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Sulfoxide-Directed Enantioselective Synthesis of Functionalized Tetrahydropyridines

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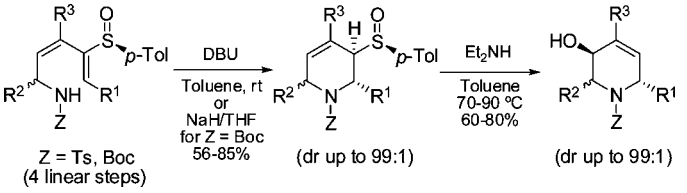
ABSTRACT



The highly selective base-promoted cyclization of enantiopure sulfinyl dienamines provides stereodefined sulfinyl 1,2,3,6-tetrahydropyridines (dr up to 99:1). Subsequent sigmatropic rearrangement affords tetrahydropyridin-3-ols in good yields and selectivities.

Piperidines and 3-hydroxypiperidines are prevalent motifs within nature[1] as well as in conformationally restricted peptidomimetics[2] and synthetic drugs.[3] Their presence in numerous bioactive compounds and their pronounced pharmacological properties have attracted considerable attention to the asymmetric syntheses of these targets.[4] One of the most versatile routes to these nitrogen-containing frameworks is the aza-Diels–Alder reaction involving either aza-dienophiles or aza-dienes.[5] Alternatively, addition–cyclization to imines,[6] ring expansion of furan derivatives,[7] reduction of pyridine scaffolds,[8] ring closing metathesis[9] (RCM) on dialkyl substituted nitrogen substrates, or several approaches via nucleophilic attack of nitrogen onto different acceptors have been extensively employed to furnish the piperidine skeleton.[10] Many of these strategies require the use of amino acids or substrates bearing chiral auxiliaries to

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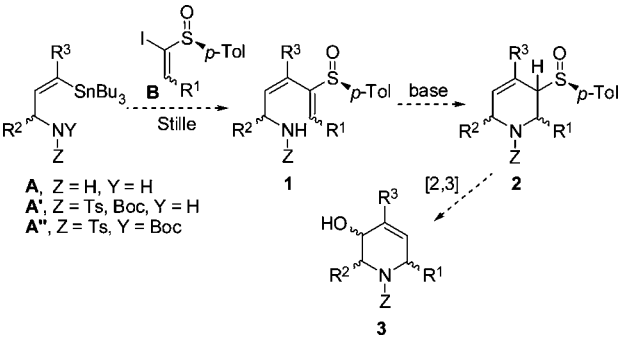
give access to these valuable scaffolds. The sulfinyl group, broadly used in organic synthesis as a stereodirecting functionality,[11] has also been examined within this field by using sulfinimines,[12] and alkenyl sulfoxides as substrates.[13] Nonetheless, the development of new synthetic approaches to access structurally diverse and enantiopure piperidine derivatives through simple and general experimental protocols remains a challenge.

Previously, we have reported the stereocontrolled cyclization of hydroxy sulfinyl dienes to afford enantiopure 3-sulfinyl dihydropyrans.[14] Building upon these precedents and our interest in developing new building blocks via novel sulfoxide-based synthetic transformations, especially those that allow for multiple chirality-transfer operations,[15] we envisaged that the related aminodienes **1** might behave similarly and undergo an intramolecular conjugate addition to provide a diverse range of stereodefined allylic sulfinyl 1,2,3,6-tetrahydropyridines **2**. We detail herein our preliminary studies aimed at this goal, as well as the [2,3]-sigmatropic rearrangement of a range of these unexplored allylic sulfoxides **2** to afford functionalized tetrahydropyridin-3-ols **3** (Scheme 1).[16]

Our initial investigations focused upon the generation of unmasked amino dienyl sulfoxides by Stille coupling between stannanes **A**,[17] and stereodefined iodo alkenyl sulfoxides **B**, available in three steps from commercially available menthyl sulfinate. However, after considerable fruitless experimentation,[18] we decided to examine the coupling with protected stannanes **A′** (Z = Ts, Boc), prepared uneventfully under standard conditions, to afford moderate to good yields of dienes **1** (63−83%).[19] Dienes **1f** and **1g** (R^2 = Me, R^3 = H) were prepared from stannane **A″**, by coupling with **B**, subsequent diastereomer separation, and *N*-Boc deprotection with TFA.

Scheme 1. Proposed Reaction Pathway To Access Stereodefined 3-Sulfinyl and 3-Hydroxyl Tetrahydropyridines, **2** and **3**



The viability of the proposed cyclization was then examined as sulfinyl diene **1a** (R^1 = *n*-Bu, R^2 = R^3 = H) was treated with LDA or NaH in THF to provide allylic sulfoxide **2a** with high selectivity but in low yields (27% and 19% respectively) along with uncharacterized byproducts. The use of DBU was next evaluated to give allylic sulfoxide **2a** in 60% yield, which further improved to 69% by switching to CH_2Cl_2 (Table 1, entries 1 and 2). Carrying out the cyclization in toluene (16 h, 0 °C to rt) provided the optimal yield (78%, Table 1, entry 3) of the desired *N*-tosyl sulfinyl tetrahydropyridine **2a**, as essentially a single isomer that could be stored for months without noticeable loss of diastereomeric purity.

In contrast, *N*-Boc-dienyl sulfoxide **1b** required the use of NaH in THF to promote the cyclization to *N*-Boc-tetrahydropyridine **2b** in good yield (Table 1, entry 4). The presence of rotamers in this case entailed further transformations to accurately determine the diastereomeric ratio.[20] Thus, we chose to carry on this study with *N*-tosyl amino dienyl sulfoxides and substrates **2c**−**h** were selected to evaluate the effect of representative R^1−R^3 groups on the feasibility and selectivity of the cyclization (Table 1, entries 5−10).

The transformation is compatible with alkyl and aryl substitution at R^1 with good yields and excellent stereoselectivities (Table 1, entries 3, 5−7). The presence of an additional stereocenter in the dienamine skeleton (R^2) is also tolerated (Table 1, entries 8 and 9), but diastereoisomer **1g** required heating at 70 °C to afford **2g** in lower yield, along with a small amount of an isomeric vinyl sulfoxide. Moreover, the methodology could also accommodate an additional substituent on the diene (R^3) with **1h** leading to **2h** that underwent a slight epimerization at sulfur upon standing in solution (Table 1, entry 10).[21]

The influence of the geometry of the amino dienyl sulfoxide was also addressed, and the less reactive *Z*,*E*-diene **1i** gave a moderate yield of *cis*-tetrahydropyridine **2i**, along with a substantial amount of the undesired cyclic vinyl sulfoxide (Table 1, entry 11). The high stereoselectivity

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(17) Amino vinyl stannane **A** (R^2 = R^3 = H) was prepared as described in Corriu, R. J. P.; Geng, B.; Moreau, J. J. E. *J. Org. Chem.* **1993**, *58*, 1443–1448. Vinyl stannane **A″** (R^2 = Me, R^3 = H) was prepared from the related alcohol by a Mitsunobu reaction with TsNHBoc.

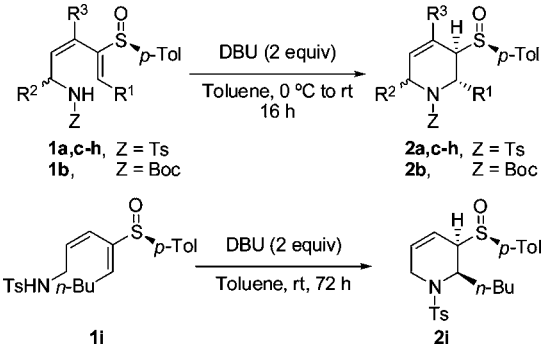
(18) Different catalysts ($Pd_2(dba)_3 \cdot CHCl_3$, $Pd(PPh_3)_4$, $Pd(CH_3CN)_2Cl_2$), solvents, and temperatures were tested under standard Stille coupling conditions. None of them provided the desired *N*-unprotected aminodiene. In all cases, vinyl iodide **B** was recovered whereas amino vinyl stannane **A** was consumed.

(19) See the Supporting Information for further details on the synthesis and spectroscopic data of all new compounds.

(20) Sequential [2,3]-sigmatropic rearrangement of **2b** followed by *N*-Boc deprotection to give **3j** was required to verify the diastereoisomer ratio.

(21) A parallel behavior was observed for the related dihydropyran (see ref 14).

Table 1. DBU-Promoted Cyclization of Amino Dienyl Sulfoxides



entry	**2**	R^1	R^2	R^3	*trans*/*cis*[a]	yield[b]
1	**2a**[c]	*n*-Bu	H	H	97/3	60
2	**2a**[d]	*n*-Bu	H	H	>98/2	69
3	**2a**	*n*-Bu	H	H	>98/2	78
4	**2b**[e]	*n*-Bu	H	H	90/10	81
5	**2c**	*n*-Pr	H	H	>98/2	85
6	**2d**	Ph	H	H	>98/2	71
7	**2e**	4-MeO-C_4H_6	H	H	>98/2	68
8	**2f**	*n*-Bu	(*S*)-Me	H	>98/2	77
9	**2g**[f]	*n*-Bu	(*R*)-Me	H	>98/2	56
10	**2h**[g]	*n*-Bu	H	Me	96/4	64
11	**2i**[g]	*n*-Bu	H	H	>98/2	51

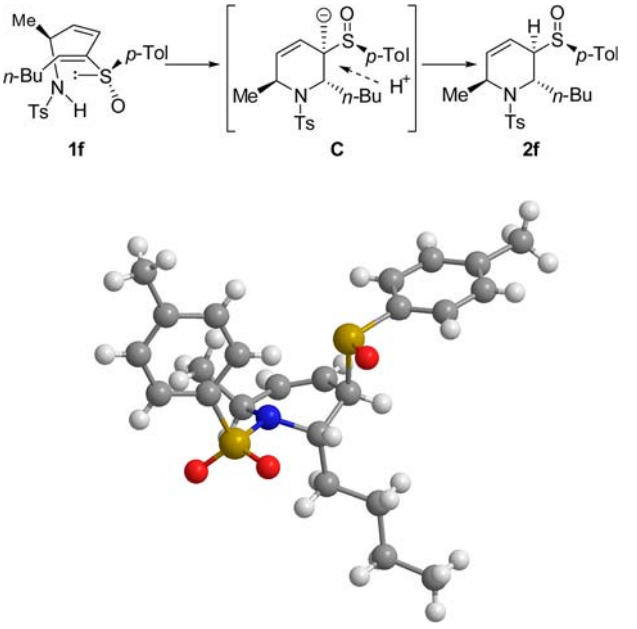
[a] Determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Yield of isolated major diastereoisomer of **2**. [c] THF was used as solvent. [d] CH_2Cl_2 was used as solvent. [e] *N*-Boc-substrate **1b** was successfully cyclized under optimized conditions with NaH (1.3 equiv)/THF, rt, 2 h (90/10). [f] 3 h at 70 °C was required to cyclize **1g**. [g] 72 h at rt was required to obtain **2h** and **2i** under optimal conditions.

found for these cyclizations and the configurational stability of the resulting allylic sulfoxides are noteworthy.

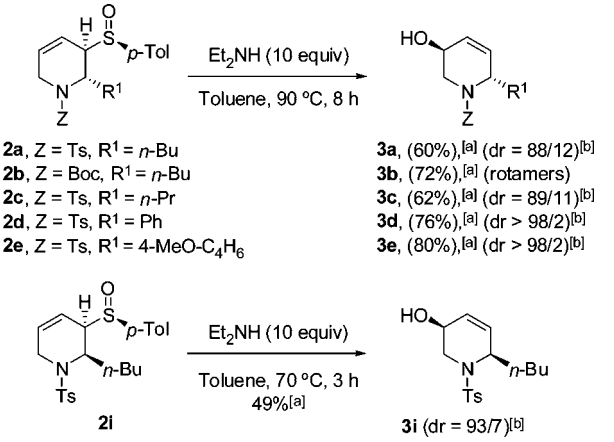
While these sulfinyl allylic tetrahydropyridines **2** were fully characterized by standard techniques, the 2,3-*trans* or 2,3-*cis* stereochemistry could not be firmly established. Examination of the values of the coupling constants between H-2 and H-3 was not conclusive, since both *trans*- and *cis*-isomers had similar small values. These stereochemical assignments were secured by an X-ray crystal structure determination of **2f** and subsequent comparison of the data.[22] In addition, the results of the [2,3]-sigmatropic rearrangements of these allylic sulfoxides to produce allylic alcohols (see below) provided further evidence supporting these assignments.

We postulate that the formation of 2,3-*trans* or 2,3-*cis* tetrahydropyridines **2** proceeds through the initial nucleophilic attack of nitrogen on the α-face of dienamines **1** and subsequent protonation of the allylic sulfoxide on the same face (Scheme 2). It should be pointed out that this stereochemical outcome is parallel to our findings in the cyclization

Scheme 2. Stereochemical Outcome and ORTEP of **2f**



Scheme 3. Sigmatropic Rearrangement of 2,3-*trans* and 2,3-*cis* 3-Sulfinyl Tetrahydropyridines



[a] Yield of isolated major diastereoisomer of **3**. [b] *Trans*/*cis* ratio determined by ^{1}H NMR analysis of crude reaction mixtures. **3a**, **3c**, and **3i** were isolated in >95/5 dr.

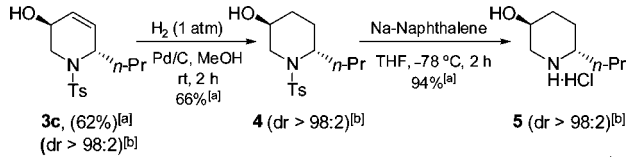
of hydroxy dienyl sulfoxides,[14] as well as other literature precedents.[23]

At this stage we examined the [2,3]-sigmatropic rearrangement of our allylic sulfinyl tetrahydropyridines **2** under a variety of reaction conditions. Thus, with Et_2NH in warm toluene, these allylic sulfoxides afforded synthetically useful 3,6-*trans* and 3,6-*cis* *N*-protected tetrahydropyridin-3-ols **3** in moderate to good yields and high diastereoselectivities (Scheme 3).[19] The relative configuration of allylic alcohols **3** was assigned on the basis of the coupling constants measured between H_3-H_{2eq} and H_3-H_{2ax}, typically small

(22) The relative and absolute configuration of **2f** was established by X-ray crystal structure analysis (see Scheme 2). CCDC number: 951220 (**2f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(23) (a) See ref 13b. (b) Iwata, C.; Maezaki, N.; Hattori, K.; Fujita, M.; Moritani, Y.; Takemoto, Y.; Tanaka, T.; Imanishi, T. *Chem. Pharm. Bull.* **1993**, *41*, 339–345.

Scheme 4. Synthesis of (+)-Pseudoconhydrine Hydrochloride **5**



[a] Yield of isolated product. [b] *Trans*/*cis* ratio determined by ^{1}H NMR analysis of crude reaction mixtures.

(1−3.3 Hz) for *trans*-isomers **3a**−**e** and larger (6.4, 9.9 Hz) for *cis*-isomer **3i**. Additionally, **3a** was transformed smoothly into ***ent*-3i** via the Mitsunobu protocol.[24]

Having demonstrated the suitability of this methodology for the preparation of tetrahydropyridin-3-ols **3**, we further applied this process to the synthesis of (+)-pseudoconhydrine **5** (Scheme 4). Hydrogenation of **3c**, obtained uneventfully on a 1 g scale, over Pd/C gave **4** in good yield. Subsequent removal of the *N*-tosyl group provided **5** as a single isomer with identical spectroscopic data to those in the literature.[1a,25] Moreover, the synthesis of natural product **5** allowed the determination of the absolute configuration of our tetrahydropyridin-3-ols **3**.

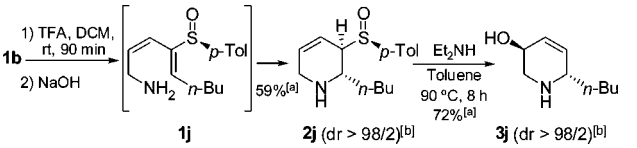
The decreased selectivity found for the sigmatropic rearrangements of alkyl substituted (R^1) sulfinyl tetrahydropyridines **2a,c** was tentatively attributed to either a base-mediated epimerization at the sulfur bearing center (C-3) or a ring-opening−closing sequence with diminished selectivity. The tosyl protecting group on nitrogen could influence these processes by conformational biases or by facilitating the ring-opening pathway. To test this hypothesis we briefly examined the possibility of carrying out our cyclization−sigmatropic rearrangement methodology without protection at nitrogen, and the results are gathered in Scheme 5. Deprotection of *N*-Boc-diene **1b** with TFA

(24) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164. The specific optical rotations measured were: **3i** (−80.2, *c* = 1, $CHCl_3$), ***ent*-3i** (+78.4, *c* = 1, $CHCl_3$, obtained via Mitsunobu of **3a**).

(25) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249–1251.

(26) Amino diene **1j** could be detected by a rapid ^{1}H NMR of the mixture.

Scheme 5. Cyclization−Sigmatropic Rearrangement Sequence with Unprotected Nitrogen



[a] Yield of isolated product. [b] *Trans*/*cis* ratio determined by ^{1}H NMR analysis of crude reaction mixtures.

followed by basic workup gave amino diene **1j**[26] that underwent spontaneous cyclization to tetrahydropyridine **2j**. The subsequent sigmatropic rearrangement took place in good yield and excellent selectivity to afford tetrahydropyridin-3-ol **3j** (72% yield and > 98/2 dr).

In conclusion, the first examples of the base-promoted intramolecular cyclization of a range of 4-sulfinyl dienamines to afford novel sulfinyl tetrahydropyridines have been described. This transformation sets two new stereogenic centers in one step and gives rise to configurationally stable allylic sulfoxides. Subsequent stereoselective sigmatropic rearrangement yields tetrahydropyridin-3-ols. The methodology has been applied to the synthesis of enantiopure hemlock alkaloid (+)-pseudoconhydrine. The scope and limitations of these transformations and the synthetic applications of our intermediates are currently under investigation.

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Supporting Information Available. Experimental procedures and spectroscopic data for compounds **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.