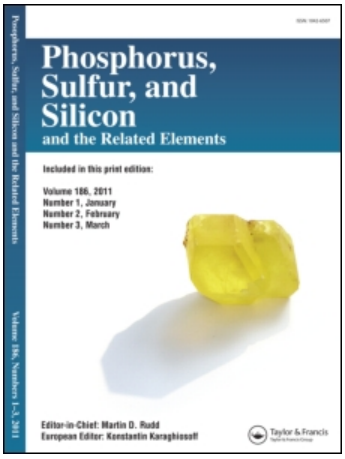

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Highly Diastereoselective [3 2] Cycloadditions Between Non-Racemic *p*-Tolylsulfinimines and Iminoesters: An Efficient Entry to Enantiopure Imidazolidines and Vicinal Diaminoalcohols

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Readily available p-*tolylsulfinimines undergo highly stereoselective [3 + 2] cycloadditions with azomethine ylides generated from α-iminoesters and LDA to produce* N-*sulfinylimidazolidines. In the presence of Lewis acids,* p-*tolylsulfinimines react with glycine iminoester enolates to produce* N-*sulfinylimidazolidines, after cyclization of open chain intermediates. These mechanistically diverse processes take place with excellent regio-, stereo-, and facial selectivities, and the latter is opposite to most known reactions involving sulfinimines. Some of the resulting imidazolidines have*

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been transformed into examples of a novel class of nonsymmetrical vicinal diamines using reductive and/or hydrolytic protocols.

Keywords 1,2-Diamines; asymmetric cycloadditions; imidazolidines; sulfinimines

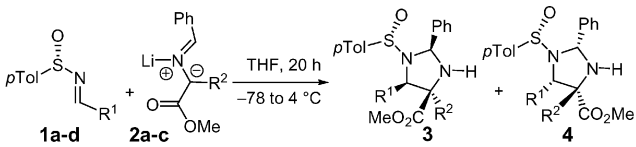
INTRODUCTION

Vicinal diamino compounds have attracted the attention of many organic chemists because of their vast applications. Indeed, vicinal diamino compounds are frequently found among bioactive compounds either from natural or nonnatural sources and many of them have found multiple applications within the pharmaceutical industry.[1] Alternatively, enantiopure imidazolidines and imidazolidinones have also been used as chiral auxiliaries in a number of different processes, and 1,2-diamino compounds have played a pivotal role in the development of asymmetric synthesis.[1] For these reasons, we have focused our attention on the development of a new and general route for the synthesis of 1,3-imidazolidines and 1,2-diamines based on the enantioselective construction of the imidazolidine ring that will be used subsequently as a source of vicinal diaminocompounds. Most of the known routes to obtain enantiopure imidazolidines involve the condensation between aldehydes and chiral 1,2-diamines, which is often limited to the use of C2-symmetrical diamines to reduce the number of resulting stereoisomers. However, the success of this strategy requires an efficient access to optically pure vicinal diamines.

Enantiopure sulfinimines, readily available in both enantiomeric forms, are versatile intermediates for enantioselective syntheses of a variety of targets.[2] These desirable features, along with our interest in the development of sulfur-directed methodology, attracted our attention to these intermediates as potential precursors to chiral nonracemic imidazolidines. Our methodology entails the highly diastereoselective [3 + 2] cycloaddition between sulfinimines **1**, and α-iminoesters derived azomethine ylides **2**, to produce enantiopure *N*-sulfinylimidazolidines (Scheme 1). Subsequently, some of these cycloadducts were readily transformed into nonsymmetrical vicinal diamino compounds.

RESULTS AND DICUSSION

To carry out our study we selected sulfinimines **1a–d** and iminoesters **2a–c** (Scheme 1). After considerable experimentation it was found that generating the azomethine ylides with LDA at 0°C, followed by adding the sulfinimines and allowing the reaction to warm up to approximately



3a	55%[a]	(95:5)[b]	**4a**	R^1 = Ph, R^2 = CH_2Ph
3b	53%	(95:5)	**4b**	R^1 = Ph, R^2 = Me
3c	80%	(97:3)	**4c**	R^1 = $pNO_2C_6H_4$, R^2 = CH_2Ph
3d	70%	(98:2)	**4d**	R^1 = $pNO_2C_6H_4$, R^2 = *i*Bu
3e	80%	(99:1)	**4e**	R^1 = 3-pyr, R^2 = CH_2Ph
3f	37%	(98:2)	**4f**	R^1 = 2-fur, R^2 = CH_2Ph

SCHEME 1 1,3-Dipolar cycloaddition between azomethine ylides and enantiopure sulfinimines. [a]Except for **3e** and **3f**, combined yields are given. [b]Ratios measured by integration of the crude ^{1}H NMR spectra.

4°C, produced just two of the eight possible 1,3-imidazolidines, **3a–f** and **4a–f**, as a highly diastereoselective mixture (from 95:5 to 98:2) with yields between 53% and 80%.[3] The definitive proof of the facial outcome of the process was established by an X-ray diffraction analysis of **3a**. Furthermore, to secure that both imidazolidines **3a** and **4a** were diastereofacial isomers with respect to the sulfinyl group, they were independently oxidized to enantiomeric *N*-sulfonylimidazolidines with identical optical rotation but opposite sign.

The remarkably high stereoselectivity found, along with the absence of any detectable open chain intermediates in the reaction, made us consider a 1,3-dipolar pathway for the process with an endo approach that allows for an overlap of the ester (ylide) and the aromatic group R^1 (sulfinimine) to the less-hindered *si* face of sulfinimines **1** on the side of the sulfur lone pair, as shown in Figure 1, to provide **3a–f** as the predominant cycloadducts. Additionally, we found that our process displayed a remarkable facial selectivity opposite to that observed for most other additions of enolates to *p*-tolylsulfinimines.

To extend the scope of our methodology, a number of different Lewis acids was tested[4] and we found that the use of freshly distilled $BF_3{\cdot}OEt_2$ gave rise to a satisfactory isolated yield of a mixture of diastereomeric imidazolidines **6a–j** and **7a–j** along with small amounts (5–10%) of

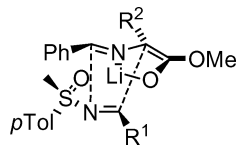
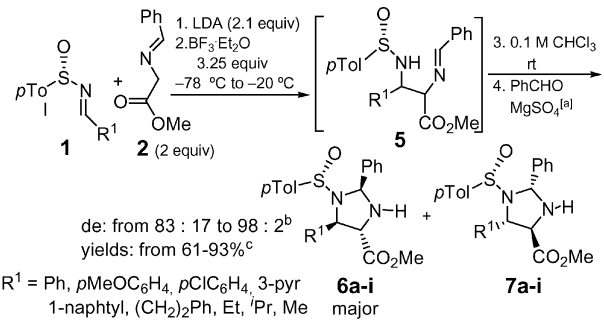


FIGURE 1 Stereochemical outcome for the 1,3-dipolar cycloaddition process.



SCHEME 2 Lewis acid-mediated cyclizations between glycine iminoesters and *p*-tolylsulfinimines. [a]Optionally, step 4 can accelerate (1–2 h) the cyclization with comparable ratios and yields. [b]Measured by integration of the ^{1}H NMR spectra of the crude. [c]Combined yield of pure imidazolidines **6** and **7**.

N-sulfinyldiaminoesters produced by hydrolysis of iminoester intermediate **5** (Scheme 2). It should be pointed out that cycloadducts **6a–i** and **7a–i** are not the primary reaction products (^{1}H NMR) but they are formed fairly rapidly upon standing in $CHCl_3$ solution at room temperature. These results may be rationalized in terms of a stepwise process initiated by addition of an iminoester-derived enolate to the sulfinimine and followed by cyclization of the open chain intermediate **5**, presumably promoted by the presence of trace amounts of acidic species in solution.

The predominant facial outcome was establised by an X-ray analysis of a derivative of **6a.** This process may be accounted for in terms of addition of the chelated iminoester enolate on the less hindered *si* face of sulfinimines **1**, upon activation by the Lewis acid (Figure 2). The trans stereochemistry around the C_4—C_5 bond may be accounted for by an open transition state with the less crowded arrangement of the substituents, although at this point we cannot rule out coordination of the sulfinyl oxygen with the lithium atom of the enolate.

The *N*-sulfinylimidazolidines obtained are nicely functionalized since both nitrogen atoms are already differentiated and the ester group should be an additional handle for synthetic applications. Consequently we envisioned that selective removal of the aminal moiety would

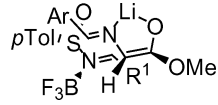
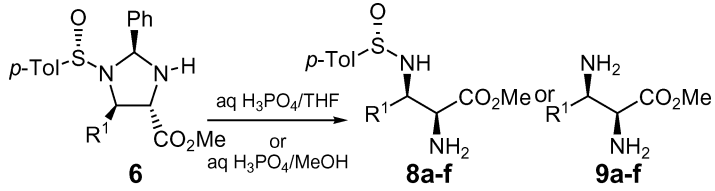


FIGURE 2 Stereochemical outcome of the Lewis acid-mediated condensation.

provide an efficient access to *syn N*-sulfinyldiaminoesters (Scheme 3).[5] However, because the sulfinamide group is labile to acidic media, finding selective conditions was an additional challenge.

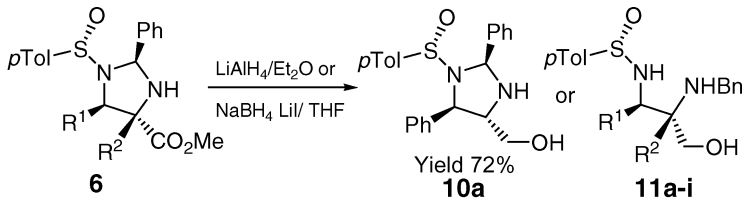


Yield: 76-88%, R^1 = Ph, 1-Naph, pFC_6H_4, $(CH_2)_2Ph$, ^{i}Pr, Me

SCHEME 3 Synthesis of *syn* α,β-diaminoesters from *N*-sulfinylimidazolidines.

Consequently, we focused on the search of optimal conditions for the selective hydrolysis process and we found that treatment of imidazolidines **6** with aqueous H_3PO_4 in THF provided good yields of *N*-sulfinyldiaminoesters **8a–f**. In contrast, when using aqueous HCl, TFA/MeOH, or H_3PO_4/MeOH, the simultaneous removal of the sulfinamide and the aminal took place, affording good yields of diaminoesters **9a–f**. These results point to H_3PO_4 as the reagent of choice for these transformations because of a combination of a suitable acidity and a low nucleophilicity of the phosphate counterion that prevents the attack on the sulfur atom.

Alternatively, reductive conditions appeared to be suitable to transform our 1,3-imidazolidines **6** into 1,2-diamines. The carboxylate moiety reacted smoothly with $LiAlH_4$ to produce *N*-benzyl-*N*-sulfinyldiaminoalcohols **11a–i** (Scheme 4).[6] This unexpected finding allowed for the straightforward differentiation of both nitrogen atoms with synthetically useful protecting groups. This process may be understood in terms of initial reduction of the ester functionality followed by aminal cleavage via an *N*-metalated intermediate and reduction of the



Yields = 63-83%; R^1 = Ph, 1-Naphtyl, 3-pyr, pFC_6H_4, Et, ^{i}Pr, Me, $(CH_2)_2Ph$
R^2 = H, Me

SCHEME 4 Reductive cleavage of the aminal moiety.

transient imino group thus generated. To further probe this hypothesis we surveyed a number of reducing agents in pursuit of the selective reduction of the ester while preserving the heterocyclic structure. Thus, the use of $NaBH_4$/LiI gave a good yield of imidazolidine **10a** which, upon treatment with $LiAlH_4$ in Et_2O, afforded diaminoalcohol **11a**.

In summary, we have developed two new, highly diastereoselective methods for the synthesis of enantiopure *N*-sulfinylimidazolidines that rely on a diastereoselective [3 + 2] cycloaddition of enantiopure sulfinimines and α-iminoesters promoted or not by the presence of $BF_3{\cdot}OEt_2$. Subsequently, we have undertaken the study of the transformation of the resulting *N*-sulfinylimidazolidines into a variety of differentially protected vicinal diamines using reductive and/or hydrolytic protocols.

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