

Sml₂-Promoted Intramolecular Asymmetric Pinacol-Type Ketone—*tert*-Butanesulfinyl Imine Reductive Coupling: Stereoselectivity and Mechanism

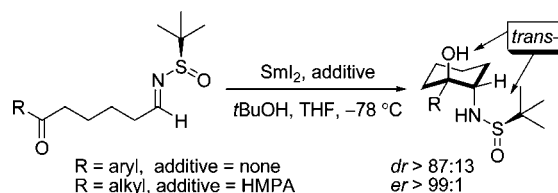
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ABSTRACT



The asymmetric ketone—*tert*-butanesulfinyl (*t*-BS) imine pinacol-type reductive coupling promoted by SmI₂ is described. *Trans*-1,2-vicinal amino alcohols were formed predominantly in excellent er and high dr. The stereochemical outcome provided evidence for a radical mechanism for SmI₂-induced reductive couplings of *t*-BS imines.

1,2-Amino alcohol is a ubiquitous structural feature in natural products as well as a key pharmacophore in therapeutical agents possessing a wide spectrum of biological activities.¹ Moreover, it is also a pivotal moiety in chiral ligands and auxiliaries for asymmetric synthesis.² In view of its importance in both organic synthesis and medicinal chemistry, numerous efforts have been devoted to the stereoselective construction of this key unit.^{1,3} One of the most straightforward methods to construct vicinal amino alcohols is the direct pinacol-type aldehyde—imine reductive coupling. Recently,

an efficient and highly enantioselective SmI₂-induced⁴ reductive coupling of aldehydes with *N*-*tert*-butanesulfinyl (*t*-BS hereafter) imines⁵ has been reported.⁶ However, although reactions of ketone with other C=N functions (imine,⁷ nitron,⁸ hydrazone,⁹ oxime¹⁰) have been studied, mostly in racemic form, the asymmetric ketone—sulfinimine coupling is very rare, and only a single example using the symmetric

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(6) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, 127, 11956. However, the mechanism of this reaction has not been rationalized.

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acetone has been reported so far.¹¹ Conceivably, such a reaction would afford a chiral amine juxtaposed with a tertiary carbinol, a challenging key structure of many chiral ligands (**I–III**) as well as natural products (**IV**) (Figure 1).

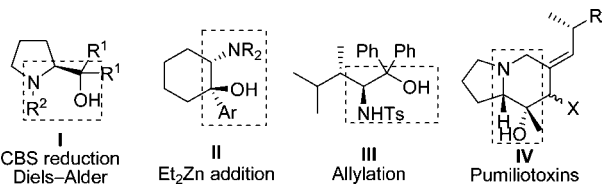
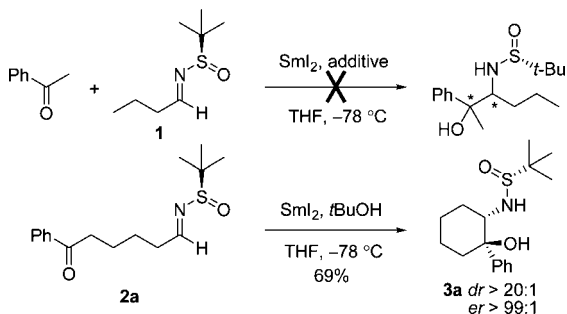


Figure 1. Representative chiral ligands and natural products possessing juxtaposed tertiary carbinol and amine.

Furthermore, results obtained in ketone–sulfinimine coupling might provide clues to the origins of stereoselectivity in closely related reactions and improve our understanding of the chemistry of Ellman's imine. As part of our continuing interest in the area of amino alcohols,¹² herein we describe the asymmetric intramolecular reductive coupling between ketones and *t*-BS imines.

Our initial attempt to effect intermolecular SmI₂-mediated coupling between acetophenone and *t*-BS imine **1** was unsuccessful. Under various conditions (additives, proton sources), only the reduction and pinacol coupling of acetophenone were observed, whereas **1** was untouched. Apparently, the ketyl radical anion formed upon single-electron reduction of acetophenone was much less reactive toward *t*-BS imine as compared to aldehyde-derived analogues, due to the profound steric and electronic effects of the extra methyl. Nevertheless, it is still of interest to fathom the reactivity of ketyls toward imines in an intramolecular fashion, as in this way favorable spatial proximity of the reacting partners could possibly overcome unfavorable thermodynamics. Thus, a simple substrate **2a**, a chimera joining acetophenone and **1**, was prepared and subjected to conditions employed in the aldehyde–imine coupling⁶ (Scheme 1). To our delight, a cyclization product **3a** was

Scheme 1. Pinacol-Type Ketone–Imine Reductive Coupling



obtained in good yield (69%) and excellent stereoselectivity (dr > 20:1, er > 99:1).¹³

The absolute configuration of **3a** was determined by single-crystal X-ray diffraction (Figure 2, top).¹⁴ It turned out that

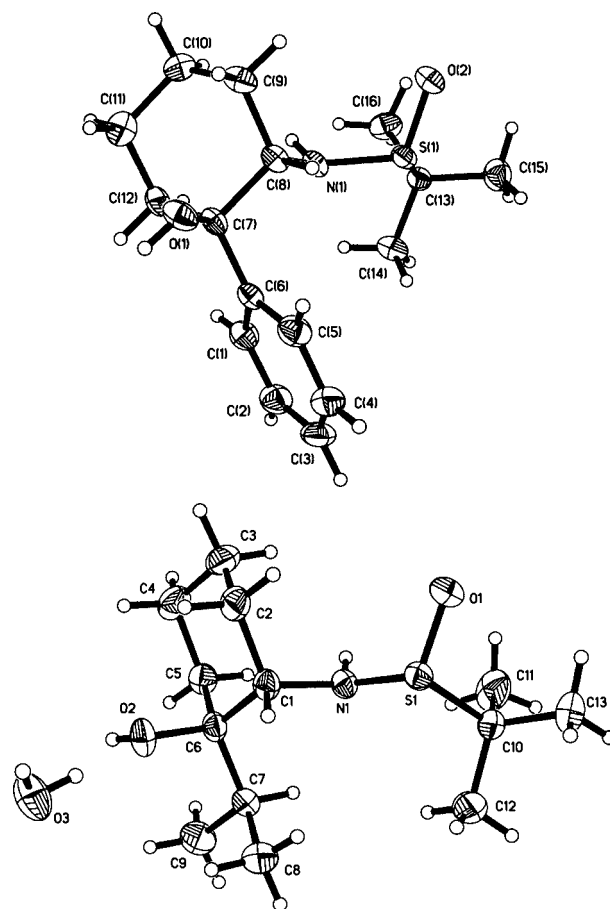


Figure 2. X-ray crystal structures of **3a** (top) and **3b** (bottom).

the hydroxyl and the sulfinylamino groups were *trans* to each other, showing a diaxial substitution pattern. This might

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(11) Lin, X.; Bentley, P. A.; Xie, H. *Tetrahedron Lett.* **2005**, *46*, 7849.

(12) (a) Wang, B.; Zhong, Z.; Lin, G.-Q. *Org. Lett.* **2009**, *11*, 2011. (b) Wang, B.; Liu, R.-H. *Eur. J. Org. Chem.* **2009**, 2845. (c) Liu, R.-H.; Fang, K.; Wang, B.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2008**, *73*, 3307. (d) Wang, B.; Fang, K.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 7981. (e) Wang, B.; Yu, X.-M.; Lin, G.-Q. *Synlett* **2001**, 904. (f) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2000**, *65*, 9114.

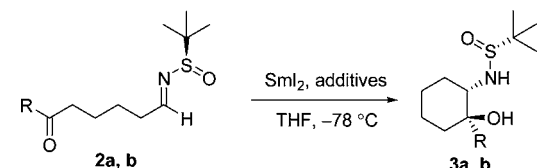
(13) The dr was determined by ¹H NMR, and the er was determined by chiral HPLC of *N*-Ac derivatives of **3**; see the Supporting Information.

(14) Enantiopure **3a** did not afford suitable single crystals for X-ray analysis; instead, the racemic sample (1:1 mixture of *R*_S,1*R*,2*S*- and *S*_S,1*S*,2*R*-isomers) was used. Nevertheless, it is safe to conclude that *R*_S-**2a** produced *R*_S,1*R*,2*S*-**3a**, since the absolute configuration of sulfur was not disturbed during the reaction.

suggest that chelation of the heteroatoms of the sulfinylamino group to the Sm(III) cation did not play a significant role for the stereoselection during the course of the reaction, and the high dr was the result of inherent stereoelectronic effects.

With this promising result, the reaction conditions were then optimized with regard to the amount of reductant, the additive and the proton source across both aryl and alkyl ketones (Table 1). It was found that the reaction of **2a** did

Table 1. Optimization of Coupling Conditions

				
entry	2 , R	SmI ₂ (equiv)	additives (equiv)	3 (%) ^a
1	2a , Ph	2.0	<i>t</i> -BuOH (2)	63
2	2a	3.0	<i>t</i> -BuOH (3)	69
3	2a	3.0	none	42 (64)
4	2a	2.0	<i>t</i> -BuOH (2), HMPA (8)	NR
5	2b , <i>i</i> -Pr	2.0	<i>t</i> -BuOH (2)	NR
6	2b	3.0	HMPA (12)	11 (22)
7	2b	4.0	<i>t</i> -BuOH (4), HMPA (16)	76
8	2b	4.0	<i>t</i> -BuOH (4), DMPU (16)	18 (35)

^a Isolated yields; conversion indicated in parentheses.

not require HMPA as an additive, while for alkyl substrate **2b**, 4 equiv of *t*-BuOH and 16 equiv of HMPA were both necessary to obtain the optimal results, and the latter could not be replaced by DMPU.¹⁵ For alkyl ketones, 4 equiv of SmI₂ was employed, while a further increase of its amount would not improve the yield. The structure of **3b** was also determined to be the diaxial *trans*- configuration by single-crystal X-ray analysis (Figure 2, bottom). The fact that the sense of diastereoselection remained the same for both types of substrates, with or without HMPA, suggested that the course of reaction was not affected by this additive.

With the optimum conditions in hand, we probed the scope and limitation of this reductive coupling reaction (Table 2). Unlike the nitron-*t*-BS imine coupling,¹⁶ little restriction in the nature of ketone appendages was observed. Both aryl and alkyl ketones gave moderate to excellent yields. The reaction of an aryl ketone bearing multiple halogen nucleus substitutions was more complex and gave a lower yield (entry 7), probably due to its higher oxidative potential which favored further reduction of the ketyl to carbanion before cyclization. Such an α -oxygenated carbanion was too reactive and prone to cause side reactions. A bulky 2-naphthyl appendage also decreased the yield (entry 8). In the alkyl ketone series, even the highly hindered *tert*-butyl ketone gave a 36% yield of the expected product at an eroded dr. Cyclohexanone **2m** (1:1 diastereomeric

Table 2. Intramolecular Asymmetric Ketone–Imine Coupling^a

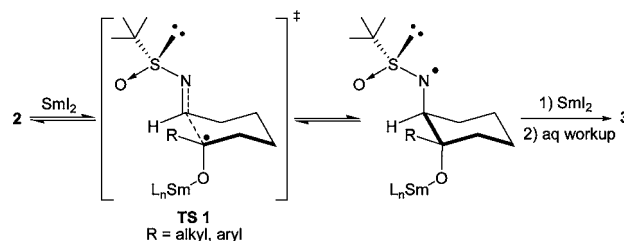
entry	ketoimine 2	product 3	yield (%), dr ^b
1	2a R = Ph	3a	69, > 20:1
2	2b R = <i>i</i> Pr	3b	76, 9:1
3	2c R = <i>p</i> -CH ₃ C ₆ H ₄	3c	95, > 20:1
4	2d R = <i>p</i> -CH ₃ OC ₆ H ₄	3d	96, > 20:1
5	2e R = <i>p</i> -BrC ₆ H ₄	3e	56, > 20:1
6	2f R = <i>p</i> -ClC ₆ H ₄	3f	63, > 20:1
7	2g R = <i>m,p</i> -Cl ₂ C ₆ H ₃	3g	28, > 20:1
8	2h R = 2-C ₁₀ H ₇	3h	35, > 20:1
9	2i R = Me	3i	70, > 20:1
10	2j R = Et	3j	66, 14:1
11	2k R = <i>t</i> Bu	3k	36, 6.6:1
12	2l R = BnO(CH ₂) ₃	3l	80, 12:1
13	2m	3m	82, ^c nd
14	2n	3n	45, > 20:1
15	2o	3o	28, > 20:1

^a Conditions: For aryl ketones, see Table 1, entry 2; for alkyl ketones, see Table 1, entry 7. ^b Isolated yields of pure major diastereomers; dr determined by ¹H NMR of the crude products. ^c dr 2.4:1 at C-6.

mixture) afforded fused bicyclic products in 82% yield, with a dr of 2.4:1 at the former ketonic α -position. This significant deviation from statistical product distribution suggested that there was a certain equilibrium before the event of cyclization. Notably, the oxa-heterocyclic product **3n** can be obtained in a moderate yield (45%), while analogous ketone–alkene coupling was reportedly overridden by SmI₂-promoted α -deoxygenation.¹⁷ Unfortunately, formation of a 5-membered ring was less effective (28%), whereas attempts to form 7-membered rings failed.

The interesting stereoselectivity of this ketone–imine reductive coupling can be best elucidated without invoking complicated chelation models (Scheme 2). The ketone carbonyl was first reduced to a ketyl via SET from 1 equiv of SmI₂. In the transition state for the cyclization (**TS 1**),

Scheme 2. Plausible Ketyl Cyclization Mechanism



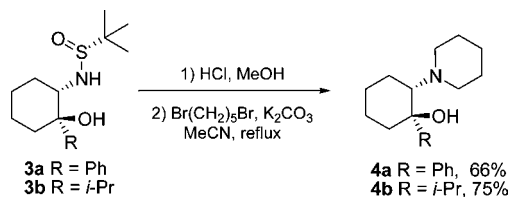
(15) For recent studies on the role of HMPA, see: (a) Faran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 865. (b) Sadasivam, D. V.; Antharjanam, P. K. S.; Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2008**, *130*, 7228.

the *t*-BS imine adopted its less energetic conformation,¹⁸ whereas the ketone appendage R occupied the more stable equatorial orientation^{17a,19} and the attack of the ketyl occurred at the less hindered face of the imine. Both the carbonyl reduction and C–C bond formation may be reversible,²⁰ which could be key to the high dr. In the extreme case of **3k** where the exceedingly bulky R (*t*-Bu) caused appreciable R–*t*-BS interaction and partially altered the imine orientation, a lower dr was observed, while in general such interaction was tolerated.²¹ Postcyclization reduction of the *N*-centered radical afforded product **3**. The resemblance of **TS 1** to that of ketyl–olefin cyclization^{17a} and the absence of chelation between Sm(III) and the sulfinylamino moiety²² both argue for the radical mechanism instead of an anionic pathway.²³

The synthetic utility of this ketone–imine reductive coupling was demonstrated by the facile synthesis of **4a**, an

effective chiral catalyst for the asymmetric addition of Et₂Zn to aldehydes.²⁴ Removal of *t*-BS followed by double *N*-alkylation with 1,5-dibromopentane afforded the piperidine derivatives **4a,b** in one pot (Scheme 3). Unfortunately, in

Scheme 3. Utility of the Coupling Products



our preliminary tests the alkyl analogue **4b** did not show catalytic activity for this reaction.²⁵

To summarize, we have achieved an asymmetric intramolecular pinacol-type ketone–imine reductive coupling. The substrate scope covers both aryl and alkyl ketones, and the reaction of the former did not require HMPA as the additive. For both types of substrates, the resulting tertiary β -amino alcohols possessed a diaxial (*trans*) substitution pattern, which provided the backbones of some excellent chiral ligands. From a mechanistic point of view, the stereochemical outcome favors the ketyl cyclization mechanism via single-electron transfer, instead of the alternative anionic pathway via a two-electron reduction. Potential applications of this protocol along with its products in asymmetric synthesis are currently under investigation.

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Supporting Information Available: Characterization data, ¹H and ¹³C NMR spectra for **3a–o** and **4b**. X-ray structures of **3a**, **3b**, and **3k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(21) The tolerance of the R–sulfinyl *gauche*-interaction in this reaction could be due to the fact that an *N*-radical might be roughly trigonal (*sp*²), similar to its imine precursor; while for polar 1,2-addition to sulfinimines directly yielding a sterically demanding tetrahedral (metallated) *N*-anion, such R–sulfinyl interaction becomes the determining factor (ref 18a). In the latter case, the shift in hybridization state of nitrogen could also affect the conformation of the sulfinyl group.
(22) In most polar additions to sulfinimines, coordination of substrate O/N atoms to metal cation was proposed to explain the observed stereoselectivity. If anionic cyclization mechanism predominated in the present case, chelation of the hydroxyl and the sulfinylamino groups to Sm(III) would afford either the *cis*- products or the *opposite* sense of chiral induction.
(23) We tentatively interpret the diastereoselectivity for aldehyde–*t*-BS imine coupling (ref 6) by an analysis along the same line: the unfavorable R–R' *gauche*-interaction in **TS 3** was avoided in **TS 2**, which produced the observed *anti*-diastereomer. It should be noted that in **TS 1**, OSmL_n occupied the axial orientation as the result of stereoelectronic effects in cyclic systems (ref 17a), and this does not reflect its bulk relative to R in acyclic systems (OSmL_n > R>H).

