Asymmetric Hydrogenation

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Asymmetric Hydrogenation of α,β-Unsaturated Nitriles with Base-Activated Iridium N,P Ligand Complexes**

*Marc-André Müller and Andreas Pfaltz**

Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *Although many chiral catalysts are known that allow highly enantioselective hydrogenation of a wide range of olefins, no suitable catalysts for the asymmetric hydrogenation of α,β-unsaturated nitriles have been reported so far. We have found that Ir N,P ligand complexes, which under normal conditions do not show any reactivity towards α,β-unsaturated nitriles, become highly active catalysts upon addition of N,N-diisopropylethylamine. The base-activated catalysts enable conjugate reduction of α,β-unsaturated nitriles with H_2 at low catalyst loadings, affording the corresponding saturated nitriles with high conversion and excellent enantioselectivity. In contrast, alkenes lacking a conjugated cyano group do not react under these conditions, making it possible to selectively reduce the conjugated C=C bond of an α,β-unsaturated nitrile, while leaving other types of C=C bonds in the molecule intact.*

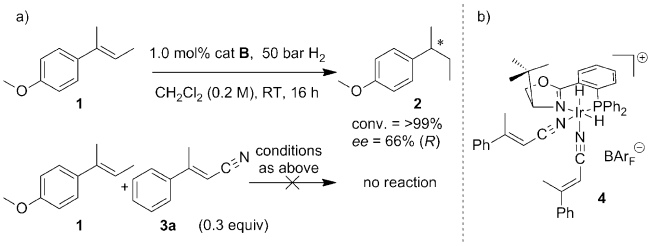
Asymmetric hydrogenation is one of the most general, most widely applied reactions to generate enantiomerically enriched products from prochiral starting materials.[1] Many efficient chiral rhodium and ruthenium diphosphine catalysts are available and hydrogenate C=C bonds bearing an adjacent coordinating group with high enantioselectivity.[2] More recently, iridium complexes derived from chiral N,P, C,N or O,P ligands were developed to extend the application range of asymmetric hydrogenation to olefins lacking a coordinating group.[3] Although a very broad range of functionalized and unfunctionalized olefins can be converted into highly enantioenriched products using rhodium, ruthenium, or iridium catalysts, asymmetric hydrogenation of α,β-unsaturated nitriles has met limited success so far. The challenges imposed by this substrate class are related to the linear geometry of the nitrile group, which keeps a coordinated catalyst away from the C=C bond, and the strong binding affinity of the cyano group to transition-metal complexes results in catalyst deactivation.

Hence, only a few examples of asymmetric reductions of α,β-unsaturated nitriles have been reported so far, despite the considerable synthetic value of the enantioenriched nitriles produced in this way.[4] Conjugate reduction with sodium borohydride and semicorrin cobalt catalysts led to the saturated nitriles with only moderate enantioselectivity (up to 69% *ee*).[5] Better enantioselectivities of up to 99% *ee* were achieved with copper diphosphine catalysts and polymethylhydrosiloxane (PMHS) as the reducing agent, but relatively high catalyst loadings (3 mol%), a fourfold excess of PMHS, and strongly basic work-up conditions (aq. NaOH) are drawbacks of this method.[6] For rhodium-catalyzed hydrogenation with hydrogen gas, high enantioselectivities have only been observed for unsaturated nitriles with an additional coordinating acetamido or carboxylate group at the C=C bond.[7]

Herein we report that chiral iridium N,P ligand complexes can be activated by addition of a base, thus enabling the hydrogenation of α,β-unsaturated nitriles with high enantioselectivities at low catalyst loadings.

Our initial attempts to apply iridium-based complexes to the asymmetric hydrogenation of α,β-unsaturated nitriles under standard conditions, which had proved optimal for a wide variety of functionalized and unfunctionalized alkenes,[3] were unsuccessful. None of the many iridium catalysts tested showed any reactivity towards this class of substrate. Moreover, addition of α,β-unsaturated nitriles to other substrates which were known to be fully hydrogenated by iridium catalysts under standard conditions, resulted in complete catalyst deactivation (Scheme 1A). Further investigation of the interaction of α,β-unsaturated nitriles with an Ir/PHOX catalyst under a hydrogen atmosphere led to the identification and isolation of the iridium(III) dihydride complex **4** with two bound nitrile molecules (Scheme 1B; BAr_F = tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate). Apparently, coordination of the two cyano groups leads to an 18-electron complex lacking a free coordination site, which is necessary for catalytic activity.

Semeniuchenko et al. recently found that addition of *N,N*-diisopropylethylamine (DIPEA) markedly enhanced the reactivity of Ir/PHOX catalysts for the hydrogenation of



Scheme 1. Inhibition of the activated iridium catalyst by the substrate.

[*] M.-A. Müller, Prof. Dr. A. Pfaltz
Department of Chemistry, University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
E-mail: andreas.pfaltz@unibas.ch

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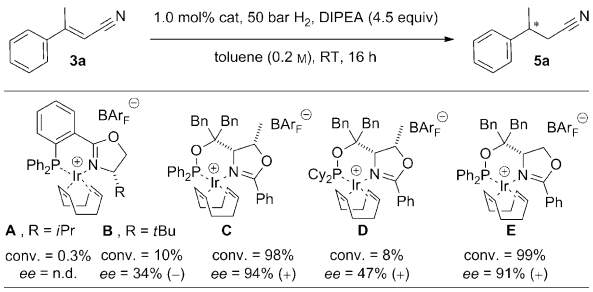
electron-deficient olefins such as benzylidenemalononitrile or α,β-unsaturated ketones,[8] and is in contrast to the general experience that amine bases deactivate iridium catalysts.[3d,9] These results prompted us to evaluate the effect of DIPEA on the hydrogenation of **3a** with various iridium catalysts (Scheme 2).



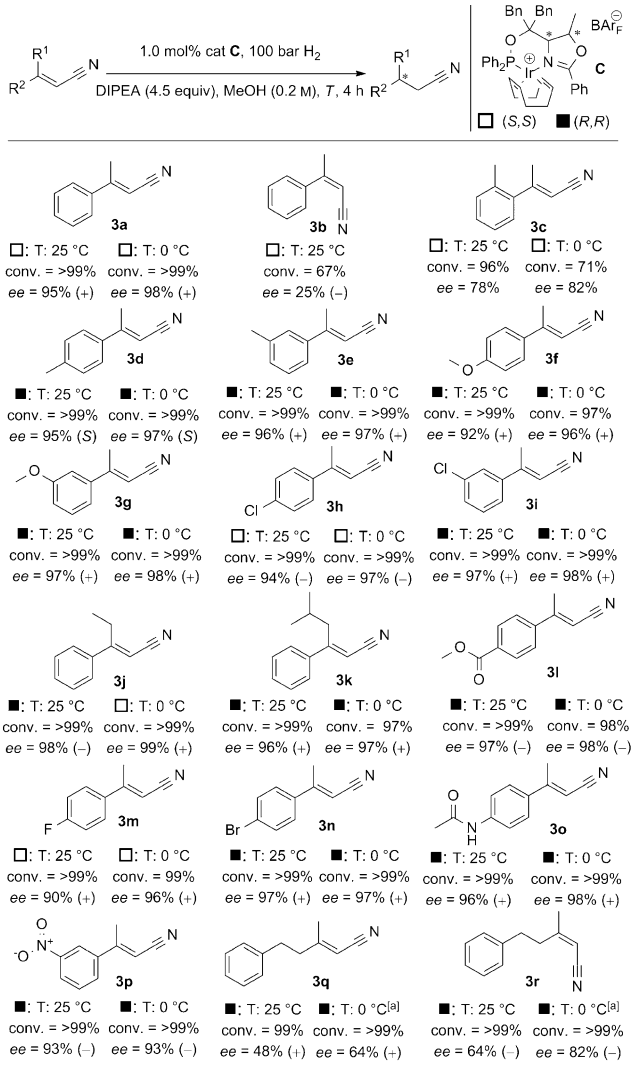
Scheme 2. Selected catalysts used in the hydrogenation of (*E*)-3-phenylbut-2-enenitrile (**3a**).

Although the first experiment with catalyst **A** gave only minimal conversion of less than 1%, further studies covering a broad selection of iridium complexes (see the Supporting Information) led to more reactive and more selective catalysts. By far the best results were obtained with the commercially available ThrePHOX complex **C** and the SerPHOX analogue **E**. The reactivity and enantioselectivity showed extreme variation from catalyst to catalyst. Even small changes in the ligand structure had a strong impact on catalyst performance (compare **A** vs. **B** or **C** vs. **D**). Both steric and electronic factors seem to play a role, but no clear trends could be deduced from the data.

We next studied the influence of the various reaction parameters in the hydrogenation of **3a**. An increase of the hydrogen pressure from 50 to 100 bar resulted in full conversion without affecting the enantioselectivity. Variation of the amount of DIPEA added to the reaction mixture had a very strong effect. The 4.5 equivalents originally chosen were found to be optimal. Both an increase or reduction of the amount of DIPEA impaired catalyst performance. With 1.5 equivalents of DIPEA the reaction still went to completion, but the *ee* value dropped from 94% to 88%, whereas reduction to 0.1 equivalent led to a significant loss of *ee* value and incomplete conversion. Raising the amount of DIPEA from 4.5 to 18 equivalents also caused a drop in *ee* value and conversion.

The range of solvents tolerated proved to be remarkably broad. To our surprise, even in strongly coordinating solvents such as methanol or acetonitrile, which are known to inhibit iridium catalysts such as **C**, catalytic activity was retained. Among the polar protic and aprotic solvents that were tested, only DMSO was found to be unsuitable. The highest *ee* value was observed in DMF, but the reaction did not go to completion. Full conversion and excellent enantioselectivities of 94–95% *ee* were achieved in alcoholic solvents and in water.[10] The remarkable water tolerance of this catalyst system is an attractive feature enhancing its scope and practicality. By lowering the temperature to 0 °C the enantioselectivity could be further improved, thus reaching 98% *ee* and full conversion in methanol (see the Supporting Information, Table 1).

To establish the scope of this catalyst system, we examined a broad selection of α,β-unsaturated nitriles under optimized reaction conditions (Scheme 3). Changing the double-bond



Scheme 3. Catalytic asymmetric hydrogenation of α,β-unsaturated nitriles. [a] 2.0 mol% catalyst loading and 16 h reaction time.

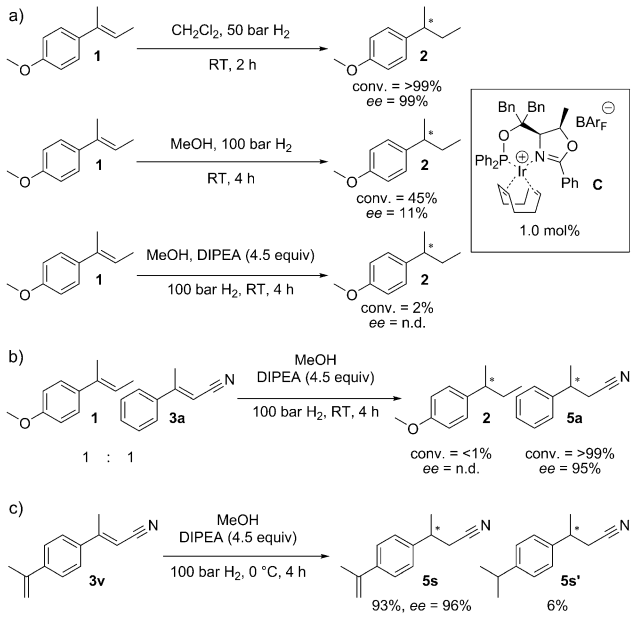
geometry of **3a** from *trans* to *cis* caused a large drop in conversion and enantioselectivity, with a reversal of the absolute configuration (**3b**). Introduction of an *ortho* substituent onto the phenyl group, which destabilizes a coplanar arrangement of the C=C bond and the aromatic π-system, also reduced the reactivity and *ee* value, but to a lower extent (**3c**). Electron-donating or electron-withdrawing groups in the *meta* or *para* position of the aryl substituent had no or only small effects (**3d–i**, **3l–p**). The substrates **3j**,**k**, having larger alkyl substituents at the C=C bond, gave full conversion with similar or even higher enantioselectivity compared to the methyl-substituted compound **3a**. Overall this catalyst system showed high functional-group tolerance, as exemplified by

the fluoro-, chloro-, bromo-, acetamido-, carbomethoxy-, cyano-, and nitro-substituted compounds which were all successfully hydrogenated.

The β,β-dialkyl-substituted acrylonitriles **3q** and **3r** exhibited lower reactivity and required 2 mol% of catalyst and longer reaction time for full conversion at 0°C. The enantioselectivities were also lower than in the hydrogenation of the phenyl methyl analogue **3a**. Interestingly, the *cis*-isomer **3r** afforded a higher *ee* value than the *trans*-isomer **3q**, contrary to the results obtained with **3a** and **3b**. The best results were achieved in the hydrogenation of **3r** at 0°C, which led to the saturated nitrile with 82% *ee* and full conversion. At −15°C the *ee* value was increased to 88%, but conversion reached only 51%.

We next investigated to what extent the catalyst loading and the amount of DIPEA could be reduced without affecting the enantioselectivity and conversion. In methanol containing 0.23 equivalents of DIPEA as little as 0.05 mol% of catalyst was necessary to achieve 99% to full conversion within 18 hours. With the exception of **3d** (91% *ee*), the enantioselectivities for **3a**, **3g**, **3i**, **3j**, **3n**, and **3o** remained at the same levels as those observed in reactions with 1 mol% of catalyst. At longer reaction times of 112 hours, 96.5% conversion with 95% *ee* was observed for **3a** on a 1.5 mmol scale using only 0.005 mol% catalyst (corresponding to 19300 turnovers). In methanol with 1 mol% catalyst, the amount of DIPEA could be reduced to 0.1 equivalents without affecting the *ee* value and conversion. In this solvent, even in the absence of DIPEA, the reaction went to completion, but the *ee* value dropped from 95% to 86% (see the Supporting Information, Table 2).

We wondered how standard substrates lacking a nitrile group behaved under these reaction conditions in methanol with and without addition of DIPEA. We therefore studied the hydrogenation of the typical alkene **1** shown in Scheme 4,



Scheme 4. Reactivity and selectivity studies of α,β unsaturated nitriles and other alkenes.

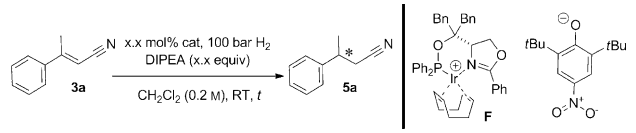
which is known to give full conversion with catalyst **C** in CH_2Cl_2 (Scheme 4A).[12] In pure methanol some reactivity remained, but conversions were significantly lower than in CH_2Cl_2 and the *ee* value fell from 99% to 11%. Addition of DIPEA quenched the reaction almost completely. Notably, when a 1:1 mixture of (*E*)-3-phenylbut-2-enenitrile (**3a**) with **1** was subjected to these reaction conditions, the unsaturated nitrile was fully hydrogenated, while **1** did not react (Scheme 4B). Apparently, DIPEA enhances the reactivity of the catalyst towards the electrophilic C=C bond of an α,β-unsaturated nitrile while inhibiting hydrogenation of more-electron-rich, less polarized C=C bonds.[12] Thus, selective hydrogenation of α,β-unsaturated nitriles containing additional C=C bonds becomes possible, as demonstrated by the reduction of **3s** (Scheme 4C). The cyano-substituted C=C bond was almost fully hydrogenated to afford 93% of the monohydrogenation product **5s** with 96% *ee*, and only 6% of the fully hydrogenated product **5s′**. The high preference for reduction of the trisubstituted C=C bond is remarkable in view of the very high reactivity of terminal C=C bonds under normal hydrogenation conditions.[11]

Obviously, this base-modified catalyst system must operate through a different mechanism than under standard base-free conditions. In view of the pronounced Brønsted acidity of cationic iridium hydride complexes,[13] a deprotonated neutral iridium(I) monohydride may be postulated as a reactive intermediate which is generated by deprotonation of a dihydride complex such as **4** (Scheme 1). A neutral hydride complex would be expected to be less electrophilic and, consequently, to release a bound nitrile more easily, thus opening up a free coordination site, which is required for the reaction. Moreover, the hydride would be more nucleophilic than hydrides in a cationic dihydride complex, thus facilitating hydride transfer to the electrophilic C=C bond of an α,β-unsaturated nitrile. However, experimental evidence for such a mechanism is difficult to obtain because of the high reactivity and sensitivity of iridium hydride species,[14] and attempts to characterize intermediates other than **4** (Scheme 1) were unsuccessful so far.

Considering the dramatic influence of an added external base, we wondered whether replacement of the BAr_F ion by a basic weakly coordinating anion would bring about a similar effect.

Indeed complex **F**, having the sterically hindered 2,6-ditert-butyl-4-nitrophenolate anion, showed high catalytic activity in the hydrogenation of **3a** in CH_2Cl_2 and afforded essentially the same conversion and enantioselectivity as the corresponding BAr_F salt **E** in the presence of DIPEA (Table 1). High conversion was achieved down to 0.2 mol% catalyst loading. When the catalyst loading was further reduced, the *ee* value remained high, however, conversions were much lower than that with catalyst **E** and 0.23 equivalents of DIPEA. This can be explained by degradation of the phenolate complex **F**, and was observed over time in solution. Although the maximum achievable turnover numbers are lower than those with the DIPEA-modified catalyst systems, the phenolate complex **F** offers the advantage to carry out hydrogenations without addition of excess base under nearly neutral conditions.

Table 1: Comparison of catalyst **F** and **E**/DIPEA in the hydrogenation of (*E*)-3-phenylbut-2-enenitrile (**3a**).



Entry	Cat.	Cat. loading [mol%]	DIPEA [equiv]	*t* [h]	Conv. [%][a]	*ee* [%][b]
1	**E**	1.0	4.5	4	>99	94 (+)
2	**F**	1.0	0	4	>99	94 (+)
3	**E**	0.2	0.9	4	95	95 (+)
4	**F**	0.2	0	4	92	92 (+)
5	**E**	0.05	0.23	16	74	91 (+)
6	**F**	0.05	0	72	7	94 (+)

[a] Determined by GC on an achiral stationary phase. [b] Determined by HPLC on a chiral stationary phase.

In summary, we have found that addition of an external sterically hindered amine base or the presence of a basic counterion in the catalyst dramatically enhances the catalytic activity of iridium N,P ligand complexes in the hydrogenation of α,β-unsaturated nitriles. While these catalysts show no reactivity towards α,β-unsaturated nitriles under normal base-free conditions, the base-activated catalyst systems allow smooth hydrogenation at low catalyst loadings, thus affording the corresponding saturated nitriles with high conversion and excellent enantioselectivity. In contrast, other alkenes lacking a conjugated cyano group do not react under these reaction conditions. So it becomes possible to selectively reduce the cyano-substituted C=C bond of an α,β-unsaturated nitrile, thus leaving less electrophilic C=C bonds in the molecule intact. Thus the catalyst systems described herein enable enantio- and chemoselective hydrogenations, for which no suitable catalysts were available before.

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