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Reversal of diastereoselection in the addition of Grignard reagents to chiral 2-pyridyl *tert*-butyl (Ellman) sulfinimines

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Abstract—Addition of Grignard reagents to chiral *tert*-butyl sulfinimines derived from pyridine 2-carboxaldehyde affords protected 2-pyridyl amines in high yields and diastereoselectivities. The sense of chiral induction is opposite to that predicted via a chelation-controlled transition state.

We recently required a practical method to access chiral 2-substituted pyridyl amines. Among the approaches, we considered is the addition of an organometallic reagent to a nonracemic imine derived from pyridine-2-carboxaldehyde (Fig. 1). Ellman has demonstrated that chiral *tert*-butyl sulfinimines are attractive substrates for a variety of nucleophiles, yielding the desired adducts in excellent diastereoselectivities.[1] Subsequent cleavage of the sulfinyl group under mildly acidic conditions affords enantio-enriched products in high yields. Since this general strategy had already been successfully carried out in a related context, we sought to adapt this procedure to our specific needs.[2]

The initial experiments to probe optimum conditions were carried out using MeMgCl and *tert*-butyl sulfinimine **1**.[3]

Combination of these reactants in tetrahydrofuran at −40 °C provided the expected diastereomers **2a** (R_S, R) and **2b** (R_S, S) with good selectivity (2a:2b = 10:1) but in the opposite sense of the predicted stereochemistry (Scheme 1).

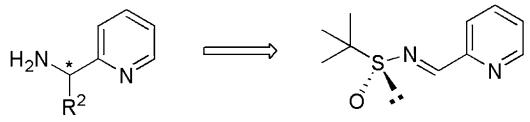

Figure 1.

We attribute the reversal of the expected stereochemical outcome in this reaction to the α-coordinating ability of the pyridine nitrogen as depicted in Figure 2. According to precedent, the coordination of an organometallic moiety with the sulfoxide oxygen would be expected to form a chelation controlled, chair-like transition state (model **A**).[4] However, this model would predict diastereomer **2b** to be the predominant product. Based on the reaction product distribution, we propose that in the case of 2-pyridyl imines, coordination of the metal is favored between the imine and the pyridine nitrogens to afford organo-magnesium complex **B**.[5] Subsequent addition of the nucleophile then occurs via an open transition state.[6] A similar rationalization was invoked to explain the high stereoselectivities observed in the addition of organometallic reagent to *tert*-butyl sulfinimines under nonchelating conditions.[7]

In order to gain additional insight into the factors that govern this transformation, we systematically modified reaction conditions, the most relevant of which are collated in Table 1.

A perusal of the data indicates that solvent effects were modest. Whereas reactions carried out in methylene chloride and toluene resulted in marginally higher yields (entries 7 and 9), those performed in ethereal solvents gave higher diastereoselectivities (entries 2 and 5). As

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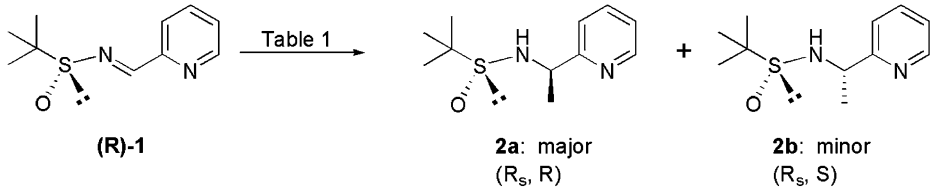


Scheme 1.

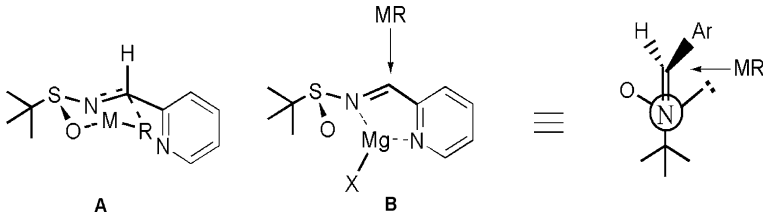


Figure 2.

Table 1.

Entry	Nucleophile	Solvent	Additive	Temp (°C)	Ratio (R_SR:R_SS)[a]	Yield[b] (%)
1	CH_3MgCl	THF	—	−40	10:1	85
2	CH_3MgCl	THF	—	−78	14:1	85
3	CH_3MgCl	THF	$Cu(OTf)_2$	−40	—	<2
4	CH_3MgCl	THF	$ZnBr_2$	−40	—	<2
5	CH_3MgCl	Et_2O	—	−40	9:1	82
6	CH_3MgCl	CH_2Cl_2	—	−40	7.4:1	>99
7	CH_3MgCl	CH_2Cl_2	—	−78	8.8:1	>99
8	CH_3MgCl	Toluene	—	−40	7:1	98
9	CH_3MgCl	Toluene	—	−78	9.4:1	95
10	CH_3MgCl	Toluene	Me_3Al	−40	1:2.5	63
11	CH_3Li	Toluene	—	−78	1.6:1	89
12	CH_3Li	THF	—	−78	1.2:1	97

[a] Ratio of the crude reaction mixture determined by HPLC.[8]
[b] Isolated yield of analytically pure material.

anticipated, diastereoselectivities were increased at lower temperatures (cf. entries 1 and 2). The inclusion of additives such as $Cu(OTf)_2$ and $ZnBr_2$ (entries 3 and 4) was detrimental to reaction yields, a result attributable to the attenuated reactivities of the corresponding transmetallated species. When other organometallic species were employed, diastereoselectivities were eroded (entries 11 and 12) or reversed (entry 10).[9] The foregoing results are consistent with the transition state exemplified by model **B**. The poor coordination of lithium relative to magnesium results in substantially lower diastereoselectivities. On the other hand, the moderate reversal of selectivity observed in entry 10 can be ascribed to pre-coordination of the aluminum moiety with the pyridine nitrogen, followed by attack with MeMgCl according to model **A**.

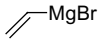
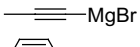
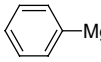
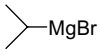
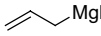
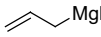
In order to explore the scope of the Grignard addition to 2-pyridyl *tert*-butyl sulfinimines, we substituted methyl Grignard with other commonly available Grignard reagents. All reactions were carried out in tetrahydrofuran utilizing the conditions summarized in Table 2.

In general, the improved diastereoselectivities that were observed relative to methyl Grignard correlated with increasing steric bulk of the Grignard reagent (entries 2–4). The anomalous result obtained with allyl Grignard (entries 5 and 6) can be rationalized by invoking a magnesium chelate, as in transition state **C**, wherein intramolecular transfer of the allyl group competes with the intermolecular pathway (Fig. 3).

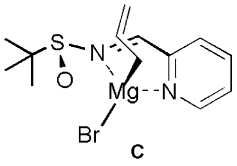
The reversal of selectivity observed in the addition of organometallic reagents to chiral 2-pyridyl *tert*-butyl sulfinimines is analogous to the results obtained with *N*-sulfinyl imines containing an α-coordinating group.[6,10] For example, an α-alkoxy group[11,12] has recently been proposed to alter the transition state in a manner illustrated by model **D** (Fig. 4). However, in the present case, the pyridine nitrogen (model **B**) is not strictly equivalent to the α-coordinating group depicted in model **D**.[13] This is predicated on the observations that diastereoselectivities in the α-alkoxy sulfinimine manifold are manifestly influenced by solvent effects and metal additives such as trimethylaluminum.[14]

In summary, we have developed a viable synthetic route to chiral 2-pyridyl amines in high yields and diastereo- selectivities.[15] The observed sense of chiral induction is opposite to that predicted via a chelation-

Table 2.

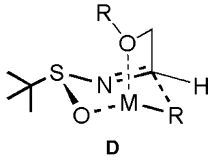
Entry	R^2MgBr	Temp (°C)	Time (min)	Ratio (R_SR:R_SS)[a,b]	Yield[c] (%)
1		−40	60	8:1	74
2		−20	180	15:1[d]	90
3		−40	60	28:1	70
4		−40	30	15:1[d]	72
5		−40	30	2:1	81
6		−78	30	2:1	>99

[a] Ratio of the crude reaction mixture determined by HPLC.[8]
[b] The absolute configurations were confirmed after deprotection of the reaction product and comparison of the optical rotation with literature values.
[c] Isolated yield of analytically pure material.
[d] Ratio determined by ^1H NMR.



C

Figure 3.



D

Figure 4.

controlled transition state and provides another example of the reversal of selectivity in the addition of nucleophiles to chiral imines bearing an α-coordinating group.

Acknowledgements

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8. The diastereomeric ratios were determined on a Delta Pak C-18 column using 55% water (containing NH_4OAc)-45% MeOH.
9. Me_3Al (2.2 equiv) was premixed with **1** prior to the addition of MeMgCl. A similar reversal of selectivity (1:2) was obtained with 1.1 equiv Me_3Al.
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13. The reaction of lithium enolates with 3-pyridyl *tert*-butyl sulfinimines did not exhibit reversal of selectivity. See: Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.
14. In the case of α-alkoxy sulfinimines, Me_3Al enhances diastereoselectivity via chelation with the imine nitrogen (Ref. 11a). Solvent plays a role in determining the sense of addition to α-alkoxy sulfinimines: coordinating solvents such as THF give the predicted product, whilst CH_2Cl_2leads to the reverse addition product (Ref. 12). The 2-pyridyl sulfinimines described herein are essentially unaffected by solvent effects.
15. Representative procedure: To a solution of **1** (1.25 mmol) in THF at −78 °C was added 0.75 mL of a 3 M solution of MeMgCl in THF (Aldrich). After 10 min, the reaction was quenched by the addition of 10 mL of saturated aqueous ammonium chloride and extracted with EtOAc (3×40 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography of the crude reaction mixture on silica gel (50–100% EA/Hex) afforded a 14:1 mixture of **2a**:**2b** (0.24 g, 85%). **2a**: ^1H NMR ($CDCl_3$, 400 MHz) d 8.55 (d, J = 4.9 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.29–7.16 (m, 2H), 4.82 (bd, J = 4.9 Hz, 1H), 4.82–4.57 (m, 1H), 1.51 (d, J = 6.8 Hz, 3H), 1.26 (s, 9H); LRMS (electrospray): *m/z* 227.2 (MH^+).