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Iridium(I) Complexes with Anionic N-Heterocyclic Carbene Ligands as Catalysts for H/D Exchange in Nonpolar Media

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Abstract. A series of neutral iridium(I) complexes of the general type [(WCA-NHC)]IrL(COD)] (COD = 1,5-cyclooctadiene; L = phosphine, pyridine), bearing anionic N-heterocyclic carbenes (WCA-NHC) with a weakly coordinating anionic (WCA) borate moiety, were prepared by addition of phosphines and pyridine to [(WCA-NHC)]Ir(COD)], in which the available coordination site is stabilized by intramolecular metal-arene interaction (π -face donation). The solvent and substrate scope of the neutral

complexes as catalysts for H/D exchange was investigated, revealing their suitability for promoting efficient deuteration in nonpolar solvents such as cyclohexane.

Keywords: Hydrogen Isotope Exchange; Deuterium; Iridium Catalysis; N-Heterocyclic Carbenes; Weakly Coordinating Anions

Introduction

Hydrogen isotope exchange (HIE) is commonly used to label molecules by introducing heavier isotopes of hydrogen (deuterium or tritium) through C-H functionalization.^[1-3]Though numerous heterogeneous homogeneous methods for HIE have been or described, ^[1,3,4]selective *ortho*-directed HIE catalyzed by iridium(I) complexes has become particularly prominent (Scheme 1).^[5]This process has distinct advantages over the classic preparation of labelled compounds, since it is possible to label the desired molecule after its synthesis under mild conditions with commercially available catalysts. The use of gas $(D_2 \text{ or } T_2)$ as an isotope source is especially advantageous for tritiation reactions, since it is readily available in high isotopic purity (>99%), and the preparation of alternative tritiated precursors requires special care because of their radioactive nature.^[6]



Scheme 1. General iridium-catalyzed HIE reaction. DG = directing group.

Crabtree's catalyst $[(COD)Ir(PCy_3)(py)]PF_6$ (1, COD = 1,5-cyclooctadiene, Cy = cyclohexyl, py =pyridine)^[7] is a well-established and effective HII iridium catalyst (Figure 1)^[8] that is commercially available and widely used to date.^[9] By replacing the pyridine ligand with an N-heterocyclic carbene (NHC), Kerr introduced highly efficient, air- and moisture-stable catalysts the of type 1,3-bis(2,4,6- $[(IMes)Ir(PR_3)(COD)]X$ (IMes = trimethylphenyl)imidazolin-2-ylidene; $PR_3 = PPh_3$, PBn₃, PPhMe₂, etc.),^[10] which are able to introduce hydrogen isotopes into a large variety of substrates, for example primary sulfonamides, ketones, amides, esters and heterocycles.^[10-13,14] Counterion variations of the "flagship" catalyst [(IMes)Ir(PPh₃)(COD)]PF₆ (IIa) had a substantial influence on the catalytic activity, with the tetrakis[3,5bis(trifluoromethyl)phenyl]borate (BArF₂₄) complex **IIb** showing a superior solubility profile and applicable solvent scope in HIE processes.[13] In addition to these cationic species, neutral complexes of the type [(NHC)IrCl(COD)] were also succesfully employed.^[15] Similar anion effects were observed for the iridium(I) catalysts III supported by P,N ligands, which were developed in the course of our work with highly basic imidazolin-2-imine ligands.[16] Hence, the BArF₂₄ derivative **IIIb** showed remarkable performance in H/D exchange with a broad range of aromatic substrates, including ketones, amides, esters, heterocycles and nitro compounds, and also promoted H/D exchange in



Figure 1. Selected examples of iridium complexes active in HIE; Mes = 1,3,5-trimethylphenyl, Dipp = 2,6-diisopropylphenyl.

aromatic Boc-protected anilines, benzylamines and methoxy derivatives.^[17] Moreover, HIE reactions with sulfonamides, N-oxides, phosphonamides^[18] and phenylacetic acid esters and amides were accomplished.^[19]

Anionic N-heterocyclic carbenes that bear a weakly coordinating anion (WCA) are another class of ligands introduced by our group,^[20] which were used for the preparation of homogeneous WCA-NHC gold(I),^[21] iridium(I)^[22] and palladium(II)^[23] (pre-)catalysts. The iridium(I) systems IV can be regarded as carbene analogues of Crabtree's catalyst I, with overall neutral charge allowing olefin their hydrogenations in nonpolar media.^[22] Notably, intramolecular π -face donation is an important feature of complexes **IV**, and stabilizes а coordination site that is potentially available for the introduction of donor ligands. Accordingly, the reaction of complexes IV with phosphines should afford neutral congeners of Kerr's catalysts II, which could be used in nonpolar solvents. In contrast, most HIE reactions with cationic iridium(I) complexes are performed in chlorinated solvents such as dichloromethane, which is considered unfavourable because of its associated hazards, including suspected carcinogenicity and high vaporisability.^[11]

To the best of our knowledge, no catalyst suitable for HIE in nonpolar solvents such as cyclohexane or n-hexane has been described to date, and in this contribution, we wish to present the application and solvent scope of the complexes **IV** and their derivatives [(WCA-NHC)IrL(COD)] (1–4) in *ortho*-directed H/D exchange reactions.

Results and Discussion

Synthesis and Characterization. The complex [(WCA-IMes)Ir(COD)] (IVa, WCA = $B(C_6F_5)_3$, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2ylidene) was treated with the phosphines PPh₃, PPh₂Me, PPhMe₂, and PMe₃ in tetrahydrofuran (THF). Simple addition and formation of the complexes [(WCA-IMes)IrL(COD)] was observed only for $L = PPh_3$ (1) and $L = PPh_2Me$ (2), whereas the reaction with the smaller, more electron-rich phosphines PPhMe₂ and PMe₃ afforded cyclooctenyl complexes of the composition [(WCA-IMes-COE)IrL₃] by COD insertion into the Ir–C_{carbene} bond These complexes exhibit three ³¹P NMR signals, and for $L = PMe_3$, the molecular structure could be established by X-ray diffraction analysis, revealing a distorted trigonal-bipyramidal coordination sphere; see the Supporting Information for the crystal structure of [(WCA-IMes-COE)Ir(PMe₃)₃]·CH₂Cl₂. Similar insertion reactions have been observed for indenvl complexes of the type [(Ind)Ir(COD)].^[24]

The complexes 1 ($L = PPh_3$) and 2 ($L = PPh_2Me$) were isolated as red-orange powders in 83% and 80% yield (Figure 1). The $31\hat{P}$ NMR spectra exhibit singlets at 16.1 ppm (1) and 0.4 ppm (2), while the ¹³C NMR spectra of **1** and **2** show doublets at 171. ppm (${}^{2}J_{CP} = 7.5 \text{ Hz}$) and 176.4 ppm (${}^{2}J_{CP} = 8.1 \text{ Hz}$), respectively. These chemical shifts fall in the expected range in comparison with Kerr's catalysts such as **IIa** and are in accordance with the expected cis arrangement of the carbene and phosphine ligands.^[10] Addition of pyridine to a THF solution of $\mathbf{IV}\mathbf{a}$ afforded the pyridine complex **3** as a yellow powder in moderate yield (50%). 3 gave rise to similar ¹H and ¹³C NMR signals for the WCA-IMes and COD ligands; e.g., the carbene carbon atom resonates at 175.8 ppm. Similar addition reactions with the sterically more demanding complex [(WCA-IDipp)Ir(COD)] (**IVb**, WCA = $B(C_6F_5)_3$, IDipp = 1,3bis(2,6-diisopropyllphenyl)imidazolin-2-ylidene) proved successful only for $L = PPhMe_2$, and the resulting complex 4 was isolated as a red-orange solid in 67% yield (Figure 1). Like compounds 1-3, the low symmetry (C_1) of **4** leads to complicated ¹H and ¹³C NMR spectra, and hindered rotation around the B–C₆F₅ bonds creates additional complexity. The ³¹P NMR signal is found at –16.5 ppm.

The molecular structures of $1 \cdot \text{Et}_2O$, $3 \cdot \text{CH}_2\text{Cl}_2$ and $4 \cdot 2\text{CH}_2\text{Cl}_2$ were determined by X-ray diffraction analyses (Figure 2, Table 1), revealing that the iridium atom exhibits in all cases a slightly distorted square-planar coordination sphere with C1–Ir1–P/N angles of 98.5(1)° (1), 88.7(1)° (3) and 94.0(1)° (4). The Ir–C1 and Ir–P1 bond lengths in the phosphine complexes



Figure 2. Molecular structures of the iridium complexes in $1 \cdot \text{Et}_2\text{O}$, $3 \cdot \text{CH}_2\text{Cl}_2$ and $4 \cdot 2\text{CH}_2\text{Cl}_2$. Thermal ellipsoids drawn at 50% probability. Co-crystallized solvent and hydrogen atoms were omitted for clarity. For selected bond lengths and angles, see Table 1.

1/4 are 2.090(2)/2.131(3) Å and 2.368(1)/2.333(1) Å and fall in the ranges established for related cationic complexes of type **II**,^[10,13] indicating that the overall neutral nature of the WCA-NHC complexes does not affect the structural parameters significantly. The pyridine complex **3** shows a slightly shorter Ir–C1 bond length of 2.077(2) Å and an Ir–N3 bond length of 2.104(2) Å, which are in good agreement with the values established for similar cationic NHC complexes, e.g., Ir–C = 2.076(4) and Ir–N = 2.103(4) in [(IDipp)Ir(py)(COD)]BF4,^[25] whereas the Ir–N bond in Crabtree's catalyst **I** is slightly shorter at 2.089(2) Å.^[26]

Table 1. Table Caption. Selected bond lengths (Å) and angles (°) of compounds 1, 3 and 4.

	1	3	4
Ir-C _{carbene}	2.090(2)	2.077(2)	2.131(3)
Ir-P/N	2.368(1)	2.103(2)	2.333(1)
C1–Ir1–P/N	98.5(1)	88.7(1)	94.0(1)

Catalytic Studies. Since weakly coordinating anions (WCA) are known to improve the solubility and therefore the activity of ionic complexes in solvents of low polarity,^[13,27] we aimed at investigating the influence of the solvent on H/D exchange. Acetophenone (5) was employed as a common substrate for screening H/D exchange reactions, with 5 mol% of the catalyst in each solvent. The catalysts and substrates were handled in air and treated with commercially available HPLC grade solvents. All H/D exchange reactions were carried out in a 12-vial reactor equipped with a 3-way stopcock connected to a vacuum line and a balloon filled with deuterium gas. To start the deuteration, the atmosphere in the vials was exchanged several times with deuterium gas. After a reaction time of 16 h, the solvent was reduced to a minimum and the residue filtered through a short silica column. Deuterium

incorporation was determined by $^{1}\mathrm{H}$ NMR spectroscopy (see the Supporting Information for details). Initial screenings revealed that the WCA-IMes complex IVa does not promote deuteration of acetophenone, presumably because of its significantly lower stability in comparison with the air-stable WCA-IDipp complex IVb.^[22] Complex 4 gave only very low deuterium incorporation (6%-17%), which corresponds to Kerr's finding that all attempts to form HIE catalysts containing a phosphine and the sterically more encumbered carbene IDipp failed.^[15] Therefore, compounds IVa and 4 were excluded from further screening, which was performed with IVb and **1–3** (Figure 1).

The results of the solvent screening are summarized in Figure 3. In dichloromethane (DCM), high degrees of deuteration were found for all four catalysts (90%–95%). In contrast, only IVb performed well in tetrahydrofuran (THF), which agrees with the observation that THF represents a challenging solvent for Kerr-type catalysts.^[13] Complex 3 gave inconclusive results, presumably because of the lability of the pyridine ligand in THF solution. Methyl tert-butyl ether (MTBE) is used in industry as a safer alternative to diethyl ether,^[11] and complexes IVb and 2 performed well with ca. 95% deuterium incorporation, whereas only mediocre performance was found for 1 and 3. Notably, almost quantitative deuteration ($\geq 96\%$) was achieved with 1 and 2 even in cyclohexane and *n*-hexane, which confirms our initial hypothesis that the WCA-NHC complexes act as neutral analogues of Kerr's catalysts II for HIE in nonpolar solvents. A slightly lower degree of deuteration was found for **IVb** in *n*-hexane, while the pyridine complex 3 again proved inferior.

For a better understanding of the activity of the new catalysts in cyclohexane, deuteration of acetophenone (5) was studied with a reduced catalyst loading of 0.5 mol%. The reaction mixtures were



Figure 3. Solvent screening of H/D exchange with acetophenone (5, 0.083 mmol). The reactions were set up under ambient conditions with commercially available HPLC grade solvents; 5 mol% catalyst loading, 16 h reaction time at room temperature under 1 atm D_2 gas. Total amount of solvent used: 1 mL (DCM, THF, MTBE), 2 mL (cyclohexane), 4 mL (*n*-hexane). Results are reported as an average of two runs. [a] = No conclusive results could be obtained.

prepared under inert conditions to avoid catalyst decomposition. Remarkably, deuterium incorporation dropped significantly only for catalyst **1**, whereas almost the same level of deuteration was reached with **IVb** and **2** even after shortening the reaction time from 16 h to 90 min (Figure 4). These results indicate that the extremely high level of catalytic activity reported for cationic Kerr-type catalysts can be attained by neutral WCA-NHC complexes even in the nonpolar solvent cyclohexane.



Figure 4. Screening of H/D exchange with acetophenone (5, 0.083 mmol) at 0.5 mol% catalyst loading in cyclohexane (2 mL). Results are reported as an average of two runs.

To assess the substrate scope of the new iridium catalysts for H/D exchange reactions in nonpolar solvents, a series of selected substrates was screened in the presence of **IVb**, **1** and **2** with 5 mol% catalyst loading under the same conditions as described above (Figure 5). Even though our complexes proved to be

highly active in *n*-hexane, we opted for a screening in cyclohexane, since some commonly used substrates are poorly soluble in *n*-hexane, e.g., ethyl 4-dimethylaminobenzoate (8). 2-Phenylpyridine (6) is often used to assess the tolerance of HIE catalyst towards N-heterocycles as directing groups. A high level of deuterium incorporation (94%) was realised with complex 1, which is in the range reported for Kerr's catalysts.^[10] The lower degree observed for **IVb** and 2 can probably be ascribed to stronger binding of the substrate to the sterically less encumbered catalysts.

To test whether the new complexes can accept a nitro group as a directing group, deuteration of 4nitroanisole (7) was investigated. Thereby, the ether group might act as a second directing group via a four-membered metallacyclic intermediate (4-mmi) in contrast to the generally preferred 5-mmi mechanism.[12,17] Deuterium was selectively incorporated in *ortho*-position to the nitro group with high (98% for 1 and 2) or moderate (62% for IVb) deuterium levels. Likewise, exclusive orthodeuteration was found next to the ester group in ethyl 4-dimethylaminobenzoate (8), with IVL outperforming the IMes complexes 1 and 2. Pyrrole 9 and indole 10 were also tested, since general methods Boc-protected for labelling (Boc tertbutyloxycarbonyl) anilines are still rare.[17] Again, only IVb achieved good levels of deuterium incorporation up to 93%. The ferrocene-based diester 11 was chosen as another unusual substrate, with a high degree of deuteration (95%) being observed only in the presence of IVb.^[28]

Another remarkable feature of catalyst **IVb** is the tolerance of anilines and benzylamines, as demonstrated by the efficient deuteration of 1-

naphthylamine (12), 4-dimethylaminobenzylamine

(13) and 1-naphthylmethylamine (14), since primary



Figure 5. Substrate screening of H/D exchange in cyclohexane with various substrates (0.083 mmol of each substrate); 5 mol% catalyst loading, 16 h reaction time at room temperature under 1 atm D₂ gas. Total amount of solvent used: 1 mL (**5**, **6**), 5 mL (**7** – **11**, **13**), 6 mL (**12**, **15**), 10 mL (**14**). Values in square brackets denote the degree of deuteration [%] in the indicated position (D); multiple deuteration sites are assigned in the order $[D^1]/[D^2]/[D^3]$ (**14**) and $[D^1]/[D^2]$ (**15**); % values indicate isolated yields. Results are reported as an average of two runs. * Almost quantitative yield of material containing solvent impurities.

amino groups generally coordinate strongly to the iridium atom and thus lead to deactivation of the catalyst.^[8,17,29] Deuteration of 1-naphthylamine (12) can be achieved adequately with all three catalysts, whereas the benzylamines 13 and 14 were efficiently deuterated only in the presence of **IVb**. Moreover, **IVb** enables efficient labelling of 14 in both the D¹-(83%) and D²-position (87%), which indicates that this catalyst is able to promote deuteration via five-(5-mmi)and six-membered metallacyclic intermediates (6-mmi).^[19,30,31] To confirm this ability, 2-phenylacetophenone (15) was chosen as a final substrate to . As expected, given the results obtained for the deuteration of acetophenone (5, vide supra), all three catalysts lead to high degrees of deuteration via a 5-mmi, whereas labeling via a 6-mmi is only observed for IVb, albeit to a smaller extent (91%

versus 41%). The observation that only **IVb** is capable of labelling in positions consistent with the formation of six-membered metallacycles can be ascribed to a higher tendency to accommodate these larger rings in comparison with the sterically more congested carbene-phosphine complexes **1** and **2**.

Conclusion

We have described a new class of stable iridium(I) complexes with anionic N-heterocyclic carbenes that contain a weakly coordination anionic borate moiety and have investigated their ability to promote H/D exchange in nonpolar media. Phosphine introduction into the previously reported hydrogenation catalysts [(WCA-NHC)Ir(COD)] (**IV**) affords neutral carbene-

phosphine complexes, with [(WCA-IMes)IrL(COD)] (1, L = PPh₃; 2, L = PPh₂Me) demonstrating a similar level of catalytic activity to that reported for established cationic Kerr-type HIE catalysts. Because of the overall neutral charge of the new complexes, efficient deuteration could be achieved even in nonpolar solvents such as cyclohexane. Moreover, the well-established hydrogenation catalyst [(WCA-IDipp)Ir(COD)] (**IVb**) proved to be particularly useful for deuterium incorporation into a wide scope of substrates, including primary and Boc-protected anilines, and its sterically less congested nature creates a higher tendency to promote H/D exchange involving not only the preferred five-membered, but also six-membered metallacycles.

Experimental Section

Full experimental procedures, including the synthesis and characterization of compounds 1-4 can be found in the Supporting Information.

Labelling reactions: General remarks. All labelling experiments were carried out in a Radleys carousel reactor and HPLC grade solvents without further purification. Exceptions are experiments with low catalyst loading (0.5 mol%) and naphthylmethylamine **14** (air-sensitive), which were prepared under standard Schlenk conditions with purified solvents. Deuterium incorporation was determined by ¹H NMR spectra via correlation of the respective integrals of the undeuterated starting material *versus* the deuterated product. Both integrals of the starting material and product were calibrated against a peak corresponding to a position not expected to be labelled (see equation 1 in the Supporting Information). All degrees of deuteration were determined by the average of two reactions.

General screening procedure. A stock solution of the substrate is prepared by dissolving 0.083 mmol of the substrate per reaction in a specific amount of solvent (0.5–5 mL). After transfer of the substrate, the corresponding catalyst (0.00415 mmol IVb = 5.0 mg, 1 = 5.7 mg, 2 = 5.5 mg, 3 = 4.9 mg, 5 mol%) is added as a solution to the Radleys Reactor (0.5–5 mL). The reactor caps are closed, and the atmosphere is exchanged four times with deuterium gas via a balloon. With tightly closed caps, the reaction is stirred for 16 h at room temperature. To terminate the deuteration process, the atmosphere is exchanged twice with argon prior to careful removal of the corresponding solvent *in vacuo*. For volatile substrates, the solvent is reduced to a minimum before work-up. Details of the work-up procedures and solvent amounts are available in the Supporting Information.

Crystal structures. CCDC 1995319 (1·Et₂O), CCDC 1995320 (3·CH₂Cl₂), CCDC 1995321 (4·2 CH₂Cl₂), CCDC 1995322 ([(WCA-IMes-COE)Ir(PMe₃)₃]·CH₂Cl₂), and CCDC 1995323 ([(WCA-IMes)Ir(14)(COD)]·CH₂Cl₂) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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FULL PAPER

Iridium(I) Complexes with Anionic N-Heterocyclic Carbene Ligands as Catalysts for H/D Exchange in Nonpolar Media

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