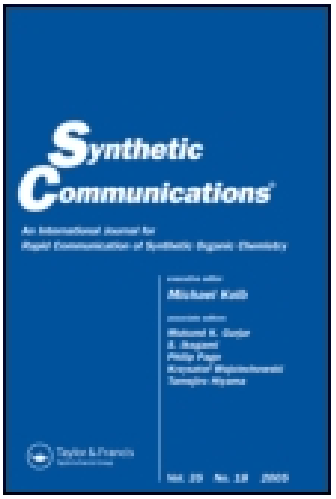

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Reversal Diastereoselectivity Between the Organomagnesium and Organolithium Reagents on Chiral N-Tert-Butylsulfinylaldimines for the Preparation of Chiral Amines

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REVERSAL DIASTEREOSELECTIVITY BETWEEN THE ORGANOMAGNESIUM AND ORGANOLITHIUM REAGENTS ON CHIRAL *N-TERT*-BUTYLSULFINYLALDIMINES FOR THE PREPARATION OF CHIRAL AMINES

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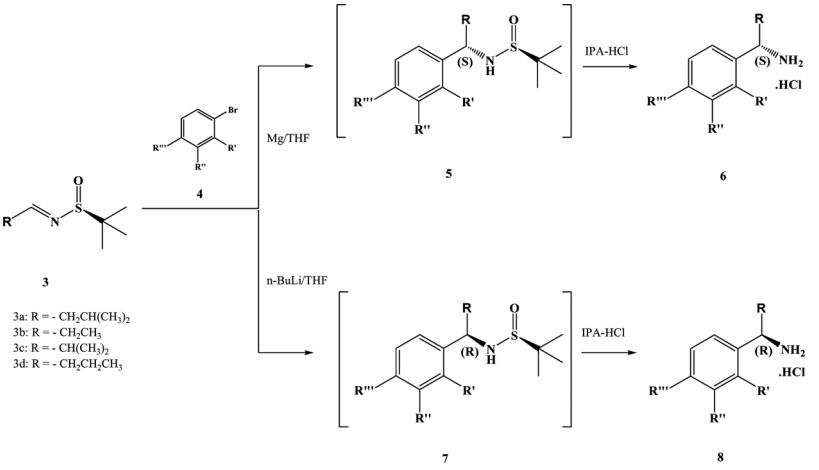
GRAPHICAL ABSTRACT



Abstract *The asymmetric synthesis of both the enantiomer of chiral amines from the single chiral source of N-*tert*-butylsulfinylaldimines (**3**) by simply changing the organometallic reagents through diastereoselective addition. An efficient enantioselective synthesis of chiral amines including (S)-3-methyl-1-(2-piperidin-1-yl-phenyl)butyl amine (**6a**), a key intermediate to prepare antidiabetic drug repaglinide (**1**), is reported.*

Keywords 1-(2-Bromophenyl)piperidine; isobutyraldehyde; isovaleraldehyde; n-butyraldehyde; n-propionaldehyde; S(–)-*tert*-butanesulfinamide; titanium tetraethoxide

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INTRODUCTION

In recent years the asymmetric synthesis of chiral amines occupied a prominent place in synthetic organic chemistry. The diasteroselective addition of organometallic reagents to chiral sulfinimines is a useful method for the preparation of chiral amine as a building block for many pharmaceutically important chiral drugs and intermediates. Ellman's groups has popularized the use of chiral auxiliaries *tert*-butanesulfinamide for the synthesis of optically active amines.[1] Both enantiomers of (*R*)- and (*S*)-*tert*-butane sulfinamide are readily available, easy to remove by acidic conditions, and excellent asymmetric chiral auxiliaries for the preparation of enantiopure amines.

Recently we have reported[2] the diastereoselective synthetic method for the preparation of both enantiomers of chiral amines (**6a** and **8a**) from a single chiral aromatic *N*-*tert*-butyl sulfinylaldimines source by simply changing the aliphatic organometallic reagents such as isobutyl magnesium bromide and isobutyllithium. (*S*)-3-Methyl-1-(2-piperidin-1-yl-phenyl)butylamine (**6a**) is a key raw material for the preparation of the drug repaglinide (**1**), which is used for lowering the blood glucose levels in patients suffering from type II diabetes mellitus (NIDDM)[3–7] (Figs. 1 and 2).

In continuation of our studies on chiral amine synthesis, we further investigated an efficient method to synthesize chiral amines that would enable us to prepare both the product antipodes in high stereoselectivity and also could be amenable to preparing a variety of chiral amine of both isomers. The studies relate to the preparation of chiral amines from aliphatic aldehydes of the general formula **2** and aromatic halides of the general formula **4** as starting materials. As expected we found that the reverse diastereoselective nucleophilic addition of organic metallic reagents to aliphatic *N*-*tert*-butylsulfinylaldimines (**3**) gave chiral amines. Herein we report the diastereoselective addition of organomagnesium reagents and organolithium reagents to same chiral aliphatic *N*-*tert*-butylsulfinylaldimines as the key step in the construction of both enantiomers of the same chiral amines.

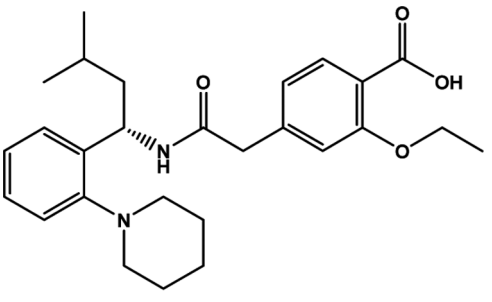

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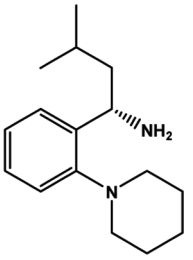
Figure 1. Structure of repaglinide.



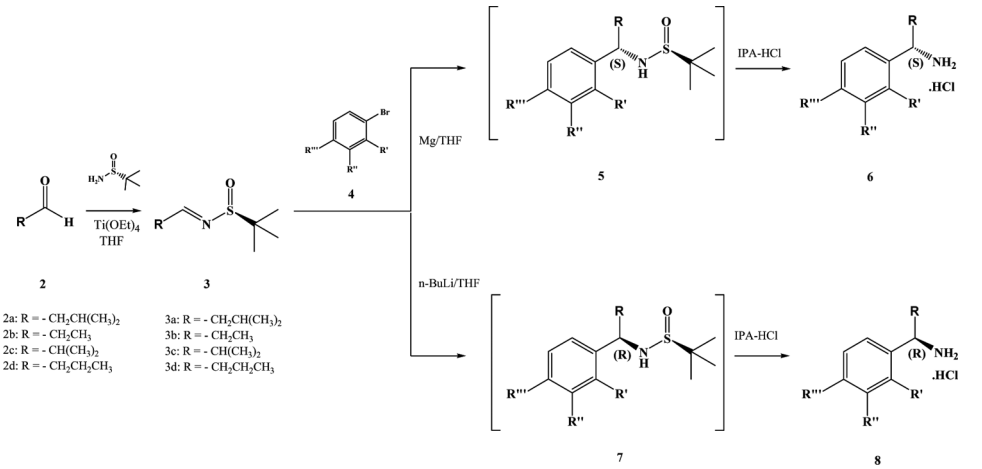
6a

Figure 2. Structure of (*S*)-3-methyl-1-(2-piperidin-1-yl-phenyl)butylamine.

RESULTS AND DISCUSSION

Several resolution methods have been reported for the preparation of enantiopure chiral amine **6a**.[8–13] Kinetic resolution of racemic mixture of enantiomers is one of the current method for preparing enantiomerically pure chiral amines. However, these processes suffer from disadvantages of poor yields and required multiple purifications. As part of our research program we aimed to develop the stereocontrolled synthesis of chiral amines used in the bioactive molecules. We previously reported good results on diastereoselectivity in preparing the chiral amines in our earlier research using chiral aromatic *N-tert*-butylsulfinylaldimines. Herein we attempted to use the same strategy by using aliphatic *N-tert*-butylsulfinylaldimines of the formula **3** to get the both the enantiomers by changing the nucleophilic sources.

Condensation of isoveraldehyde (**2a**) with *S*(–)-*tert*-butanesulfinamide in the presence of titanium tetraethoxide as a water scaventure in tetrahydrofuran (THF)



Scheme 1. Diastereoselective reaction of organometallic reagents with *N-tert*-butylsulfinylaldimines.

Table 1. Diastereoselective reaction of organomagnesium reagents with *N-tert*-butylsulfinylaldimine (**3a–3d**)

Entry	R	R′	R″	R‴	Product	Chiral HPLC (%) *R*	Chiral HPLC (%) *S*	SOR	Yield (%)
1	$-CH_2CH(CH_3)_2$		-H	-H	**6a**	10.29	89.71	+5.4	76.8
2	$-CH_2CH(CH_3)_2$	-H	-H		**6b**	6.66	92.82	+17.8	61.4
3	$-CH_2CH(CH_3)_2$	-H	-H	-H	**6c**	8.44	91.56	+20.4	47.4
4	$-CH_2CH(CH_3)_2$	-Cl	-H	-H	**6d**	19.17	80.83	+15.3	62.6
5	$-CH_2CH(CH_3)_2$	-H	-Cl	-H	**6e**	10.67	85.94	+17.0	53.9
6	$-CH_2CH(CH_3)_2$	-H	-H	-Cl	**6f**	7.69	92.31	+6.0	70.0
7	$-CH_2CH(CH_3)_2$	$-CH_3$	-H	-H	**6g**	14.84	85.16	+16.9	53.1
8	$-CH_2CH(CH_3)_2$	-H	$-CH_3$	-H	**6h**	6.33	93.67	+5.5	73.8
9	$-CH_2CH(CH_3)_2$	-H	-H	$-CH_3$	**6i**	13.00	87.00	+5.7	65.0
10	$-CH_2CH(CH_3)_2$	-H	$-OCH_3$	-H	**6j**	1.88	98.12	+21.8	70.0
11	$-CH_2CH(CH_3)_2$	-H	-H	$-OCH_3$	**6k**	0.95	99.05	+14.8	68.6
12	$-CH_2CH(CH_3)_2$		-H	-H	**6l**	38.72	61.28	+4.1	44.8
13	$-CH_2CH(CH_3)_2$		-H	-H	**6m**	13.76	86.24	+18.5	61.9
14	$-CH_2CH(CH_3)_2$	-H	-H		**6n**	3.05	96.95	+14.3	72.7
15	$-CH_2CH_3$		-H	-H	**6o**	1.30	98.70	+5.1	62.1
16	$-CH_2CH_3$	-H	-H	-H	**6p**	—	100.0	+15.7	72.3
17	$-CH_2CH_3$	$-CH_3$	-H	-H	**6q**	4.85	95.15	+15.3	76.4
18	$-CH_2CH_3$	-H	-H	$-CH_3$	**6r**	10.94	89.06	+11.2	75.0
19	$-CH(CH_3)_2$		-H	-H	**6s**	39.57	60.43	+2.7	57.6
20	$-CH(CH_3)_2$	-H	-H	-H	**6t**	—	100.0	+3.6	81.7
21	$-CH(CH_3)_2$	$-CH_3$	-H	-H	**6u**	3.23	96.77	+8.3	73.8
22	$-CH(CH_3)_2$	-H	-H	$-CH_3$	**6v**	15.84	84.16	+3.5	80.3
23	$-CH_2CH_2CH_3$		-H	-H	**6w**	1.54	98.46	+5.8	58.7
24	$-CH_2CH_2CH_3$	-H	-H	-H	**6x**	0.98	99.02	+14.6	87.8
25	$-CH_2CH_2CH_3$	$-CH_3$	-H	-H	**6y**	—	100.0	+10.0	79.3
26	$-CH_2CH_2CH_3$	-H	-H	$-CH_3$	**6z**	3.71	96.29	+12.4	76.0

solvent at reflux temperature gave *N-tert*-butylsulfinylaldimine (**3a**). The addition of Grignard reagent 2-piperidin-1-yl-phenylmagnesium bromide (prepared from 1-(2-bromophenyl)-piperidine (**4a**) and magnesium in THF solvent) to sulfinylaldimine (**3a**) to get diastereosulfinamine (**5**) and hydrolysis with alcoholic hydrochloric acid gave a major chiral amine *S*-Isomer (**6a**). Similarly the addition of 2-piperidin-1-yl-phenyllithium reagent (prepared from 1-(2-bromophenyl)-piperidine (**4a**) and n-butyllithium in THF solvent at -40 to $-60\,^{\circ}C$) to sulfinylaldimine (**3a**) to get sulfinamine (**7**) followed by hydrolysis gave the major *R*-chiral amine (**8a**). Hence we could achieve both enantiomers of chiral amines (**6a** and **8a**) from the single chiral sulfinylaldimine (**3a**) source. Further we confirmed the product of (*S*)-chiral amine (**6a**) obtained from this method by making the drug repaglinide (**1**).

Having discovered the encouraging results from our results, we have extended our studies to generalize and understand the diastereoselectivity on *N-tert*-butyl

Table 2. Diastereoselective reaction of organolithium reagents with *N*-tert-butylsulfinyl aldimine (**3a–3d**)

Entry	R	R′	R″	R‴	Product	Chiral HPLC (%) *R*	Chiral HPLC (%) *S*	SOR	Yield (%)
1	$-CH_2CH(CH_3)_2$		-H	-H	**8a**	67.38	32.62	−2.5	69.2
2	$-CH_2CH(CH_3)_2$	-H	-H		**8b**	82.13	17.87	−10.1	65.3
3	$-CH_2CH(CH_3)_2$	-H	-H	-H	**8c**	66.87	33.13	−10.4	58.7
4	$-CH_2CH(CH_3)_2$	-Cl	-H	-H	**8d**	54.98	45.02	−2.4	64.7
5	$-CH_2CH(CH_3)_2$	-H	-Cl	-H	**8e**	71.70	28.30	−8.5	56.6
6	$-CH_2CH(CH_3)_2$	-H	-H	-Cl	**8f**	68.38	31.62	−7.9	61.9
7	$-CH_2CH(CH_3)_2$	$-CH_3$	-H	-H	**8g**	54.25	45.75	−1.1	47.8
8	$-CH_2CH(CH_3)_2$	-H	$-CH_3$	-H	**8h**	72.89	27.11	−2.1	79.7
9	$-CH_2CH(CH_3)_2$	-H	-H	$-CH_3$	**8i**	72.21	27.79	−8.3	59.0
10	$-CH_2CH(CH_3)_2$	-H	OCH_3	-H	**8j**	73.85	26.15	−8.9	57.7
11	$-CH_2CH(CH_3)_2$	-H	-H	$-OCH_3$	**8k**	82.66	17.34	−5.8	60.4
12	$-CH_2CH(CH_3)_2$		-H	-H	**8l**	62.48	37.42	−3.1	38.4
13	$-CH_2CH(CH_3)_2$		-H	-H	**8m**	59.54	40.46	−8.2	66.1
14	$-CH_2CH(CH_3)_2$	-H	-H		**8n**	85.95	14.05	−9.3	75.9
15	$-CH_2CH_3$		-H	-H	**8o**	54.86	45.14	−1.2	65.7
16	$-CH_2CH_3$	-H	-H	-H	**8p**	100.0	–	−15.3	88.6
17	$-CH_2CH_3$	$-CH_3$	-H	-H	**8q**	95.11	4.89	−13.7	82.3
18	$-CH_2CH_3$	-H	-H	$-CH_3$	**8r**	87.85	12.15	−9.9	79.5
19	$-CH(CH_3)_2$		-H	-H	**8s**	83.52	16.48	−3.5	66.5
20	$-CH(CH_3)_2$	-H	-H	-H	**8t**	98.09	1.91	−4.2	80.1
21	$-CH(CH_3)_2$	$-CH_3$	-H	-H	**8u**	66.44	33.56	−4.5	78.4
22	$-CH(CH_3)_2$	-H	-H	$-CH_3$	**8v**	77.02	22.98	−3.2	75.6
23	$-CH_2CH_2CH_3$		-H	-H	**8w**	57.21	42.19	−1.1	63.2
24	$-CH_2CH_2CH_3$	-H	-H	-H	**8x**	62.90	37.10	−3.7	88.7
25	$-CH_2CH_2CH_3$	$-CH_3$	-H	-H	**8y**	53.01	46.99	−0.3	85.2
26	$-CH_2CH_2CH_3$	-H	-H	$-CH_3$	**8z**	52.91	47.91	−0.9	81.1

sulfinylaldimine (**3a**) by carrying out the experiments with different aromatic halides (**4b–4n**). All the halides gave the expected reverse diastereoselectivity in the reactions. Further we extended with different aliphatic *N-tert*-butylsulfinylaldimines (**3b–3d**) prepared from *n*-propanaldehyde (**2b**), isobutyraldehyde (**2c**), and *n*-butyraldehyde (**2d**), which were reacted with organometallic reagents prepared from aromatic halides (**4a, 4c, 4g**, and **4i**) and gave the expected distereoselectivity. In brief the organomagnesium reagents provided greater diastereoselectivities and organolithium reagents substantially lower diastereoselectivities in the preparation of chiral amines. These reactions are summarized in Scheme 1, and the results are tabulated in Tables 1 and 2.

CONCLUSIONS

In conclusion, we have demonstrated and expanded our earlier study to reverse the diastereoselectivity of organometallic anions to chiral *N-tert*-butylsulfinylaldimines

to get the enantiomers of chiral amines. This procedure gives good yield with good diastereoselectivity and can be applied to prepare the optically active pure chiral amines of both enantiomers, which is highly useful for synthetic organic chemistry.

EXPERIMENTAL

Melting points were taken on a Branstead melting-point apparatus (model 9300) in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded as neat or KBr using a Perkin-Elmer 2000 FT-IR spectrometer. Both ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker NMR spectrometer instrument. Deuterated reagents were used as solvents and tetramethylsilane (TMS) was used as internal reference standard. Chemical shift values are expressed in parts per million (δ) values and coupling constants are expressed in hertz. All mass spectra were recorded using the electrospray ionization (ESI) technique on an API 2000, ABS triple quadrupole instrument. Chiral high-performance liquid chromatography (HPLC) was done using a chiral Cel OD-H 250 × 436 mm column. The purity of all the compounds was routinely checked by thin-layer chromatography (TLC) on silica-gel-coated plates. Column chromatography was performed using 60- to 120-mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions, using commercial grade solvents as eluents. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified.

General Procedure for Making N-*tert*-Butylsulfinylaldimine (3a–3d)

Titanium tetraethoxide (2.0 eq.) was added to a stirred solution of aldehydes (**2a–2d**) and *S*(–)-*tert*-butanesulfinamide (1.1 eq.) in THF at room temperature. The mixture was refluxed until completion, the reaction mass was cooled, and saturated sodium chloride solution was added. The reaction mass was filtered through celite and the aqueous layer was extracted with ethyl acetate. The organic layer was concentrated and purified through column chromatography to get **3a–3d**.

General Procedure for the Reaction of Grignard Reagents with *N-tert*-Butyl Sulfinylaldimines

The Grignard reagents were prepared from aromatic halides (**4a–4n**) (3.0 eq.) using magnesium (3.05 eq.) in THF and then added to a stirred solution of *N-tert*-butylsulfinylaldimines (**3a–3d**) (1.0 eq.) in THF at −5 to 5 °C. The mixture was stirred for 1.0 h and warmed to room temperature. The reaction mass was quenched in saturated ammonium chloride solution and stirred at room temperature. The organic layer was separated and the aqueous layer was extracted in dichloromethane. The organic extracts were washed with water and concentrated. This sulfinylamine (**5**) was treated with IPA-HCl and stirred for 1.0 h. After completion of the reaction, the mass was concentrated, stirred with ethyl acetate, and filtered to get **6a–6z**.

General Procedure for the Reaction of Organolithium Reagents with *N-tert*-Butyl Sulfinylaldimines

N-Butyllithium in hexanes (1.6 M, 2 eq.) was added slowly to a stirred solution of aromatic halides (**4a–4n**) (2.0 eq.) in THF at −40 to −50 °C, and the mass was stirred for 1.0 h at −40 to −50 °C. *N-tert*-Butylsulfinylaldimines (**3a–3d**) was added slowly at 40 to −50 °C and stirred for 1–2 h. The reaction mass was quenched by adding saturated ammonium chloride solution, warmed to room temperature, and extracted in toluene. The organic extracts were washed with water and concentrated. This sulfinylamine (**7**) was treated with IPA-HCl and stirred for 1.0 h. After completion of the reaction, the mass was concentrated, stirred with ethyl acetate, and filtered to get **8a–8z**.

ACKNOWLEDGMENT

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SUPPORTING INFORMATION

Full experimental details, ^{1}H NMR and ^{13}C NMR spectra, and chiral HPLC data can be accessed on the publisher's website.

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