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Highly Diastereoselective Addition of Lithio Vinyl Sulfoxides to *N*-Sulfinimines: An Entry to Enantiopure 3-Sulfinyl-2,5-*cis*-dihydropyrroles

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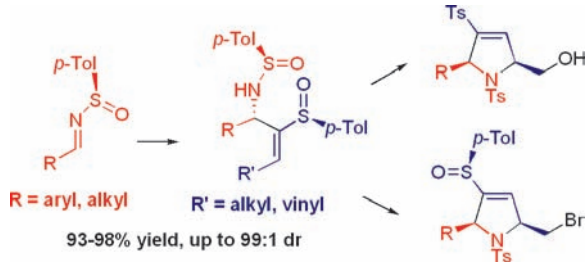
ABSTRACT



The addition of enantiopure α-metalated vinyl and dienyl sulfoxides to enantiomerically pure *N*-sulfinimines takes place with high diastereoselectivity primarily directed by the *N*-sulfinimine sulfur. The resulting allylic amines have been further transformed into highly functionalized 3-sulfinyl and 3-sulfonyl 2,5-*cis*-dihydropyrroles by reaction with electrophiles.

Pyrroles and pyrrolidines constitute an important class of heterocyclic compounds, and numerous methods have been developed for their preparation. However, few syntheses offer high efficiency and generality when applied to the assembly of polysubstituted and enantiopure heterocycles. Strategies that provide direct access to these five-membered rings are of great interest nowadays.[1] Some of these routes rely on the cyclization of enantiopure γ,δ-unsaturated amines,[2] with the straightforward synthesis of these precursors being a current challenge.[3]

Alternatively, *N*-sulfinimines have been applied to the synthesis of β-amino-α-methylene carbonyl adducts through the aza-Morita−Baylis−Hillman reaction (Aza-MBH).[4] Although nonracemic *N*-sulfinimines have proven to be efficient chiral auxiliaries for this reaction, the loss of selectivity for

(1) For recent reports on the syntheses of enantiopure pyrrolidines, see: (a) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201. (b) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996–2003. (c) Jiang, C.; Frontier, A. J. *Org. Lett.* **2007**, *9*, 4939–4942. For recent synthesis using the sulfinyl group as chiral auxiliary: (d) Davis, F. A.; Zhang, J.; Qiu, H.; Wu, Y. *Org. Lett.* **2008**, *10*, 1433–1436. (e) Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 1501–1504. (f) Dong, C.; Mo, F.; Wang, J. *J. Org. Chem.* **2008**, *73*, 1971–1974. (g) García Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981–987.

(2) (a) Donohoe, T. J.; Churchill, G. H.; Wheelhouse, K. M. P.; Glossop, P. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 8025–8028. (b) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938–2941. (c) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453. (d) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896–3905.

(3) For recent examples of stereoselective preparation of γ,δ-unsaturated amines: (a) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Scarponi, C.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2007**, *18*, 2758–2767. (b) Lee, C. L. K.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2965–2967. (c) Kumar Pandey, S.; Kumar, P. *Synlett* **2007**, 2894–2896.

(4) Reviews: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628. (b) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905–2916. *N*-Sulfinimines in Aza-MBH: (c) Aggarwal, V. K.; Martin Castro, A. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577–1581. (d) Shi, M.; Xu, Y.-M. *Tetrahedron: Asymmetry* **2002**, *13*, 1195–1200.

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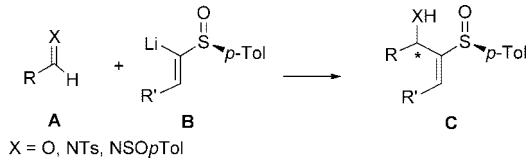
trisubstituted double bonds and the long reaction times are still drawbacks to be overcome. Besides, in contrast to sulfonimines,[5] Lewis acids are required for the less electrophilic sulfinimines.

As an alternative to the diastereoselective version of the Aza-MBH reaction and due to our experience in chiral sulfur chemistry,[6] we envisioned the reaction between metalated vinyl sulfoxides **B** and enantiopure *N*-sulfinimines **A**[7] (Scheme 1) as an efficient access to analogous chiral sulfinamides **C** (X = NSO*p*-Tol).[8]

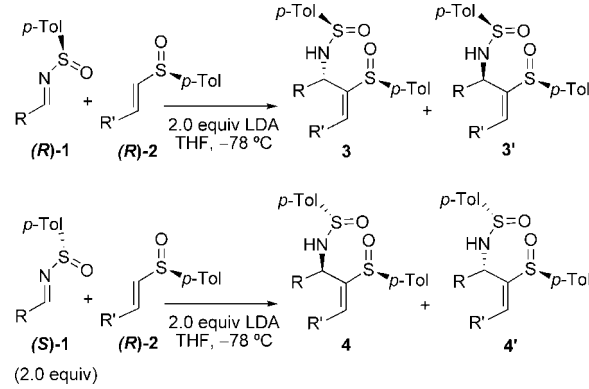
Scheme 1. Nucleophilic Addition of Lithio Vinyl Sulfoxides



Previous results revealed a poor stereocontrol for the addition of lithio vinyl sulfoxides **B** to aldehydes to afford equimolecular mixtures of allylic alcohols (**C**, X = O).[9] Moreover, our first attempt to achieve the analogous nitrogen adducts using sulfonimines led to a 50:50 mixture of sulfonamides (**C**, X = NTs). However, the additional chiral sulfur of sulfinimines could provide a double diastereoselection scenario based on two chiral sulfur atoms that could render sulfinamides (**C**, X = NSO*p*Tol) with stereocontrol. Thus, we now report the diastereoselective addition of vinyl and dienyl sulfoxides to chiral sulfinimines to provide 2-sulfinyl allylic sulfinamides. In addition, we have examined the reactivity of dienyl sulfinamides **C** (R′ = CH=CH$_2$) finding an efficient entry to enantiopure 3-sulfinyl and 3-sulfonyl 2,5-*cis*-disubstituted dihydropyrroles.

We submitted a number of enantiomerically pure sulfinimines **(*R*)-1** and **(*S*)-1** to treatment with (R_S,*E*)-lithio vinyl sulfoxides [generated from **(*R*)-2** and LDA][10] obtaining in all cases good to excellent yields (69−98%) and moderate to high diastereoselectivities of allylic sulfinamides **3** and **4** (Table 1). Moreover, undesired byproducts from self-addition

Table 1. Addition of Lithio Vinyl and Dienyl Sulfoxides to *N*-Sulfinimines ***R*-1** and ***S*-1**[d]



entry	**1** (R)	**2** (R′)	product (yield %)[a]	dr (**3**:**3′** or **4**:**4′**)[b]
1	***R*-1a** (Ph)[c]	***R*-2a** (*n*-Bu)	**3a**(90)	91:9
2	***S*-1a** (Ph)[c]	***R*-2a** (*n*-Bu)	**4a**(69)	82:18
3	***R*-1a** (Ph)	***R*-2b** (CH=CH$_2$)	**3b**(95)	99:1
4	***S*-1a** (Ph)	***R*-2b** (CH=CH$_2$)	**4b**(91)	87:13
5	***R*-1b** (*i*-Pr)	***R*-2b** (CH=CH$_2$)	**3c**(93)	99:1
6	***S*-1b** (*i*-Pr)	***R*-2b** (CH=CH$_2$)	**4c**(69)	75:25
7	***R*-1c** (*n*-Bu)	***R*-2b** (CH=CH$_2$)	**3d**(98)	99:1

[a] Combined yield. [b] Ratio determined by ^{1}H NMR analysis. [c] 3.0 equiv of LDA and **1** was employed. [d] Comparative matched vs mismatched pair.

of vinyl sulfoxides **(*R*)-2** were not observed under these conditions. These results highlight the crucial role of the absolute configuration of the sulfinimine in the process since both yields and selectivities increased when **(*R*)-1** was employed (entries 1, 3, 5, and 7, matched pair).

The scope of the reaction was examined by varying the nature of R in sulfinimines (Table 1, **(*R*)-1a**−**c**, **(*S*)-1a**,**b**). In addition, alkyl and alkenyl substitution at vinyl sulfoxide **(*R*)-2a**,**b** gave outstanding yields and selectivities (91:9−99:1) for the matched pair.

The synthesis of sulfinamide **3b** has been carried out on a 3 g scale uneventfully using 3.5 g of *N*-sulfinimine **(*R*)-1a**. It should be mentioned that the excess of imine is recovered without racemization after purification of the crude by flash chromatography.

The stereochemical outcome for the addition can be understood in terms of a rigid transition state depicted in Scheme 2, where the lithium coordinates the two oxygen atoms of sulfoxide **(*R*)-2** and sulfinimine **1**.[11] The nucleophilic addition would take place mostly *anti* to the *p*-tolyl

(5) Tosyl imines in Aza-MBH: (a) Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 4119–4122. (b) Qi, M. J.; Shi, M. *Tetrahedron* **2007**, *63*, 10415–10424. (c) Shi, Y. L.; Shi, M. *Tetrahedron* **2006**, *62*, 461–475. (d) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2002**, *67*, 2329–2334.

(6) (a) Fernández de la Pradilla, R.; Alhambra, C.; Castellanos, A.; Fernández, J.; Manzano, P.; Montero, C.; Ureña, M.; Viso, A. *J. Org. Chem.* **2005**, *70*, 10693–10700. (b) Fernández de la Pradilla, R.; Castellanos, A.; Fernández, J.; Lorenzo, M.; Manzano, P.; Méndez, P.; Priego, J.; Viso, A. *J. Org. Chem.* **2006**, *71*, 1569–1575. (c) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A.; Tortosa, M.; López-Rodríguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448. (d) Viso, A.; Fernández de la Pradilla, R.; García, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martínez-Ripoll, M.; Fonseca, I.; André, I.; Rodríguez, A. *Chem.*−*Eur. J.* **2003**, *9*, 2867–2876. (e) Fernández de la Pradilla, R.; Tortosa, M.; Lwoff, N.; del Águila, M. A.; Viso, A. *J. Org. Chem.* **2008**, *73*, 6716–6727.

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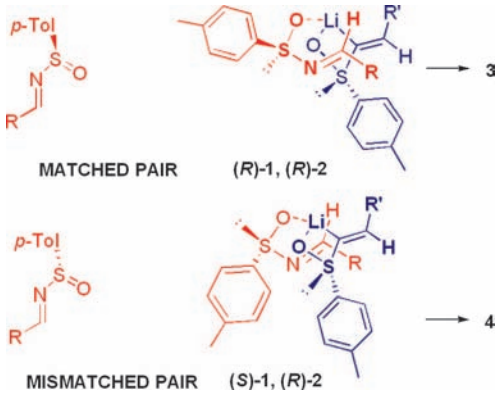
(8) Precedents of diastereoselective reactions of imines and α-sulfinyl carbanions: (a) García Ruano, J. L.; Alcudia, A.; del Prado, M.; Barros, D.; Maestro, M. C.; Fernández, I. *J. Org. Chem.* **2000**, *65*, 2856–2862. (b) García Ruano, J. L.; Alemán, J.; del Prado, M.; Fernández, I. *J. Org. Chem.* **2004**, *69*, 4454–4463. (c) Midura, W. H. *Tetrahedron Lett.* **2007**, *48*, 3907–3910.

(9) Marino, J. P.; Anna, L. J.; Fernández de la Pradilla, R.; Martínez, M. V.; Montero, C.; Viso, A. *J. Org. Chem.* **2000**, *65*, 6462–6473.

(10) Vinyl and dienyl sulfoxides **2** are available in one step by the procedure of Craig: Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263−11304.

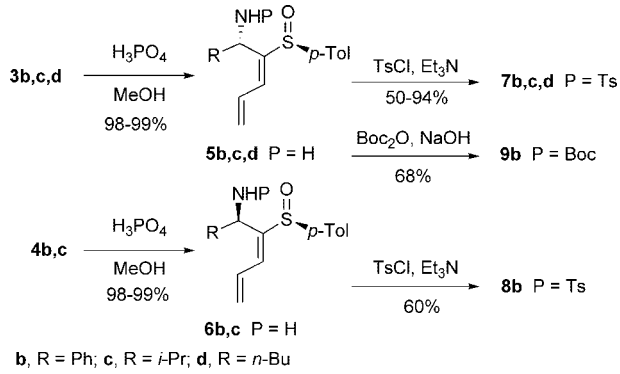
Scheme 2. Stereochemical Outcome of the Addition of Lithio Vinyl Sulfoxides **(*R*)-2** to *N*-Sulfinimines **(*R*)-1** and **(*S*)-1**



group of the sulfinimine arranged in an *s-cis* conformation, onto the *re* face of **(*R*)-1** for the matched pair or the *si* face of **(*S*)-1** for the mismatched pair. Interestingly, in terms of facial discrimination, sulfinimines behave as in the addition of α-sulfinyl carbanions[8a] and α-imino enolates[6d] but opposite to Baylis−Hillman nucleophiles[4c,d] and other enolates.[7a]

Subsequent cleavage of the sulfinamides by acidic treatment[12] provided very good yields of allylic amines **5** and **6** (Scheme 3). Removal of the sulfinamide stereogenic center

Scheme 3. Selective Cleavage of Sulfinamides and Protection of the Allylic Amines



allowed us to identify compounds **5** and **6** as diastereomers at the allylic carbon. In addition, the minor isomer from the mismatched pair (**4′**) and the major isomer from the matched pair (**3**) afforded allylic amine **5**. Finally, the structural assignment was secured by X-ray analysis of a derivative of **3b** (see below).

At this point, we focused our attention on adducts with a diene functionality in the structure. The isolation of a single *E* isomer at the double bond after the addition process, in contrast to other base-catalyzed procedures,[5c,13] allowed us to address the synthesis of nitrogen heterocycles. For this purpose, we examined the protection of amines **5** and **6** with different groups, and Ts (**7**, **8**) and Boc (**9**) moieties were uneventfully installed using standard protocols (Scheme 3).

With these products in hand, we studied their behavior under two conditions for intramolecular cyclization (Scheme 4). We first treated sulfinamide **3b** with *m*-CPBA[14] in toluene resulting in a fast oxidation of both sulfinyl groups followed by slow epoxidation at the distal double bond and producing a mixture of diastereomeric epoxides that was not isolated.[15] Cyclization in situ of these epoxides with a catalytic amount of CSA afforded a 75:25 mixture of sulfonyl dihydropyrroles **10** and **11** in good yield, where 2,5-*cis* stereochemistry resulted predominant. Pursuing to preserve the sulfoxide moiety, after considerable experimentation, we tried the halocyclization by using tetrabutylammonium tribromide (TBATB) as a halogen source. The reaction of TBATB with sulfinamide **3b** in the presence of K_2CO_3 produced only a small amount of a complex mixture of pyrrolines. Besides, no reaction was observed when carbamate **9b** was tested.

In contrast, we could obtain 3-sulfinyl dihydropyrroles through the use of the more acidic sulfonamido group, **7b**. Moreover, we were delighted to detect the formation of a major product **12b** initially assigned as a 2,5-*cis* isomer by 1D-NOE experiments. To generalize the reaction, dienyl sulfonamides **7c** and **7d** (R = *n*-Bu, *i*-Pr) were submitted to halocyclization with TBATB rendering sulfinyl pyrroles **12c** and **12d** in moderate yields and good diastereoselectivities.

Additional efforts to obtain similar structures from diastereomer **8b** or from the related dienyl sulfone (prepared by oxidation of **7b**) failed in giving the expected dihydropyrroles. This suggests that both the oxidation state and the relative stereochemisty of the substrate are crucial for a successful cyclization.

To confirm the stereochemical pathway for both cyclizations, pyrroline **12b** was oxidized to obtain 3-sulfonyl dihydropyrrole **14** in good yield. On the other hand, treatment of hydroxymethyl dihydropyrrole **10** with CBr_4/PPh_3 led also to compound **14**, thus correlating the stereochemistries of the major products **10** and **12**.

The absolute configuration of the new stereogenic carbons as well as the configurational stability of the sulfinyl group under the reaction conditions were secured by X-ray crystallography of 3-sulfinyl dihydropyrrole **13b** (Figure 1).

In conclusion, we have developed a very useful synthetic route for the preparation of functionalized 2-sulfinyl allylic

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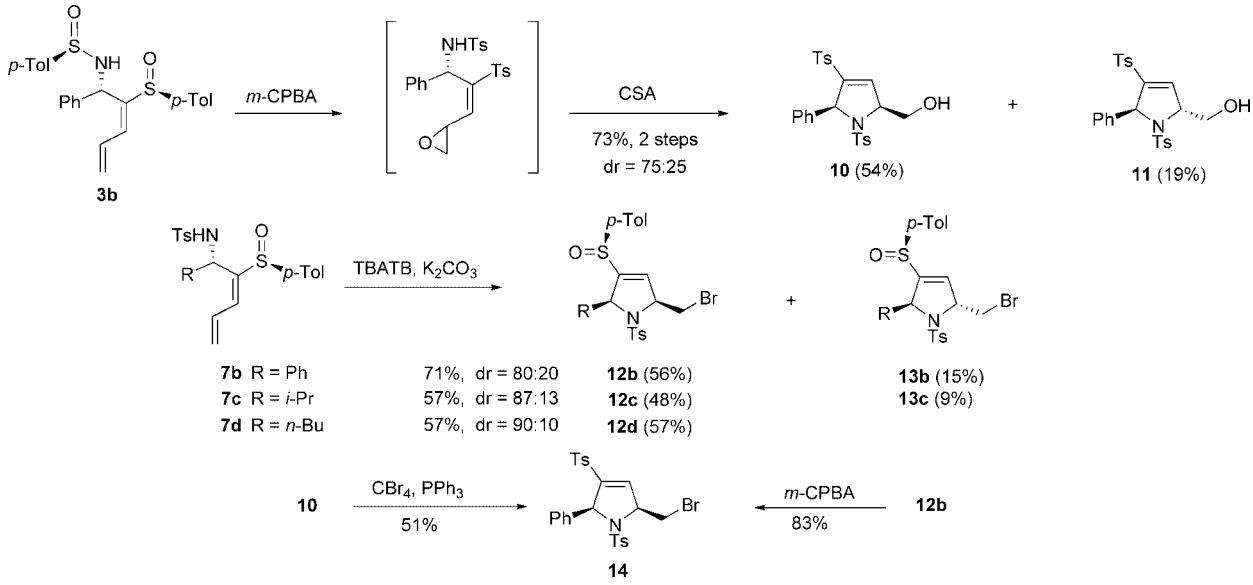
(13) (a) Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett.* **2005**, *7*, 2377–2379. (b) Sorbetti, J. M.; Clary, K. N.; Rankic, D. A.; Wulff, J. E.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3326–3331.

(14) Previous epoxidation−cyclization procedures with analogous nitrogenated structures: (a) Wipf, P.; Stephenson, C. R. J.; Walczak, M. A. A. *Org. Lett.* **2004**, *6*, 3009–3012. (b) Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349–6352.

(15) In related epoxidation experiments with other reagents, we have observed that isolated mixtures of epoxides cyclized to mixtures of *cis*- and *trans*-hydroxymethyl pyrrolines in identical ratio to the oxiranes. Some examples of epoxidation of dienyl sulfoxides: (a) Fernández de la Pradilla, R.; Manzano, P.; Montero, C.; Priego, J.; Martínez-Ripoll, M.; Martínez-Cruz, L. A. *J. Org. Chem.* **2003**, *68*, 7755–7767. (b) Fernández de la Pradilla, R.; Castellanos, A. *Tetrahedron Lett.* **2007**, *48*, 6500–6504.

Scheme 4. Synthesis of Enantiopure 2,5-*cis*-Disubstituted Dihydropyrroles



sulfinamides from readily available chiral sulfinimines and α-metalated vinyl and dienyl sulfoxides. The two chiral sulfinyl groups in both starting materials contributed to the formation of a new carbon−carbon bond in a highly diastereoselective manner. Electrophilic cyclizations of dienyl sulfonamides **7** provide a valuable application of the reaction to the diastereoselective synthesis of 3-sulfonyl and 3-sulfinyl *cis*-2,5-disubstituted dihydropyrroles **10** and **12**. Further explorations on these reactions are now underway in our laboratory.

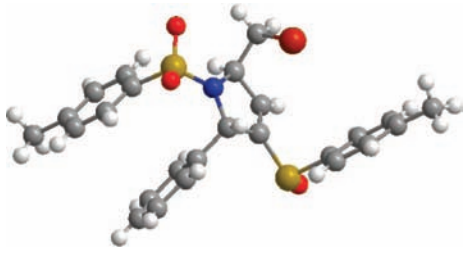


Figure 1. X-ray structure of *trans* isomer **13b**.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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