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Sulfinamide Phosphinates as Chiral Catalysts for the Enantioselective Organocatalytic Reduction of Imines

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Supporting Information

ABSTRACT: A new type of chiral sulfinamide phosphinate catalysts with up to three stereogenic centers, readily accessible from commercially available starting materials, is reported. The naphthyl derivative SulPhos proved to be highly efficient in the organocatalytic asymmetric imine reduction, leading to a wide range of arylmethylamines in high yields with up to 99% ee under 10% catalyst loading. The synthetic utility of this method was demonstrated by the expeditious enantioselective synthesis of the calcimimetic NPS-R568.

Chiral nitrogen-containing substrates in general, and chiral methyl aryl amines in particular, are extremely useful synthons in the synthesis of numerous synthetic drugs and natural products with unique properties.[1] Catalytic asymmetric imine reduction is among the most efficient approaches for the synthesis of enantiopure amines.[2] In this sense, one of the most developed metal-free processes toward the enantioselective reduction of ketoimines relies on the use of the inexpensive and readily available trichlorosilane as the reducing agent in the presence of a chiral Lewis base.[3] The most successful catalysts developed so far are those derived from proline,[4] pipecolinic acid,[5] picolinamides,[6] valine,[7] phosphine oxides,[8] and *tert*-butylsulfinamides.[9] Most of these ligands are bidentate in which the coordinating oxygen atoms are distant from the stereogenic center. Very recently, Wang and Sun demonstrated that the use of a mixed SO/CO ligand with a single S-chiral sulfinamide was beneficial for the enantioselectivity outcome.[9d] We conceived that a doubly chiral SO/PO ligand would provide further opportunities for catalyst performance improvement (Figure 1).

In the present work, we report on the design and the synthesis of the first mixed SO/PO bidentate organocatalyst of type **I** (Figure 1) where both stereogenic centers, sulfur and phosphorus, are in adjacent positions to the coordinating oxygens. The two stereogenic heteroatoms are connected by a three-atom spacer,[10] with an additional C-stereogenic atom which could optimize the asymmetric environment in the transition state, with the consequent improvement in chiral induction.[11] Indeed, this ligand design afforded one of the most efficient organocatalysts for the enantioseletive hydrosilylation of ketoimines in terms of both enantioselectivity and catalyst loading.

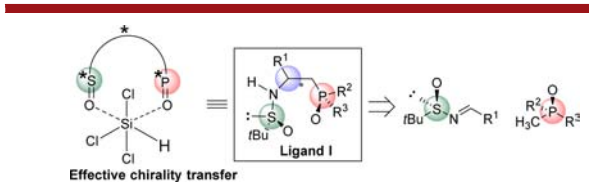
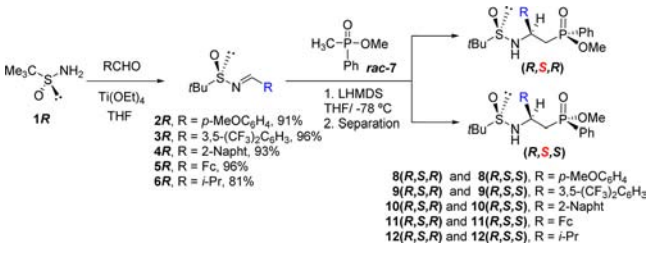


Figure 1. Ligand design and retrosynthetic scheme.

The synthesis of the new SO/PO bidentate ligands is easily achieved by a nucleophilic addition of methylphosphinyl carbanions to the C=N double bond of different sulfinylimines (Figure 1). Starting from commercially available (*R*)-*tert*-butanesulfinamide **1*R***, *N*-*tert*-butylsulfinylaldimines **2*R*−6*R*** were prepared via a standard method[12] (Scheme 1). Addition of *rac*-methyl phenyl metanephosphinate, ***rac*-7**, in the presence of LHMDS led to the corresponding sulfinamide phosphinates **8**−**12** as a mixture of two of the four possible diastereomers,

Scheme 1. Synthesis of Sulfinamide Phosphinates Ligands



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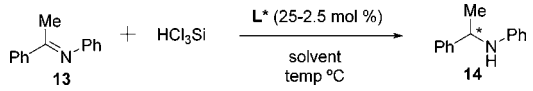
which were purified either by column chromatography or by recrystallization (Scheme 1). In this process, the stereochemistry of the new stereogenic center was controlled by the *tert*-butylsulfinyl group, regardless of the configuration of the phosphinate.[7] Thus, the two diastereomers obtained in these additions are epimers that only differ in the chirality at phosphorus. This straightforward and experimentally simple synthesis allowed the preparation of different sulfinamide-phosphinate derivatives in good yields and in enantiopure form (Scheme 1). These derivatives are small yet complex molecules containing three stereogenic centers, two of which are also Lewis basis.

The prepared catalysts were then assayed in the model reaction of hydrosilylation of the *N*-phenylimine of acetophenone **13** (Table 1) under previously reported conditions: 2 molar equiv of trichlorosilane and 20−25 mol % of the catalyst in dichloromethane at −20 °C.[9a]

Table 1. Hydrosilylation of the *N*-Phenylimine of Acetophenone 13 with Different Ligands



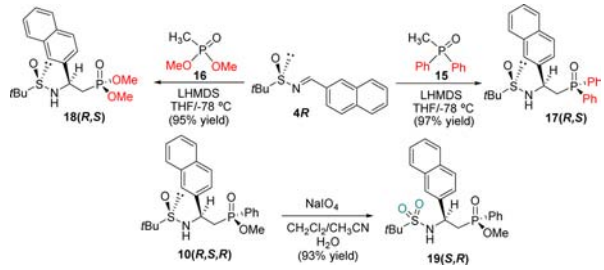
entry	ligand	temp (°C)	solvent	L* (mol %)	yield[a,b] (%)	ee[c] (% *R*)
1	**8**(*R,S,R*)	−20	CH_2Cl_2	25	86	16
2	**9**(*R,S,R*)	−78	Tol[d]	10	81	56
3	**10**(*R,S,R*)	−20	CH_2Cl_2	25	93	56
4		−40	CH_2Cl_2	25	91	72
5	**11**(*R,S,R*)	−20	CH_2Cl_2	25	77	32
6	**12**(*R,S,R*)	−20	CH_2Cl_2	25	89	24
7	**10**(*R,S,R*)	−78	Tol	20	90	98
8		−78	Tol	10	91	98
9		−78	Tol	5	89	96
10		−78	Tol	2.5	92	96

[a]Isolated by column chromatography. [b]All of the reactions were stirred overnight. [c]ee's were determined by chiral stationary phase HPLC. [d]The catalyst was not soluble in dichloromethane (CH_2Cl_2).

As can be seen, chemical yields were from good to excellent; however, the enantioselectivities in CH_2Cl_2 were far from competing with the gold standard catalysts reported in the literature.[9] The highest induction was obtained with the sulfinamide naphthyl phosphinate derivative **10**(*R,S,R*), which we have named SulPhos (Table 1, entry 3). Lowering the temperature to −40 °C led to an increase of the enantioselectivity to 72% ee (Table 1, entry 4). Replacing CH_2Cl_2 by toluene afforded the product **30***R* with an excellent 98% ee (Table 1, entry 7), one of the best enantiomeric excesses reported for this transformation to date. Interestingly enough, SulPhos catalyst **10**(*R,S,R*) maintained its performance at 5 mol % loading or even at 2.5 mol % loading (entries 9 and 10, Table 1), yielding the chiral amine **14***R* with 96% ee. The use of 10 mol % catalyst at −78 °C seems to fulfill the best reactivity−enantioselectivity compromise (entry 8, Table 1) and was used as the optimized reaction conditions in the rest of our study.

To determine the role of each stereogenic center present in the SulPhos organocatalyst, we prepared the analogues **17**−**19** (Scheme 2) and assayed them in the model reaction of hydrosilylation of the *N*-phenylimine of acetophenone **13**.

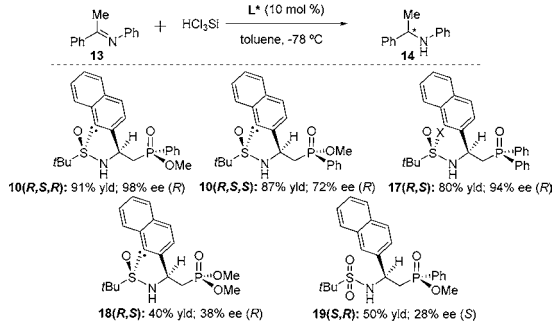
Scheme 2. Synthesis of Organocatalysts 31−33 with Only Two Stereogenic Centers



The phosphine oxide **17**(*R,S*) and the dimethyl phosphinite **19**(*R,S*) were obtained by addition of **15** and **16**, respectively to the sulfinylimine **4***R* (Scheme 2). As in the case of the addition of methyl phosphinate ***rac*-7**, the *R* configuration of the new stereogenic center could be determined by X-ray analysis. The stereocourse of the reaction can be explained by assuming a nonchelated model for the addition of the methyl carbanion to the less hindered face of the CN double bond.[13] On the other hand, sulfonamide **19**(*S,R*) was obtained by oxidation of **10**(*R,S,R*) with $NaIO_4$ (Scheme 2).

The enantioselectivity with the SulPhos ligand, **10**(*R,S,R*), with *R* configuration at phosphorus was clearly better than that obtained with the epimer derivative **10**(*R,S,S*) (Scheme 3). It is

Scheme 3. Hydrosilylation of *N*-Phenylimine of Acetophenone 13 with Different Naphthyl Derivative Ligands



noteworthy that the phosphine oxide **17**(*R,S*) with an achiral phosphorus center led to the desired amine with an excellent enantioselectivity (Scheme 3). However, poor chemical and stereochemical yields were obtained with the methyl phosphinite **18**(*R,S*). Finally, the stereocourse of the reaction was just the opposite with the sulfonamide **19**(*S,R*), where the chirality at the sulfur function was not present but the rest of the stereogenic centers were maintained (Scheme 3). Taken together, these results clearly demonstrate the prevalent role of the *tert*-butylsulfinyl group on the stereochemical outcome of this process.

Given the excellent results obtained with the SulPhos organocatalyst, we decided to evaluate the substrate scope of the reaction using a variety of *N*-aryl aryl methyl ketimines under the optimal reaction conditions (Table 2).

Both electron-deficient and electron-rich aromatic *N*-arylketimines **20**−**29** underwent reduction to yield the desired products **30**−**39** in high yields and with excellent enantioselectivities, generally higher than 97% ee (entries 1−10, Table 2). It is noteworthy that, except for the *ortho*-substituted

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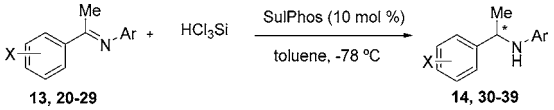
Table 2. Asymmetric Hydrosilylation of Aryl Methyl Ketimines with SulPhos Organocatalyst



entry	imine	amine	yield (%)[a,b]	ee (%*R*)[c]
1			91	97
2			96	99
3			95	99
4			93	>99
5			94	97
6			93	50
7			90	>99
8			92	97
9			97	99
10			97	99
11			97	>99

[a]Isolated by column chromatography. [b]All the reactions were stirred overnight. [c]ee's were determined by chiral stationary phase HPLC.

arylimine **24** (entry 6, Table 2), the presence of a substituent at the *meta* or *para* position on the aromatic ring did not significantly affect the enantioselectivity of the process (90–98% yield and 97 to ≥99% ee; Table 2 entries 1–5 and 7–11). In a tentative explanatory model of the observed stereoselection, we propose a bidentate coordination where both Lewis bases present in the ligand, i.e., the sulfinyl and phosphinyl oxygens, activate trichlorosilane (Figure 2). Two

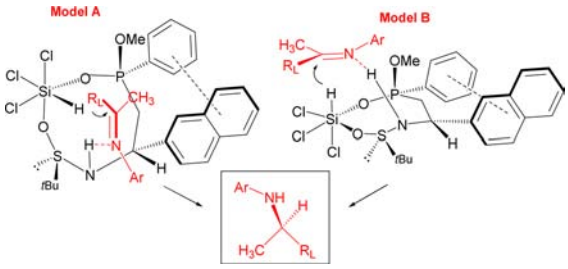
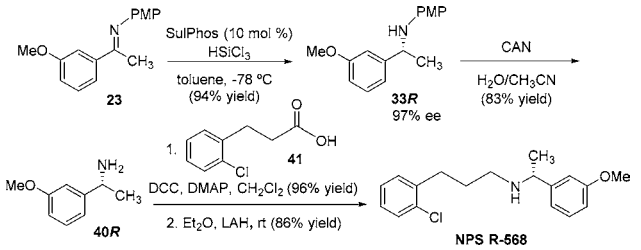


Figure 2. Proposed models for the observed stereoselection.

possible models can be considered as the lowest energy structures leading to the formation of the *R* amine, model A with the coordination in apical and equatorial positions and model B with both coordinated oxygens in equatorial positions. In both models, we have incorporated hydrogen bonding and π-stacking as noncovalent interactions.[14] The hydrogen bond between the sulfinamide and the iminic nitrogen guarantees the proximity of all reactants (Figure 2). The presence of the bulky *tert*-butyl group forces the aryl group of ketimine to be positioned in a distant position.

Finally, to demonstrate the synthetic applicability of the new catalyst, we applied it in a short synthesis of a product of pharmaceutical interest, namely the calcimimetic NPS R-568, an effective drug against both primary and secondary hyperparathyroidism. The reduction of imine **23** (Scheme 4)

Scheme 4. Stereoselective Synthesis of the Calcimimetic NPS R-568



led to the expected chiral amine **33*R*** in 94% yield and 97% ee. Subsequent removal of the PMP protecting group yielded amine **40*R***, which reacted with the carboxylic acid **41** to give the corresponding amide that was reduced with LAH to yield the target drug[15] in only four steps with 64% overall yield. It is noteworthy that our approach compares favorably with the best approaches developed for the synthesis of this compound.

In summary, we have developed the highly effective organocatalyst SulPhos, which promotes the enantioselective reduction of a broad range of *N*-aryl aryl methyl ketimines with trichlorosilane in high chemical yields and enantioselectivities. This new chiral bidentate organocatalyst can be easily prepared and, to our knowledge, provides the highest enantioselectivity hitherto described in the literature for this asymmetric reduction with only a 10 mol % ligand loading. The synthetic utility of this method was demonstrated by the expeditious enantioselective synthesis of the calcimimetic NPS-R568.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01509.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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