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Asymmetric synthesis of 1-substituted-1-(pyridin-2-yl)methylamines by diastereoselective reduction of enantiopure *N*-*p*-toluenesulfinyl ketimines

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Abstract—Reduction of enantiopure *N*-*p*-toluenesulfinyl ketimines derived from 2-pyridyl ketones affords *N*-*p*-toluenesulfinyl amines with good yields and diastereoselectivities.

In some recent reports, we have pointed out that ruthenium(II) complexes having achiral 2-pyridyl amines as co-ligands, namely RuCl[(2-CH_2–6-MeC_6H_3)PPh_2]-(CO)(L),[1a,b] *cis*-$RuCl_2$(PP)(L)[1c] (L = 1-(pyridin-2-yl)-methylamine; PP = diphosphine) and RuCl(*CNN*)-[$Ph_2P(CH_2)_4PPh_2$] (H*CNN* = 1-(6-phenylpyridin-2-yl)-methylamine),[2] exhibit high activity in transfer hydrogenation of ketones in 2-propanol. In order to prepare the related chiral 2-pyridyl amine metal complexes, we required a practical procedure for accessing chiral nonracemic 1-substituted-1-(pyridin-2-yl)methylamines. Among the approaches,[3] we considered the diastereoselective reduction of enantiopure pyridyl imines derived from 2-pyridyl ketones.[4] For this purpose the proper choice of the nitrogen chiral substituent is of crucial importance, since it not only must enable the preparation of stable imine, but also must be inexpensive and straightforward to remove without loss of optical purity from the amine product. The *N*-*p*-toluenesulfinyl substituent pioneered by Davis and co-workers[5] satisfies many of these criteria.[6] Moreover, high diastereofacial selectivity has been obtained in the reduction of *N*-*p*-toluenesulfinyl ketimines derived from both dialkyl and aryl alkyl ketones.[7,8] Therefore, we sought to adapt this procedure to our specific needs (Fig. 1).

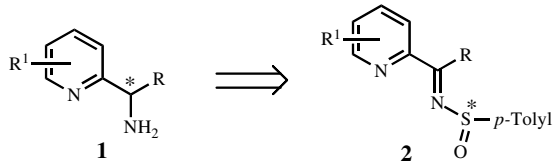

Figure 1.

Herein, we report the preliminary results obtained in the reduction of a number of chiral *N*-*p*-toluenesulfinamides **2** derived from 2-pyridyl ketones **3** (Scheme 1).

N-*p*-Toluenesulfinyl ketimines (S_S)-**2a**–**f** were obtained by condensation of commercially available (*S*)-(+)-*p*-toluenesulfinamide (S_S)-**4** (1 equiv) with a series of 2-pyridyl ketones **3a**–**f** (1.1 equiv) with varying steric and electronic demand about the carbonyl. The reactions were performed[9] employing $Ti(OEt)_4$ (2 equiv) in CH_2Cl_2 at 40 °C for **2a** (45%) and **2b** (37%) or THF at 70 °C for **2c** (40%), **2d** (75%), **2e** (34%) and **2f** (67%). All imines were obtained as a single isomer as determined by the ^{1}H NMR spectra.

The reduction of (S_S)-**2a**–**f** with three hydride transfer reagents under a variety of conditions was examined (Table 1). The extent of the asymmetric induction was determined directly by ^{1}H NMR on the diastereoisomeric mixture of sulfinamides **5a**–**f**. All reductions were initially carried out using $NaBH_4$,[10] which afforded good yields of the sulfinamides **5a**–**f**, but low diastereoselectivities.

Keywords: Pyridyl amines; *N*-*p*-Toluenesulfinyl ketimines; Nitrogen heterocycles; Diastereoselective reduction.
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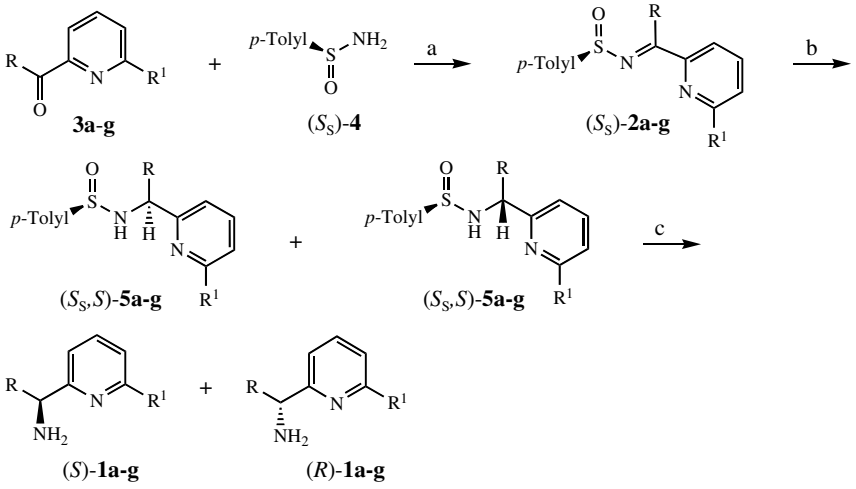

a: R = Me, R^1 = H; **b**: R = *i*-Pr, R^1 = H; **c**: R = *t*-Bu, R^1 = H; **d**: R = Ph, R^1 = H
e: R = 2-furyl, R^1 = H; **f**: R = 2-thienyl, R^1 = H; **g**: R = Me, R^1 = Br.

Scheme 1. Reagents and conditions: (a) $Ti(OEt)_4$, CH_2Cl_2 (40 °C) or THF (70 °C), 24–36 h, 34–75%; (b): Table 1; (c) CF_3COOH, MeOH, rt, 6 h.

Table 1. Reduction of (S_S)-**2a**–**g**

Entry	Compound	Reducing agent/conditions	Reaction time (h)	Ratio[a] (S_S,*R*):(S_S,*S*)-**5**	Yield[b] (%)
1	**2a**	$NaBH_4$, MeOH, 25 °C	1	55:45	95
2	**2a**	L-Selectride, THF, −78 °C	3	74:26	77
3	**2a**	L-Selectride, THF, 0 °C	3	68:32	75
4	**2a**	DIBAL, THF, −78 °C	6	16:84	90
5	**2b**	$NaBH_4$, MeOH, 25 °C	1	47:53	—
6	**2b**	L-Selectride, THF, −78 °C	3	97:3	77
7	**2b**	DIBAL, THF, −78 °C	6	71:29	87
8	**2c**	$NaBH_4$, MeOH, 25 °C	1	53:47	95
9	**2c**	L-Selectride, THF, −78 °C	10	—	No reaction
10	**2c**	L-Selectride, THF, 0 °C	24	1:1	40
11	**2c**	DIBAL, THF, −78 °C	6	96:4	92
12	**2c**	DIBAL, THF, −20 °C	6	92:8	91
13	**2c**	DIBAL, THF, 25 °C	6	92:8	45
14	**2d**	$NaBH_4$, MeOH, 25 °C	1	54:46	88
15	**2d**	L-Selectride, THF, −78 °C	3	67:33	93
16	**2d**	DIBAL, THF, −78 °C	6	60:40	91
17	**2e**	$NaBH_4$, MeOH, 25 °C	1	1:1	87
18	**2e**	L-Selectride, THF, −78 °C	3	71:29	32
19	**2e**	DIBAL, THF, −78 °C	24	1:1	40
20	**2f**	$NaBH_4$, MeOH, 25 °C	1	1:1	89
21	**2f**	L-Selectride, THF, −78 °C	10	75:25	35
22	**2f**	DIBAL, THF, −78 °C	24	—	No reaction
23	**2f**	DIBAL, THF, −20 °C	48	72:28	57
24	**2g**	DIBAL, THF, −78 °C	6	<2:>98	90

[a] Ratio of the crude reaction mixture determined by ^1H NMR.
[b] Isolated yields.

Using L-Selectride[11] or DIBAL,[12] yields and diastereoselectivities were greatly dependent on the nature of the substituent on the imino moiety. Thus, with **2a** (R = Me) higher selectivity was obtained with DIBAL (68% de), whereas L-Selectride was the better stereoselective reducing agent with **2b** (R = *iso*-propyl) (94% de). Moreover, with DIBAL as the reducing agent, the diastereoselectivity was reversed in going from **2a** to **2b**, yielding (S_S,*R*)-**5** as the major isomer in the reduction of **2b**. L-Selectride gave no reaction with **2c** (R = *tert*-butyl) whereas DIBAL gave high yield and diastereoselectivity (up to 92% de), with minimal effect of reaction temperature on the stereoselective outcome. With **2d** and **2f** (R = phenyl and thienyl, respectively) both L-Selectride and DIBAL gave similar stereochemical results (up to 50% de). Finally, with **2e** (R = furyl) diastereoselective reduction occurred only with L-Selectride (42% de).

In order to determine the configuration of the new stereocentre in the reduction products, an enriched mixture

of the diastereoisomers of **5a**,**b** and **5d** was converted (CF_3COOH, MeOH, rt, 6 h, 85–90%)[13] to the optically active amines **1a**,[14] **1b**[15] and **1d**,[14] respectively, for which the correlation between configuration and sign of the optical rotation has previously been established. In this way, it has been possible to determine that in the ^1H NMR spectra the resonances of the protons at the 6-position of the pyridine ring of the (S_S,*R*)-diastereomers of **5a**,**b** and **5d** are shifted downfield with respect to those of the related (S_S,*S*)-diastereomers. By analogy, the configurations to the diastereomers of **5c** and **5e**–**g** have been tentatively assigned.

It has been reported than the diastereoselectivity of addition reactions involving functionalised pyridines depends on the position of the functional group with respect to the pyridine nitrogen. For instance, the Michael addition of chiral nonracemic lithium amides to *tert*-butyl 3-(pyridin-3-yl)- and 3-(pyridin-4-yl)prop-2-enoates afforded the addition product in good yields and diastereoselectivities (84%), whereas the application of this methodology to the analogous β-2-pyridyl system afforded very low levels of stereoselectivity (6% de) unless the pyridine ring was also substituted at the 6-position.[16]

In order to probe the influence on the diastereoselectivity of a substituent at the 6-position of the pyridine ring in our system, the 4-methyl-*N*-[1-(6-bromopyridin-2-yl)ethylidene]benzenesulfinamide (S_S)-**2g** was prepared in the usual way ($Ti(OEt)_4$, THF, 60 °C, 4 h, 85%) from 1-(6-bromopyridin-2-yl)ethanone (**3g**). Reduction of **2g** with DIBAL at −78 °C afforded a 1.5:98.5 mixture of diastereomers. The increase in facial selectivity observed upon reduction relative to the unsubstituted system **2a**, appears to indicate that the group at the 6-position of the pyridine ring serves to sterically impede the competing coordination of the pyridyl nitrogen to the aluminium. This reduced coordination to the pyridyl nitrogen would then minimise disruption of the normal chelation-controlled transition state,[7a,8] thus disfavouring the competing nonstereoselective pathway for the reduction.

In conclusion, we have developed a method for the preparation of 2-pyridyl amines with moderate to good diastereoselectivities. This procedure, which complements existing ones, has been particularly successful for the preparation of a *tert*-butyl substituted pyridyl amine, where all other methods failed. Moreover, the finding that 1-substituted *N*-toluenesulfinyl 1-(6-bromopyridin-2-yl)methylamines (such as **5g**) can be obtained with very high diastereoselectivity and the consideration that the *N*-toluenesulfinyl group can be considered as a *N*-protecting group,[17] should allow for further elaboration of the 6-bromo substituent (e.g., via Ni(0)-catalysed homocoupling, Suzuki-type heterocoupling, etc.). Further studies on this subject are currently in progress.

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10. Representative procedure for the reduction with $NaBH_4$: A solution of (S_S)-**2a** (52.0 mg, 0.20 mmol) in MeOH (3 mL) was treated with $NaBH_4$ (15.0 mg, 0.40 mmol) at 0 °C. After 1 h at 25 °C the reaction was quenched with saturated aqueous ammonium chloride (4 mL). The crude mixture was extracted with ethyl acetate, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate = 1:1) to afford a 55:45 mixture of (S_S,*R*)-**5a**: (S_S,*S*)-**5a** (49.4 mg, 95%), mp 73–75 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, 1H, J = 4.8 Hz, major isomer), 8.49 (d, 1H, J = 4.8 Hz, minor isomer), 7.70–7.42 (m, 1H, overlapping), 6.64 (d, 2H, J = 7.8 Hz, major isomer), 7.53 (d, 2H, J = 7.8 Hz, minor isomer), 7.35–7.10 (m, 2H, overlapping), 7.31 (d, 2H, J = 7.8 Hz, minor isomer), 7.00 (d, 1H, J = 7.8 Hz, minor isomer), 5.58 (d,

1H, $J = 7.2$ Hz, major isomer), 5.31 (d, 1H, $J = 6.9$ Hz, minor isomer), 4.65–4.10 (m, 2H), 2.42 (s, 3H, major isomer), 2.37 (3H, minor isomer), 1.60 (d, 3H, $J = 6.9$ Hz, minor isomer), 1.30 (d, 3H, $J = 6.9$ Hz, major isomer). Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19; N, 10.76. Found: C, 63.86; H, 6.42; N, 10.65.

11. Representative procedure for the reduction with L-Selectride: A solution of (S_S)-**2a**(52.0 mg, 0.20 mmol) in THF (2 mL) was treated with L-Selectride (0.2 mL of a 1.0 M solution in THF, 0.20 mmol) at −78 °C. After 3 h the reaction was quenched with saturated aqueous ammonium chloride (3 mL) and extracted with ethyl acetate. The mixture was filtered through a Celite pad that was washed with ethyl acetate. The organic phase was separated, dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography to give a 74:26 mixture of (S_S,*R*)-**5a**: (S_S,*S*)-**5a** (40.0 mg, 77%).
12. Representative procedure for the reduction with DIBAL: DIBAL (0.45 mL of a 1.0 M solution in THF, 0.45 mmol) was added to a solution of (S_S)-**2a** (52.0 mg, 0.20 mmol) in THF (2 mL) at −78 °C. After 6 h MeOH (1 mL) was added to the mixture, which was then evaporated under reduced pressure. Aqueous 2 M NaOH (2 mL) was added to the residue and the crude mixture was extracted with ethyl acetate. The reaction was worked up as above to give a 16:84 mixture of (S_S,*R*)-**5a**:(S_S,*S*)-**5a** (46.8 mg, 90%).
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