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A facile three-step synthesis of 1,2-amino alcohols using the Ellman homochiral *tert*-butylsulfinamide

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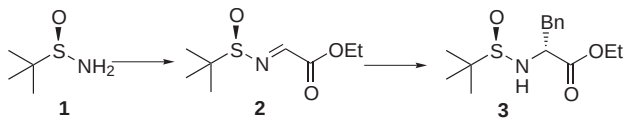
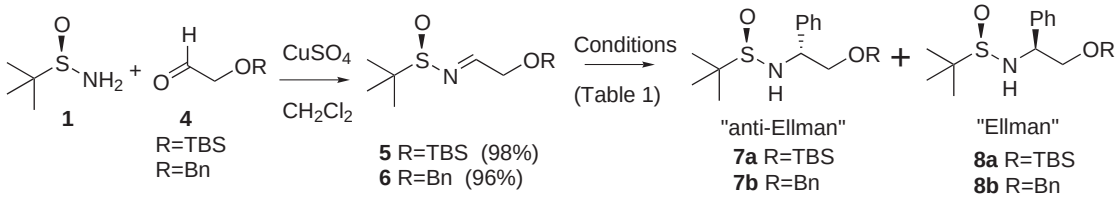
Abstract—Addition of organometallic reagents to *tert*-butylsulfinimines derived from *tert*-butyldimethylsiloxyacetaldehyde stereoselectively generates protected 1,2-amino alcohols. Removal of the acid labile protecting groups affords amino alcohols in high yield. The predominant diastereomer is opposite to that predicted by the traditional Ellman model; therefore, a chelation model invoking rapid E/Z isomerization of the imine is proposed to rationalize the observed selectivity.

Optically active 1,2-amino alcohols and their derivatives have seen widespread use in synthetic chemistry[1] as chiral auxiliaries,[2] ligands for asymmetric catalysis,[3] and building blocks for natural products and medicinal agents. Accordingly, many different methods have been developed for their preparation with the most common involving reduction of optically active α-amino acids.[4] Recently, Sharpless has developed a catalytic method for asymmetric olefin aminohydroxylation which is most effectively applied to styrenes and α,β-unsaturated esters.[5] In analogy to pioneering work by Davis,[6] Ellman has developed optically active *tert*-butylsulfinamide **1** (Scheme 1) as a convenient chiral auxiliary for the asymmetric synthesis of amines.[7] This reagent readily condenses with aldehydes and ketones to form sulfinimines which react with organometallic reagents in a highly stereoselective manner. The resulting adducts can then be purified to optical purity before removal of the auxiliary. Davis has reported condensation of **1** with ethyl glyoxylate and reaction of the resulting imine **2** with benzylmagnesium chloride to selectively produce optically active phenylalanine derivatives[8] (Scheme 1). Herein we describe an adaptation of the Ellman and Davis methodologies that allows for the direct preparation of amino alcohols using sulfinimines **5** and **6**.



Scheme 1.

Using copper sulfate mediated conditions developed by Ellman,[7a] sulfinimines **5** and **6** were prepared in good yield from the reaction of optically pure (*R*)-**1**[9] with either commercially available benzyloxyacetaldehyde or



Scheme 2.

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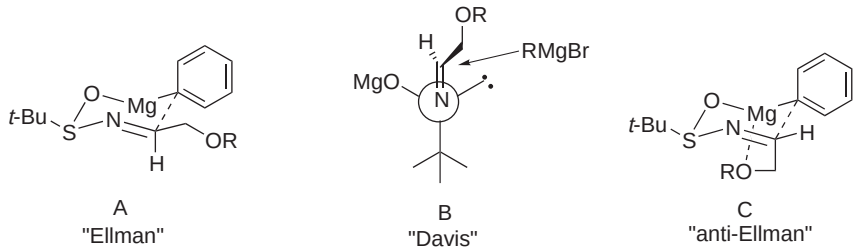
Table 1. Addition of PhMgBr or PhLi to **5**

Entry	Reaction solvent	Temp. (°C)	Ph-X	Solvent for Ph-X	Ratio[a] **7a**:**8a**	Yield%[b]
1	CH_2Cl_2	0	PhMgBr	Et_2O	1:1	92
2	CH_2Cl_2	−50	PhMgBr	Et_2O	2.7:1	97
3	CH_2Cl_2	−78	PhMgBr	Et_2O	3:1	96
4	CH_2Cl_2	−78	PhMgBr	THF	1:1.6	89
5	THF	0	PhMgBr	Et_2O	–	<10
6	THF	−78	PhMgBr	Et_2O	1:3.5	89
7	THF	0	PhMgBr	THF	–	<10
8	THF	−78	PhMgBr	THF	1:2.5	84
9	Et_2O	−78	PhMgBr	Et_2O	1:2.4	85
10	CH_2Cl_2	−78	PhLi	Chx/Et_2O	2.7:1	81
11	Et_2O	−78	PhLi	Chx/Et_2O	3.8:1	65
12	Hexane	−78	PhLi	Chx/Et_2O	4.4:1	79

[a] Ratio determined by 400 MHz ^{1}H NMR of the unpurified reaction mixture.
[b] Combined isolated yield after silica gel chromatography.



Scheme 3.

Table 2. Addition of PhMgBr or PhLi to **6**

Entry	Reaction solvent	Temp. (°C)	Ph-X	Solvent for Ph-X	Ratio[a] **7b**:**8b**	Yield%[b]
1	CH_2Cl_2	−78	MgBr	Et_2O	>10:1	90
2	Hexane	−78	MgBr	Et_2O	8:1	53
3	THF	−78	MgBr	Et_2O	9:1	96
4	Et_2O	−78	MgBr	Et_2O	4:1	78
5	CH_2Cl_2	−78	MgBr	THF	4:1	95
6	Hexane	−78	Li	Chx/Et_2O	2.4:1	70

[a] Ratio determined by 400 MHz ^{1}H NMR of the unpurified reaction mixture.
[b] Combined isolated yield after silica gel chromatography.

tert-butyldimethylsilyloxyacetaldehyde (Scheme 2). As summarized in Table 1, several conditions were initially screened for the addition of phenylmagnesium bromide or phenyllithium to the potentially enolizable sulfinimine **5**.

Under most of these conditions, the yield of the desired adduct was high (>80%). Common side products were oligomers of **5**, resulting from enolization and self-condensation. These pathways were favored in ethereal solvents and at higher temperatures.[10] Interestingly, the ratio of **7a** to **8a** was highly dependent on the reaction conditions. In the presence of THF (used as either the reaction solvent or as the solvent for the Grignard reagent, entries 4–8), there was modest selectivity for the expected product **8a**, presumably via the chair-like transition state proposed by Ellman (Scheme 3, A).[7c] In contrast, reactions performed in CH_2Cl_2 (entries 1–3) or with phenyllithium (entries 10–12) favored **7a**. Davis observed a similar reversal of selectivity in additions to **3** (Scheme 1). To explain this stereochemical turnover, he proposed an open transition state (Scheme 3, B), speculating that chelation prevents the traditional transition state from forming.[8] However, this 'anti-Ellman' selectivity can also be explained by a bicyclic-chelated transition state (Scheme 3, C).

Although this mechanism would require initial isomerization of the imine to the *Z* configuration prior to addition, Ellman has demonstrated this type of behavior in the addition of Grignard reagents to sulfinimines derived from ketones.[7c] While the thermodynamic preference for the *E* isomer is higher for aldimines, components in the reaction mixture may catalyze the isomerization. We favor the latter model to explain the results since it correlates well with the observed substituent (vide infra) and solvent effects.

Further supporting the model, imine **6** proved to be even more selective than **5** and less dependent on the

reaction solvent, most likely due to the superior coordinating ability of the benzyloxy group (Table 2). Surprisingly, phenyllithium was less selective than phenylmagnesium bromide, in contrast to the trend seen with **5**.

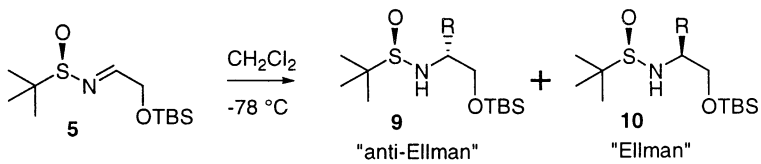
Using the optimal reaction conditions developed for phenylmagnesium bromide (CH_2Cl_2, −78°C), we then examined the addition of other organometallic reagents to **5** for their effect on yield and selectivity as shown in Table 3.

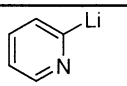
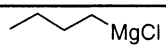
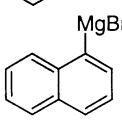
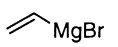
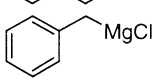
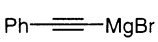
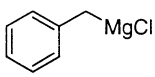
Addition of 2-pyridyllithium (generated from 2-bromopyridine and *n*-BuLi) to sulfinimine **5** proceeded in good yield and selectivity suggesting that this methodology might be applied to other heteroaromatic analogs. Interestingly, the addition of 1-napthylmagnesium bromide was virtually unselective under the standard conditions, as was that of benzylmagnesium chloride (entries 2 and 3, Table 3). Contrary to previous results, reverting to THF as the solvent for the Grignard reagent restored some of the selectivity for the 'anti-Ellman' product (entry 4, Table 3 versus entry 4, Table 1). The reason for this apparent contradiction is not clear although the degree of aggregation of the Grignard reagent in solution may be playing a subtle, confounding role.

Other results shown in Table 3 suggest that this methodology can be extended to a variety of organometallics. Reaction of sulfinimine **5** with butylmagnesium chloride proceeded in quantitative yield with high selectivity. Similarly, addition of vinylmagnesium bromide to **5** afforded good stereoselectivity, albeit in lower yield. This represents a simple preparation of optically active vinylglycinol after separation of product diastereomers and deprotection. Even the relatively small alkynyl Grignard generated from phenylacetylene and EtMgBr underwent addition with an acceptable degree of selectivity and in good yield. While the degree of selectivity may differ from substrate to substrate, the results in Table 3 demonstrate that this methodology is quite general and should be amenable to the preparation of a wide variety of amino alcohols.

Similar to a *tert*-butylcarbamate, the *tert*-butylsulfinamide can be conveniently removed under mildly

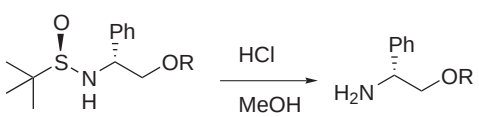
Table 3. Addition of organometallics to **5**



Entry	R-X	Solvent for R-X	Ratio[a] **9:10**	yield[b] %	Entry	R-X	solvent for R-X	Ratio[a] **9:10**	yield[b] %
1		Et_2O	5.3:1	82	5		Et_2O	>10:1	100
2		Et_2O	1.6:1	65	6		THF	5.9:1	44
3		Et_2O	1:1	65	7		Et_2O	3.4:1	93
4		THF	3.1:1	84					

[a] Ratio determined by 400 MHz ^{1}H NMR of the unpurified reaction mixture. Stereochemical assignments were obtained by acid mediated removal of the auxiliary and silyl protecting group followed by comparison of the optical rotation with literature values.[11,12] For entry 5, the stereochemical assignment was made by comparison to (2*R*)-2-aminohexan-1-ol prepared by reduction of (*R*)-2-aminohexanoic acid. Entries 2 and 7 are tentatively assigned by analogy.

[b] Combined isolated yield after silica gel chromatography.



7a R=TBS
7b R=Bn

11a R=H (92%)
$[\alpha]_D$= -26.7° (c = 0.075, 1N HCl);
(lit.[13a] $[\alpha]_D$ = -31.7° (c = 0.76, 1N HCl)
11b R=Bn (81%)
$[\alpha]_D$ = -26.0° (c = 1.1, $CHCl_3$);
(lit.[13b] $[\alpha]_D$ = -28.3° (c = 1.1, $CHCl_3$)

Scheme 4.

acidic conditions. For example, treatment of **7a** with HCl in MeOH followed by removal of the volatile by-products provided phenylglycinol in high yield and purity (Scheme 4). Alternatively, if the synthetic sequence requires a protected alcohol, similar treatment of **7b** provides **11b**. Comparison of optical rotation for **11a** and **11b** to literature values[13] established the stereochemical assignment for the addition step.

In summary, addition of Grignard or lithium reagents to **5** and **6** stereoselectively generates protected 1,2-amino alcohols in high yield and diastereomeric purity after silica gel chromatography. Removal of the acid labile protecting groups affords free or *O*-benzyl protected 1,2-amino alcohols.[14] Since factors that traditionally favor chelate-controlled selectivity (non-coordinating solvents, smaller oxygen protecting groups) improve the observed product ratios, a bicyclic transition state model which invokes rapid *E*/*Z* isomerization of the imine is proposed to rationalize the observed selectivity.[15] This methodology serves as a convenient means of arriving at 1,2-amino alcohols for which the optically active α-amino acids are not commercially available or otherwise readily accessible.

Acknowledgements

We thank Professor D. A. Evans for helpful discussions.

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9. Both enantiomers of **1** are commercially available from Aldrich Chemical Company or can be prepared as described in Ref. 7b.
10. Older bottles of Grignard reagent also caused more of this type of side reaction, presumably due to increased amounts of $Mg(OH)_2$.
11. 2-Pyridylglycinol: Cossu, S.; Conti, S.; Giacomelli, G.; Falorni, M. *Synthesis* **1994**, *12*, 1429–1432.
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13. (a) **11a**: *Aldrich Catalog* **1996–1997**, p. 1162; (b) **11b**: *Tetrahedron: Asymmetry* **1996**, *7*, 3397.
14. **Representative procedure**: To a solution of 3.02 g (24.9 mmol) (*R*)-*tert*-butylsulfinamide (**1**) and 5.21 mL (27.4 mmol) of *tert*-butylsilyloxyacetaldehyde in 30 mL of CH_2Cl_2 was added 8.74 g (54.7 mmol) $CuSO_4$. The reaction mixture was stirred at room temperature for 17 h and then filtered through Celite (400 mL CH_2Cl_2 rinse). The filtrate was concentrated in vacuo. Purification on the ISCO CombiFlash (120 g silica gel, 90 mL/min flow rate, linear gradient 0–30% EtOAc:hexane over 30 min) afforded 6.80 g (98%) of **5** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (t, 1H, $J=3.05$ Hz); 4.55 (d, 2H, $J=3.05$ Hz); 1.21 (s, 9H); 0.92 (s, 9H); 0.10 (s, 6H). To a −78°C solution of 0.300 g (1.08 mmol) of **5** in 5.4 mL of CH_2Cl_2 was slowly added 0.720 mL (2.16 mmol) of a 3 M solution of phenylmagnesium bromide in diethyl ether. After 5 h at −78°C, the reaction mixture was warmed to room temperature. After 17 h at room temperature, the reaction was quenched with 15 mL of a saturated NH_4Cl solution and extracted with EtOAc (15 mL×3). The combined EtOAc fractions were washed with 15 mL of brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash chromatography (40×105 mm silica gel, linear gradient 30–50% EtOAc:hexane) yielded 0.260 g (66%) of **7a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.28 (m, 5H); 4.544–4.511 (m, 1H); 3.784 (dd, 1H, $J=4.12$ Hz, 10.07 Hz); 3.619 (t, 1H, $J=9.62$ Hz); 1.234 (s, 9H); 0.908 (s, 9H); 0.062 (d, 6H, $J=8.06$ Hz); MS (Electrospray): m/z 356.1 (M^+H).
To a 0°C solution of 0.258 g (0.725 mmol) of **7a** in 4 mL of MeOH was added 0.720 mL (2.90 mmol) of a 4 M solution of HCl in 1,4-dioxane. After 5 min at 0°C, the reaction mixture was concentrated in vacuo to give 0.166 g (92%) of **11a** in the form of a yellow solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.48–7.40 (m, 5H); 4.335 (dd, 1H, $J=4.30$ Hz, 8.43 Hz); 3.887 (dd, 1H, $J=4.35$ Hz, 11.58 Hz); 3.800 (dd, 1H, $J=8.47$ Hz, 11.58 Hz); MS (Electrospray): m/z 138.1 (M^+H); $[\alpha]_D^{23}=-26.7$ ($c=0.075$, 1N HCl); (lit.:[13a] $[\alpha]^{24}=-31.7$ ($c=0.76$, 1N HCl).
15. Since completion of this work, addition of ethylaluminum cyanoisopropoxide to α-hydroxy sulfinimines has been reported: Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonova, P. *J. Org. Chem.* **2000**, *65*, 7663.