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View Article Online

Cite this: Chem. Sci., 2013, 4, 2760

Discovery of an iridacycle catalyst with improved reactivity and enantioselectivity in the hydrogenation of dialkyl ketimines†

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Received 1st March 2013 Accepted 9th April 2013

DOI: 10.1039/c3sc50587a

www.rsc.org/chemicalscience

Catalytically active iridacycles are formed by cyclometalation of acetophenone imines with Ir–PHOX complexes under hydrogen atmosphere. These complexes show unusually high reactivity and enantioselectivity in the hydrogenation of alkyl methyl ketimines. The structure of the cyclometalated imine has a strong effect on the conversion and enantiomeric excess.

Introduction

Chiral amines play an important role as building blocks for the synthesis of pharmaceuticals and agrochemicals. They are also of great importance as chiral auxiliaries, catalysts and resolving agents. Therefore, asymmetric hydrogenation of ketimines has received much attention as an attractive, very direct route to enantiomerically enriched amines. High yields, perfect atom economy and mild conditions make this approach ideal for industrial applications. This is impressively demonstrated by the multi-ton scale production of the herbicide metolachlor, based on an extremely active and productive Ir-diphosphine catalyst.²

During the last two decades a wide range of chiral Ti, Rh, Ir, Pd, Ru,¹ and most recently Fe¹,³ complexes have been developed that catalyze the hydrogenation of various imines with high enantioselectivity. However, the scope of most catalysts is rather narrow and there are still important classes of imines that give unsatisfactory results with the available catalysts. Especially the hydrogenation of imines derived from dialkyl ketones remains a challenging problem. With the exception of the dual catalyst system reported by Xiao and co-workers,⁴ consisting of a chiral Ir(Cp*)-diamine complex and an elaborate chiral binaphtholderived phosphoric acid (TRIP), most catalysts give very low enantioselectivities with these substrates. Organocatalytic asymmetric imine reduction and reductive amination has also been developed to afford chiral aliphatic amines with high enantioselectivities.⁵ However, these reactions generally suffer

from lower yields and very long reaction times compared to transition-metal catalyzed hydrogenations. Furthermore, they require hydride donors such as dihydropyridines that generate stoichiometric waste products. So a practical readily accessible catalyst for the asymmetric hydrogenation of dialkyl ketimines remains elusive.

We have recently begun to reinvestigate Ir–phosphinooxazoline complexes that we originally introduced as catalysts for imine hydrogenation in 1997. ^{6a} After evaluation of a wide range of phosphinooxazoline (PHOX) derivatives and careful optimization of the reaction conditions, excellent enantioselectivities and high turnover numbers have been achieved in the hydrogenation of aryl alkyl *N*-arylketimines such as **I1** (Scheme 1). ^{6b}

However, analogous dialkyl ketimines still gave disappointing results. We therefore decided to conduct a mechanistic study, in the hope that it would guide the development of improved catalysts with broader substrate scope.

Results and discussion

Here we report the outcome of this study that led to surprising insights into the structure of the catalytic intermediates and, ultimately, to a new catalyst system that gave promising results in the hydrogenation of dialkyl ketimines.

Experimental mechanistic studies of imine hydrogenation with Ir-PHOX complexes have not been reported. However,

Scheme 1 Asymmetric hydrogenation of acetophenone N-phenylimine I1.

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 \uparrow Electronic supplementary information (ESI) available: Protocols for procedures and experimental data. CCDC 916564. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc50587a

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^{0.5} mol%
H₂ (10 bar)
CH₂Cl₂, -20 °C, 6 h

A1

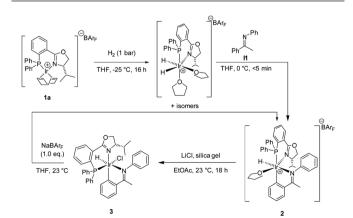
Hopmann and Bayer⁷ carried out DFT calculations with catalyst **1a** on nine different catalytic cycles based on proposed mechanisms for imine hydrogenations with other types of Ir complexes. The computed energies of the turnover-limiting transition states indicated a pathway involving proton transfer from an Ir-hydride complex to a free, uncoordinated imine, followed by hydride transfer to the resulting iminium ion. As all proposed mechanisms included Ir-dihydride complexes as intermediates, we decided to prepare a dihydride complex from the Ir(PHOX) precursor **1a** following the procedure of Mazet *et al.*⁸ and to study its reactivity with **11** as a typical substrate (Scheme 2).

When the dihydride complex, generated by reaction of 1a with $\rm H_2$ in THF at -25 °C, was treated with I1 at 0 °C, rapid formation of an iridacycle 2 was observed. This complex proved to be very sensitive and rapidly decomposed upon exposure to air. Attempts to obtain suitable crystals for X-ray analysis failed and, therefore, the BAr_F (tetrakis[(3,5-trifluoromethyl)phenyl]borate) counterion that, in our experience, often impedes crystallization, was exchanged with chloride or hexafluorophosphate. The chloride complex 3 was readily obtained by treatment with LiCl and silica gel in ethyl acetate and purified by flash chromatography on silica gel. Ion exchange with NaBAr_F in THF led back to the BAr_F complex 2.

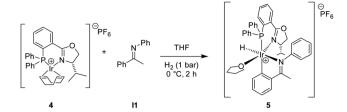
While crystallization attempts of 3 were unsuccessful, the hexafluorophosphate salt 5 furnished suitable crystals for X-ray analysis (Scheme 3 and Fig. 1). Furthermore, a preliminary crystal structure of the analogous iridacycle 7 prepared from SimplePHOX complex 6 (Scheme 4 and Fig. 2) could also be determined. 10

An analogous cyclometalation reaction of [Ir(H)₂(PPh₃)₂-(acetone)₂]PF₆ with benzaldehyde *N*-benzylimine has been reported by James and co-workers.¹¹ The resulting iridacycle was tested in the hydrogenation of imines but showed no catalytic activity.¹¹a

When complex 3 was tested as catalyst for the hydrogenation of I1, no reaction was observed. However, when the chloride was replaced with the non-coordinating anion BAr_F by addition of an equimolar amount of $NaBAr_F$, an active catalyst was generated that furnished the same enantiomer of amine A1 with identical enantioselectivity as the reduction catalyzed by the parent complex 1a (Scheme 5).



Scheme 2 Formation of cyclometalated imine complexes



Scheme 3 Preparation of iridacycle 5.

What are the possible conclusions that can be drawn from these results? The iridacycle formed under hydrogenation conditions could be an inactive species outside the catalytic cycle that is in equilibrium with an active catalytic intermediate through reversible cyclometalation/reductive elimination, similar to the reaction scheme proposed by Marcazzan and James.¹²

Alternatively, it could be directly involved in the catalytic cycle. In this case, it could either react *via* reduction of the cyclometalated imine, followed by reductive elimination releasing the saturated amine, or the cyclometalated imine could serve as a stable ligand that remains bound throughout the catalytic cycle.

To distinguish between these possibilities we carried out the cross-over experiment shown in Scheme 6. If a catalytic intermediate derived from 3 would release the free imine I1, the cyclometalation product of substrate I2 along with amine A1 would be formed. However, we did not observe even traces of I1 or A1 in the course of the hydrogenation reaction by GC analysis. These results are consistent with the hypothesis that cyclometalation is irreversible and the imine remains bound to iridium throughout the catalytic reaction. The enantiomeric excess of A2 remained constant throughout the reaction. The

We speculated that the cyclometalated complex formed under hydrogenation conditions could be a superior catalyst compared to complex 1a and that the poor results in the hydrogenation of aliphatic ketimines could be a consequence of the inability of these substrates to form cyclometalated complexes.

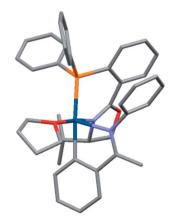


Fig. 1 Crystal structure of **5** (PF₆ counterion omitted for clarity).

Cy Po N Ph Ph THF LiCI, silica gel, Cy Po N Cy Print N C Cy Print N C

Scheme 4 Preparation of iridacycle 7.

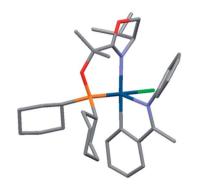


Fig. 2 Preliminary crystal structure of 7

Scheme 5 Comparison of complexes ${\bf 1a}$ and ${\bf 3}$ as precatalysts for the hydrogenation of imine ${\bf 11}$.

Scheme 6 Hydrogenation of imine ${\bf 12}$ with iridacycle ${\bf 3}$ in combination with NaBAr_F.

Indeed, the catalyst generated *in situ* from the iridacycle 3 by treatment with NaBAr $_{\rm F}$ gave much higher conversion and enantioselectivity (Table 1, entry 1) in the hydrogenation of cyclohexyl methyl ketimine I3 than the parent Ir–PHOX complex 1a (entry 2) or iridacycle 3 alone (entry 3). Identical ee and higher conversion was obtained when the catalyst was generated by treating complex 1a with $\rm H_2$ and an equimolar amount of acetophenone imine I1 (entry 4). At 50 bar $\rm H_2$ pressure 71% ee and full conversion were observed after activation with imine I1 (entry 5), compared to 27% conversion and 35% ee with complex 1a alone (entry 6).

These findings clearly indicate that the new more efficient catalyst is a cationic cyclometalated complex that arises by chloride abstraction from 3 or by reaction of precatalyst 1a with H₂ and imine I1 (*cf.* structure 2 in Scheme 2). Because cationic complexes such as 2 or 5 with very weakly coordinating anions proved to be too unstable and impractical to be used as catalysts, *in situ* activation of precatalyst 1a with acetophenone imine I1 or derivatives thereof was the method of choice for further experiments.

If the imine remains bound to the catalyst throughout the catalytic cycle, it is also involved in the enantiodiscriminating step. Cyclometalation of a chiral additive to an achiral complex would thus provide a chiral imine hydrogenation catalyst. We therefore prepared chiral complex (*S*)-11 derived from an achiral iridium–PHOX complex 8 and a chiral imine 9 (Scheme 7).

NMR analysis indicated the presence of two diastereomers of complex (S)-10. However, upon treatment with an equimolar amount of NaBAr_F in CD₂Cl₂, a single hydride species (S)-11 was observed.

Both enantiomers of complex **11**, formed *in situ* from the diastereomeric mixture of (*S*)-**10ab** or (*R*)-**10ab**, were tested as catalysts for the hydrogenation of **I1** (Table 2). While low conversion was observed at atmospheric hydrogen pressure, hydrogenation at 5 bar afforded **A1** with 54% conversion (entry 3).

The resulting ee values showed a weak but reproducible influence of the chiral imine 9. Analogous catalysts derived from 1,3-benzoxazines were tested as well (Table 3) and gave reproducible enantioselectivities of up to 23% ee.

Table 1 Hydrogenation of imine **I3** using catalyst **1a** in the presence or absence of imine **I1** or using iridacycle **3** in the presence or absence of NaBAr $_{\rm F}$

Entry	Catalyst	Additive	$p(H_2)/bar$	Conv. ^a (%)	ee ^b (%)
1	3	$NaBAr_{F}$	1	40	73 (R)
2	1a	_	1	5	69 (R)
3	3	_	1	0	_ ` ´
4	1a	I1 (2 mol%)	1	50	73 (R)
5	1a	I1 (2 mol%)	50	>99	71 (R)
6	1a		50	27	35 (R)

 $[^]a$ Determined by GC analysis. b Determined by HPLC analysis on a chiral stationary phase.

Scheme 7 Preparation of chiral iridium complexes (S)-10 derived from achiral Ir-PHOX complex 8 and chiral imine 9. Upon addition of NaBAr_F, chloride abstraction results in the formation of one single hydride complex (S)-11 in solution.

(S)-11 (S = CD₂Cl₂)

Table 2 Hydrogenation of imine I1 using iridacycle 10

Entry	Catalyst	H ₂ /bar	Conv. ^a (%)	ee ^b (%)
1	(S)- 10	1	16	4 (S)
2	(R)-10	1	18	6 (R)
3	(S)-10	5	54	4 (S)
4	(R)- 10	5	44	6 (R)

 $[^]a$ Determined by GC analysis. b Determined by HPLC analysis on a chiral stationary phase.

Erosion of enantioselectivity was observed when hydrogenations were conducted at 5 bar (entries 2 vs. 3 and 4 vs. 5). Furthermore, complex 14 gave higher conversion but lower enantioselectivity than complex 13 (entries 2, 4 and 6). To get a more accurate correlation of the ee with conversion, the reaction was followed by GC and HPLC analysis (Fig. 3).

While complex 13 reacted with almost constant enantioselectivity, 14 showed a strong erosion of the enantioselectivity with increasing conversion. Furthermore, an overall higher conversion and faster reaction was observed for 14.

The following conclusions were drawn from these observations: while in 13 the benzoxazine remains bound to the iridium center throughout the reaction, complex 14 is not stable under the reaction conditions. As a consequence the benzoxazine

Table 3 Hydrogenation of imine I1 using iridacycle 12–14

Entry	Catalyst	H ₂ /bar	Conv. ^a (%)	ee ^b (%)
1	(S)-12	1	63	15 (S)
2	(S)-13	1	31	23 (R)
3	(S)-13	5	97	14 (R)
4	(R)-13	1	20	23 (S)
5	(R)-13	5	99	14 (S)
6	(R)-14	1	40	17 (S)

^a Determined by GC analysis. ^b Determined by HPLC analysis on a chiral stationary phase.

ligand is replaced by imine I1 resulting in a complex with two achiral ligands, which produces racemic product. However, the high initial enantioselectivity of 44% ee clearly demonstrates that the cyclometalated ligand is involved in the enantiodiscriminating step of the reaction.

Attempts to improve the enantioselectivity by using catalysts prepared from a combination of chiral PHOX complexes with chiral benzoxazines gave disappointing results. However, systematic evaluation of various achiral *N*-aryl acetophenone imines as additives was more successful (Table 4).

The influence of substituents in the acetophenone phenyl ring showed no apparent trends that could be correlated with steric or electronic effects. Surprisingly, *meta*-substituents distinctly lowered the enantioselectivities (entries 4–8),¹⁵ while an *ortho*-methyl or *ortho*-fluoro substituent had essentially no effect (entries 2 and 3). Overall, introduction of substituents in the acetophenone phenyl ring did not improve the enantioselectivity. In contrast, *ortho*-alkyl groups in the *N*-aryl ring resulted in enhanced

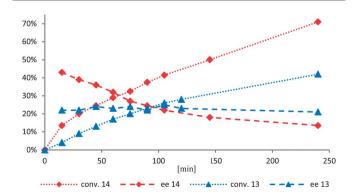


Fig. 3 Conversion (dotted) and enantioselectivity (dashed) of **A1** using iridacycle **13** (blue triangles) and **14** (red diamonds) as the catalyst.

 Table 4
 Screening of different imines as additives

$\begin{array}{cccccccccccccccccccccccccccccccccccc$	^b (%)	ee^b	Conv. ^a (%)	R'	R	Additive	Entry
3 I5 2-F H $90-95$ 71 4 I6 $3-NO_2$ H $75-99$ 48 5 I7 $3,5-(NO_2)_2$ H 10 15 6 I8 $3,5-Me_2$ H >99 3 7 I9 $3,5-Pe_2$ H 34 42 8 I10 $3,5-Pe_2$ H 11 10 9 I2 4-MeO H >99 67 10 I11 4-Pe H >99 64 11 I12 4-Me H >99 63 12 I13 4-Cl H >99 66 13 I14 4-F H >99 66 14 I15 4-CF ₃ H 95 50 15 I16 4-NO ₂ H 40 45 16 I17 4-Me 2-Br >99 78 18 I19 H 2-MeO >99 71 19 I20 <	(R)	71 (>99	Н	Н	I1	1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	(R)	69 (>99	Н	2-Me	I4	2
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(R)	71 (90-95	H	2-F	I 5	3
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(R)	48 (75-99	H	$3-NO_2$	16	4
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(R)	15 (10	H	$3,5-(NO_2)_2$	I 7	5
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(S)	3 (>99	H	$3,5$ -Me $_2$	18	6
9	(S)	42 (34	H	$3,5^{-i}$ Pr ₂	I9	7
10 I11 4-tBu H >99 64 11 I12 4-Me H >99 63 12 I13 4-Cl H >99 56 13 I14 4-F H >99 66 14 I15 4-CF ₃ H 95 50 15 I16 4-NO ₂ H 40 45 16 I17 4-Me 2-Br >99 68 17 I18 H 2-Me >99 71 18 I19 H 2-MeO >99 71 19 I20 H 3-MeO >99 68	(R)	10 (11	Н	$3,5$ - t Bu ₂	I10	8
11 I12 4-Me H >99 63 12 I13 4-Cl H >99 56 13 I14 4-F H >99 66 14 I15 4-CF ₃ H 95 50 15 I16 4-NO ₂ H 40 45 16 I17 4-Me 2-Br >99 68 17 I18 H 2-Me >99 71 18 I19 H 2-MeO >99 71 19 I20 H 3-MeO >99 68	(R)	67 (>99	Н	4-MeO	I 2	9
12 I13 4-Cl H >99 56 13 I14 4-F H >99 66 14 I15 4-CF ₃ H 95 50 15 I16 4-NO ₂ H 40 45 16 I17 4-Me 2-Br >99 68 17 I18 H 2-Me >99 71 18 I19 H 2-MeO >99 71 19 I20 H 3-MeO >99 68	(R)	64 (>99	Н	4- ^t Bu	I11	10
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(R)	63 (>99	H	4-Me	I12	11
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	(R)	56 (>99	H	4-Cl	I13	12
15 I16 4-NO2 H 40 45 16 I17 4-Me 2-Br >99 68 17 I18 H 2-Me >99 78 18 I19 H 2-MeO >99 71 19 I20 H 3-MeO >99 68	(R)	66 (>99	Н	4-F	I14	13
16 I17 4-Me 2-Br >99 68 17 I18 H 2-Me >99 78 18 I19 H 2-MeO >99 71 19 I20 H 3-MeO >99 68	(R)	50 (95	H	$4\text{-}\mathrm{CF}_3$	I15	14
17 I18 H 2-Me >99 78 18 I19 H 2-MeO >99 71 19 I20 H 3-MeO >99 68	(R)	45 (40	Н	$4-NO_2$	I16	15
18 I19 H 2-MeO >99 71 19 I20 H 3-MeO >99 68	(R)	68 (>99	2-Br	4-Me	I17	16
19 I20 H 3-MeO >99 68	(R)	78 (>99	2-Me	H	I18	17
	(R)	71 (>99	2-MeO	H	I19	18
20 121 H 4 MaO >00 60	(R)	68 (>99	3-MeO	H	I20	19
20 121 n 4-MeO >99 69	(R)	69 (>99	4-MeO	H	I21	20
21 I22 H 4-CF ₃ >99 59	(R)	59 (>99	$4-CF_3$	Н	I22	21
22 I23 H 2- ⁱ Pr >99 81	(R)	81 (>99	2- ⁱ Pr	Н	I23	22
23 I24 H 2,6-Me ₂ >99 85	(R)	85 (>99	$2,6-Me_2$	H	I24	23

 $[^]a$ Determined by GC analysis. b Determined by HPLC analysis on a chiral stationary phase.

enantioselectivity (entries 17, 22 and 23). Other iridium complexes were screened as well, but none of them reached the enantioselectivities achieved with PHOX complex 1a.¹³

With an optimized catalyst system in hand we studied the scope for the hydrogenation of aliphatic ketimines (Table 5). Higher conversions and enantioselectivities were obtained in all cases compared to reactions using complex 1a alone. The high reactivity of this catalyst system allowed lowering the reaction temperature to -5 °C. Under these conditions imine I3 furnished the product A3 with an improved ee of 92% and full conversion (entry 4). Isopropyl methyl ketimine I25 gave 84% ee but only 33% conversion (entry 5). The ee was further improved when the more bulky complex 1b was used as precatalyst for isobutyl methyl ketimine I26 and benzyl methyl ketimine I27 (entries 8 and 10). However, for α -branched alkyl methyl ketimines such as I3, I25, I31 and I32, no reaction was observed with complex **1b**. The sterically less demanding *n*-alkyl methyl ketimines I28, I29 and I30 gave markedly lower enantioselectivity (entries 11-13). Chemoselective hydrogenation of an imine double bond in the presence of a trisubstituted olefin can be achieved as shown in **I29** (entry 12).

 Table 5
 Asymmetric hydrogenation of N-phenyl aliphatic imines

					1b R = ^t Bu		
Entry	Substrate	Catalyst	Additive	T/°C	Conv. ^a (%)	ee ^b (%)	
1 2 3 4	N Ph	1a 1a 1a 1a	I1 I1 I24 I24	23 -5 23 -5	>99 >99 >99 >99	71 (<i>R</i>) 73 (<i>R</i>) 85 (<i>R</i>) 92 (<i>R</i>)	
5	N Ph	1a	I24	-5	33	84 (R)	
6 7 8	N Ph	1a 1a 1b	I1 I24 I24	-5 -5 -5	>99 >99 >99	49 (-) 70 (-) 80 (-)	
9 10	Ph Ph	1a 1b	I24 I24	-5 -5	>99 94	62 (+) 72 (+)	
11	N Ph	1b	I24	-5	>99	52 (-)	
12	N. Ph	1b	124	-5	>99 ^c	56 (-)	
13	N Ph 5 130	1b	I24	-5	>99	57 (R)	
14	N Ph	1 a	I24	-5	8	63 (-)	
15	N Ph	1a	11	-5	8	46 (R)	

^a Determined by GC analysis. ^b Determined by HPLC analysis on a chiral stationary phase after purification by flash chromatography. ^c Contained <3% of fully saturated product.</p>

To see whether the *N*-phenyl group was essential for achieving high enantioselectivity, we investigated *N*-alkyl imines **I33–I36** as substrates (Table 6). Asymmetric hydrogenation of imines of this

type has not been reported yet apart from I33. As these substrates proved to be less reactive, hydrogenations were conducted at room temperature. Using imine I1 as additive the *N*-benzylimine I33 furnished a moderate ee of 44% (entry 1). An even lower enantioselectivity is observed for the *N*-*n*-butylimine I34 (entry 2). On the other hand almost the same ee as for corresponding *N*-phenylimine I3 was observed in the hydrogenation of I35 (entry 3). The *N*-cyclohexyl analogue I34 reacted with even higher enantioselectivity of 77% ee (entry 4), demonstrating that purely alkyl-substituted imines are suitable substrates for this catalyst system. The more bulky complex 1b and the sterically demanding *N*-(2,6-dimethylphenyl)imine I24 afforded lower yields and enantioselectivities with these substrates.

Conclusions

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We have found that the active catalyst in the hydrogenation of acetophenone-derived imines with Ir–PHOX precatalysts is an iridacycle generated under hydrogenation conditions by cyclometalation of the substrate. Cyclometalated complexes of this type, formed *in situ* by addition of an equimolar equivalent of acetophenone imine, show higher reactivity and better enantioselectivity in the hydrogenation of *N*-phenyl and *N*-alkyl aliphatic ketimines than the corresponding Ir-PHOX complex alone. Obviously, the reaction proceeds through a pathway that differs from the catalytic cycles proposed in the literature. Although at present the scope is still limited, our findings indicate many opportunities for further improvement of this catalyst system by structural variation of both the chiral P,N ligand and the cyclometalated imine.

Experimental section

Screening

Imine (0.1 mmol), catalyst (2 μ mol), additive (2 μ mol), and a stir bar were added to an oven-dried glass vial that had been placed

 Table 6
 Asymmetric hydrogenation of N-alkyl aliphatic imines

Entry	Substrate (R)	Conv. ^a (%)	ee ^b (%)
1	I33 (CH ₂ Ph)	>99	44 (R) ^c
2	I34 (ⁿ Bu)	>99	33 (R)
3	I35 (ⁱ Pr)	>99	73 $(R)^d$
4	I36 $(c-C_6H_{11})$	>99	$77 (R)^c$

 $[^]a$ Determined by GC analysis. b Determined by GC or HPLC analysis on a chiral stationary phase after derivatisation. c Determined after derivatisation to the 1-naphthoyl amide. d Determined after derivatisation to the acetamide.

in an autoclave (60 mL) and purged with argon for 5 min. Anhydrous CH_2Cl_2 (1 mL) was added by syringe under a stream of argon and the autoclave was closed. For reactions at low temperature the autoclave was immersed in a cooling bath for 60 min before starting the reaction. The autoclave was pressurized with hydrogen gas, hydrogen was released and the autoclave pressurized again. It was then placed on a stirring plate for the time indicated. After releasing the pressure, the solvent was evaporated under a stream of nitrogen. The residue was suspended in pentane–diethyl ether (5:1) and filtered through a short elution plug (cotton bottom, 40×5 mm silica gel). The crude filtrate was analysed by GC for conversion before being purified by flash chromatography (SiO₂, pentane–diethyl ether (20:1), 15×2 cm) and analysed by HPLC on a chiral stationary phase for determination of the enantiomeric excess.

Preparative reaction

Imine I3 (1.005 g, 5 mmol), 1a (0.1 mmol), I24 (0.1 mmol), and a stir bar were added to a 25 mL Pyrex oven-dried glass vial that had been placed in an autoclave (60 mL) and purged with argon for 5 min. Anhydrous CH_2Cl_2 (5 mL) was added by syringe under a stream of argon and the autoclave was closed. The autoclave was immersed in a cooling bath for 60 min at -5 °C before it was pressurized with hydrogen gas. Hydrogen was released and the autoclave pressurized again before being placed on a stirring plate for 18 h. After pressure release the reaction mixture was transferred to a 50 mL round-bottom flask and solvents removed under reduced pressure. The residue was suspended in pentane–diethyl ether (20 : 1) and purified by flash chromatography (SiO₂, pentane–diethyl ether (10 : 1), 21 × 3 cm). Solvents were removed under reduced pressure and the residue was dried *in vacuo* to afford A3 (998 mg, 4.92 mmol, 98%).

Acknowledgements

Support of this work by the *Swiss National Science Foundation* (*SNF*) and the *Federal Commission for Technology and Innovation* (*KTI*) is gratefully acknowledged. We thank Dr Markus Neuburger for the crystal structure analysis, Robin Wehlauch for synthetic contributions and Prof. Dr Klaus Dittrich from *BASF* for generous gifts of chemicals.

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