Highly Diastereoselective [3+2] Cycloadditions between Nonracemic *p*-Tolylsulfinimines and Iminoesters: An Efficient Entry to Enantiopure Imidazolidines and Vicinal Diaminoalcohols

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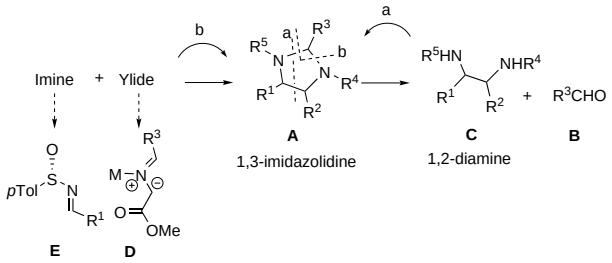
Abstract: A new procedure for the asymmetric synthesis of imidazolidines and vicinal diamines is reported. The 1,3-dipolar cycloaddition between nonracemic *p*-tolylsulfinimines and azomethine ylides generated in situ from α-iminoesters and LDA produces *N*-sulfinylimidazolidines with a high degree of stereocontrol. In contrast, the presence of Lewis acids promotes formation of the cycloadducts through a highly diastereoselective process with opposite stereochemistry. Subsequent transformations of the imidazolidines including oxidative, reductive, and hydrolytic processes that provide easy access to vicinal diaminoalcohols have been explored. Among these, reductive cleavage of the aminal with $LiAlH_4$ is an extremely efficient and general reaction for the synthesis of enantiopure *N*-sulfinyl-*N*′-benzyldiaminoalcohols.

Keywords: cycloadditions · heterocycles · imidazolidines · sulfinimines · ylides

Introduction

The 1,3-dipolar cycloaddition between alkenes and dipoles is one of the most powerful tools for the synthesis of 5-membered heterocycles.[1] In particular, azomethine ylides which are commonly generated in situ, have proved to be versatile intermediates for the reaction with alkenes to produce pyrrolidines[2] with high stereocontrol, and this well-established methodology allows the use of a variety of chiral auxiliaries or chiral catalysts in the synthesis of nonracemic pyrrolidines.[1d, e, 3] In contrast, the majority of the routes towards enantiopure 1,3-imidazolidines **A** utilize the condensation of aldehydes **B** and chiral 1,2-diamines **C** and are often limited to the use of C_2-symmetric diamines to reduce the number of possible final diastereomers (Scheme 1, route a). Consequently, the success of this approach relies on an efficient access to optically pure vicinal diamines.[4] Notwithstanding the well-established synthetic usefulness of enantiopure imidazolidines,[5] reports on dipolar cycloadditions between azomethine ylides and imines are scarce (Scheme 1, route b)[6] and the asymmetric variant of this process had not been documented.[7]



Scheme 1. Strategies for the synthesis of enantiopure 1,3-imidazolidines.

Chiral sulfinimines are readily available in both enantiomeric forms and have proved to be valuable intermediates for the synthesis of different nitrogen-containing targets.[8] These compounds display excellent facial selectivity towards nucleophiles, and removal of the chiral sulfinyl auxiliary is easy.[9] The above facts along with our interest in the development of sulfur-directed methodology prompted us to consider sulfinimines as precursors to enantiopure 1,3-imidazolidines by 1,3-dipolar cycloadditions with azomethine ylides. Thus, here we disclose a full description of the first examples of the asymmetric 1,3-dipolar cycloaddition of azomethine ylides **D**

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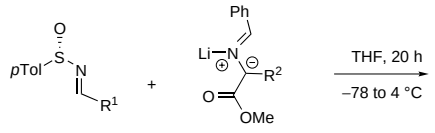
with enantiopure sulfinimines **E** to produce enantiopure imidazolidines **A**.[10] In this account we will also report in full the Lewis acid mediated stepwise condensation between enolates derived from α-iminoesters and sulfinimines[10b] as well as expedient and novel transformations of the resulting *N*-sulfinylimidazolidines **A** into enantiopure nonsymmetrical vicinal diamines **C** (Scheme 1).

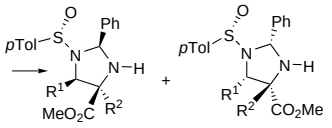
Results and Discussion

1,3-Dipolar cycloadditions: To begin our study we selected sulfinimine **1a** ($R^1 = Ph$, Scheme 2) and iminoester **2a**, derived from benzaldehyde and phenylalanine methyl ester. To our dismay many of the common conditions used to generate the dipole did not lead to the desired cycloaddition ($LiBr/Et_3N/CH_3CN$, NaHMDS/THF, etc.). Instead starting material was recovered from the reaction mixtures. After considerable experimentation we found that generation of the dipole with LDA (*n*BuLi, *i*Pr_2NH),[11] followed by addition of



1a: R^1 = Ph
1b: R^1 = *p*-$NO_2C_6H_4$
1c: R^1 = 3-pyr
1d: R^1 = 2-fur

2a: R^2 = CH_2Ph
2b: R^2 = Me
2c: R^2 = *i*Bu



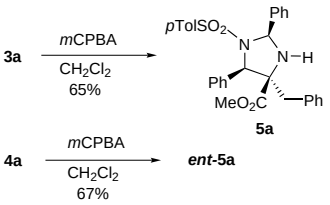
3a:	55%[a]	(95:5)[b]	**4a:** R^1 = Ph, R^2 = CH_2Ph
3b:	53%	(95:5)	**4b:** R^1 = Ph, R^2 = Me
3c:	80%	(97:3)	**4c:** R^1 = *p*-$NO_2C_6H_4$, R^2 = CH_2P
3d:	70%	(98:2)	**4d:** R^1 = *p*-$NO_2C_6H_4$, R^2 = *i*Bu
3e:	80%	(99:1)	**4e:** R^1 = 3-pyr, R^2 = CH_2Ph
3f:	37%	(98:2)	**4f:** R^1 = 2-fur, R^2 = CH_2Ph

Scheme 2. 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 ^1H NMR spectra.

Abstract in Spanish: *En este trabajo se describe un nuevo procedimiento de síntesis de imidazolidinas y diaminas vecinales que implica la cicloadicion 1,3-dipolar entre p-tolilsulfiniminas no racémicas e iluros de azometino, generados in situ a partir de α-iminoésteres y LDA, y que transcurre con alto grado de estereocontrol. Por otra parte, la presencia de ácidos de Lewis promueve la formación de las imidazolidinas con estereoquímica opuesta. Se han estudiado procesos de oxidación, reducción e hidrólisis de las imidazolidinas que en algunos casos permiten el acceso a diaminoalcoholes vecinales. En este contexto, la apertura reductora del aminal con $LiAlH_4$, es una reacción eficiente y general que da lugar a N-sulfinil-N′-bencildiaminoalcoholes enantiopuros.*

the sulfinimine and allowing the reaction to warm up to approximately 4 °C produced just two of the eight possible 1,3-imidazolidines, **3a** and **4a**, as a 95:5 mixture along with small amounts of starting material (ca. 15%). The major isomer **3a** was isolated in 50% yield from this mixture by crystallization.[12] Comparable behavior was found when the α-iminoester derived from alanine methyl ester was employed. Thus, 1,3-imidazolidines **3b** and **4b** were obtained in a 95:5 ratio and the major isomer was isolated in 47% yield. By placing a nitro group at the *para* position of the aromatic ring attached to the sulfinimine ($R^1 = p$-$NO_2C_6H_4$, **1b**), a more reactive dipolarophile was obtained which underwent complete conversion to cycloadducts **3c** and **4c** with a slight improvement in the facial selectivity (97:3). Similar behavior was observed when the dipole was generated with LDA and the α-iminoester derived from leucine methyl ester and benzaldehyde (**3d**:**4d** 98:2). We also obtained excellent diastereocontrol with the sulfinimines **1c** (R^1 = 3-pyr) and **1d** (R^1 = 2-furyl) under the reaction conditions, and 1,3-imidazolidines **3e** and **3f** were obtained as practically single isomers; however, again the more electron-deficient sulfinimine (**1c**) provided a better yield of the cycloadducts.

The structural determination of the cycloadducts was based on their spectral features. Thus, for *N*-sulfinylimidazolidines **3a**–**f**, the unusually upfield signals attributed to protons of the carbomethoxy groups at C4 (s, 2.97–3.27 ppm) indicated a *cis* relative arrangement to the phenyl group at C5. Further proof of the relative stereochemistry of the new chiral centers was found by D-NOE (**3a**: H2–H5 = 1.3%, CH_2Ph–H2 = 4.3%). However, the definitive proof of the facial outcome of the process was established by an X-ray diffraction analysis of **3a**.[13] Furthermore, to confirm that **3a** and **4a** were facial isomers regarding the sulfinyl group, they were independently oxidized to *N*-sulfonylimidazolidines **5a** and ***ent*-5a** respectively with identical optical rotation but opposite sign (Scheme 3).



Scheme 3. Oxidation of *N*-sulfinylimidazolidines **3a** and **4a** with *m*CPBA.

The remarkably high stereoselectivity and 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, which allows an overlap between the ester (ylide) and the aromatic group R^1 (sulfinimine), to the less hindered β face of sulfinimines **1**[14a] on the side of the sulfur lone pair, as shown in Figure 1, to provide **3a**–**f** as the predominant cycloadducts. It should be pointed out that our process displayed a re-

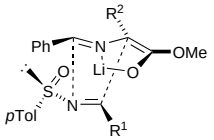


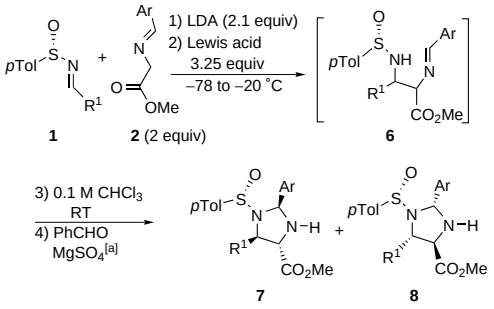
Figure 1. Stereochemical outcome of the 1,3-dipolar cycloaddition process.

markable facial selectivity opposite to that observed for most other additions of enolates to sulfinimines.[14b–f]

Lewis acid mediated cyclizations: At this stage we focused our efforts on the extension of the scope of our methodology to other substrates and a variety of conditions were tested with benzylidene glycinate (**2d**) ($R^2 = H$) as the azomethine ylide precursor and *p*-tolylsulfinimines derived from aliphatic and aromatic aldehydes as dipolarophiles. Unfortunately, most experiments did not give the desired imidazolidines[15] and therefore we examined the effect of Lewis acids as potential promoters of the cycloadditions.[16] Initially, we selected $BF_3 \cdot OEt_2$, and after considerable experimentation[17] we found that the reaction of **1a** and **2d** indeed provided a satisfactory isolated yield (85%) of an 83:17 mixture of diastereomeric imidazolidines **7a** and **8a** along with a small amount (5%) of the corresponding *N*-sulfinyldiaminoester (Table 1, entry 1). In contrast to the cycloadditions previously studied, we observed a rapid disappearance of the starting material (10 min, at $-78\,^{\circ}C$), but when the ^1H NMR spectrum of the crude reaction mixture was recorded immediately after workup, the desired cycloadducts could barely be detected. However, when we recorded subsequent ^1H NMR spectra of the same sample, increasing amounts of cycloadducts **7a** and **8a** and the disappearance of a number of other signals, tentatively attributed to iminoesters **6**, were observed. These observations prompted us to allow the crude mixtures to stand in 0.1M $CHCl_3$ solution and monitor the progress of the cyclization by ^1H NMR spectroscopy at intervals of about 24 h. In most cases, after 2–4 d we could not detect significant changes in the composition of the mixture. These results may be rationalized in terms of a stepwise process initiated by addition of an iminoester derived enolate to the sulfinimine followed by cyclization of the open-chain intermediate **6**, presumably promoted by the presence of trace amounts of acidic species in solution.[18] Additionally, the isolation of variable amounts of *N*-sulfinyldiaminoesters derived from **6** also supports a stepwise mechanism under these conditions.[19]

A number of different Lewis acids were then tested leading to comparable diastereoselectivities. The generality of the reaction was then explored by using $BF_3 \cdot OEt_2$ as an acidic promoter, and the results are gathered in Table 1. The increase in facial selectivity found for glycine derivative **2e**, which has a more electron-rich imine moiety ($Ar = p$-$CH_3OC_6H_4$), is noteworthy. On the other hand, a decrease of facial selectivity was observed when sulfinimine **1e** was treated with iminoester **2d** ($R^1 = p$-$CH_3OC_6H_4$). A significant improvement in facial selectivity was accomplished when electron-poor sulfinimines (**1f**, $R^1 = p$-ClC_6H_4 and **1c**, R^1 = 3-pyr) were tested, while other aromatic groups (**1g**, $R^1 = p$-FC_6H_4, **1h**, R^1 = 1-naphthyl) behaved as **1a** (R^1 = Ph) in terms of facial selectivity. In addition, these reaction conditions led to excellent yields and selectivities when sulfinimines **1i–l**, which have aliphatic groups ($R^1 = CH_2CH_2Ph$, Et, *i*Pr, Me), were used as starting materials. Finally, despite the considerable generality of our methodology for the preparation of *N*-sulfinylimidazolidines, some substrates failed to give the expected products; *p*-tolylsulfinimines derived from furfural, cinnamaldehyde, and pivalaldehyde provided complex reaction mixtures under the above conditions.[20] Additionally, the *tert*-butylsulfinimine analog of **1a** (R^1 = Ph) again produced a complex reaction mixture.

Table 1. Lewis acid mediated cyclizations between glycine iminoesters and *p*-tolylsulfinimines.



Entry	**1** (R^1)	**2** (Ar)	Lewis acid	Ratio **7**:**8**[b]	Yield [%][c]
1	**1a** (Ph)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7a** (83):**8a** (17)	85
2	**1a** (Ph)	**2d** (Ph)	Et_2AlCl	**7a** (83):**8a** (17)	43
3	**1a** (Ph)	**2d** (Ph)	$Ti(OiPr)_3Cl$	**7a** (60):**8a** (40)	40
4	**1a** (Ph)	**2d** (Ph)	$SnCl_4$	**7a** (70):**8a** (30)	55
5	**1a** (Ph)	**2e** (p-$MeOC_6H_4$)	$BF_3 \cdot Et_2O$	**7b** (87):**8b** (13)	53
6	**1e** (p-$MeOC_6H_4$)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7c** (76):**8c** (24)	67
7	**1f** (p-ClC_6H_4)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7d** (90):**8d** (10)	61
8	**1g** (p-FC_6H_4)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7e** (83):**8e** (17)	66
9	**1c** (3-pyr)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7f** (90):**8f** (10)	60
10	**1h** (1-naphthyl)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7g** (83):**8g** (17)	72
11	**1i** (-$(CH_2)_2$Ph)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7h** (98):**8h** (2)	83
12	**1j** (Et)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7i** (95):**8i** (5)	64
13	**1k** (*i*Pr)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7j** (95):**8j** (5)	93
14	**1l** (Me)	**2d** (Ph)	$BF_3 \cdot Et_2O$	**7k** (92):**8k** (8)	64

[a] Optionally, step 4 can accelerate (1–2 h) the cyclization with comparable ratios and yields. [b] Measured by integration of the ^1H NMR spectra of the crude. [c] Combined yields of pure imidazolidines **7** and **8**.

The gross structure of these adducts (**7a–k**), including the relative stereochemistry around the ring, was established by detailed inspection of their spectroscopic features. The *trans* relative stereochemistry (C4–C5) was secured by the coupling constant ($J_{4,5} = 4–6$ Hz) along with the ^1H NMR chemical shifts observed for the carbomethoxy group (s, 3.75–3.82 ppm). However, these studies did not allow a conclusive stereochemical assignment relative to the chiral sulfur atom. This crucial matter was subsequently solved by an X-ray analysis of **18a**[13] (see below), a derivative of **7a**, which established the predominant facial outcome of our enolate addition/cyclization protocol. This may be accounted for in terms of addition of the chelated iminoester enolate to the less hindered β face of sulfinimines **1**, *anti* to the *p*-tolyl group, upon activation by the Lewis acid (Figure 2). On the other hand, the *trans* stereochemistry around the C4–C5 bond may be accounted for by an open transition state with a less crowded arrangement of the substituents, although at this point we cannot rule out coordination of the sulfinyl oxygen atom with the lithium atom of the enolate.

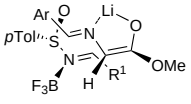


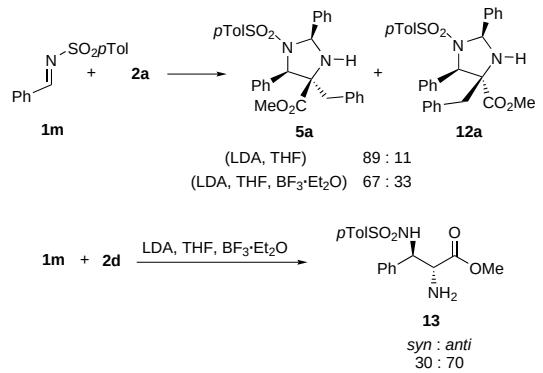
Figure 2. Stereochemical outcome of the Lewis acid mediated condensation of sulfinimines **1** and glycine-derived enolates.

The effect of Lewis acid catalysis on the cycloaddition between sulfinimines and α-substituted iminoesters **2a** and **2b** (R^2 = Bn and CH_3) paralleled the previous observations for glycinate derivatives (R^2 = H) although with diminished *syn*/*anti* selectivity at C4 and C5. Thus, the treatment of **1a** with **2a** in the presence of $BF_3 \cdot OEt_2$ or Cp_2TiCl_2 resulted in a mixture of cycloadducts in which **9a** was the major product (Table 2). In addition, the use of $TiCl_4$ provided a remarkably high diastereo and facial selectivity even though deoxygenation to sulfenamide **10a**[13] was simultaneously observed (entry 3, (**9a**+**10a**):**11a**, 92:4). *p*-Tolylsulfinimines **1f** ($R^1 = p$-ClC_6H_4) and **1k** ($R^1 = i$Pr) showed similar behavior upon reaction with iminoester **2b** to give **9b** and **9c** as major products, respectively. Interestingly, these highly substituted *N*-sulfinylimidazolidines displayed lower rates of epimerization (see footnote [b] in Table 2) at the aminal upon standing in solution or purification by chromatography (silica gel).

The general structure of adducts **9a–c** was readily derived from their spectral features.[21] However, a definitive proof of the relative configuration of the ring and the sulfur atoms for the mayor product was obtained by an X-ray analysis of **15a′**,[13] a derivative of **9a** (see below), thereby establishing the main facial sense of the process. Furthermore, an X-ray analysis of *N*-sulfenylimidazolidine **10a**[13] was also carried out to establish its structure and absolute configuration.

Given the above results, we decided to explore the reactivity of *p*-tolylsulfonimines with α-iminoesters under both uncatalyzed and catalyzed conditions. Thus, the treatment of **1m** with **2a** in the presence of LDA resulted in an 89:11 mixture of racemic *N*-sulfonylimidazolidines **5a** and **12a**; this suggests that both concerted and stepwise mechanisms are operative to some extent. In addition, in the presence of $BF_3 \cdot OEt_2$ this substrate provided an even lower selectivity (**5a**:**12a** 67:33). In contrast, the reaction between sulfonimine **1m** and the glycine-derived iminoester **2d** gave just monotosyldiaminoesters **13** and with a fairly low *syn*:*anti* selectivity (*syn*:*anti* 30:70) (Scheme 4).

The structural assignment of *N*-sulfonylimidazolidines **5a** and **12a** was mainly based on their spectral data. Furthermore, chemical correlations with the corresponding *N*-sulfinylimidazolidines **3a** and **9a** by oxidation at sulfur (*m*CPBA) provided **5a** and **12a** as enantiopure materials; this provided a definitive structural proof and a complementary route to **5a** and **12a**.

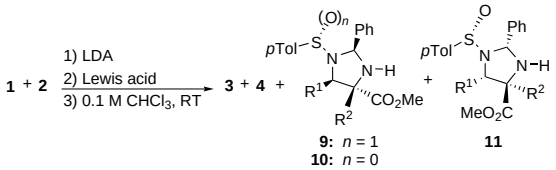


Scheme 4. Condensation of sulfonimine **1m** with iminoesters.

Synthesis of 1,2-diamines: The *N*-sulfinylimidazolidines produced by our methodology are nicely functionalized for subsequent manipulations. Indeed, both nitrogen atoms are already differentiated and both aryl rings can be readily varied. Furthermore, the ester group should be an additional "handle" for synthetic applications. Our studies on the reactivity of these imidazolidines will be discussed next. Initially, acidic hydrolysis of *N*-sulfinylimidazolidine **3a** with TFA in methanol[22] led to desulfinylation and fragmentation of the molecule to phenylalanine methyl ester. This observation prompted us to explore the reduction of the ester to the primary alcohol with the expectation that this adjustment of functionality would avoid the undesired fragmentation.

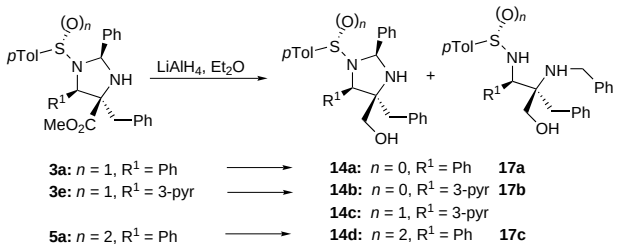
After a number of failed experiments with different reducing agents,[23] we found that the treatment of cycloadduct **3a** with a large excess of $LiAlH_4$ (9 equiv, 18 h) in Et_2O resulted in concurrent deoxygenation at sulfur and ester reduction to afford sulfenamide **14a** (65%, $n = 0$, Scheme 5). Shorter reaction times provided a substantial amount of starting material (**3a**), and forcing reaction conditions allowed the isolation of variable amounts of *N*-sulfinyldiaminoalcohol **17a** derived from the simultaneous reduction of the ester and reductive opening of the aminal. A more erratic behavior was observed for *N*-sulfinylimidazolidine **3e** and *N*-sulfonylimi-

Table 2. Lewis acid mediated cyclizations of alanine and phenylalanine iminoesters and *p*-tolylsulfinimines.



Entry	**1** (R^1)	**2** (R^2)	Lewis acid	*syn* **3**+**4** [%][a]	*anti* **9** [%][a,b]	*anti* **10** [%][a]	*anti* **11** [%][a]	Yield [%][c]
1	**1a** (Ph)	**2a** (CH_2Ph)	$BF_3 \cdot OEt_2$	**3a**+**4a** (24)	**9a** (64)	–	**11a** (12)	87
2	**1a** (Ph)	**2a** (CH_2Ph)	Cp_2TiCl_2	**4a** (30)	**9a** (60)	–	**11a** (10)	88
3	**1a** (Ph)	**2a** (CH_2Ph)	$TiCl_4$	**4a** (4)	**9a** (30)	**10a** (62)	**11a** (4)	54
4	**1f** (p-ClC_6H_4)	**2b** (Me)	$BF_3 \cdot OEt_2$	**3g** (22)	**9b** (63)	–	**11b** (15)	80
5	**1k** (iPr)	**2b** (Me)	$BF_3 \cdot OEt_2$	**3h** (16)	**9c** (84)	–	–	80

[a] Stereochemistry referred to the relative positions of R^1 and CO_2CH_3 groups at the imidazolidine ring. Ratio of isomers measured by integration of the ^1H NMR spectra of the crude; except for entries 1–3, the structural assignments are tentative. [b] Minor amounts (5–20%) of the epimer at the aminal (C2) are included; for **9c** this epimer at C2 can reach 40% of the total product. [c] Combined yield.

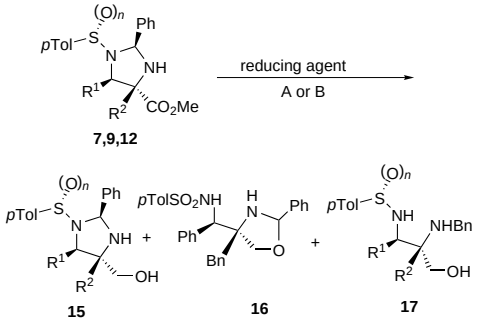


Scheme 5. Reductive transformations of 4-benzyl-*N*-sulfinyl- and 4-benzyl-*N*-sulfonylimidazolidines.

dazolidine **5a** which yielded mixtures of unreacted starting materials, hydroxymethylimidazolidines **14b–d**, and *N*-tosyl- or *N*-sulfinyl-*N*-benzyldiaminoalcohols **17b**, **c**. We found these reductions to be very sluggish presumably due to the carboxylate being very hindered.

In contrast, substrate **9a**, in which the relative arrangement of R^1 and the ester is *trans*, displayed a more reproducible behavior and gave a good yield of hydroxymethylimidazolidine **15a** (Table 3). Subsequently, we found that **9c** ($R^1 = i$Pr, $R^2 = $Me) reacts with $LiAlH_4$ in Et_2O to give a 63% yield of **17e**; although shorter reaction times may produce the hydroxymethylimidazolidine, we cannot rule out that the bulky aliphatic isopropyl group accelerates the reductive cleavage. Finally, *N*-tosylimidazolidine **12a** provided a good yield of **17d** (63%, 0 °C to RT, 2 h); however, after a short time and at low temperature (−20 °C to 0 °C, 10 min), **12a** selectively gave hydroxymethylimidazolidine **15b**[24] (entries 3 and 4). A definitive structural proof for this family of imidazolidines was provided by an X-ray analysis of *para*-nitrobenzoate **15a′**, which was derived from **15a** by selective esterification.

Table 3. Reductive transformations of *N*-sulfinyl- and *N*-sulfonylimidazolidines.

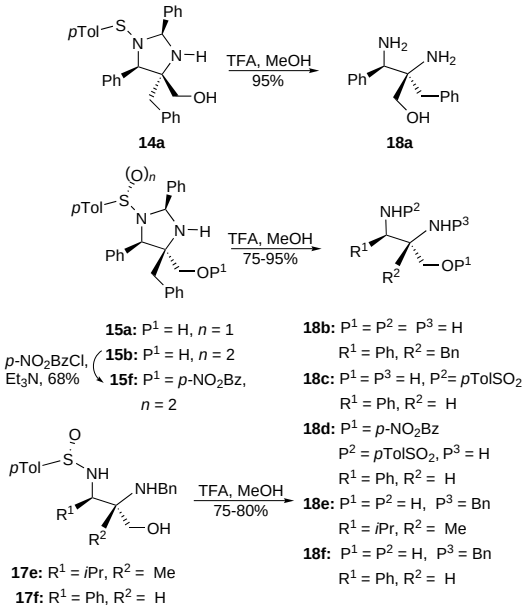


Entry	Substrate	Method[a]	**15** [%][b]	**17** [%][b]
1	**9a** ($n=1$, $R^1=$Ph, $R^2=$Bn)	A	**15a** (75)	
2	**9c** ($n=1$, $R^1=i$Pr, $R^2=$Me)	A[c]		**17e** (63)
3	**12a** ($n=2$, $R^1=$Ph, $R^2=$Bn)	A[d]	**15b** (82)	**17d** (17)
4	**12a** ($n=2$, $R^1=$Ph, $R^2=$Bn)	A		**17d** (63)
5	**7a** (n = 1 $R^1=$Ph, $R^2=$H)	A		**17f** (83)
6[e]	**7a**	B	**15c** (78)	
7[e]	**7e** ($n=1$, $R^1=p$-FC_6H_4, $R^2=$H)	A		**17g** (72)
8[e]	**7e**	B	**15d** (71)	
9	**7f** ($n=1$, $R^1=$3-pyr, $R^2=$H)	A		**17h** (71)
10	**7h** ($n=1$, $R^1=(CH_2)_2$Ph, $R^2=$H)	A		**17i** (68)
11	**7h**	B	**15e** (79)	
12	**7i** ($n=1$, $R^1=$Et, $R^2=$H)	A		**17j** (79)
13	**7j** ($n=1$, $R^1=i$Pr, $R^2=$H)	A		**17k** (75)

[a] Method A: $LiAlH_4$, Et_2O, 0 °C to RT, 2–7 h; method B: $NaBH_4$, LiI, THF, RT. [b] Yield of pure isolated compounds. [c] 15 h. [d] THF, −20 to 0 °C, 10 min; reversible isomerization of **15b** to oxazolidine **16** was observed.[24] [e] In these cases combined yields are given, since reductions were performed with mixtures **7**/**8**.

Given our previous results, we anticipated a more straightforward behavior in the reduction of *N*-sulfinylimidazolidines **7**, derived from iminoglycine **2d**, due to the ester moiety being less hindered in these compounds. Indeed, imidazolidine **7a** reacted smoothly to produce *N*-benzyl-*N*-sulfinyldiaminoalcohol **17f**. In some experiments, particularly with short reaction times, small amounts of **15c** were obtained. Similarly, other related *N*-sulfinylimidazolidines gave *N*-sulfinyldiaminoalcohols **17g–k** in good yields. The scope of this procedure is broad with regard to the nature of R^1 (aromatic for **7a**, **7e**, and **7f** or aliphatic for **7h–j**). This process may be understood in terms of initial reduction of the ester functionality followed by aminal cleavage via an *N*-metalated intermediate and subsequent reduction of the 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 moiety. Thus, the use of $NaBH_4$/LiI gave good yields of imidazolidines **15c–e**.[25] Subsequent treatment of **15c** with $LiAlH_4$ in Et_2O afforded diaminoalcohol **17f**. As mentioned before, the structural assignments of imidazolidines **7a–k** produced under Lewis acid catalysis were established by an X-ray analysis of sulfinamide **17f**.[26]

Finally, once the ester group was removed, *N*-sulfenyl and *N*-sulfinyl hydroxymethylimidazolidines (**14a**, **15a**) underwent smooth aminal methanolysis along with sulfur–nitrogen bond cleavage under acidic conditions to produce diastereomeric diamines **18a** and **18b**, respectively. In contrast, *N*-sulfonylimidazolidines **15b** and **15f** (obtained by selective esterification of **15b**) underwent aminal cleavage with the *p*-toluenesulfonamide group remaining unaltered (Scheme 6). It



Scheme 6. Synthesis of highly substituted vicinal diaminoalcohols under acidic conditions.

should be pointed out that, to the best of our knowledge, the substitution pattern of diamines **18a–d** is unprecedented in the literature. Additionally, treatment of *N*-sulfinyldiaminoalcohols **17e** and **17f** with TFA/MeOH resulted in smooth desulfinylation to give **18e** and **18f** in good yields.

Conclusions

In summary, we have developed two new highly diastereoselective methods for the synthesis of enantiopure *N*-sulfinylimidazolidines from *p*-tolylsulfinimines. The first method relies on a diastereoselective 1,3-dipolar cycloaddition of azomethine ylides generated from α-iminoesters and enantiopure sulfinimines, and the latter involves a highly stereocontrolled stepwise condensation of iminoester-derived enolates and sulfinimines in the presence of $BF_3 \cdot OEt_2$. In addition, we have explored the reactivity of related *N*-sulfonylimines under both conditions. Subsequently, we have successfully undertaken the study of the transformation of the resulting *N*-sulfonyl- and *N*-sulfinylimidazolidines into a variety of differentially protected vicinal diamines by using reductive and/or hydrolytic protocols. Within this context, the concurrent reduction of the ester and cleavage of the aminal to produce *N*-sulfinyl-*N*′-benzyldiaminoalcohols is particularly noteworthy.

Experimental Section

General: Reagents and solvents were handled by using standard syringe techniques. Hexane, toluene, and CH_2Cl_2 were distilled from CaH_2, and Et_2O and THF from sodium. Et_3N and $i Pr_2NH$ were distilled from CaH_2. $BF_3 \cdot OEt_2$ was distilled from CaH_2 just prior to use; it was collected over granular CaH_2 and argon was bubbled through for 5 min. Crude products were purified by flash chromatography on Merck 230–400 mesh silica gel (previously treated with Et_3N, 25 μL g^{-1} silica gel) with distilled solvents (when a mixture of solvents is used, the percentage refers to the first component given). Analytical TLC was carried out on Merck (Kieselgel 60F-254) silica gel-coated plates with detection by UV light and development with iodine, acidic vanillin solution, 10% phosphomolybdic acid solution in ethanol, or 15% $KMnO_4$ in water containing 5% NaOH and 10% K_2CO_3. All reagents were commercial products purchased from Aldrich, Acros, Fluka, or Merck. Organolithium reagents were titrated prior to use.[27] Most starting materials were obtained by known procedures: **1a–n**,[28] **1m**,[29] and **2**[30]. Throughout this section, the volume of solvents is reported in mL mmol^{-1} of starting material. Infrared spectra (IR) were obtained on a Perkin–Elmer 681 and on a Perkin–Elmer Spectrum One. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-200 (200 MHz), Varian Gemini-200 (200 MHz), Varian INOVA-300 (300 MHz), and Varian INOVA-400 (400 MHz) with $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), m (multiplet), br (broad), ap (apparent). Melting points were determined on a Reichert Kofler microscope and are uncorrected. Optical rotations were measured in $CHCl_3$ solution on a Perkin–Elmer 241 polarimeter at 20 °C using a sodium lamp. Low-resolution mass spectra were recorded by direct injection onto a Hewlett Packard 5973 MSD instrument using the electronic impact technique with an ionization energy of 70 eV (EI) or on a Hewlett Packard 1100 MSD instrument using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in positive or negative modes. Elemental analyses were carried out on a Perkin–Elmer 240 C and on a Heraus CHN-O-Rapid instruments at Instituto de Química Orgánica, CSIC (Madrid).

General procedure for the 1,3-dipolar cycloaddition of sulfinimines with azomethine ylides: A 100-mL round-bottomed flask fitted with a stirrer bar and a rubber septum was charged with anhydrous THF (5 mL mmol^{-1}) and $i Pr_2NH$ (2.1 equiv) under an atmosphere of argon. The mixture was cooled to 0 °C and *n*BuLi (2.1 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min and then cooled to −78 °C and stirred for an additional 10 min. A solution of the *N*-(benzylidene)aminoester (2.0 equiv) in THF (5 mL mmol^{-1}), previously dried over 4 Å sieves, was added dropwise. The reaction mixture was stirred at −78 °C for 25 min and then a solution of the corresponding sulfinimine (1 equiv) in THF (5 mL mmol^{-1}), previously dried over 4 Å sieves, was added dropwise. The reaction vessel was sealed under argon and placed in a refrigerator (ca. 4 °C). After 20 h, the reaction was quenched with a saturated solution of NH_4Cl (4 mL mmol^{-1}), diluted with EtOAc (8 mL mmol^{-1}), and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with a saturated solution of NaCl (4 mL mmol^{-1}), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography on silica gel using the appropriate mixture of solvents.

(−)-Methyl [(2*S*,4*R*,5*R*,S_S)-4-benzyl-5-*p*-nitrophenyl-2-phenyl-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl]carboxylate (3c) and methyl [(2*R*,4*S*,5*S*,S_S)-4-benzyl-5-*p*-nitrophenyl-2-phenyl-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl]carboxylate (4c): Prepared from a solution of LDA [$i Pr_2NH$ (27 μL, 21 mg, 0.21 mmol) and *n*BuLi (1.27 M, 0.16 mL, 0.21 mmol)] with a solution of methyl 2-benzyl-2-(benzylideneamino)acetate (**2a**, 53 mg, 0.20 mmol) and a solution of (*S*)-(+)-*N*-*p*-nitrobenzylidene-*p*-toluenesulfinamide (**1b**, 30 mg, 0.10 mmol) according to the general procedure (formation of cycloadduct was observed at −78 °C) (20 h) to give a 97:3 mixture of cycloadducts **3c** and **4c** (80%) and traces of sulfinimine **1b** after purification by chromatography (5–30% EtOAc/hexane). From this mixture of **3c** and **4c**, pure **3c** (36 mg, 65%) was obtained by recrystallization (30% Et_2O/hexane) as a pale yellow solid. $R_f = 0.14$ (20% EtOAc/hexane); m.p. 155–159 °C; $[\alpha]_D^{20} = -145.6$ ($c = 1.03$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (dm, $J = 9.0$ Hz, 2H; Ar-H), 7.77 (dm, $J = 8.9$ Hz, 2H; Ar-H), 7.57–7.47 (m, 3H; Ar-H), 7.25–7.16 (m, 5H; Ar-H), 7.19 (d, $J = 8.2$ Hz, 2H; Ar-H), 7.04 (d, $J = 8.1$ Hz, 2H; Ar-H), 6.85 (d, $J = 8.1$ Hz, 2H; Ar-H), 5.93 (d, $J = 10.6$ Hz, 1H; H-2), 4.88 (s, 1H; H-5), 3.44 (d, $J = 14.2$ Hz, 1H; CH_2Ph), 3.37 (d, $J = 14.2$ Hz, 1H; CH_2Ph), 3.35 (d, $J = 10.7$ Hz, 1H; NH-3), 3.03 (s, 3H; CO_2Me), 2.16 ppm (s, 3H; Me-Tol); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.2$, 147.9, 146.5, 141.8, 138.7, 137.7, 135.7, 130.1 (2C), 129.5, 129.2 (2C), 128.7 (2C), 128.6 (2C), 128.2 (2C), 127.0, 125.2 (2C), 122.3 (2C), 77.2, 75.8, 64.5, 51.8, 41.0, 21.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3450$, 3030, 2930, 1740, 1600, 1520, 1450, 1350, 1260, 1210, 1090, 1070, 860, 810, 750, 700 cm^{-1}; MS (EI): *m*/*z* (%): 356 (5), 324 (9), 292 (26), 246 (12), 208 (20), 176 (93), 139 (84), 117 (49), 91 (100), 90 (63), 65 (45); elemental analysis calcd (%) $C_{31}H_{29}N_3O_5S$ (555.65): C 67.01, H 5.26, N 7.56, S 5.77; found: C 66.99, H 5.24, N 7.55, S 5.48.

Compound **4c** (partial data): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.80$ (d, $J = 10.7$ Hz, 1H; H-2), 5.08 (s, 1H; H-5), 3.14 (s, 3H; CO_2Me), 2.20 ppm (s, 3H; Me-Tol).

(−)-Methyl [(2*S*,4*R*,5*R*,S_S)-4-benzyl-2-phenyl-5-(3-pyridyl)-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl]carboxylate (3e): Prepared from a solution of LDA [$i Pr_2NH$ (100 μL, 79 mg, 0.78 mmol) and *n*BuLi (1.6 M, 0.45 mL, 0.72 mmol)] with a solution of methyl 2-benzyl-2-(benzylideneamino)acetate (**2a**, 160 mg, 0.60 mmol) and a solution of (*S*)-(+)-*N*-(2-pyridylmethylidene)-*p*-toluenesulfinamide (**1c**, 73 mg, 0.30 mmol) according to the general procedure (10 h). After purification by chromatography (5–65% EtOAc/CH_2Cl_2) this gave pure cycloadduct **3e** (122 mg, 80%) as a white solid, which was recrystallized from 25% CH_2Cl_2/hexane. $R_f = 0.39$ (20% EtOAc/CH_2Cl_2); m.p. 158–160 °C; $[\alpha]_D^{20} = -51.1$ ($c = 1.30$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$ (dd, $J = 4.9$, 1.7 Hz, 1H; Ar-H), 8.12 (d, $J = 1.8$ Hz, 1H; Ar-H), 7.80 (dm, $J = 8.5$ Hz, 2H; Ar-H), 7.57–7.47 (m, 3H; Ar-H), 7.26–7.19 (m, 8H; Ar-H), 6.91–6.86 (m, 3H; Ar-H), 5.94 (d, $J = 11.1$ Hz, 1H; H-2), 4.83 (s, 1H; H-5), 3.43 (AB system, 2H; C*H*$_2$Ph), 3.37 (d, $J = 10.7$ Hz, 1H; NH-3), 3.05 (s, 3H; CO_2Me), 2.19 ppm (s, 3H; Me-Tol); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.0$, 148.8, 147.6, 141.2, 138.2, 137.7, 135.7 (2C), 134.4, 129.9 (2C), 129.1, 128.8 (2C), 128.7 (2C), 127.8 (2C), 127.3 (2C), 126.6, 124.8 (2C), 121.8, 77.4, 75.5, 62.8, 51.4, 40.4, 20.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2930$, 2860, 1730 (C=O), 1640, 1600, 1530, 1490, 1450, 1340, 1270, 1160, 1100, 1010, 1000, 720, 700, 660 cm^{-1}; elemental analysis calcd

(%) $C_{30}H_{29}N_3O_3S$ (511.63): C 70.43, H 5.71, N 8.21, S 6.27; found: C 70.06, H 5.54, N 8.43, S 6.38.

General procedure for the Lewis acid catalyzed condensation between iminoester enolates and *p*-tolylsulfinimines: A 100-mL round-bottomed flask fitted with a stirrer bar and a rubber septum was charged with anhydrous THF (5 mL mmol^{-1} of sulfinimine) and *i*Pr_2NH (2.6 equiv) under an atmosphere of argon. The mixture was cooled to 0 °C and *n*BuLi (2.1 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min and then cooled to −78 °C and stirred for an additional 10 min. A solution of the *N*-(benzylidene)aminoester (2.0 equiv) in THF (5 mL mmol^{-1} of sulfinimine), previously dried over 4 Å sieves, was added dropwise. The reaction mixture was stirred at −78 °C for 25–30 min and then a solution of the corresponding sulfinimine (1 equiv) in THF (5 mL mmol^{-1}), previously dried over 4 Å sieves, was added dropwise followed by freshly distilled $BF_3 \cdot OEt_2$ (3.25 equiv). Upon addition of the Lewis acid, the orange reaction mixture turned pale yellow and the mixture was allowed to warm up slowly to approximately −20 °C until the starting material (15 min–3 h) disappeared. The reaction was then quenched with a 5% solution of $NaHCO_3$ (6 mL mmol^{-1}). When the mixture had reached about 0 °C, the layers were separated and the organic phase was washed with a saturated solution of NaCl (4 mL mmol^{-1}). The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow oil. This crude product mixture was dissolved in $CHCl_3$ (0.1M) and the ensuing cyclization was monitored by ^{1}H NMR spectroscopy. After 2–4 d, the mixture was purified by column chromatography on silica gel with the appropriate mixture of solvents as eluent. In an alternative procedure, 0.5 equiv of PhCHO and $MgSO_4$ (1.3 g mmol^{-1}) was added to the $CHCl_3$ solution to accelerate the cyclization. In all experiments, variable amounts of a related imidazolidine formed by dimerization of the iminoester were also obtained.

(−)-Methyl [(2*S*,4*S*,5*R*,S_S)-2-phenyl-5-(3-pyridyl)-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl)]carboxylate (7f) and methyl [(2*R*,4*R*,5*S*,S_S)-2-phenyl-5-(3-pyridyl)-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl)]carboxylate (8f): Prepared from a solution of LDA [*i*Pr_2NH (0.18 mL, 131 mg, 1.30 mmol) and *n*BuLi (1.42 M, 0.74 mL, 1.05 mmol)] with a solution of methyl 2-(benzylideneamino)acetate (**2d**, 177 mg, 1.00 mmol) and a solution of (*S*)-(+)-*N*-(3-pyridinemethylidene)-*p*-toluenesulfinamide (**1c**, 122 mg, 0.5 mmol) by adding $BF_3 \cdot OEt_2$ (231 mg, 0.20 mL, 1.625 mmol) according to the general procedure (3 h 30 min) to give a 90:10 mixture of cycloadducts **7f** and **8f** (126 mg, 60%) after purification by chromatography (80% $CHCl_3$/hexane, then 0–100% $Et_2O/CHCl_3$ and then 5% MeOH/Et_2O). Pure **7f** (90 mg, 40%) was obtained as a white solid from this mixture by recrystallization (Et_2O). $R_f = 0.23$ (20% EtOH/hexane); m.p. 155–158 °C; $[\alpha]_D^{20} = -48.3$ ($c = 0.46$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.19$ (dd, 1H, $J = 4.8$, 1.7 Hz; Ar-H), 7.88 (d, 1H, $J = 2.0$ Hz; Ar-H), 7.73 (d, 2H, $J = 7.5$ Hz; Ar-H), 7.50–7.40 (m, 3H; Ar-H), 7.28 (d, 2H, $J = 8.2$ Hz; Ar-H), 6.91 (d, 3H, $J = 8.0$ Hz; Ar-H), 6.80 (dd, 2H, $J = 7.9$, 4.8 Hz; Ar-H), 6.05 (d, 1H, $J = 5.6$ Hz, H-2), 4.87 (d, 1H, $J = 6.2$ Hz; H-5), 3.80 (m, 1H; H-4), 3.76 (s, 3H; CO_2Me), 3.27 (br t, 1H, $J = 7.7$ Hz; NH-3), 2.19 ppm (s, 3H; Me-Tol); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 170.8$, 148.8, 147.8, 141.6, 139.8, 138.9, 136.8, 134.3, 128.8 (2C), 127.2 (2C), 125.4 (2C), 122.5, 80.6, 68.5, 57.9, 52.6, 21.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3400$, 3300, 1725, 1550, 1430, 1180, 1110, 1070,1040, 740, 670 cm^{-1}; MS (APCI): *m*/*z* (%): 422 $[M+H]^+$ (100), 282 (77); elemental analysis calcd (%) $C_{23}H_{23}N_3O_3S$ (421.56): C 65.54, H 5.50, N 9.97, S 7.61; found: C 65.40, H 5.66, N 9.78, S 7.94.

Compound **8f** (partial data): $R_f = 0.23$ (20% EtOH/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.94$ (s, 1H; H-2), 5.09 (d, 1H, $J = 7.4$ Hz; H-5), 3.79 (s, 3H; CO_2Me), 2.32 ppm (s, 3H; Me-Tol).

(+)-Methyl [(2*S*,4*S*,5*R*,S_S)-5-methyl-2-phenyl-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl]carboxylate (7k) and methyl [(2*R*,4*R*,5*S*,S_S)-5-methyl-2-phenyl-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl]carboxylate (8k): Prepared from a solution of LDA [*i*Pr_2NH (0.64 mL, 461 mg, 4.56 mmol) and *n*BuLi (1.6 M, 2.6 mL, 4.18 mmol)] with a solution of methyl 2-(benzylideneamino)acetate (**2d**, 673 mg, 3.80 mmol) and a solution of (*S*)-(+)-*N*-ethylidene-*p*-toluenesulfinamide (**1l**, 344 mg, 1.90 mmol) by adding $BF_3 \cdot OEt_2$ (863 mg, 0.77 mL, 6.08 mmol) according to the general procedure (10 min) to give a 92:8 mixture of cycloadducts **7k** and **8k** (441 mg, 64%) as a yellowish oil after purification by chromatography (5–25% Et_2O/CH_2Cl_2). A second careful purification by chromatography (5–20% Et_2O/CH_2Cl_2) afforded pure imidazolidine **7k** (309 mg, 45%). $R_f = 0.37$ (30% Et_2O/CH_2Cl_2); $[\alpha]_D^{20} = +78.5$ ($c = 1.10$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$–7.57 (m, 4H; Ar-H), 7.40–7.23 (m, 5H; Ar-H), 5.95 (s, 1H; H-2), 3.95 (ap quint, $J = 5.9$ Hz, 1H; H-5), 3.77 (s, 3H; CO_2Me), 3.44 (m, 1H; H-4), 2.39 (s, 3H; Me-Tol), 0.67 ppm (d, $J = 6.6$ Hz, 3H; Me); DNOE between H-2/Ar-H (7.64): 0.5%, H-4/Me: 1.9%, H-5/Me: 0.9%, H-5/Ar-H (7.61): 0.3%, Me/H-4: 0.5%, Me/H-5: 0.8%, Me/Ar-H (7.64): 0.1%; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.5$, 141.5, 140.8, 140.6, 129.5 (2C), 128.4 (2C), 128.2, 127.0 (2C), 125.6 (2C), 81.4, 67.1, 53.2, 52.5, 21.9, 21.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3306$, 3030, 2952, 1745, 1644, 1596, 1492, 1448, 1376, 1351, 1276, 1206, 1130, 1089, 1068, 935, 813, 758, 737, 699 cm^{-1}; MS(ES): *m*/*z* (%): 739 $[2M+Na]^+$ (15), 359 $[M+H]^+$ (100); elemental analysis calcd (%) $C_{19}H_{22}N_2O_3S$ (358.45): C 63.66, H 6.19, N 7.82, S 8.95; found: C 63.47, H 6.12, N 8.01, S 8.68.

Compound **8k** (partial data from a 92:8 mixture): $R_f = 0.36$ (30% Et_2O/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.74$ (s, 1H; H-2), 1.30 ppm (d, $J = 6.6$ Hz, 3H; Me).

General procedure for oxidation of sulfinamides to sulfonamides with *m*CPBA: *m*CPBA (1.5–3.0 equiv, 70%) was added at 0 °C to a solution of the sulfinamide in CH_2Cl_2 (10 mL mmol^{-1}) under an argon atmosphere. The reaction mixture was allowed to warm up slowly to room temperature and was monitored by TLC. The reaction was quenched with 1M aqueous $Na_2S_2O_4$ (5 mL mmol^{-1}), a saturated solution of $NaHCO_3$ (3 mL mmol^{-1}), and H_2O (4 mL mmol^{-1}), diluted with EtOAc (8 mL mmol^{-1}); the layers were separated, and the aqueous layer was extracted with EtOAc (3×, 5 mL mmol^{-1}). The organic layer was washed with a saturated solution of NaCl (4 mL mmol^{-1}), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography.

(−)-Methyl [(2*S*,4*R*,5*R*)-4-benzyl-2,5-diphenyl-1-(*p*-tolylsulfonyl)-1,3-imidazolidin-4-yl]carboxylate (5a): Prepared from sulfinamide **3a** (11 mg, 0.02 mmol) and *m*CPBA (8 mg, 0.046 mmol) according to the general procedure (12 h) to give sulfonamide **5a** (7 mg, 65%) after chromatography (50–100% CH_2Cl_2/hexane) as a white solid that was recrystallized from Et_2O. Similarly, oxidation of **4a** gave ***ent*-5a** (62%) with comparable optical rotation of opposite sign {$[\alpha]_D^{20} = +31.8$ ($c = 0.49$) for ***ent*-5a**}. Compound **5a**: $R_f = 0.37$ (CH_2Cl_2); m.p. 115–119 °C; $[\alpha]_D^{20} = -31.2$ ($c = 0.46$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$–7.56 (m, 2H; Ar-H), 7.39–7.13 (m, 15H; Ar-H), 7.06 (d, $J = 8.2$ Hz, 2H; Ar-H), 5.77 (d, $J = 11.6$ Hz, 1H; H-2), 4.96 (s, 1H; H-5), 3.30 (d, $J = 11.8$ Hz, 1H; NH-3), 3.20 (d, $J = 14.0$ Hz, 1H; CH_2Ph), 3.05 (s, 3H; CO_2Me), 2.82 (d, $J = 13.9$ Hz, 1H; CH_2Ph), 2.31 ppm (s, 3H; Me-Tol); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 169.9$, 143.6, 139.0, 137.7, 135.9, 130.1 (2C), 129.2 (2C), 128.9, 128.5 (2C), 128.0 (4C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 126.9, 78.7, 75.4, 72.2, 51.7, 41.0, 21.5 ppm; IR (KBr): $\tilde{\nu} = 3450$, 3040, 2960, 1740, 1600, 1260, 1090, 1020, 800, 700, 660 cm^{-1}; MS (EI): *m*/*z* (%): 467 (3), 283 (2), 266 (32), 260 (9), 206 (21), 176 (18), 155 (36), 117 (14), 92 (18), 91 (100), 90 (42), 77 (36); elemental analysis calcd (%) $C_{31}H_{30}N_2O_4S$ (562.57): C 70.70, H 5.74, N 5.32, S 6.09; found: C 70.39, H 5.89, N 5.40, S 5.86.

General procedure for the reaction between sulfinylimidazolidines and $LiAlH_4$: A round-bottomed flask was charged with anhydrous Et_2O or THF (6 mL mmol^{-1} of imidazolidine) and $LiAlH_4$ (3–9 equiv). After 10 min, the resulting suspension was cooled to 0 °C and a solution of the corresponding imidazolidine in anhydrous Et_2O or THF (4 mL mmol^{-1}) was added dropwise and the reaction mixture was stirred at room temperature and monitored by TLC. When the reaction had reached completion (2–18 h), the mixture was quenched with a saturated $NaHCO_3$ solution (4 mL mmol^{-1}), H_2O (4 mL mmol^{-1}), and diluted with CH_2Cl_2 (8 mL mmol^{-1}). The resulting suspension was filtered through Celite, the residue was thoroughly washed with CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 times, 8 mL mmol^{-1}). The combined organic extracts were washed with a saturated NaCl solution (4 mL mmol^{-1}), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography on silica gel.

(−)-[(2*S*,4*S*,5*R*,S_S)-4-Benzyl-2,5-diphenyl-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl]methanol (15a): Prepared from a suspension of $LiAlH_4$ (3 equiv, 12 mg, 0.31 mmol) in Et_2O and sulfinamide **9a** (53 mg, 0.10 mmol) with further additions of $LiAlH_4$ (3 equiv) after 3 h and (3 equiv) after 12 h at room temperature according to the general procedure (16 h) to give hydroxymethylsulfinamide **15a** (37.5 mg, 75%) as a colorless oil after

chromatography (15–100% EtOAc/hexane). $R_f = 0.31$ (50% EtOAc/hexane); $[\alpha]_D^{20} = -95.4$ ($c = 1.42$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 6.9$ Hz, 2H; Ar-H), 7.54–7.45 (m, 3H; Ar-H), 7.24–7.20 (m, 2H; Ar-H), 7.13–7.10 (m, 4H; Ar-H), 7.09–6.99 (br s, 3H; Ar-H), 6.93–6.90 (m, 3H; Ar-H), 6.82 (d, $J = 8.1$ Hz, 2H; Ar-H), 5.80 (s, 1H; H-2), 4.78 (s, 1H; H-5), 3.75 (d, $J = 11.1$ Hz, 1H; CH_2OH), 3.60 (d, $J = 11.1$ Hz, 1H; CH_2OH), 2.44 (d, $J = 13.9$ Hz, 1H; CH_2Ph), 2.17 (s, 3H; Me-Tol), 2.06 (d, $J = 13.9$ Hz, 1H; CH_2-Ph), 1.70–1.50 ppm (br, 2H; NH, OH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 140.9$, 140.8, 139.7, 138.8, 136.8, 130.1 (2C), 128.9 (4C), 128.6 (2C), 128.3, 128.0 (2C), 127.4 (4C), 126.4 (2C), 125.4 (2C), 77.2, 68.6, 62.8, 62.1, 40.1, 21.1 ppm; IR (CCl_4): $\tilde{\nu} = 3400$, 3060, 3030, 2930, 1490, 1450, 1090, 1050, 700, 605 cm^{-1}; MS (EI): m/z (%): 352 (2), 311 (7), 260 (6), 223 (9), 194 (9), 168 (16), 141 (17), 139 (26), 115 (27), 91 (100), 77 (35), 65 (17), 6 (14); elemental analysis calcd (%) $C_{30}H_{20}N_2O_2S$ (482.64): C 74.66, H 6.27, N 5.80, S 6.64; found: C 74.95, H 6.54, N 5.55, S 6.48.

(−)-(2*S*,3*R*,*S*$_S$)-2-(Benzylamino)-5-phenyl-3-(*p*-tolylsulfinylamino)pentan-1-ol (17i): Prepared from a suspension of $LiAlH_4$ (149 mg, 3.66 mmol) in Et_2O and **7h** (1327 mg, 3.16 mmol) according to the general procedure (4 h 30 min). Purification by chromatography (0–5% MeOH/CH_2Cl_2) afforded diaminoalcohol **17i** (274 mg, 0.62 mmol, 68%) as a colorless oil. $R_f = 0.30$ (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20} = -117.5$ ($c = 1.60$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (d, $J = 8.2$ Hz, 2H; Ar-H), 7.34–7.22 (m, 7H; Ar-H), 7.21–7.08 (m, 3H; Ar-H), 6.78 (d, $J = 8.2$ Hz, 2H; Ar-H), 5.03 (d, $J = 8.3$ Hz, 1H; S-NH), 3.85 (d, $J = 13.1$ Hz, 1H; N-CH_2Ph), 3.70 (d, $J = 13.1$ Hz, 1H; N-CH_2Ph), 3.64 (dd, $J = 11.6$, 4.4 Hz, 1H; H-1), 3.56 (dd, $J = 11.6$, 7.3 Hz, 1H; H-1), 3.30 (m, 1H; H-3), 2.72 (ddd, $J = 7.1$, 4.4, 2.6 Hz, 1H; H-2), 2.41 (s, 3H; Me-Tol), 2.18–2.01 (m, 2H; CH_2-5), 1.72–1.59 (m, 1H; H-4), 1.44–1.34 ppm (m, 1H; H-4); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 141.5$, 141.3, 140.2, 140.1, 129.5 (2C), 128.5 (2C), 128.3 (2C), 128.2 (2C), 128.0 (2C), 127.3, 125.9 (2C), 125.7, 61.6, 58.9, 52.9, 51.3, 35.8, 32.0, 21.3 ppm; IR (film): $\tilde{\nu} = 3317$, 3060, 3026, 2925, 1601, 1494, 1453, 1086, 1046, 812, 747, 699 cm^{-1}; MS (ES): m/z (%): 423 $[M+H]^+$ (100); elemental analysis calcd (%) $C_{25}H_{30}N_2O_2S$ (422.585): C 71.06, H 7.16, N 6.63, S 7.59; found: C 70.89, H 7.34, N 6.46, S 7.33.

General procedure for the reaction between sulfinylimidazolidines and $NaBH_4$/LiI: A round-bottomed flask was charged with anhydrous THF (2 mL mmol^{-1} of imidazolidine) and LiI (2–3 equiv) was added, followed by $NaBH_4$ (2–3 equiv). The resulting suspension was cooled to 0 °C and a solution of the corresponding imidazolidine in anhydrous THF (6 mL mmol^{-1}) was added dropwise, and the reaction mixture was stirred at 0 °C (30 min) and then at room temperature and monitored by TLC. When the reaction had reached completion (2–3 h), the mixture was quenched with a 5% $NaHCO_3$ solution (2 mL mmol^{-1}) and diluted with CH_2Cl_2 (8 mL mmol^{-1}) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 times, 8 mL mmol^{-1}). The combined organic extracts were washed with a saturated NaCl solution (4 mL mmol^{-1}), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography on silica gel.

(±)-[(2*S*,4*S*,5*R*,*S*$_S$)-2-Phenyl-5-(2-phenylethyl)-1-(*p*-tolylsulfinyl)-1,3-imidazolidin-4-yl]methanol (15e): Prepared from LiI (120 mg, 0.90 mmol) in THF, with $NaBH_4$ (35 mg, 0.90 mmol) and **7h** (135 mg, 0.30 mmol) according to the general procedure (3 h). Alcohol **15e** (100 mg, 79%) was obtained after chromatography (Et_2O/EtOH 40:1) as a white solid that was recrystallized from Et_2O/CH_2Cl_2. $R_f = 0.24$ (40:1 CH_2Cl_2/EtOH); m.p. 136–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.57–7.54$ (m, 2H; Ar-H), 7.50 (d, $J = 8.3$ Hz, 2H; Ar-H), 7.43–7.34 (m, 3H; Ar-H), 7.27 (d, $J = 8.3$ Hz, 2H; Ar-H), 7.16–7.12 (m, 2H; Ar-H), 6.71 (dd, $J = 7.8$, 1.7 Hz, 2H; Ar-H), 5.75 (s, 1H; H-2), 3.79–3.64 (m, 3H; H-4, CH_2OH), 3.25 (td, $J = 7.1$, 2.3 Hz, 1H; H-5), 2.78 (br s, 1H; NH-3), 2.42 (s, 3H; Me-Tol), 2.27–2.06 (m, 2H; CH_2-2′), 1.38 (m, 1H; H-1′), 1.00 ppm (m, 1H; H-1′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 141.5$, 140.8, 140.3, 140.1, 129.5 (2C), 128.7 (2C), 128.6, 128.2 (2C), 128.0 (2C), 127.0 (2C), 125.8, 125.1, 80.4, 64.8, 62.4, 54.8, 37.8, 32.7, 21.4 ppm; IR (KBr): $\tilde{\nu} = 3435$, 2933, 1656, 1500, 1454, 1058, 960, 811, 753, 697 cm^{-1}; MS (ES): m/z (%): 863 $[2M+Na]^+$ (33), 443 $[M+Na]^+$ (41), 421 $[M+H]^+$ (100); elemental analysis calcd (%) $C_{25}H_{28}N_2O_2S$ (420.62): C 71.38, H 6.72, N 6.66, S 7.62; found: C 71.19, H 7.02, N 6.75, S 7.54.

General procedure for desulfinylation and solvolysis with TFA: Trifluoroacetic acid (5–10 equiv) was added to a solution of substrate (1 equiv) in MeOH (10–20 mL mmol^{-1}; for poorly soluble substrates, 10–20% of CH_2Cl_2 was employed) and the reaction mixture was stirred at room temperature and monitored by TLC (this often required spotting from aliquots worked up with saturated aqueous K_2CO_3). Upon completion (5–24 h), the solvent was removed in vacuo, the residue was diluted with CH_2Cl_2 (10 mL mmol^{-1}), and extracted with 15% aqueous HCl (2 × 10 mL mmol^{-1}); the combined aqueous layer was cooled to 5 °C, and CH_2Cl_2 (10 mL mmol^{-1}) was added. The resulting biphasic solution was carefully neutralized with solid $NaHCO_3$ (to pH 7.5–9), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL mmol^{-1}). The combined organic extracts were washed with water (4 mL mmol^{-1}) and brine (6 mL mmol^{-1}), dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel. Alternatively, upon completion of the reaction, solid NaOH (ca. 7.5 mmol mmol^{-1}) was added and the mixture was stirred at room temperature (ca. 10 h), the solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 and then 10–20% EtOH/CH_2Cl_2 and filtered through a short plug of silica gel.

(+)-(2*R*,3*R*)-2-Benzyl-2,3-diamino-3-phenyl-propan-1-ol (18a): Prepared from sulfenamide **14a** (10 mg, 0.021 mmol), with TFA (5 equiv, 8 μL, 11.8 mg, 0.103 mmol) in MeOH according to the general procedure (5 h). Chromatography (0–65% MeOH/Et_2O) gave diamine **18a** (5.2 mg, 95%) as a colorless oil. $R_f = 0.18$ (30% MeOH/Et_2O); $[\alpha]_D^{20} = +11.0$ ($c = 0.55$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42–7.10$ (m, 10H; Ar-H), 4.12 (s, 1H; H-3), 3.60 (d, $J = 11.5$ Hz, 1H; CH_2OH), 3.25 (d, $J = 11.2$ Hz, 1H; CH_2OH), 2.68 (d, $J = 13.4$ Hz, 1H; CH_2Ph), 2.56 (d, $J = 13.4$ Hz, 1H; CH_2Ph), 2.40–2.10 ppm (br s, 5H; $2NH_2$, OH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 141.2$, 136.3, 130.7 (2C), 128.5 (2C), 128.3 (2C), 128.1 (2C), 128.0, 126.7, 67.6, 65.0, 57.0, 40.6 ppm; IR (CCl_4): $\tilde{\nu} = 3350$, 3060, 3030, 2930, 1725, 1600, 1590, 1500 cm^{-1}; MS (ES): m/z (%): 225 (2), 208 (3), 195 (5), 177 (3), 165 (14), 150 (100), 133 (22), 106 (34), 91 (87), 77 (23), 69 (23), 57 (37); elemental analysis calcd (%) $C_{16}H_{20}N_2O$ (256.34): C 74.97, H 7.86, N 10.93; found: C 74.73, H 7.65, N 10.82.

(−)-(2*S*,3*R*)-3-Amino-2-benzylamino-3-phenylpropan-1-ol (18f): Prepared from sulfinyldiaminoalcohol **17f** (17 mg, 0.04 mmol) with TFA (5 equiv, 16 μL, 23 mg, 0.20 mmol) in MeOH according to the general procedure (24 h). Chromatography (CH_2Cl_2 to 50% EtOH/CH_2Cl_2) gave diaminoalcohol **18f** (7.0 mg, 75%) as a white solid that was recrystallized from Et_2O. Similarly, from a 50:50 mixture of **17f** and **17f′** racemic **18f** was obtained. Compound **18f**: $R_f = 0.20$ (25% EtOH/CH_2Cl_2); m.p. 176–177 °C; $[\alpha]_D^{20} = -46.3$ ($c = 0.80$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35–7.23$ (m, 10H; Ar-H), 4.06 (d, $J = 6.7$ Hz, 1H; H-3), 3.87 (d, $J = 13.2$ Hz, 1H; CH_2Ph), 3.70 (d, $J = 13.2$ Hz, 1H; CH_2Ph), 3.65 (dd, $J = 11.5$, 4.0 Hz, 1H; CH_2OH), 3.45 (dd, $J = 11.4$, 3.2 Hz, 1H; CH_2OH), 2.81 ppm (m, 5H; H-2, NH_2, NH, OH); ^{1}H NMR (300 MHz, 40 °C, $CDCl_3$): $\delta = 7.35–7.23$ (m, 10H; Ar-H), 4.06 (d, $J = 6.6$ Hz, 1H; H-3), 3.87 (d, $J = 13.2$ Hz, 1H; CH_2Ph), 3.71 (d, $J = 13.2$ Hz, 1H; CH_2Ph), 3.65 (dd, $J = 11.4$, 4.1 Hz, 1H; CH_2OH), 3.45 (dd, $J = 11.4$, 3.4 Hz, 1H; CH_2OH), 2.81 (ddd, $J = 6.7$, 3.5 Hz, 1H; H-2), 2.75 ppm (br s, 4H; NH_2, NH, OH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 143.2$, 138.9, 128.7 (2C), 128.5 (2C), 128.3 (2C), 127.6, 127.4, 126.6 (2C), 62.7, 61.1, 57.3, 51.7 ppm; IR (KBr): $\tilde{\nu} = 3320$, 2930, 2860, 1735, 1650, 1540, 1455, 1375, 1360, 1335, 1290, 1125, 1065, 1040, 1010, 740, 695 cm^{-1}; MS (APCI): m/z (%): 257 $[M+H]^+$ (100); elemental analysis calcd (%) $C_{16}H_{20}N_2O$ (256.34): C 74.97, H 7.86, N 10.93; found: C 75.13, H 7.35, N 10.72.

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[13] CCDC 188087, -188088, REBHAH, CEZSUV contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

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[19] Variable amounts of *N*-sulfinyldiaminoesters derived from **6** were frequently isolated (5–20%). Their quantitative conversion to the corresponding imidazolidines **7** and **8** upon treatment with PhCHO and $MgSO_4$ provided a definitive structural proof for these side products along with an increase of the global yield of **7** and **8**.

[20] Decomposition of the starting materials upon prolonged reaction times has been tentatively proposed. For cinnamaldehyde-derived sulfinimine we cannot rule out a competition between C=N and C=C bonds as electrophiles.

[21] To establish that **9a** and **11a** were facial isomers an equimolecular mixture of both was oxidized at sulfur with *m*CPBA to produce racemic *N*-sulfonylimidazolidine **12a**.

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