ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: *Chem. Commun.*, 2013, **49**, 7052

Received 18th June 2013,
Accepted 21st June 2013

DOI: 10.1039/c3cc44567d

www.rsc.org/chemcomm

# Robust cyclometallated Ir(III) catalysts for the homogeneous hydrogenation of N-heterocycles under mild conditions†‡

Jianjun Wu, Jonathan H. Barnard, Yi Zhang, Dinesh Talwar, Craig M. Robertson and Jianliang Xiao*

**Cyclometallated Cp*Ir(N^C)Cl complexes derived from N-aryl ketimines are highly active catalysts for the reduction of N-heterocycles under ambient conditions and 1 atm $H_2$ pressure. The reaction tolerates a broad range of other potentially reducible functionalities and does not require the use of specialised equipment, additives or purified solvent.**

The hydrogenation of organic substrates is one of the great success stories of homogeneous catalysis. Building on the pioneering work of Wilkinson, Crabtree, Knowles and Noyori, highly effective hydrogenations of C=C and C=O bonds have been developed and widely adopted by the synthetic community.[1] However, the field of C=N hydrogenation is much less well developed and utilised, particularly for N-heterocycles. Reduced heterocyclic compounds are present in many pharmaceuticals, natural products, organic dyes, fragrances and hydrogen storage materials, and as a result, efficient methods for the synthesis of these compounds are desirable.[2] Of the methods developed, the catalytic hydrogenation of the parent unsaturated N-heterocycles with hydrogen gas is an attractive route to these products due to the lack of stoichiometric waste products associated with the use of reactive metals and metal hydrides or other hydrogen sources.[3]

In comparison to the hydrogenation of olefins, carbonyls and imines, the hydrogenation of N-heterocycles is more challenging due to the aromaticity of the N-heterocycles. Transition metal catalysts based on Rh, Ir, Ru, Os, Mo and Fe have been applied to the homogeneous hydrogenation of N-heterocycles.[4,5] Unfortunately, these reactions are often characterised by the use of high temperatures or hydrogen pressures, and many systems require the use of additives such as Brønsted acids,[5g] chloroformates[5h] or $I_2$.[5f] Furthermore, to the best of our knowledge, there is no single reported homogeneous catalyst capable of hydrogenating quinolines, 3,4-dihydroisoquinolines, quinoxalines and indoles. Crabtree and co-workers reported that a $[Ir(NHC)(PPh_3)(COD)][PF_6]$ complex is active for the reduction of N-heterocycles at room temperature and low $H_2$ pressures (1–5 atm).[5d] However, additional $PPh_3$ was required for catalytic activity and the substrates were limited mainly to quinolines.

We recently reported that cyclometallated Cp*Ir(N^C)Cl complexes are highly active catalysts for a range of hydrogen transfer reactions.[6] We now report that related complexes, if appropriately functionalised, catalyse the selective reduction of N-heterocycles at room temperature and 1 atm $H_2$, allowing for the operationally simple synthesis of various reduced N-heterocyclic compounds.

Initially we screened complexes **1a–1l** (Fig. 1) for the reduction of 2-methylquinoline **2a** in as-received 2,2,2-trifluoroethanol (TFE) at ambient temperature (Table 1). A hydrogen balloon was used as the hydrogen source. Surprisingly, of all the complexes **1a–1f**, only the electron rich 3,4-methylenedioxy-substituted **1f** showed any activity (entries 1–8). To assess the effect of the N-donor substituent, complexes **1g–1l** were screened,[6] but all showed diminished activity in comparison to **1f** (entries 9–14). No reaction was observed when $[Cp^*IrCl_2]_2$ or no catalyst was used (entries 1–7). Notably, ligands bearing the 3,4-methylenedioxy group underwent selective cyclometallation with $[Cp^*IrCl_2]_2$ (ref. 7) to give the more hindered products with 85 : 15–95 : 5 isomeric ratios (Fig. 2), due to the *ortho*-directing effect of the oxygen atoms.[8] In contrast, the 3-OMe group of **1e** resulted in selective cyclometallation *para* to the OMe, and **1e** proved to be inactive (entries 1–7).

Screening a variety of different solvents suggested that the use of TFE was essential for good catalytic activity at 1 atm $H_2$

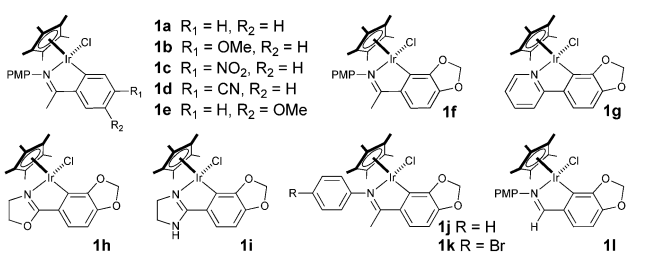


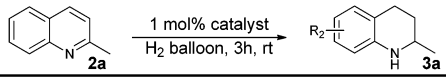

**Fig. 1** Catalysts examined in this study (see Table 1), PMP = *p*-methoxyphenyl.

*Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD, UK. E-mail: jxiao@liv.ac.uk; Fax: +44 (0)151-7943588*

† In memory of Dr Phil Hogan.

‡ Electronic supplementary information (ESI) available: Characterisation data for Ir complexes, ligands and hydrogenation products. CCDC 933833 and 933834. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc44567d

**Table 1** Optimisation of the hydrogenation of 2-methylquinoline[a]




| Entry | Complex | Solvent | Conversion[b] (%) |
|---|---|---|---|
| 1–7 | **1a–1e**, $[Cp^*IrCl_2]_2$, none | TFE | N.R. |
| ***8*** | ***1f*** | ***TFE*** | ***>98*** |
| 9 | **1g** | TFE | 9 |
| 10 | **1h** | TFE | 21 |
| 11 | **1i** | TFE | 77 |
| 12 | **1j** | TFE | 87 |
| 13 | **1k** | TFE | 88 |
| 14 | **1l** | TFE | 6 |
| 15–17 | **1f** | MeOH, EtOH, iPrOH | N.R. |
| 18–20 | **1f** | DCM, THF, toluene | N.R. |
| 21, 22 | **1f** | $H_2O$, EtOAc | N.R. |

[a] Conditions: **2a** (0.5 mmol), complex (1 mol%), solvent (3 mL), rt, 3 h, $H_2$ balloon. [b] Conversion determined by $^1$H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%. A conversion of >98% was assigned when the substrate was not observable in the spectrum. N.R. = no reaction.

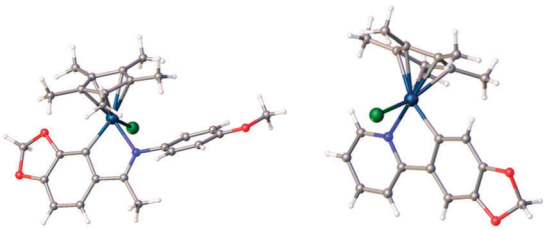
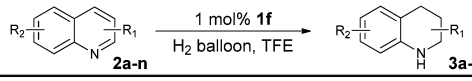


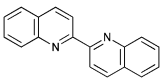
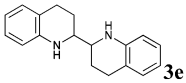
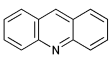
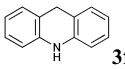
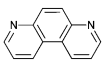
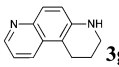
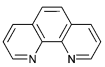
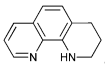
**Fig. 2** Molecular structures of **1f** (major isomer, left) and **1g** (minor isomer, right) determined by X-ray diffraction. See the ESI‡ for details.

pressure (entries 15–22). However, the reaction was found to occur slowly in MeOH at 20 bar (see the ESI,‡ S1.5 for full details), although TFE remained the most effective solvent. TFE is known to solvate chloride ions much more strongly than MeOH,[9] and so may enhance the dissociation of chloride from the coordinatively saturated 18 electron complexes **1**, creating a vacant, active site on Ir(III) for $H_2$ coordination. In line with this, the hydrogenation in TFE was found to be inhibited by the addition of chloride ions (6 fold decrease in conversion with 10% $NBu_4Cl$) or $PPh_3$ (no reaction with 1% $PPh_3$) (see ESI,‡ S1.8 for further details). In addition, as TFE ($pK_a$ 12.4) is more acidic than MeOH ($pK_a$ 15.5) or EtOH ($pK_a$ 15.8),[10] it can hydrogen bond to substrate or product more effectively, and thereby may help prevent them from competing with $H_2$ for the single vacant site on Ir(III). Indeed, $^1$H NMR showed that upon mixing **2a** with TFE in $CDCl_3$, the chemical shift of the TFE hydroxyl proton changed from 2.5 to 3.5 ppm, suggesting that TFE hydrogen bonds to **2a** (see ESI,‡ S1.6 for further details). Not entirely surprisingly, the use of chloride abstracting agents ($AgSbF_6$ and $NaBAr^F{}_4$) did not allow the reaction to proceed in MeOH at 1 atm $H_2$ pressure (see ESI,‡ Table S2), given the weaker hydrogen bonding ability of MeOH.

Using the optimised conditions, a variety of quinolines (including substitutions at 2-, 3-, 4-, 6- and 8-positions), were hydrogenated to give the 1,2,3,4-tetrahydroquinoline products in good to excellent yields (Table 2). The reaction was found to be highly tolerant of other functionalities, such as halides, esters, and free hydroxyl groups (entries 10 and 12–14). It is worthy to note that 3- and

**Table 2** Hydrogenation of quinolines with **1f**[a]




| Entry | $R_1$ | $R_2$ | Prod. | Temp (°C) | Time (h) | Conv.[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 2-Me | H | **3a** | rt | 3 | >98 (96) |
| 2[c] | 2-Me | H | **3a** | 85 | 16 | 92 (85) |
| 3 | H | H | **3b** | rt | 3 | >98 (95) |
| 4 | 3-Me | H | **3c** | 40 | 20 | >98 (97) |
| 5 | 4-Me | H | **3d** | 40 | 20 | >98 (98) |
| 6 |  |  **3e** | | rt | 3 | >98 (97), 4 : 1 dr |
| 7 |  |  **3f** | | rt | 3 | >98 (99) |
| 8 |  |  **3g** | | 40 | 20 | >98 (93) |
| 9 |  |  **3h** | | 40 | 20 | >98 (80) |
| 10 | H | 6-$CO_2$Et | **3i** | rt | 3 | >98 (97) |
| 11 | 2-Me | 6-OMe | **3j** | 40 | 3 | 95 (92) |
| 12 | H | 6-Br | **3k** | rt | 3 | >98 (97) |
| 13 | H | 6-Cl | **3l** | rt | 3 | >98 (96) |
| 14 | H | 8-OH | **3m** | rt | 3 | >98 (98) |
| 15 | H | 8-Me | **3n** | 40 | 3 | >98 (97) |

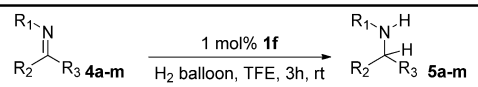
[a] Conditions: substrate (0.5 mmol), **1f** (1 mol%), TFE (3 mL), $H_2$ balloon. [b] As for Table 1. A conversion of >98% was assigned when the substrate was not observable in the spectrum. Isolated yields in parentheses. [c] 0.01 mol% **1f**.

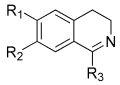
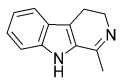
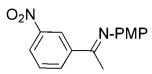
4-methylquinolines, which are often challenging substrates,[5b,e] were reduced with full conversion, although a slightly elevated temperature and prolonged time was necessary. Reduction of phenanthrolines gave the partially hydrogenated 1,2,3,4-tetrahydrophenanthrolines as the exclusive products (entries 8 and 9).[11] Notably, entry 6 represents the 1st homogeneous hydrogenation of 2,2′-biquinoline. Acridine was reduced to the 9,10-dihydro product (entry 7). The presence (or lack of) 2-substituents did not unduly affect the reaction, suggesting that the substrate and/or product does not coordinate or affect the coordination of $H_2$ to the single active site in TFE. The catalyst loading can be lowered. For instance, in the reduction of **2a**, a TON of 9200 (85% isolated yield) was achieved at 85 °C in 16 h and 1 atm $H_2$ pressure, showing the robust nature of the hydrogenation catalyst (entry 2).

We also investigated the reduction of a variety of other N-heterocycles and imines (Table 3). Quinoxalines were reduced with full conversions, which is, to our knowledge, the first example of homogeneous hydrogenation of these substrates under ambient conditions (entries 1–3). Cyclic and acyclic imines were also efficiently hydrogenated (entries 4–10). The presence of a nitro group was well tolerated (entry 10). Unprotected indoles (entries 11–13), which are often challenging substrates for homogeneous hydrogenation,[12] could be reduced to the corresponding indolines. However, no reaction was observed for either ketone or styrene substrates (entries 14 and 15), showing the chemoselectivity of **1f** for the reduction of C=N bonds over C=O and C=C bonds.

To further demonstrate the utility of complex **1f** for the reduction of N-heterocycles, three widely used heterogeneous

**Table 3** Hydrogenation of other C=N bonds with **1f**[a]




| Entry | Substrate | Prod. | Conv.[b] (%) |
|---|---|---|---|
| 1[c] | Quinoxaline | **5a** | >98 (95) |
| 2 | 2-Me-quinoxaline | **5b** | >98 (93) |
| 3 | 6-Me-quinoxaline | **5c** | >98 (95) |
| 4–8 |  | **5d–5h** | See below |
| 4 | $R_1$, $R_2$ = H, $R_3$ = Me | **5d** | >98 (88) |
| 5 | $R_1$, $R_2$ = H, $R_3$ = $^i$Pr | **5e** | >98 (93) |
| 6 | $R_1$, $R_2$ = H, $R_3$ = Cy | **5f** | >98 (89) |
| 7 | $R_1$, $R_2$ = MeO, $R_3$ = Cy | **5g** | >98 (91) |
| 8 | $R_1$, $R_2$ = MeO, $R_3$ = Ph | **5h** | >98 (90) |
| 9 |  | **5i** | 96 (85) |
| 10 |  | **5j** | >98 (99) |
| 11 | 2-Me-indole | **5k** | 86 (83) |
| 12 | Indole | **5l** | 82 (78) |
| 13[d] | 5-MeO-indole | **5m** | >98 (95) |
| 14 | 4-MeO-acetophenone | **5n** | N.R. |
| 15 | 4-MeO-styrene | **5o** | N.R. |

[a] Conditions: substrate (0.5 mmol), **1f** (1 mol%), TFE (3 mL), rt, 3 h, $H_2$ balloon. [b] As for Table 1. A conversion of >98% was assigned when the substrate was not observable in the spectrum. Isolated yields in parentheses. [c] 0.5 mol% **1f**. N.R. = no reaction. [d] 40 °C, 20 h.

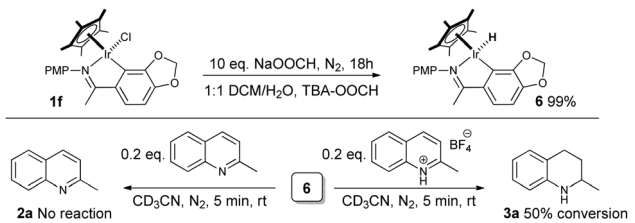



**Fig. 3** Synthesis and reactions of hydride **6**.

hydrogenation catalysts[13] and five homogeneous catalysts, including systems that have been shown to be extremely effective for quinoline hydrogenations,[5c,d,i] were compared to **1f** for the reduction of **2a** (see ESI,‡ Table S3). Complex **1f** was found to be over 14 times more active than Rh/C which was the most active of the heterogeneous catalysts and 6 times as active as $[IrCl(COD)]_2$/P-Phos/$I_2$, which was the most active of the other homogeneous catalysts previously reported.[5i]

In order to gain further information about the reaction mechanism, we prepared the iridium hydride[14] species **6** by treating **1f** with an excess of sodium formate in DCM–$H_2O$ (Fig. 3). Treatment of **6** with 0.2 equivalents of 2-methylquinoline **2a** did not lead to the formation of **3a**. However, the reaction of **6** with 0.2 equivalents of 2-methyl quinolinium tetrafluoroborate led to the rapid formation of the fully reduced product **3a** (see ESI,‡ S1.4 for further details). Repeating the reactions in the presence of TFE did not alter the results. These results suggest that the protonated, instead of the neutral quinoline, is the species that is reduced in the reaction (Fig. 3).

In conclusion, we report the reduction of a diverse range of N-heterocyclic compounds under mild conditions (ambient temperature, 1 atm $H_2$) without the use of any additives. Key to the success of the reaction is the choice of ligand and the use of TFE as solvent. The reaction was found to be tolerant of a wide range of other, potentially reducible, functional groups and could be carried out using standard laboratory glassware and non-purified solvent. Thus, our results demonstrate a simple, yet highly selective reduction of N-heterocycles and imines with hydrogen gas as a highly effective alternative to the heterogeneous metal catalysts and borohydrides commonly used for these reactions, whilst offering greatly increased reactivity and selectivity.

We thank the University of Liverpool (JHB) and Pfizer (JW) for funding. Mass spectrometry data was acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

## Notes and references

1 *The Handbook of Homogeneous Hydrogenation*, ed. J. G. de Vries and C. J. Elsevier, Wiley-VCH, Weinheim, 2007.
2 (*a*) V. Sridharan, P. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157; (*b*) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669; (*c*) R. H. Crabtree, *Energy Environ. Sci.*, 2008, **1**, 134.
3 (*a*) M. R. Pitts, J. R. Harrison and C. J. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 2001, 955; (*b*) G. W. Gribble, *Chem. Soc. Rev.*, 1998, **27**, 395.
4 D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557.
5 (*a*) E. Baralt, S. J. Smith, J. Hurwitz, I. T. Horvath and R. H. Fish, *J. Am. Chem. Soc.*, 1992, **114**, 5187; **Ru**: (*b*) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu and A. S. C. Chan, *J. Am. Chem. Soc.*, 2011, **133**, 9878; (*c*) S.-M. Lu, X.-W. Han and Y.-G. Zhou, *J. Organomet. Chem.*, 2007, **692**, 3065; **Ir**: (*d*) G. E. Dobereiner, A. Nova, N. D. Schley, N. Hazari, S. J. Miller, O. Eisenstein and R. H. Crabtree, *J. Am. Chem. Soc.*, 2011, **133**, 7547; (*e*) R. Yamaguchi, C. Ikeda, Y. Takahashi and K. Fujita, *J. Am. Chem. Soc.*, 2009, **131**, 8410; (*f*) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 10536; (*g*) Z.-W. Li, T.-L. Wang, Y.-M. He, Z.-J. Wang, Q.-H. Fan, J. Pan and L.-J. Xu, *Org. Lett.*, 2008, **10**, 5265; (*h*) S.-M. Lu, Y.-Q. Wang, X.-W. Han and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2006, **45**, 2260; (*i*) W.-J. Tang, J. Tan, L.-J. Xu, K.-H. Lam, Q.-H. Fan and A. S. C. Chan, *Adv. Synth. Catal.*, 2010, **352**, 1055; **Os**: (*j*) R. A. Sánchez-Delgado and E. González, *Polyhedron*, 1989, **8**, 1431; **Mo**: (*k*) G. Zhu, K. Pang and G. Parkin, *J. Am. Chem. Soc.*, 2008, **130**, 1564; **Fe**: (*l*) T. J. Lynch, M. Banah, H. D. Kaesz and C. R. Porter, *J. Org. Chem.*, 1984, **49**, 1266.
6 (*a*) C. Wang, A. Pettman, J. Bacsa and J. Xiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 7548; (*b*) J. H. Barnard, C. Wang, N. G. Berry and J. Xiao, *Chem. Sci.*, 2013, **4**, 1234; (*c*) Y. Wei, D. Xue, Q. Lei, C. Wang and J. Xiao, *Green Chem.*, 2013, **15**, 629; (*d*) Q. Lei, Y. Wei, D. Talwar, C. Wang, D. Xue and J. Xiao, *Chem.–Eur. J.*, 2013, **19**, 4021; (*e*) J. Wu, D. Talwar, S. Johnston, M. Yan and J. Xiao, *Angew. Chem., Int. Ed.*, 2013, DOI: 10.1002/anie.201300292.
7 D. L. Davies, O. Al-Duaij, J. Fawcett, M. Giardiello, S. T. Hilton and D. R. Russell, *Dalton Trans.*, 2003, 4132.
8 K. Gao, P.-S. Lee, C. Long and N. Yoshikai, *Org. Lett.*, 2012, **14**, 4234.
9 R. R. Ryall, H. A. Strobel and M. C. R. Symons, *J. Phys. Chem.*, 1977, **81**, 253.
10 (*a*) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, 1959, **81**, 1050; (*b*) http://evans.harvard.edu/pdf/evans_pka_table.pdf.
11 J. Wu, D. Talwar, S. Johnston, M. Yan and J. Xiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 6983–6987.
12 (*a*) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou and X. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 8909; (*b*) A. Kulkarni, W. Zhou and B. Török, *Org. Lett.*, 2011, **13**, 5124.
13 *Heterogeneous Catalysis for the Synthetic Chemist*, ed. R. L. Augustine, Marcel Dekker, New York, 1996.
14 C. Wang, H.-S. T. Chen, J. Bacsa, R. A. Catlow and J. Xiao, *Dalton Trans.*, 2013, **42**, 935.