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Asymmetric α-Alkylation of *N′-tert*-Butanesulfinyl Amidines. Application to the Total Synthesis of (6*R*,7*S*)-7-Amino-7,8-dihydro-α-bisabolene

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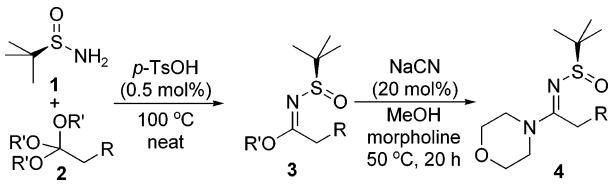
The addition of nucleophiles to imines[1] and metalloenamine additions to electrophiles[2] are two of the most important methods for the preparation of diverse amine structures. The addition of a variety of nucleophiles to *N*-sulfinyl imines is increasingly being used for the asymmetric synthesis of a broad range of amine-containing compounds,[3,4] and recently, the highly diastereoselective addition of metalloenamines derived from *N*-sulfinyl ketimines to aldehydes has been developed for the asymmetric synthesis of 1,3-amino alcohols.[5] However, in the course of studies on the applicability of the *N*-sulfinyl metalloenamine additions to other electrophiles, α-alkylations of the metalloenamines with alkyl halides were not successful. We attributed these results to the strong electron-withdrawing character of the sulfinyl group, which attenuates the nucleophilicity of the metalloenamine. Therefore, we envisioned that the significantly more basic metalloenamines derived from *N′*-sulfinyl amidines would be sufficiently reactive to enable α-alkylation. Herein we describe the highly diastereoselective α-alkylation of *N′-tert*-butanesulfinyl amidines and the versatility of the resulting α-alkylation products in the asymmetric synthesis of amines that contain both α- and *β*-stereocenters. The utility of this chemistry is further demonstrated by the first asymmetric synthesis of the antimicrobial marine natural product (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene.[6]

Synthesis of *N′-tert*-butanesulfinyl amidines **4** can be achieved in two steps from ortho esters (Table 1).[7] Condensation of *tert*-butanesulfinamide **1** and ortho esters **2** with 0.5 mol % *p*-TsOH, followed by the reaction of the imidate products **3** with morpholine using NaCN as a catalyst, afforded **4** in high yields.

Examination of the α-alkylation of *N′-tert*-butanesulfinyl amidines with a number of bases and solvents established that deprotonation of **4** with KHMDS in THF/toluene, followed by reaction with alkyl halides, provided the alkylated amidine products **5** in high yields and with excellent diastereoselectivities (Table 2). The alkylation of amidine **4a** was performed at −78 °C with several allyl bromides and benzyl bromide to afford **5a**−**d** in high yields with >98:2 diastereoselectivities. Reactions with the more hindered amidines **4b** and **4c** required an increase in the reaction temperature to −40 °C, but the alkylation products were still obtained with >96:4 diastereoselectivities (entries 5−7).

Successful transformation of the amidine α-alkylation products to *N*-sulfinyl aldimines and ketimines was essential to achieving a powerful and versatile method for the asymmetric synthesis of amines. Among a number of reducing agents examined to convert the amidines to aldimines, Red-Al was found to be the most effective, with reaction of **5d** with Red-Al at −40 °C providing the desired aldimine **6d** in 86% yield (Scheme 1).[8] Addition of a mixture of an organolithium reagent and $CeCl_3$ proved to be most effective for converting the amidines to ketimines,[9] with the reaction of **5d** with MeLi and $CeCl_3$ at −48 °C affording methyl ketimine **7d** in 87% yield. It is noteworthy that no epimerization occurred

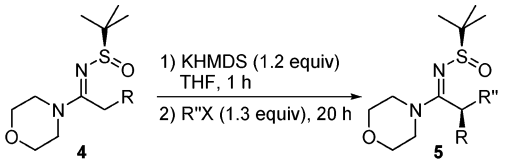
Table 1. Synthesis of *N′-tert*-Butanesulfinyl Amidines **4**

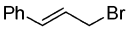


entry	R	R′	yield of **3** (%)[a]	product **4**	yield of **4** (%)[a]
1[b]	Me	Et	94	**4a**	88
2[c]	Ph	Me	97	**4b**	83
3[c]	Bn	Me	97	**4c**	88

[a] Isolated yield. [b] First step was carried out with 1 equiv of **1** and 3 equiv of **2** for 3 h. [c] First step was carried out with 1 equiv of **1** and 1.5 equiv of **2** for 12 h.

Table 2. Asymmetric α-Alkylation of *N′*-Sulfinyl Amidines **4**



entry	R	R"X	temp (°C)	product **5**	dr	yield (%)[b]
1	Me		−78	**5a**	99:1	82
2	Me		−78	**5b**	99:1	86
3	Me		−78	**5c**	98:2	78
4	Me	BnBr	−78	**5d**	98:2	86
5	Ph	BnBr	−40	**5e**	96:4	82
6	Bn		−40	**5f**	99:1	92
7[c]	Bn	MeI	−40	**5g**	97:3	82

[a] Diastereomeric ratio. [b] Isolated yield. [c] Performed with 3 equiv of MeI.

in either the Red-Al reduction or the methyl cerium addition reactions. As previously reported, *N-tert*-butanesulfinyl imines are versatile precursors for the asymmetric synthesis of protected chiral amines.[3] For example, the addition of MeMgBr to **6d** provided ***anti*-8d** in 95% yield with 99:1 dr.[10] Moreover, reduction of ketimine **7d** could be accomplished with high selectivity to obtain either amine stereoisomer, with L-Selectride affording ***anti*-8d** in 89% yield with 96:4 dr and with $NaBH_4$ in the presence of $Ti(OEt)_4$ affording ***syn*-8d** in 86% yield with 96:4 dr.[11] The structure of ***anti*-8d** has been determined by X-ray crystallography and thus establishes both the sense of induction in the alkylation step (Table

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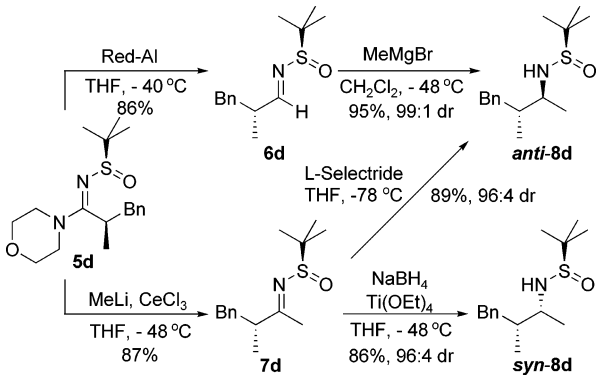
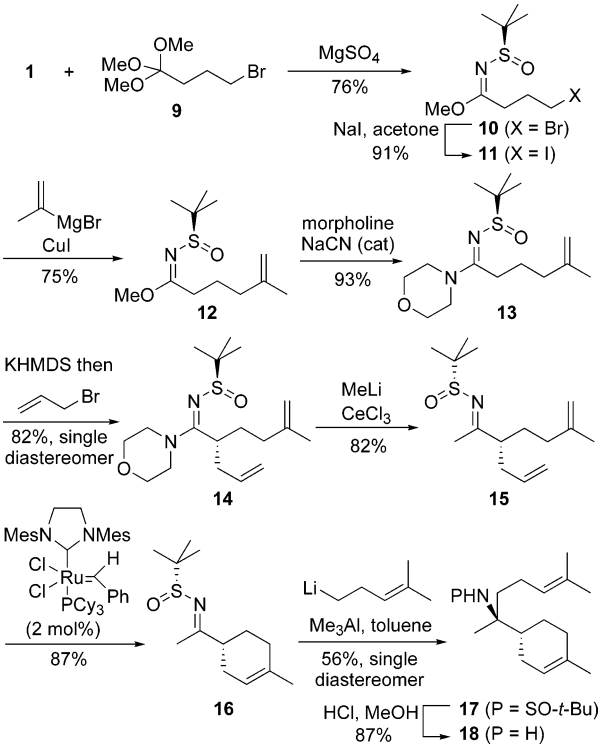
Scheme 1



Scheme 2



2) and the relative stereochemistry obtained in the imine addition steps (Scheme 1).

To demonstrate the utility of this methodology, the first asymmetric total synthesis of (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene[6] **18** was carried out (Scheme 2). The amidine substrate **13** for α-alkylation was synthesized in four steps from commercially available ortho ester **9**. Condensation of **1** with **9** afforded imidate **10** in 76% yield. Because the coupling of **10** with isopropenylmagnesium bromide did not provide **12**, bromide **10** was converted to iodide **11**, which was successfully coupled with the Grignard reagent and CuI. Imidate **12** was converted to **13** in 93% yield under the standard reaction conditions for the conversion of the imidates to the amidines. Allylation of **13** was then performed at −78 °C to afford a single diastereomer of **14** in 82% yield, and amidine **14** was subsequently converted to ketimine **15** with MeLi and $CeCl_3$ in 82% yield. Ring-closing metathesis with the Grubbs second-generation catalyst then gave **16** in high yield.

One of the key steps in the synthesis was organolithium addition to **16** to provide the tertiary carbinamine **17**. Notably, organometallic reagent addition to *N*-sulfinyl ketimines provides the only general method for the asymmetric synthesis of tertiary carbinamines.[12] Gratifyingly, precomplexation of imine **16** with Me_3Al in toluene at −78 °C, followed by addition of the organolithium reagent in hexanes, provided **17** as a single diastereomer in 56% yield. Both the Me_3Al activating agent and the use of noncoordinating solvents were essential for suppressing competitive α-deprotonation. Cleavage of the *N*-sulfinyl group from **17** under acidic conditions then provided (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene **18** in 87% yield.

In summary, the highly diastereoselective α-alkylation of *N*′-*tert*-butanesulfinyl amidines has been developed along with methods for converting the alkylation products to enantiomerically enriched amines that incorporate both α- and *β*-stereocenters. As evidenced by the first asymmetric synthesis of (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene, this method should provide for the efficient asymmetric syntheses of a wide variety of amine-containing compounds.

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Supporting Information Available: Synthetic procedures, characterization, and stereochemical determination of new compounds (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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