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Evaluating dynamic kinetic resolution strategies in the asymmetric hydrosilylation of cyclic ketimines

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ABSTRACT

Attempts at performing dynamic kinetic resolution on a series of cyclic ketimines by making use of an asymmetric organocatalysed hydrosilylation gave modest conversion and moderate to good enantioselectivities. In the case of α-tetralone derivatives, the use of an *N*-benzyl protecting group was found to be crucial in obtaining enhanced levels of selectivity.

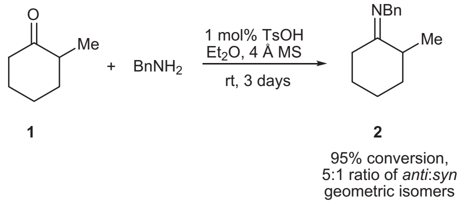
1. Introduction

Chiral amines are an important class of organic compounds, and are widely used as building blocks in synthetic chemistry. A large number of active pharmaceutical ingredients (API's) are amines or contain functional groups derived from amines, making up about one-third of the total chiral API market. It is not surprising then that many of the developments in modern catalytic asymmetric synthesis have targeted the synthesis of this class of molecules and, in particular, over the past 15 years, there have been many new organocatalysts developed that facilitate the reduction of ketimines with trichlorosilane.[1] A wide range of catalyst systems have been developed from a number of research groups and evaluated against a series of benchmark ketimine substrates to compare reactivity and selectivity. More recently, there have been sporadic and innovative examples of the application of this methodology to access more challenging target molecules containing a more diverse array of functional groups such as benzoxazinones and quinoxalinones.[2,3]

Although studies of the mechanism of the organocatalysed reduction of ketimines with trichlorosilane have not been reported in any substantial detail, there are numerous experimental observations that are of interest. Our research and that from others has noted that there is no linear relationship between the stereochemical outcome of the reaction and the initial *E*/*Z* ratio of the ketimine.[4] This in turn must mean that inter-conversion of the ketimine geometric isomers must occur during the reaction, presumably via an enamine intermediate. Thus it is reasonable to assume that a substrate bearing a stereogenic centre adjacent to the ketimine might be suitable for conducting dynamic kinetic resolution, hence setting up two new contiguous stereogenic centres. Such an approach has previously been adopted and successfully employed by Kocovsky et al. using their L-valine-derived formamide as an organocatalyst, providing direct access to a range of β-amino acid derivatives in high yield and with good diastereoselectivities and enantioselectivities.[4e] Zheng et al. also made similar observations with cyclic β-enamino esters.[4f] However, no investigation has been made of substrates bearing stereogenic centres with no adjacent electron withdrawing group. Herein we report on the potential efficacy of such substrates for this class of reaction.

2. Results and discussion

The initial benchmark substrate was imine **2**, which was formed by condensation of α-methylcyclohexanone **1** and benzylamine in good yield as a mixture in a 5:1 ratio of *anti*:*syn* geometric isomers (Scheme 1).[5]



Scheme 1. Preparation of substrate **2**.

The asymmetric reduction of imine **2** was performed with 2 equiv of $HSiCl_3$ in dry CH_2Cl_2 for 24 h at 0 °C in the presence of 5 mol % of catalyst **4**. This afforded amine **3** in moderate yield and diastereoselectivity (7:1), but with low enantioselectivity (25% ee) for the major *syn*-product (Scheme 2). The relative stereochemistry of this product was confirmed by COSY and nOe studies, and the absolute configuration was determined as (1*R*,2*S*) by removal of the benzyl protecting group, formation of the hydrochloride salt **5** and comparison of the specific rotation with that in the literature.[6]

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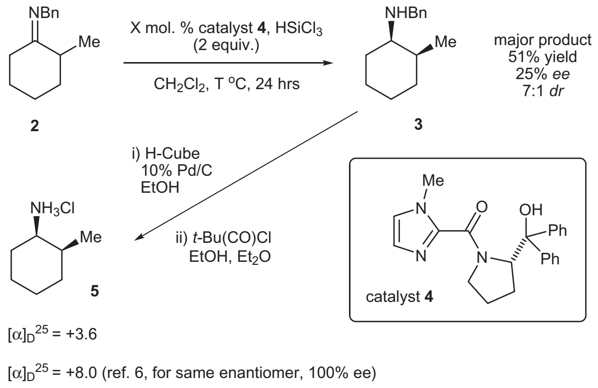

Scheme 2. Asymmetric reduction of ketimine **2**.

A variety of reaction conditions were then evaluated in an attempt to better understand the reaction parameters and hence optimise the yield and selectivity (Table 1).

Table 1
Optimisation of the asymmetric reduction of α-methyl cyclohexylimine **2** as described in Scheme 2

Entry[a]	Catalyst loading (mol %)	T (°C)	Yield[b] (%)	ee[c] (%)	*syn:anti*[d]
1	1	0	42	27	8:1
2	5	0	51	25	7:1
3	10	0	67	17	7:1
4[e]	5	0	43	32	6.5:1
5	1	−78	Trace	NA	NA
6	5	−78	18	63	5.4:1
7	10	−78	36	77	6.2:1
8[f]	10	−78	25	77	6.7:1
9	100	−78	37	79	9.9:1
10	10	−15	57	15	4.6:1
11	10	−40	48	17	5:1
12	0	0	85	NA	2.2:1
13	0	−78	0	NA	NA

[a] Reactions were performed with 2 mmol of imine **2** and 2 equiv of $HSiCl_3$ in 10 mL of dry CH_2Cl_2 and stirred for 24 h unless otherwise stated.

[b] Refers to yield of the major isomer after purification by silica gel chromatography.

[c] Determined by chiral phase HPLC analysis of the major isomer after purification by silica gel chromatography.

[d] Determined from the ratio of appropriate signals in the ^1H NMR spectrum of the unpurified reaction mixture.

[e] Reaction was performed in 20 mL of dry CH_2Cl_2.

[f] Reaction was pretreated with $HSiCl_3$ at −78 °C, the mixture of imine **2** and catalyst **4** was stirred at 0 °C for 30 min.

The yield of product **3** was improved by increasing the catalyst loading from 1 to 5%, and to 10 mol % at 0 °C. However, the enantioselectivity did not improve, and the diastereoselectivity of reactions essentially remained unchanged at approximately 7:1 (Table 1, entries 1–3). Decreasing the concentration of catalyst **4** provided similar results (entry 4). Performing the reaction at low temperature led to a significant increase in the enantioselectivity compared with those obtained at 0 °C, but reaction yields were significantly lower (entries 5–7). Increasing the catalyst loading to 100 mol % showed no significant improvement in the performance of the reaction, but slightly increased the diastereoselectivity (entry 9). Alternative temperatures (−15 °C and −40 °C) (entries 10 and 11) provided similar results to those obtained at 0 °C. Background reactions were performed at 0 °C and −78 °C, with very good conversion obtained at 0 °C whilst no reaction occurred at −78 °C.

The data imply that the high yields and low selectivities at ambient temperature are a function of a highly competitive background reaction, whilst at a much lower temperature (<−40 °C and >−78 °C), this background reaction is suppressed, thus facilitating stereoselective reduction.

The optimum reaction conditions were then studied in more detail. When the course of the reaction was examined with respect to time (Table 2), within experimental error, the diastereoselectivity essentially remained unchanged over the course of the reaction, with the enantiomeric excess decreasing with increasing conversion.

This is consistent with the data obtained in Table 1, where, within experimental error, the diastereomeric ratio remains fairly constant under different reaction conditions. The constant diastereomeric ratio over the course of the reaction indicated that the reaction may not be proceeding through the proposed dynamic kinetic resolution process, but instead proceed via equilibration of the ketimine at the kinetically more accessible centre, removing any $A_{1,3}$ strain between the nitrogen atom and adjacent methyl group (Fig. 1). This would then mean that the reaction would most likely proceed via a parallel kinetic resolution process.[7] Unfortunately, further evidence to corroborate this based on the enantiomeric excesses of the recovered ketimine and minor diastereoisomer could not be obtained due to the instability of the recovered ketimine and the small amounts of minor isomer that were produced.

Table 2
Examination of asymmetric reduction of ketimine **2** over time as described in Scheme 2 (10 mol % catalyst **4**, T = 0 °C)

Entry[a]	Time (h)	Conv.[b] (%)	ee[c] (%)	*syn:anti*[b]
1	1	16	85	–
2	3	22	83	–
3	12	23	82	7:1
4	36	24	81	5:1
5	48	28	78	4:1
6	72	52	77	6:1

[a] Reactions were performed with 2 mmol of imine **2** and 2 equiv of $HSiCl_3$ in 10 mL of dry CH_2Cl_2 and stirred for 24 h unless otherwise stated.

[b] Determined from the ratio of appropriate signals in the ^1H NMR spectrum of the unpurified reaction mixture.

[c] Determined by chiral phase HPLC analysis of the major isomer after purification by silica gel chromatography.

Attempting to apply our ‘one-pot’ reductive-amination protocol[8] failed to provide any significant improvement, giving a moderate 37% yield of the same *syn*-isomer as the major product, but with only 15% enantioselectivity (Scheme 3). The major product of this one-pot procedure was the same as that of the reaction in Scheme 2.

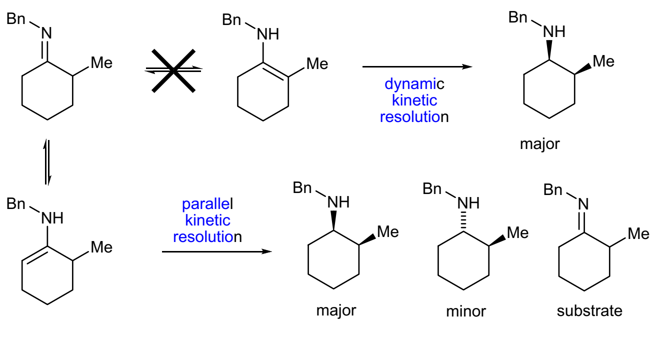

Figure 1. Possible mechanisms for the selectivity.