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Iridium(I) N-Heterocyclic Carbene (NHC)/Phosphine Catalysts for Mild and Chemoselective Hydrogenation Processes

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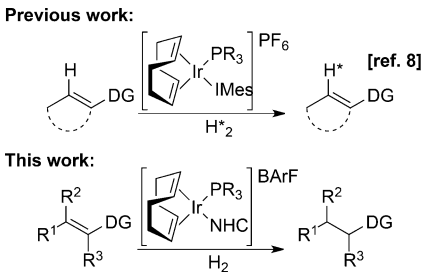
Abstract: The directed chemoselective hydrogenation of olefins has been established by using iridium(I) catalysts, which feature a tuned NHC/phosphine ligand combination. This selective reduction process has been demonstrated in a wide array of solvents, including more environmentally acceptable media, also allowing further refinement of hydrogenation selectivity.

The catalytic hydrogenation of olefins continues to be a prominent and important tool in the repertoire of the organic chemist,[1] and methods utilising heterogeneous[1b] and homogeneous[2] catalysts have been widely developed. The foremost homogeneous catalysts in this area, established by Wilkinson and co-workers[3] and Crabtree and co-workers,[4] are applied extensively in organic synthesis. Having stated this, Crabtree's catalyst, although able to facilitate mild hydrogenation processes, is thermally unstable and prone to deactivation by the formation of inactive clusters.[5] To overcome this drawback, Nolan and co-workers[6] and Buriak and co-workers[7] have both developed elegant Ir-based catalyst systems capable of olefin hydrogenation; however, the substrate scope and solvent applicability is still largely undeveloped, whilst the general effectiveness of these complexes remains similar to that of Crabtree's catalyst. More recently, we have reported the development of a series of iridium(I) N-heterocyclic carbene (NHC)/phosphine species as excellent catalysts for hydrogen isotope exchange (HIE) directed by a wide array of functionalities.[8] Similarly, these developed iridium catalysts have shown excellent activity with a preliminary array of substrates in olefin hydrogenation processes.[9]

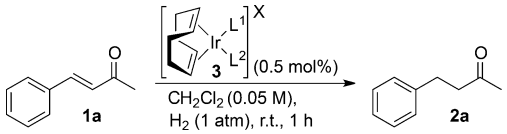
Through our on-going studies, we have now established that non-aromatic unsaturated moieties containing a suitable donor group can also undergo selective C–H activation and hydrogen-isotope exchange (Scheme 1).[8f] Pairing this process with the improved solvent applicability we have reported for HIE when utilising a less coordinating counterion,[8d] we postulated that a donor-group-assisted process[10] could deliver selective olefin hydrogenation[11] under mild reaction conditions. Furthermore and importantly, we envisaged that the developed method would be applicable in a wide variety of more environmentally acceptable solvents.[12]



Scheme 1. Research overview.

We initiated our studies by examining the nature of our developed catalyst species and evaluated a range of NHC/phosphine complexes **3** in the hydrogenation of (*E*)-4-phenylbut-3-en-2-one **1a** (Table 1). For comparison, we examined the reaction with Crabtree's catalyst **3a** and found that only 31% conversion was achieved at the low applied catalyst loading

Table 1. Catalyst screen for the hydrogenation of enone **1a**.



Entry[a]	Catalyst	L^1, L^2	X	Conversion [%][b]
1	**3a**	py, PCy_3	PF_6	31
2	**3b**	IMes, PPh_3	PF_6	27
3	**3c**	IMes, PBn_3	PF_6	94
4	**3d**	IMes, $PnBu_3$	PF_6	94
5	**3e**	IMes, PEt_3	PF_6	100
6	**3f**	IMes, PMe_2Ph	PF_6	100
7	**3g**	IMe, PPh_3	PF_6	1
8	**3h**	IBn, PPh_3	PF_6	2
9	**3i**	ICy, PPh_3	PF_6	1
10	**3j**	IMes, PMe_2Ph	BArF	100

[a] **1a** (0.4 mmol), **3** (0.002 mmol), CH_2Cl_2 (8 mL), H_2 (balloon). [b] Conversion to **2a** calculated from ^1H NMR spectroscopic analysis of the crude product.

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(entry 1). With the bulky 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene ligand (IMes) as the NHC in our catalyst series, we found the reactivity to be strongly linked to the size of the partner phosphine ligand (entries 2–6). The large rigid catalyst **3b**, in which the phosphine is triphenylphosphine, delivered only 27% conversion (entry 2). Utilising more flexible catalysts bearing tribenzylphosphine (**3c**) and tri-*n*-butylphosphine[7] ligands (**3d**) resulted in a large increase in activity, giving near quantitative conversion (Table 1, entries 3–4). However, the best results were obtained with catalysts bearing smaller ligands, such as triethylphosphine (**3e**) and dimethylphenylphosphine (**3f**) (entries 5–6). Having established that catalysts bearing small phosphine ligands gave increased activity, we sought to further improve activity with less encumbered, *N*-alkyl-substituted NHCs. However, each catalyst of this type (**3g–i**; entries 7–9) failed to deliver any hydrogenated product **2a**.

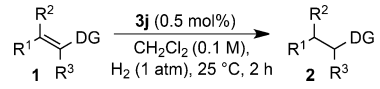
It was proposed that these complexes **3g–i** exhibited poor activity due to a strong substrate–catalyst binding that limits the recycling of the activated catalyst. In contrast, we have shown that more encumbered IMes/phosphine catalysts paired with a less coordinating counter ion (BArF) have increased activity at lower catalyst loading and an appreciably enhanced range of applicable reaction solvents in HIE processes.[8d] Accordingly, using the success of catalyst **3f** as a foundation, we synthesised BArF complex **3j** by a recently developed procedure circumventing difficult inert atmosphere filtration methods (see the Supporting Information, Section 7).[8d] As shown for entry 10, this new complex (**3j**) gave complete conversion in the hydrogenation of **1a** to **2a**; furthermore, the hydrogenation process was shown to proceed more rapidly with the BArF complex than with the equivalent PF_6 species (see the Supporting Information, Section 10).

With complex **3j** chosen for further study due to its superior performance, we turned our attention to understanding the factors affecting this overall process. To this end, we utilised a two-level, three-factor, full factorial design of experiments (see the Supporting Information, Section 11). The three factors chosen for observation were catalyst loading, reaction concentration and reaction time. The study showed, perhaps unsurprisingly, that increasing catalyst loading and reaction time both strongly enhanced the reaction efficiency. More interestingly, the study also revealed that overly increasing the concentration was detrimental to the reaction, plausibly indicating that the substrate complexation and subsequent product decomplexation is inhibiting catalyst turnover,[2] in accordance with our observations on the inactivity of catalysts **3g–i**.

Following on from this experimental design process, we applied the optimised conditions (0.5 mol% **3j**, 2 h, 0.1 M in CH_2Cl_2), to a broad range of unsaturated substrates (Table 2). After the initial success in the reduction of **1a**, further enone substrates **1b–d** all performed well, with no hindrance to the reduction by *para*-, *meta*- or *ortho*-substitution of the aromatic ring. Increasing the steric bulk adjacent to the donor group also resulted in full conversion (**1e**). Pleasingly, alkyl-substituted enones **1f** and **g** also readily underwent hydrogenation; however, the increased steric bulk in **1g** required moderately increased catalyst loading and extended reaction time (1 mol% and 16 h) for complete conversion. In contrast, the standard optimised conditions proved to be effective in the hydrogenation of the chalcone derivative **1h**. More challenging α-substituted enones **1i** and **j** required both higher catalyst loading and longer reaction times (1 mol% and 16 h), but, notably, complete conversion was still achieved at 1 atm of H_2 pressure. Furthermore, β-disubstituted enone **1k** initially proved to be problematic under the optimised conditions, but a modest increase in temperature, along with catalyst loading and reaction time (2 mol%, 35 °C, 40 h), gave quantitative conversion to the reduced product.

Following the selective reduction of a range of ketones, we next investigated a range of alternative directing groups. Notably, the sensitive carbonate group in **1l** remained intact under

Table 2. Substrate scope and chemoselectivity.



Conversion, (Yield)[a,b]

X = **1a** H 100%, (98%)
X = **1b** *p*-OMe 100%, (97%)
X = **1c** *m*-OMe 100%, (98%)
X = **1d** *o*-OMe 100%, (98%)

1e 100%, (95%)

1f 100%, (95%)

1g 32 %
100%, (95%)[c]

1h 100%, (99%)

1i 21 %
100%, (98%)[c]

1j 29%
100%, (99%)[c]

1k 0%
100%, (99%)[d]

1l 100%, (97%)

1m 100%, (95%)

1n 100%, (95%)

1o 87%
100%, (96%)[e]

1p 36%
100%, (95%)[c]

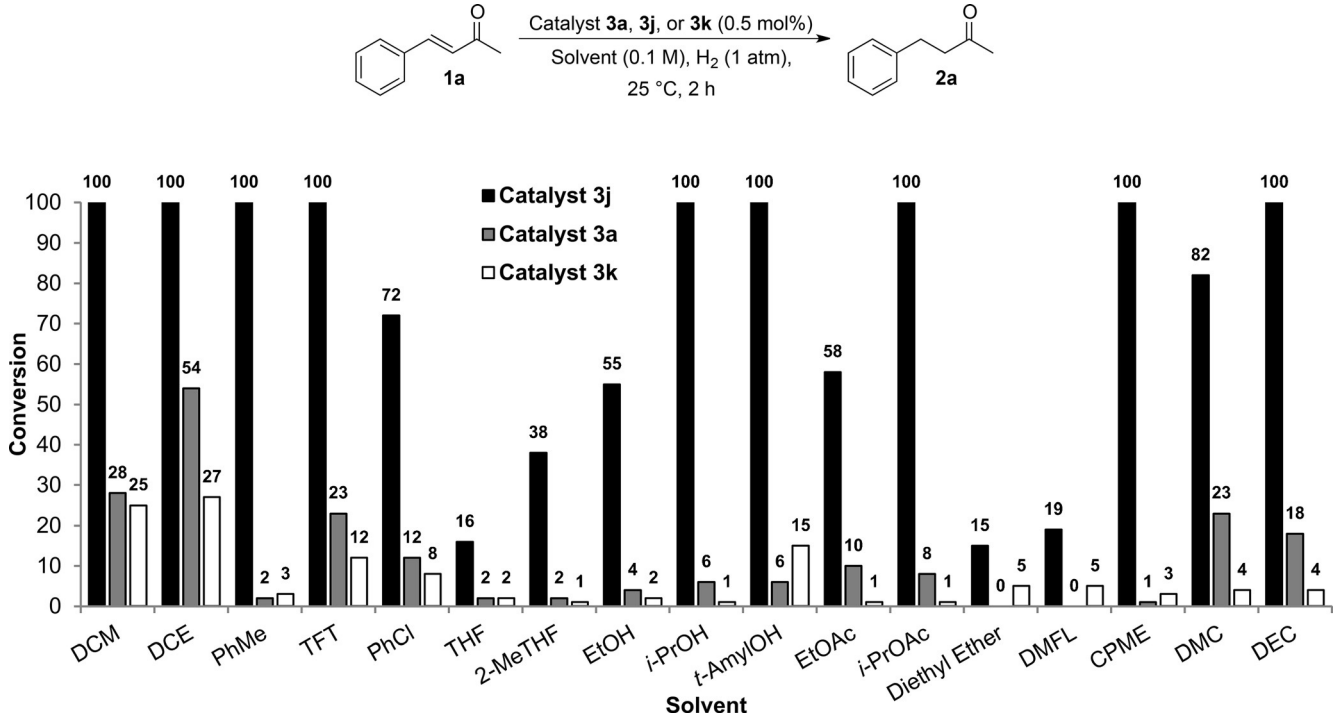
1q 23%
100%, (98%)[c]

[a] **1** (0.4 mmol), **3j** (0.002 mmol, 0.5 mol%), CH_2Cl_2 (4 mL), H_2 (1 atm). [b] Conversion calculated from ^{1}H NMR analysis of the crude product. [c] **3j** (0.004 mmol, 1.0 mol%) for 16 h. [d] **3j** (0.008 mmol, 2.0 mol%) at 35 °C for 40 h. [e] **3j** (0.004 mmol, 1.0 mol%).

the standard reaction conditions, giving an excellent yield of reduced olefin, and both cinnamic acid **1m** and its *p*-brominated ethyl ester derivative **1n** proceeded to complete conversion in excellent yields under the optimised conditions. However, the presence of a strongly coordinating amide donor group in **1o** required a slightly elevated catalyst loading of 1 mol%, again indicating that decomplexation of the substrate from the catalyst is of key importance in catalyst turnover. The hydrogenation of the less coordinating, nitro-containing compound **1p** required an extended reaction time and moderately increased catalyst loading (1 mol%, 16 h), but still proceeded without any observed NO_2 reduction. We have recently shown that a competing C–H insertion at the β-position of the olefin can also occur with this compound (**1p**),[8f] plausibly reducing the rate of hydrogenation. Similarly, vinyl benzoate **1q** can undergo a competing *ortho*-aryl-C–H activation,[8c] again reducing the rate of hydrogenation, although reduction still proceeds effectively with only 1 mol% catalyst loading.

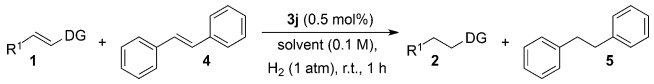
With a good substrate scope established, we turned our attention to a key parameter that limits many hydrogenation methods: the narrow scope of applicable solvents.[12] Our recent work in the area of hydrogen isotope exchange has shown that the catalysts featuring the more non-coordinating BArF counterion can perform in a much broader range of solvents than the parent PF_6 complexes.[8d] Therefore, to extend and improve the solvent scope in the present study, the hydrogenation of **1a** was performed under our optimised protocol in 17 different solvents (including chlorinated, aromatic, cyclic ether, non-cyclic ether, ester, alcohol and carbonate-based solvents) with complex **3j** and, for comparison, both the widely used and commercially available Crabtree's catalyst **3a** and its BArF counterion analogue, complex **3k**[13] (Scheme 2). We were pleased to find that in every case, our newly developed catalyst system **3j** outperformed both Crabtree's catalyst **3a** and the BArF counterion analogue **3k**. Secondly, and more importantly, under the optimised conditions, complete conversion was achieved by using catalyst **3j** in a practically appealing broad range of solvents. Notably, the solvents which gave the most effective reduction process are always the larger, less coordinating variant in each given class (e.g., *t*-AmylOH > EtOH; *i*PrOAc > EtOAc; and CPME > Et_2O). This trend indicates that the complexation and decomplexation of the solvent is also an important factor,[8b] and the more non-coordinating the solvent—the higher the catalyst activity.

Having established a catalyst system that can mediate the efficient, selective hydrogenation of conjugated olefins, we turned our attention to investigating the wider chemoselectivity of this process. To ascertain the level of effectiveness in this regard, a series of competition reactions were performed utilising (*E*)-1,2-diphenylethene **4**, as an olefin without a directing group, against unsaturated compounds **1a**, **f**, **h** and **m**–**p**, possessing a range of directing groups (Table 3). Our first comparison resulted in a high level of selectivity for reduction of the olefin within enone **1a** (entry 1). The smaller and more electron-rich enone **1f** improved upon this selectivity, with only very small amounts of **5** observed (entry 2). Utilising related chalcone **1h** resulted in a decrease in selectivity, potentially due to a weaker directing-group complexation (Table 3, entry 3). The weakly coordinating acid **1m** showed a moderate selectivity, whereas the related ester **1n** showed a reverse in selectivity to favour the reduction of **4** (entries 4–5). This reverse in selectivity can be attributed to the lack of coordina-



Scheme 2. Hydrogenation of enone **1a** in different reaction media.

Table 3. Chemoselective hydrogenation process in competition reactions.



Entry[a]	Substrate	Solvent	R^1	DG	Selectivity (**2**:**5**)[b]	Entry[a]	Substrate	Solvent	R^1	DG	Selectivity (**2**:**5**)[b]
1	**1a**	CH_2Cl_2	Ph	COMe	87:13	8	**1a**	*t*-AmylOH	Ph	COMe	81:19
2	**1f**	CH_2Cl_2	*n*-Pr	COMe	98:2	9	**1a**	*i*PrOH	Ph	COMe	86:14
3	**1h**	CH_2Cl_2	*p*-Tol	COPh	84:16	10	**1a**	EtOH	Ph	COMe	95:5
4	**1m**	CH_2Cl_2	Ph	CO_2H	76:24	11	**1a**	PhMe	Ph	COMe	94:6
5	**1n**	CH_2Cl_2	*p*-BrC_6H_4	CO_2Et	7:93	12	**1h**	PhMe	*p*-Tol	COPh	93:7
6	**1o**	CH_2Cl_2	Ph	$CONEt_2$	96:4	13	**1p**	PhMe	Ph	NO_2	77:23
7	**1p**	CH_2Cl_2	Ph	NO_2	66:34						

[a] **1** (0.4 mmol), **4** (0.4 mmol), **3j** (0.002 mmol), solvent (4 mL), H_2 (1 atm). [b] Conversions calculated from GC/MS analysis.

tion by the ester donor group in directing the hydrogenation process, with the selectivity being determined solely by the more electron-rich olefin **4** reacting preferentially. The strongly coordinating amide donor group was found to give excellent selectivity for the hydrogenation of **1o** over **4** (Table 3, entry 6), whereas the poorly coordinating nitro group in **1p** gave only a moderate selectivity for the directed hydrogenation process (entry 7).

The breadth of directing-group scope studied within this series of competition reactions allowed us to develop the hypothesis that coordination of the substrate to the catalyst is critical in determining the observed selectivity. Based on this proposal, we postulated that this selectivity could be manipulated through the choice of solvent. To test this hypothesis, a second set of competition reactions were performed, employing a series of alcohol solvents with increasing coordinating abilities, in the order *t*-AmylOH, *i*PrOH and EtOH (Table 3, entries 8–10). In the hydrogenation of **1a** versus **4**, a moderate selectivity was observed in *t*-AmylOH (entry 8). However, this selectivity was improved upon moving to the more coordinating *i*PrOH (entry 9); pleasingly, the best selectivity was observed with the most coordinating solvent, EtOH (Table 3, entry 10). This series of results suggests that the ability of a substrate to undergo hydrogenation is dependent upon displacement of the ligated solvent. Furthermore, this solvent displacement is more readily achieved by a coordinating directing group than a weaker coordinating olefin. However, further studies with a broader range of solvents showed that non-coordinating solvents, such as toluene (Table 3, entries 11–13), can also improve the chemoselectivity; this appears contrary to our hypothesis of solvent co-ordinating ability. Therefore, we propose that a low dielectric constant partially contributes to the selectivity in the absence of a coordinating group in the solvent, as was indicated by the lower dielectric constant of toluene (CH_2Cl_2 9.14, EtOH 25.3 and toluene 2.385).[14]

To conclude, we have developed a catalyst system **3j**, which outperforms Crabtree's catalyst **3a** for directed hydrogenation processes in a wide array of solvents. Exploration of a range of substrates containing other potentially reducible functionalities demonstrates the excellent chemoselectivity of our developed catalyst system, which is completely selective for the hydrogenation of olefins bearing a series of directing groups. Furthermore, by employing the non-coordinating BArF counterion in catalyst **3j**, the hydrogenation process is opened up to an appreciably broad range of solvents, in turn, providing the opportunity to use this parameter to influence the selectivity of the reduction. Indeed, through further studies, we have shown that the chemoselectivity of the process can be further tuned through appropriate choice of reaction solvent, to deliver a highly selective reduction.

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Keywords: chemoselectivity · homogeneous catalysis · hydrogenation · iridium · reduction

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