------|-------------|-----|-----|-----|-----|-----|-----|
| 1     | 23, X = PF₆| 96  | 96  | 96  | 79  | 97  |     |
| 2     | 27          | 91  | 87  | 93  | 29  | 97  |     |
| 3     | 28          | 98  | 87  | 93  | 43  | 99  |     |
| 4     | 29          | 82  | 89  | 90  | 85  | 87  |     |
| 5     | 30          | 5   | 4   | 5   | 4   | 16  |     |

3. Materials and Methods

See the Supplementary Information for details of all experimental and computational procedures, as well as all crystallographic data.

4. Conclusions

In summary, the first synthesis of the simple imidazolium-based natural product, Lepidiline A, 3-HCl, has been reported, along with a range of other counter-ion derivatives. This has been followed by the development of novel HIE catalysts and the use of a silver-NHC transmetallation approach to HIE catalyst synthesis. Detailed and combined experimental/computational analysis of the resulting iridium complexes 6 and 7 has led to quantitative insight into the parameters responsible for observed differences in the resulting catalytic reactivity of 6a versus the less substituted analogue, 7, and existing flagship HIE catalyst, 1a. Overall, dimethyl substitution on the backbone of the novel NHC was found to impart an electronic influence with a minimal impact on the steric environment. The reactivity differences between the catalysts studied are now being exploited in labelling regioselectivity studies, which will be reported in due course.

Supplementary Materials: All experimental procedures, computational calculations and X-ray structure data are available online at http://www.mdpi.com/2073-4344/10/2/161/s1: all experimental procedures along with corresponding compound characterisation; computational calculations for %V_{bur} in complexes 14–16 and C-H activation of acetophenone with catalysts 6a and 7; X-ray crystallographic parameters for compounds 3-HCl, 3-HPF₆, 12, 14–16, and 6a–6e; and copies of all NMR spectra.

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