Diastereoselective Synthesis of Enantiopure Homopropargylic *N-tert*-Butylsulfinylamines

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Abstract: The diastereoselective synthesis of enantiopure homopropargylic amines by propargylation of various *N-tert*-butylsulfinylimines (*t*BS-imines) with 1-trimethylsilyl allenylzinc bromide is presented.

Key words: amines, asymmetric synthesis, chiral auxiliaries, imines, zinc

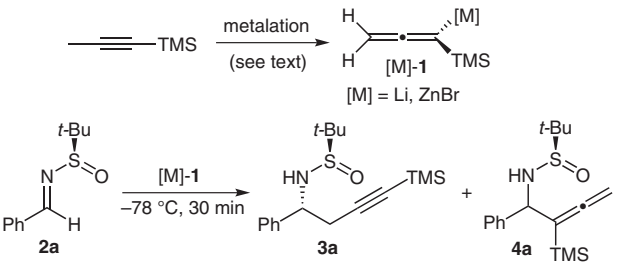
Propargylic and homopropargylic compounds, including homopropargylic amines, are of great interest in organic chemistry owing to their multiple possibilities of transformation and because of the wide range of conditions tolerated by their carbon–carbon triple bond.[1] In spite of the important place they occupy as nitrogen-containing building blocks in asymmetric synthesis, a general and practical stereoselective synthesis of homopropargylic amines is still lacking. Reported strategies[2] include Barbier-type reactions between propargylic bromides and aldimines, addition of pre-formed allenyl/propargyl metals to imines and imine derivatives,[3] and iminium-ion activation through organocatalysis.[4]

Nucleophilic addition and, more specifically, propargylation of chiral *N-tert*-butylsulfinylimines (*t*BS-imines) has proved to be a powerful way to obtain enantioenriched functionalized amine derivatives.[5] In this field, we have reported an efficient method for the stereoselective synthesis of enantioenriched acetylenic aziridines,[6] 1,2-amino alcohols,[7] and 2-amino-1,3-diols[8] by the reaction of racemic 3-chloro- and 3-methoxymethoxyallenyl zinc compounds with enantiopure *t*BS-imines. Thus, the syntheses of a number of natural products have been successfully achieved.[9]

As part of an ongoing project devoted to the synthesis of natural alkaloids, we required easy access to enantiopure α-branched homopropargylamines. Building on our experience on the synthetic use of pre-formed allenyl/propargyl zinc reagents and on two literature precedents describing the diastereoselective propargylation of enantiopure *t*BS-imines,[10,11] we reasoned that metalation of readily available 1-trimethylsilylpropyne should generate efficient *t*BS-imine propargylation reagents.

We first studied the reaction of lithium species Li-**1** with enantiopure phenyl *t*BS-imine **2a** (Scheme 1). Li-**1**, generated by treating 1-trimethylsilylpropyne with *tert*-butyllithium (1 equiv) at –78 °C in diethyl ether, reacted with **2a** almost completely within 30 minutes at –78 °C to afford adducts **3a** and **4a**. Under these conditions, both regio- and diastereoselectivities were modest; an 88:12 mixture of homopropargylic and α-allenic amines **3a** and **4a** was obtained with a diastereomeric ratio (dr) of 72:28 for amine **3a** (Table 1, entry 1). Performing the reaction in the presence of HMPA (4 equiv) gave homopropargylic amine **3a** exclusively, albeit with an incomplete conversion of 76% and a still modest dr of 76:24 (Table 1, entry 2).

Similar regio- and diastereoselectivities were attained when **2a** reacted in diethyl ether at –78 °C with zinc spe-



Scheme 1 Preparation of [M]-**1** and its subsequent reaction with *t*BS-imine **2a** (see Table 1)

Table 1 Optimization of the Reaction of [M]-**1** with *t*BS-Imine **2a**

Entry	[M]-**1** (equiv)	Solvent	Conv (%)[a]	Ratio[b] **3a**/**4a**	dr[c] of **3a**
1	Li-**1** (1)	Et_2O	98	88:12	72:28
2	Li-**1** (1)	Et_2O–HMPA	76	>98:02	76:24
3	ZnBr-**1** (1)	Et_2O	30	>98:02	80:20
4	ZnBr-**1** (1)	THF	31	>98:02	>98:02
5	ZnBr-**1** (2)	THF	100 (79)[d]	>98:02	>98:02

[a] Conversion observed in the propargylation reaction based on unreacted **2a** determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Regioselectivity determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Diastereoselectivity determined by ^{1}H NMR analysis of the crude reaction mixture
[d] Isolated yield after silica gel chromatography given in parentheses.

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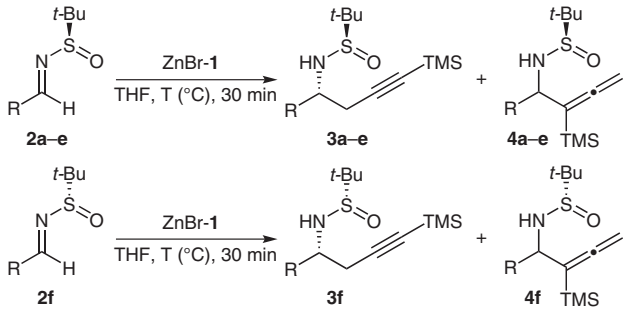
cies ZnBr-**1** (generated by the transmetalation of Li-**1** with zinc bromide at –35 °C) although, in this case, a poor conversion of 30% was observed (Table 1, entry 3).

Conversely, we found that **3a** could be obtained as the single product in dr >98:2 when the reaction was carried out between **2a** and ZnBr-**1** in tetrahydrofuran at –78 °C. In this solvent, the organozinc species was generated by metalation of 1-trimethylsiylylpropyne with *sec*-butyllithium (1 equiv) at –20 °C and subsequent transmetalation at –35 °C. However, although both regio- and stereoselectivities were excellent under these conditions, using one equivalent of ZnBr-**1** led to a poor conversion of 31% (Table 1, entry 4). Finally, full conversion of imine **2a** was observed when two equivalents of ZnBr-**1** were used, giving homopropargylic amine **3a** as a single isomer in 79% isolated yield (Table 1, entry 5).

The optimized propargylation reaction conditions (i.e., two equivalents of ZnBr-**1** in THF) were next applied to a range of *t*BS-imines (Scheme 2).[12]

Surprisingly, at –78 °C, the propargylation with alkyl-substituted imine **2b** was not completely regioselective, since a 82:18 mixture of homopropargylic and α-allenylic amines **3b** and **4b** was obtained, nevertheless, an excellent



Scheme 2 Scope of the propargylation reaction of *t*BS-imines **2a–f** (see Table 2)

diastereomeric ratio was achieved that was higher than 98:2 for **3b** (Table 2, entry 3). In contrast, a better result was obtained when the propargylation reaction was performed at room temperature. Homopropargylic amine **3b** was exclusively formed in 98% yield and dr >98:2 (Table 2, entry 4). The same conditions allowed alkyl and alkenyl homopropargylic amines **3c–f** to be isolated in high yields (70–98%) and dr >98:2 from the corresponding *t*BS-imines, meaning that steric hindrance of the R substituent of the imine had little influence on the level of the stereoselectivity (Table 2, entries 5–7 and 9). It is worthy of note that, in the case of aromatic imine **2a**, a lower dr of 84:16 was observed when the reaction was performed at room temperature (Table 2, entry 2). More unexpectedly, when the reaction was conducted at –78 °C with *t*BS-imine **2f** bearing a silyloxy substituent α to the imino group, α-allenylic amine **4f** was formed with a high regioselectivity of 95:5 as a single stereoisomer (Table 2, entry 8).

The relative configuration of the two stereocenters of **3a–c** was determined to be *anti* by transformation into known homoallylamines **5a–c**[13] and comparison of their NMR data, which were found to be identical to the reported values (Scheme 3). The *anti*-configuration of **3d–e** was inferred from these results. In contrast, the product obtained from **3f** following the same sequence had different NMR and physical data to those reported for the expected (S,S_S) stereoisomer,[13] suggesting that the relative configuration of the two stereocenters is opposite in this case. The *R* configuration of the newly created center in **3f** was further confirmed by its transformation into β-amino alcohol **6**, for which the specific rotation {$[\alpha]_D^{25}$ +6.4 (*c* 1.4, MeOH)} was found to be opposite to that reported for the antipode of **6** {$[\alpha]_D^{25}$ –6.0 (*c* 1.0, MeOH)} (Scheme 3).[14] Thus, the sense of stereoinduction is reversed between the

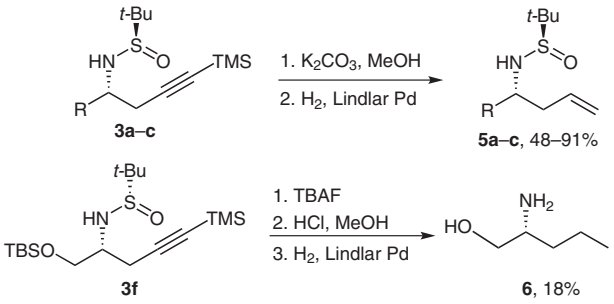
Table 2 Diastereoselective Addition of Allenylzinc ZnBr-**1** to *t*BS-Imines **2a–f**

Entry	R	*t*BS-Imine[a]	Temp (°C)	Ratio[b] **3/4**	Yield[c] (%)	Major product	dr[d]
1	Ph	**2a**	–78	>98:02	79	**3a**	>98:02
2	Ph	**2a**	r.t.	>98:02	79	**3a**	84:16
3	*n*-Pr	**2b**	–78	82:18	90	**3b**	>98:02
4	*n*-Pr	**2b**	r.t.	>98:02	98	**3b**	>98:02
5	*i*-Pr	**2c**	r.t.	>98:02	70	**3c**	96:04
6	*c*-Hex	**2d**	r.t.	>98:02	86	**3d**	>98:02
7	(*E*)-PhCH=CH	**2e**	r.t.	>98:02	98	**3e**	>98:02
8	$TBSOCH_2$	**2f**	–78	05:95	91[e]	**4f**	>98:02
9	$TBSOCH_2$	**2f**	r.t.	>98:02	81	**3f**	>98:02

[a] Propargylation reaction performed with two equivalents of ZnBr-**1** and one equivalent of imine **2a–f**.
[b] Regioselectivity determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Combined isolated yield after silica gel chromatography.
[d] Diastereoselectivity of major product determined by ^{1}H NMR analysis (400 MHz) on the crude reaction mixture.
[e] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.

addition to alkyl- or aryl-substituted *t*BS-imines and the addition to α-silyloxy-substituted imine **2f**.

Furthermore, pre-formed allenylzinc ZnBr-**1** reacts with *t*BS-imines **2a**–**e** with a stereocontrol opposite to that observed by Fandrick et al. in their zinc-catalyzed propargylation of *t*BS-imines starting from propargylborolanes, wherein the reactive species is likely to be ZnEt-**1**.[11] This interesting reversal of selectivity represents another example in which the stereoselectivity of nucleophilic addition to *t*BS-imines is controlled by the reaction conditions.[13a,15]



Scheme 3 Structural assignment of **3a**–**f**

The results obtained by Fandrick and coworkers have been rationalized by the six-membered chelated transition-state model **TS2** (Figure 1), which is similar to the model we previously proposed for the addition of a 3-chloroallenylzinc bromide to *t*BS-imines.[6a,b] The stereoselectivity observed in the reactions with ZnBr-**1** can be explained by the six-membered transition-state model **TS1**, analogous to that invoked for the addition of 3-methoxymethoxyallenylzinc bromide on *t*BS-imines,[7b,c] wherein the zinc atom is coordinated only to the nitrogen atom of the imine that adopts its lowest energy conformation.[6c]

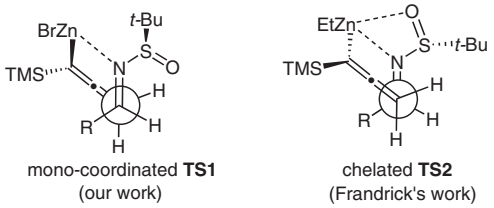
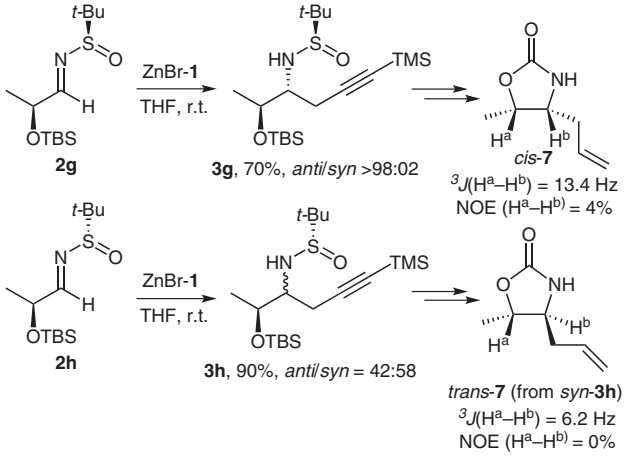


Figure 1 Transition-state model **TS1** for additions to **2a**–**e**

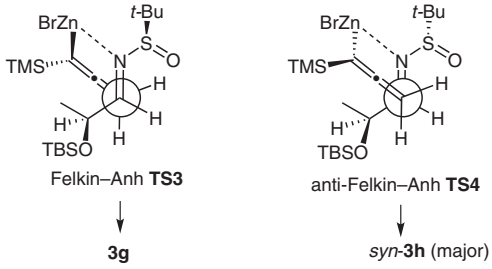
The case of the imine **2f**, bearing an α-silyloxy group, is intriguing. Reversal of facial selectivity of additions to alkyl-substituted *t*BS-imines and additions to *t*BS-imines bearing an α-coordinating group has a precedent, although no explanation has been provided.[16] Similarly, in our case, we cannot put forward a convincing explanation as to why addition on **2f** cannot be rationalized by model **TS1**.

The reactivity of *t*BS-imines **2g** and **2h**, bearing an α-oxygenated stereocenter, was also examined (Scheme 4). In both cases, propargylation in THF at room temperature proceeded with good yield and complete regioselectivity in favor of propargylic amines **3g** and **3h**. However, while the formation of *anti*-**3g** with excellent diastereoselectivity (*anti*/*syn* >98:2) was observed from imine **2g**, the propargylation of diastereoisomeric imine **2h** led to *syn*-**3h** with very low levels of selectivity (*anti*/*syn* = 42:58). The *anti*-configuration of **3g** and the *syn*-configuration of the major isomer **3h** were deduced from the $^3J(H^a–H^b)$ coupling constants measured for the corresponding *cis* (J = 13.4 Hz) and *trans* (J = 6.2 Hz) oxazolidinones *cis*-**7** and *trans*-**7** (Scheme 4). This was corroborated by NOE enhancements of 4 and 0% for *cis*-**7** and *trans*-**7**, respectively.



Scheme 4 Propargylation of α-silyloxy *t*BS-imines **2g** and **2h**

In the case of imines **2g** and **2h**, both the stereocenter α to the imino group and the *N*-*tert*-butylsulfinyl auxiliary can direct the facial selectivity of the propargylation. The *anti*-selectivity observed for the addition of ZnBr-**1** to **2g** is consistent with a Felkin–Anh model **TS3** (similar to **TS1**) as previously reported for nucleophilic additions to *N*-*tert*-butylsulfinyl-α-silyloxyacetaldimines[17] (Scheme 5). The poor selectivity observed for **2h** can be explained by an opposition of the inherent selectivity provided by the sulfinyl group and that provided by the α-stereocenter through Felkin–Anh control. The major product was thus obtained via the anti-Felkin–Anh model **TS4**, as previously reported by Ellman on enolate additions to *N*-*tert*-butylsulfinyl-α-silyloxy aldimines.[17] The stereochemical outcome of these reactions is worthy of mention since, generally, in additions to *t*BS-imines, the influence of the sulfinyl auxiliary overrides that of the α-stereocenter.[6d,8,16,18,19]



Scheme 5 Proposed transition-state models **TS3** and **TS4**

In conclusion, we have reported an efficient and highly diastereoselective propargylation of *t*BS-imines with the allenylzinc bromide derived from 1-trimethylsilyl propyne. This methodology provides a practical and competitive access to enantioenriched homopropargylic amines. Besides this, a remarkable difference of diastereofacial selectivity is observed between alkyl, aryl, and α-silyloxy *t*BS-imines. We are currently examining the rationale behind the postulated transition-state models by using theoretical calculations; the results will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) Typical procedure for the preparation of **3a**–**h** (Table 2): To a solution of 1-trimethylsilylpropyne (296 μL, 2.00 mmol) in THF (7 mL) was added *s*-BuLi (1.3 M in pentane, 1.54 mL, 2.00 mmol) at such a rate that the internal temperature did not exceed –45 °C. When the addition was complete, the reaction mixture was warmed to –20 °C over a period of 20 min. After 45 min of stirring at –20 °C, the reaction mixture turned bright yellow and was cooled to –35 °C prior to the addition of $ZnBr_2$ (1 M in THF, 2.00 mL, 2.00 mmol) over a period of 5 min. After 30 min stirring at –35 °C, the resulting colorless mixture was cooled to –78 °C (for **2a**) or warmed to 20 °C (for **2b**–**h**). Sulfinylimine **2a**–**h** (1.00 mmol) in THF (1 mL) was then added dropwise. The reaction mixture was stirred at r.t. until the reaction was complete (reaction monitored by TLC; ~30 min) then quenched by addition of NH_4Cl/NH_3 (2:1), extracted with Et_2O, dried ($MgSO_4$), and concentrated to give **3a**–**h**, which were purified by flash chromatography over silica gel

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