Asymmetric reduction of ketimines with trichlorosilane employing an imidazole derived organocatalyst†

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Organocatalysts for the asymmetric reduction of ketimines are presented that function well at low catalyst loadings providing chiral amines in good yield and enantioselectivity, the latter appearing to be independent of the ketimine substrate geometry.

Trichlorosilane is a cheap and versatile reducing agent that has been used in applications as diverse as the reduction of chiral phosphine oxides to phosphines with conservation of stereochemical information, the hydrometallation of alkynes and the synthesis of disulfide compounds.[1] Kobayashi demonstrated that it could also function as a reducing agent for aldehydes, ketones and imines if a catalytic amount of DMF was present.[2] This spurred an effort to build suitable chiral catalysts which were often derived from natural amino acids or compounds from the chiral pool. These were, from a structural point of view, chiral DMF analogues.[3]

Even though the formamide paradigm is versatile, asymmetric imine reductions using trichlorosilane have evolved further. Matsumura *et al.*, for instance, used diphenylprolinol instead of proline as a core scaffold and replaced the formyl moiety by a picolinoyl fragment to give catalyst **1** (Fig. 1).[4] Kočovský *et al.* have progressed this by preparing several catalysts containing an oxazoline attached to a quinoline **2** or pyridine **3**, the latter being particularly versatile and can be used to reduce imines and ketones with equal ease.[5]

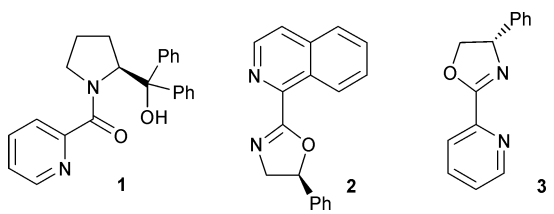

Fig. 1 Examples of chiral catalysts previously used for the asymmetric hydrosilyation of ketones and ketimines.

Our group has a long standing interest in bifunctional catalysts featuring an imidazole ring,[6] and there is a striking similarity between Kočovský's oxazoline **3** and catalyst **4** (Scheme 1), which had been previously prepared in our group but never assessed in this reaction.[7] This prompted us to investigate the use of this and related compounds **5–8** in this type of transformation.

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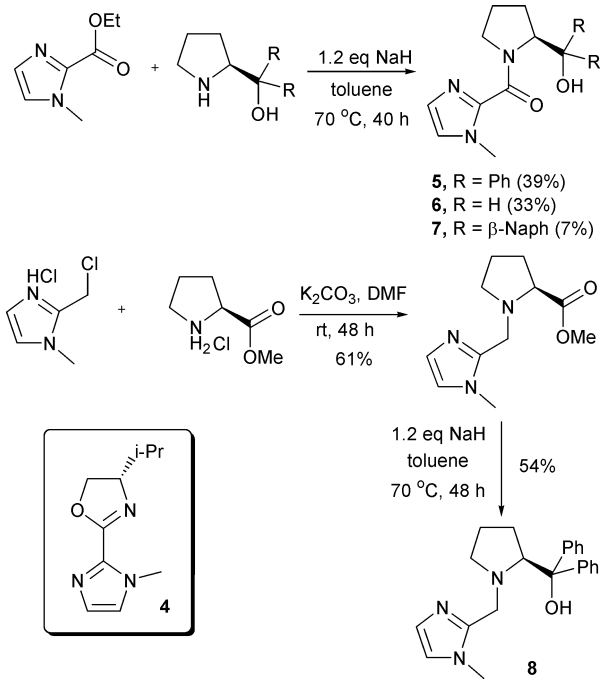
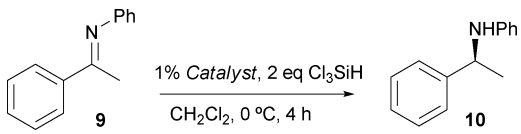
Catalysts **5–7** were prepared in acceptable yield for evaluation purposes by condensation of the appropriate prolinol derivative with ethyl 1-methylimidazole-2-carboxylate (Scheme 1). Catalyst **8** was prepared by nucleophilic displacement of 2-chloromethyl-1-methylimidazole hydrochloride, followed by reaction with excess Grignard reagent.



Scheme 1 Preparation of catalysts.

These five catalysts were then assessed in the reduction of acetophenone imine **9** to *N*-phenyl-1-phenylethanamine **10** using trichlorosilane as the reductant. Catalysts **4–7** all accelerated the rate of the reaction, with catalyst **8** showing essentially no catalytic activity and selectivity, stressing the importance of the role of the amide functionality in this reaction (Scheme 2, Table 1). The oxazoline **4** only gave modest enantioselectivity, in contrast to the *gem*-diphenyl and *gem*-β-dinaphthyl prolinol derivatives **5** and **7** which gave the best all round results. Removal of the geminal groups led to a substantial drop in ee (catalyst **6**, entry 3).



Scheme 2

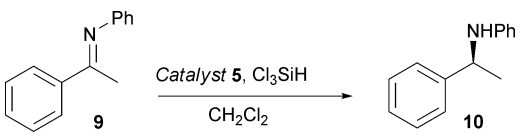
Table 1 Asymmetric hydrosilylation of *N*-phenyl acetophenone imine **9** according to Scheme 2[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]/configuration[d]
1[e]	**4**	80	23 (*R*)
2	**5**	77	86 (*S*)
3	**6**	84	47 (*S*)
4	**7**	68	87 (*S*)
5	**8**	20	3 (*S*)

[a] The reaction was performed by addition of trichlorosilane (2.0 mmol) to a stirred solution of ketimine **9** (1.0 mmol) and ligand (0.01 mmol) in dry CH_2Cl_2 (1 mL) under an atmosphere of nitrogen at 0 °C. After 4 h, the reaction was quenched with 1 M HCl (1 mL) and subjected to standard work-up procedures. [b] Based on isolated product. [c] Determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture. [d] Confirmed by comparison of HPLC retention times and specific rotations with those in the literature. [e] Reaction conducted with 10 mol% catalyst.

Catalyst **5** was taken forward for further optimization (Table 2, Scheme 3). The first and most remarkable discovery with catalyst **5** was the low loading that could be tolerated in the reaction without detrimental effects on enantioselectivity (entries 1–3). This compares well with other benchmark catalysts for *N*-aryl substrates; catalyst **1** provides 67–90% yields in 71–80% ee at 20 mol%, while catalyst **2** provides 51–67% yields in 86–87% ee at 20 mol%. At 1 mol% loading, temperature had little effect on the outcome (entries 3–5), although the initial concentration of the imine and the equivalents of Cl_3SiH used did (entries 6–9), and this could be used to offset the drop in yield when using low catalyst loadings, while additionally helping to reduce reaction times. Attempts to lower the catalyst loading of the optimized reaction conditions (entry 9) further led to erosion in both yield and selectivity of the reaction (entry 10). Switching the solvent to $CHCl_3$ gave a marginal improvement in ee (entry 11) while toluene led to a reduced yield of product (entry 12).

The applicability of the catalyst was next evaluated with a selection of diverse ketimines (Fig. 2, Table 3). Significant improvement in yield was observed when the parent substrate **9** was changed to the *N*-*p*-methoxyphenyl analogue **12** (entries 1 and 3), presumably since this more electron rich ketimine can undergo more efficient binding to the Cl_3SiH. This is also highlighted with strongly electron withdrawing aryl groups giving poor yields (entry 4). However, in this acetophenone series, essentially no improvement in selectivity was noticeable. A similar trend is also observed for propiophenone derived substrates **16** and **17** (entries 7 and 8), although a somewhat surprising low yield and selectivity is obtained with tetralone derivatives (entries 9 and 10). The ratio of the ketimine geometric isomer did not seem to have great influence on the outcome of the reaction, most remarkably demonstrated with the α-naphthyl derivative **21** (entry 12). This latter observation is of particular interest, since the substrates need not be geometrically pure, which is of significant advantage when one considers the difficulty in preparing and handling the sensitive ketimine substrates, let alone purifying them to a single geometric isomer. This is in stark contrast to oxazaborolidine catalysed borane reductions of oximes where stereospecific reduction of



Scheme 3

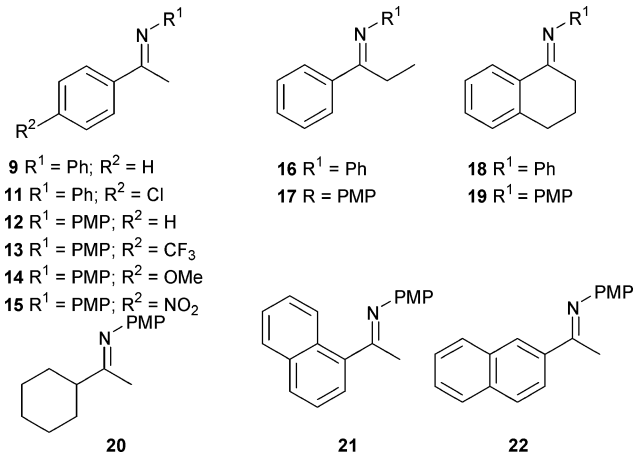


Fig. 2 Substrates used to evaluate the applicability of catalyst **5**.

Table 2 Optimisation of the asymmetric hydrosilylation of *N*-phenyl acetophenone imine **9** using catalyst **5**[a]

Entry	Time/h	T/°C	Cl_3SiH (eq)	Catalyst **5** (eq)	$[imine]_0$/mol L^{-1}	Yield (%)[b]	ee (%)[c]
1	13	0	1.5	0.1	0.4	59	87
2	13	0	1.5	0.05	0.4	65	86
3	13	0	1.5	0.01	0.4	45	85
4	13	25	1.5	0.01	0.4	39	83
5	13	–20	1.5	0.01	0.4	42	88
6	13	15	1.5	0.01	2.0	56	83
7	13	15	1.5	0.01	0.2	32	84
8	13	15	4	0.01	0.4	76	84
9	4	0	2	0.01	2.0	82	85
10	4	0	2	0.001	2.0	57	77
11[d]	4	0	2	0.01	2.0	81	86
12[e]	4	0	2	0.01	2.0	76	86

[a] The reaction was performed by addition of trichlorosilane to a stirred solution of ketimine **9** and catalyst in dry CH_2Cl_2 under an atmosphere of nitrogen. After the required time, the reaction was quenched with 1 M HCl (2 mL) and subjected to standard work-up procedures. [b] Based on isolated product. [c] Determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture. In all cases the (*S*) enantiomer was formed as the major product. [d] Reaction performed using $CHCl_3$ as solvent. [e] Reaction performed using toluene as solvent.

Table 3 Evaluation of substrate specificity and reactivity in the hydrosilylation catalysed by catalyst **5**[a]

Entry	Ketimine	Ketimine ratio[b]	Yield (%)[c]	ee (%)[d]
1	**9**	100 : 0	82	85
2	**11**	100 : 0	77	85
3	**12**	100 : 0	96	87
4	**13**	100 : 0	72	82
5	**14**	100 : 0	81	85
6	**15**	100 : 0	85	86
7	**16**	91 : 9	59	79
8	**17**	88 : 12	95	83
9	**18**	100 : 0	42	19
10	**19**	100 : 0	41	22
11	**20**	80 : 20	85	73
12	**21**	60 : 40	71	74
13	**22**	100 : 0	86	86

[a] The reaction was performed using optimized conditions as described in Table 2, entry 9. [b] Relative ratio of *E*/*Z* isomers determined by ^{1}H nmr spectroscopy. [c] Based on isolated product. [d] Determined by integration of the appropriate signals in the HPLC chromatogram of the crude reaction mixture.

each geometric isomer is observed.[8] Similar results have been remarked upon previously, but insufficient experimental data has been accrued to facilitate interpretation of this result.[9] For ketimines **9**, **12–15**, **20**, and **22**, the absolute stereochemistry of the product was confirmed to be (*S*) by comparison of the specific rotation with compounds of known configuration.[10] However, in the case of the other amine products, no unambiguous report of the absolute configuration have been reported and these are therefore assumed to be (*S*) by analogy.

In conclusion, we have developed a catalyst for the asymmetric reduction of a wide variety of ketimines at low catalyst loadings, the selectivity of which appears to be independent of the geometric purity of the substrate. Further studies which capitalize upon this reactivity and selectivity are underway.

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