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Practical Synthetic Approach to Chiral Sulfonimides (CSIs) – Chiral Brønsted Acids for Organocatalysis

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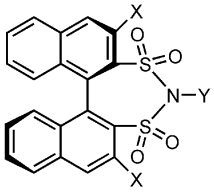
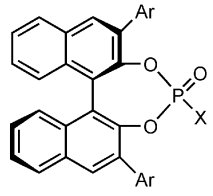
A general approach to the synthesis of optically pure 3,3′-diaryl chiral sulfonimides (CSIs) from racemic BINOL has been developed. *ortho*-Lithiation is directed by the sulfonyl groups, and the resulting dihalides serve as the common precursors for the aryl-substituted CSIs.

Introduction

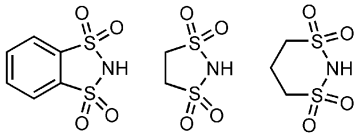
Two recent publications from the groups of List and Giernoth prompted us to report our efforts on developing binaphthyl-derived chiral sulfonimides (CSIs) as Brønsted acids in organocatalysis. Giernoth reported the synthesis of parent compound **1a** (X, Y = H),[1] whereas List demonstrated elegantly that in situ generated silylated sulfonimine **1c** (Y = $SiMe_3$, via **1b**) is a highly efficient Lewis acid organocatalyst for Mukaiyama aldol reactions.[2]



1 **a** X, Y = H
b X = 3,5-$(CF_3)_2C_6H_3$, Y = H
c X = 3,5-$(CF_3)_2C_6H_3$, Y = $SiMe_3$



2 **a** X = OH
b X = $NHSO_2CF_3$



3 **4** **5**

In recent years, the rapid development of organocatalysis has complemented the traditional organometallic and enzymatic approaches to asymmetric catalysis in the construction of chiral molecules and scaffolds.[3] With organocatalysis, synthetic chemists can construct chiral molecules in a highly efficient and stereoselective manner under rather mild conditions. In most cases, the organocatalytic reactions can be carried out under ambient conditions without the exclusion of air or moisture. Among the four types of organocatalysts,[3b] many believe that Brønsted acid catalysts have the potential to provide the reactivities and selectivities that could match up with metal-based asymmetric catalysis.[4] For example, BINOL-derived chiral phosphoric acids **2a** discovered independently by Akiyama[5a] and Terada,[5b] and the more acidic corresponding *N*-triflyl phosphoramides **2b** developed by Yamamoto,[5c,5d] are the most widely used Brønsted acid organocatalysts of today.

Recently, Barbero reported that *o*-benzenedisulfonimide **3** is a strong Brønsted acid for various acid-catalyzed transformations such as etherification, esterification, acetalization, and acylation, as well as for the acid-catalyzed Ritter, Nazarov, and Hosomi–Sakurai reactions.[6] It has been reported that the pK_a value of **3** in water is –4.1.[6b,7] For the corresponding aliphatic sulfonimides **4** and **5**, their pK_a values in water are –3.1 and –1.7, respectively.[7] We envision that a chiral version of **3** could be an effective Brønsted acid for asymmetric organocatalysis, and we selected binaphthyl as the chiral backbone in the design of the CSI.

Results and Discussion

Our approach to the synthesis of chiral sulfonimides **1** is different from those of List and Giernoth. They both started with optically pure BINOL, and Giernoth only prepared parent compound **1a** (X, Y = H). In the case of List's synthesis of **1b**, the 3,3′-substituent is already in place at the beginning of the synthesis. Instead, we started with racemic BINOL and deferred the resolution to a later stage by using readily available (*S*)-α-methylbenzylamine [(–)-**11**] as the resolving agent. In addition, we would like to explore the possibility of using the sulfonyl groups at the 2,2′-positions as the directing groups for the functionalization of the 3,3′-positions by *ortho*-lithiation.[8] Resulting dihalide **1e** could

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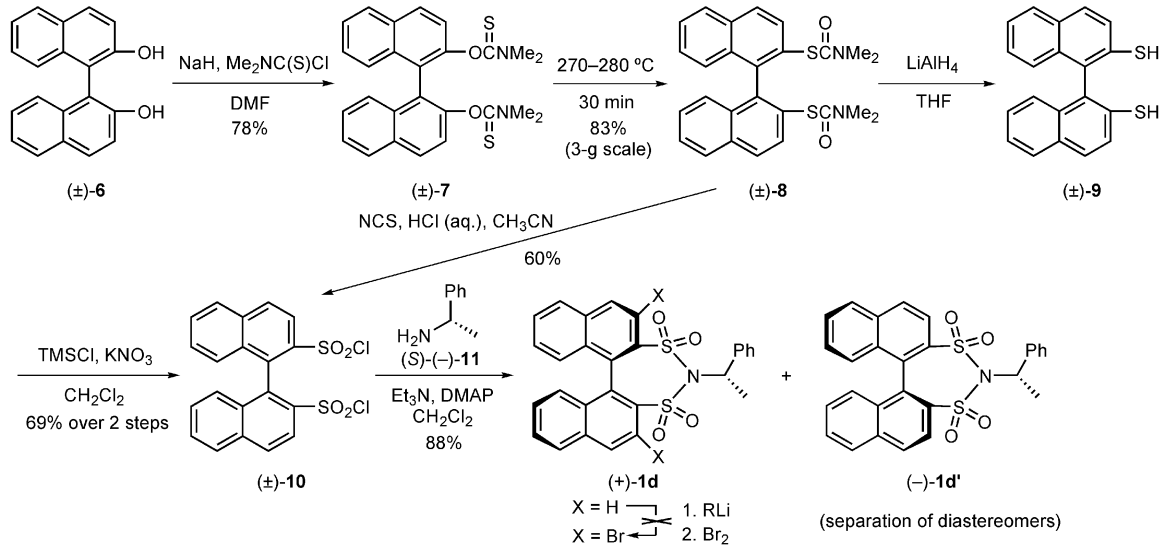
then serve as a common precursor for a series of 3,3′-substituted CSIs. Our approach should provide a more general and convergent synthesis to a wide variety of CSIs with different substituents at the 3,3′-positions by using dihalide **1e** as the common starting material.

Our synthesis of the CSIs is outlined in Scheme 1. Racemic 1,1′-binaphthalene-2,2′-dithiol [(±)-**9**] was prepared from racemic BINOL [(±)-**6**] by Newman–Kwart thermal rearrangement[9] of 1,1′-binaphthalene-2,2′-diyl *O*,*O*-bis(*N*,*N*-dimethylthiocarbamate) [(±)-**7**] into 1,1′-binaphthalene-2,2′-diyl *S*,*S*-bis(*N*,*N*-dimethylthiocarbamate) [(±)-**8**]. Under carefully controlled conditions, the Newman–Kwart rearrangement at 270–280 °C (sand bath) can be carried out in a gram scale with good overall yields. Lithium aluminum hydride reduction of (±)-**8** afforded dithiol (±)-**9** in good yield.[9a,9c,9e] Oxidative chlorination to sulfonyl chloride (±)-**10** was achieved by using potassium nitrate and TMSCl as the oxidizing and chlorinating agents, respectively.[10a] Alternatively, (±)-**10** could be obtained directly from (±)-**8** by using *N*-chlorosuccinimide (NCS), as reported by Giernoth.[1,10b]

Diastereomeric sulfonimides **1d** and **1d′**, which can be separated by silica gel column chromatography, were then formed in 88% yield with optically (*S*)-α-methylbenzylamine [(–)-**11**]. The formation of the cyclic sulfonimide has to be conduct under high-dilution conditions. Otherwise, bis(sulfonamide) will be formed as the major product. The absolute configuration of **1d** was confirmed by X-ray analysis (Figure 1). Hydrogenolysis in MeOH/EtOAc afforded the optically pure (*R*) and (*S*) enantiomers of parent CSI (*R*)-**1a** and (*S*)-*ent*-**1a** in almost quantitative yield. The X-ray structure of (*R*)-**1a** is also shown in Figure 2.

In general, bulky aryl substituents at the 3,3′-positions are needed for an effective binaphthyl-type catalyst. Therefore, functionalization of the 3,3′-positions of the binaphthyl backbone was explored. It has been reported that the sulfonamide group could serve as a director for *ortho*-lithiation in an aromatic system.[8] However, direct lithiation of *N*-substituted **1d** with various organolithium reagents was not successful. The major products were the ring-opened products of the sulfonimide, even when a bulky reagent such as *tert*-butyllithium was used. Finally, lithiation of parent CSI **1a** with an excess amount of *n*BuLi followed by bromination with either Br_2 or 1,2-dibromotetrachloroethane[11] at –40 °C afforded 3,3′-dibromo CSI **1e** in 56% yield. Iodination with I_2 also afforded the corresponding



	Ar	Yield [%]
1b	3,5-$(CF_3)_2C_6H_3$	78
1g	phenyl	87
1h	2-naphthyl	85
1i	4-$CF_3C_6H_4$	71
1j	4-CNC_6H_4	80
1k	3,5-$F_2C_6H_3$	59
1l	4-(1-naphthyl)C_6H_5	85
1m	3-PhC_6H_5	76
1n	1-naphthyl	88[a]

[a] Mixture of diastereomers

Scheme 1. Synthetic route to CSIs.

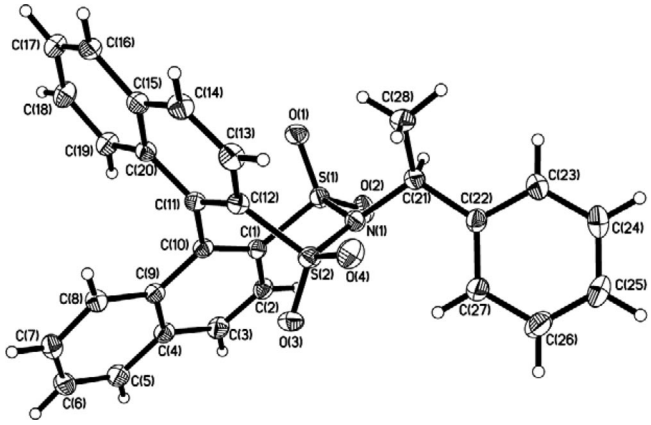


Figure 1. X-ray structures of **1d**.

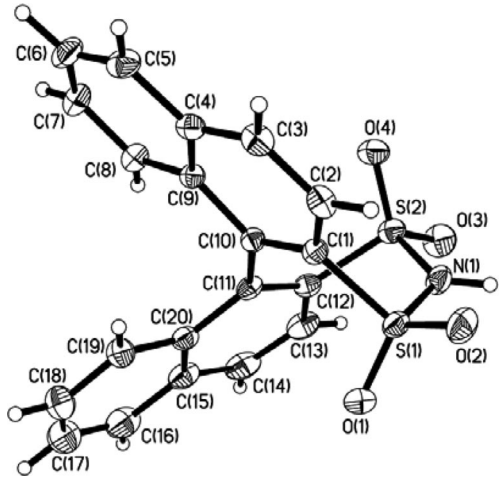


Figure 2. X-ray structures of (*R*)-CSI-**1a**.

diiodo CSI in 61% yield together with 29% of the monoiodo compound. Both dibromo **1e** and diiodo CSI **1f** could serve as the common precursors for a series of 3,3′-diaryl-substituted CSIs through coupling reactions.

Suzuki–Miyaura coupling[12] with the corresponding arylboronic acid resulted in a series of 3,3′-diaryl CSIs (**1b** and **1g**–**n**) in good yields. It is interested to note that, in the case of 1-naphthyl-substituted CSI **1n**, a mixture of inseparable diastereomers was formed (NMR spectroscopy). By examining the molecular model, it is clear that, due to the size of the sulfonyl group, restricted rotation appears between the 1-naphthyl substituent and the binaphthyl backbone.

Conclusions

In summary, we have developed a general approach to the synthesis of binaphthyl-based chiral sulfonimides with aryl substituents at the 3,3′-positions starting from racemic BINOL. *ortho*-Lithiation is directed by the sulfonyl groups, and the resulting dihalides serve as the common precursors for the aryl-substituted CSIs. The application of these CSIs and the corresponding conjugated bases[13] in organocatalysis is under investigation.

CCDC-771830 (for **1a**) and -771831 (for **1d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental details, compound characterization data, copies of the NMR spectra.

Acknowledgments

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