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Highly Stereoselective Addition of Organometallic Reagents to *N-tert*-Butanesulfinyl Imines Derived from 3- and 4-Substituted Cyclohexanones

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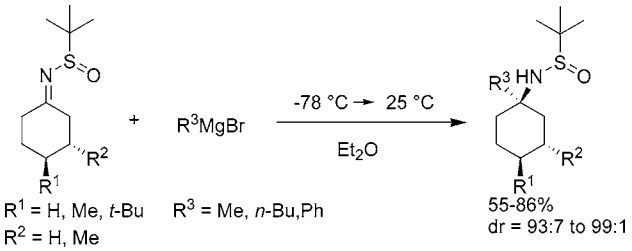
ABSTRACT



Addition of alkyl or aryl Grignard reagents to *N*-sulfinyl imines derived from 3- and 4-substituted cyclohexanones proceeds with good yields and with excellent diasteroselectivity. The selectivity of the reaction is controlled by the ring substituent rather than the sulfinyl group stereochemistry, and therefore racemic *tert*-butanesulfinamide can be employed.

The synthesis of chiral amines is of great interest due to their prevalence in biologically active molecules. Over the past several years, our laboratory has developed several methods for the asymmetric synthesis of amines using *tert*-butanesulfinamide as a chiral amine source.[1] *tert*-Butanesulfinamide can be condensed with aldehydes and ketones to form *N*-sulfinyl imines in good yields. The chiral *tert*-butanesulfinyl group directs the addition of nucleophiles to the imine and also minimizes competitive deprotonation at the α carbon. Subsequent cleavage of the sulfinamide under acidic conditions provides the chiral amines.

Organolithium reagents have been reported to add to *tert*-butanesulfinyl ketimines with high diastereoselectivity and good yields to provide one of the few general and efficient methods for the synthesis of tertiary carbinamines.[2] However, despite the prevalence of α-substituted cyclohexylamines in drugs and drug candidates, additions to *N*-sulfinyl ketimines derived from cyclic ketones have not yet been reported. Prompted by a number of inquiries on the feasibility of preparing α-substituted cyclohexylamines using *tert*-butanesulfinamide chemistry, we report here on the efficient preparation of this compound class by the addition of organometallic reagents to *N*-sulfinyl imines derived from 3- and 4-substituted cylcohexanones.[3] This study further provides the first examples of nucleophilic attack upon *N*-sulfinyl cyclic imines where both ring substituents and the sulfinyl group have the potential to control reaction diastereoselectivity.[4]

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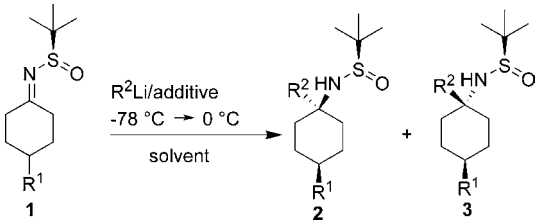
Condensation of (*R*)-*tert*-butanesulfinamide with 4-*tert*-butylcyclohexanone employing $Ti(OEt)_4$ in THF at room temperature provided imine **1** (R_1 = *t*-Bu) in 72−81% yield as a 1:1 mixture of imine isomers on the NMR time scale. When the imine was treated with BuLi using the previously reported conditions for organolithium additions to *N*-sulfinyl ketimines, a 94:6 ratio of diastereomers was obtained in 77% yield (entry 1, Table 1). The selectivity of the addition can best be rationalized if equatorial attack were to occur on the lowest energy chair conformation, which has the 4-*tert*-butyl group located equatorially.[5] The chirality at sulfur is very unlikely to play a significant role in the addition selectivity because a 1:1 ratio of diastereomeric imine isomers was observed (Figure 1).[6] As could be expected, when imine **1** (R_1 = Me) was employed, the addition product was obtained in similar yield (72%) but with a modest drop in selectivity (entry 2).

Table 1. Addition of Organolithiums to *N*-*tert*-Butanesulfinyl Imines **1**



entry	R^1	R^2	additive	solvent	**2**:**3**[a,b]
1	*t*-Bu	Bu	Me_3Al	toluene	94:6
2	Me	Bu	Me_3Al	toluene	86:14
3	*t*-Bu	Me	Me_3Al	toluene/Et_2O	2:1
4	*t*-Bu	Ph	Me_3Al	toluene/Et_2O	3:2
5	*t*-Bu	Bu	Me_3Al	toluene/Et_2O	7:3

[a] Diastereomeric ratio was determined by HPLC analysis. [b] Stereochemistry for **2** (R^1 = Me, R^2 = Ph) was determined by X-ray crystal structure. The stereochemistry of the other amine products was determined by analogy.

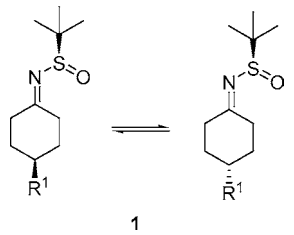


Figure 1. Equilibrium of Diastereomeric Imine Isomers **1**.

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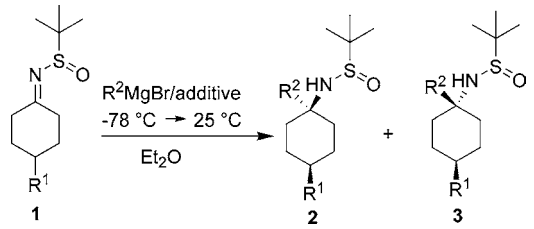
(5) Similar rationale is used to explain the selectivity of organometallic additions to cyclic ketones; see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Kluwer Academic: New York, 2001; Part B, p 457.

(6) Although the individual imine isomers cannot be isolated, they can be observed on the NMR time scale.

Table 2. Addition of Grignard Reagents to *N*-*tert*-Butanesulfinyl Imines **1**



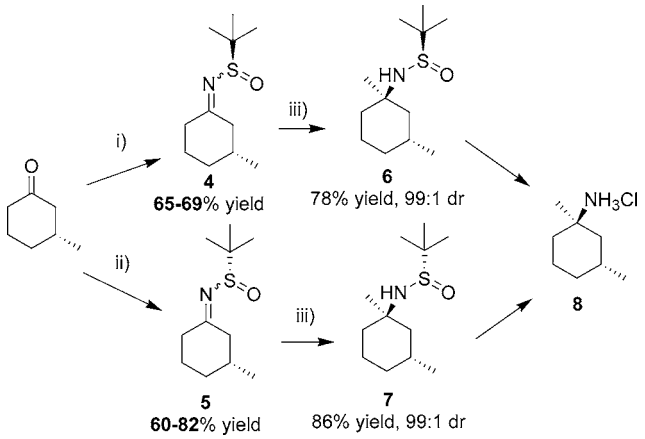
entry[a]	R^1	R^2	additive	yield	**2**:**3**[c,d]
1	*t*-Bu	Me	Me_3Al	80	98:2
2		Ph	Me_3Al	76	95:5
3		Me	none	78	98:2
4		Ph	none	69	95:5
5		Bu	none	59	97:3
6[b]		Me	none	77	>96:4[e]
7	Me	Me	Me_3Al	80	95:5
8		Ph	Me_3Al	76	95:5
9		Me	none	79	95:5
10		Ph	none	62	93:7
11		Bu	none	57	96:4

[a] Unless otherwise indicated, (*R*)-*tert*-butanesulfinamide was employed. [b] Racemic *tert*-butanesulfinamide was employed. [c] Unless otherwise indicated, the diastereomeric ratio was determined by HPLC analysis. [d] Relative stereochemistry of **2** (R^1 = Me, R^2 = Ph) was determined by X-ray crystallography, and the stereochemistry of the other addition products was inferred by analogy. [e] Diastereomeric ratio was determined by NMR of the amine hydrochloride salt after cleavage of the sulfinyl group.

Encouraged by these preliminary results, we next evaluated other organolithium reagents. Unfortunately, the selectivity of the reaction suffered when MeLi and PhLi were used as nucleophiles (entries 3 and 4, Table 1). The dramatically lower selectivities for these reactions likely resulted from an altered aggregation state of the lithium reagents.[7] While *n*-BuLi is sold as a solution in hexanes, neither MeLi nor PhLi are soluble in hydrocarbon solvents. The experiments were therefore performed using commercially available solutions of MeLi and PhLi in diethyl ether and cyclohexane/ether, respectively. The deleterious effect of the diethyl ether cosolvent was confirmed by addition of BuLi to **1** (R_1 = *t*-Bu) in toluene with a small amount of diethyl ether, equal to the percentage in the experiment in entry 4. A considerable drop in selectivity was observed (entry 5). A range of additives such as TMEDA and BF_3-Et_2O and solvents were evaluated, but reaction conditions for achieving high selectivities were not identified.

Poor selectivity was previously observed for the addition of Grignard reagents to acyclic *N*-sulfinyl ketimines.[2] However, the selectivity for additions to cyclic imines appears to depend on the low-energy chair conformation enforced by the ring substituent rather than the chirality of the sulfinyl group. We therefore explored the addition of Grignard reagents to *N*-sulfinyl-substituted cyclohexyl imines **1** (Table 2). As shown in entries 1−5, very high selectivities and good yields were observed for additions to imine **1** (R_1 = *t*-Bu), regardless of the Grignard reagent added. Due to the symmetry of 4-substituted imines **1**, racemic *tert*-

Scheme 1. Grignard Reagent Additions to *N*-*tert*-Butanesulfinyl Imines **4** and **5**[a]



[a] Reagents and Conditions: (i) (*R*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF; (ii) (*S*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF; (iii) MeMgBr, Et_2O, −78 to 25 °C.

butanesulfinamide can be employed to prepare the imines without any loss in selectivity being observed in the addition reaction (entry 6). Grignard reagent additions to imine **1** (R_1 = Me) also proceeded in good yields and with high selectivities for all of the Grignard reagents employed (entries 7−11).

We next evaluated Grignard reagent additions to *N*-sulfinyl imines derived from 3-substituted cyclohexanones (Scheme 1). Condensations of both (*R*)- and (*S*)-*tert*-butanesulfinamide with commercially available (*R*)-3-methyl cyclohexanone provided imines **4** and **5**, respectively, in good yields. Addition of MeMgBr to imines **4** and **5** each proceeded with very high (99:1) diastereoselectivity and gave comparable yields for the addition products **6** and **7**. The relative stereochemistry of **6** was established by X-ray crystallography, and the relative stereochemistry of **7** was determined by conversion of **6** and **7** to the common amine hydrochloride product **8**.[3e] The stereoselectivity of the addition reaction clearly is controlled by equatorial attack upon the low-energy chair conformation enforced by the ring substituent rather than by the chirality at sulfur.

In summary, we have shown that alkyl and aryl Grignard reagents add with high diastereoselectively and good yields to *N*-sulfinyl imines derived from 3- and 4-substituted cyclohexanones. The diastereoselectivity of the reaction is determined by equatorial attack upon the low-energy chair conformation and is independent of the stereochemistry of the sulfinyl group. Consequently, the less expensive racemic *tert*-butanesulfinamide can practically be employed for these reactions.

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Supporting Information Available: Crystallographic data, full experimental details, and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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