Silver-Catalyzed Enantioselective Sulfimidation Mediated by Hydrogen Bonding Interactions

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Abstract: An enantioselective sulfimidation of 3-thiosubstituted 2-quinolones and 2-pyridones was achieved with a stoichiometric nitrene source (PhI=N=N) and a silver-based catalyst system. Key to the success of the reaction is the use of a chiral phenanthroline ligand with a hydrogen bonding site. The enantioselectivity does not depend on the size of the two substituents at the sulfur atom but only on the binding properties of the heterocyclic lactams. A total of 21 chiral sulfimides were obtained in high yields (44–99%) and with significant enantiomeric excess (70–99% ee). The sulfimidation proceeds with high site-selectivity and can also be employed for the kinetic resolution of chiral sulfoxides. Mechanistic evidence suggests the intermediacy of a heteroleptic silver complex, in which the silver atom is bound to one molecule of the chiral ligand and one molecule of an achiral 1,10-phenanthroline. Support for the suggested reaction course was obtained by ESI mass spectrometry, DFT calculations, and a Hammett analysis.

Introduction

Sulfur compounds with two carbon–sulfur single bonds and an additional ylide-type sulfur double bond to a nitrogen substituent are called sulfimides. Alternatively, the compound class has been referred to as sulfilimines or iminosulfuranes. Their chemistry has attracted significant attention and has been studied for decades.[1] A key structural feature of sulfimides is the fact that they display a significant barrier to pyramidal inversion at the sulfur atom. As a consequence, sulfimides exist at ambient temperature as pairs of separable enantiomers, provided that the two carbon substituents are different. The stereospecific oxidation of sulfimides to sulfoximines is feasible and enables access to another class of chiral sulfur compounds with intriguing properties.[2]

Scheme 1. Top: Products I and II of previously reported enantioselective sulfimidation reactions obtained by metal catalysis (catalytically active metal and ee given). Bottom: Attempted enantioselective sulfimidation of substrates III to sulfimides IV with N-sulfonylated phenyliminoiodinanes and a chiral silver catalyst.
In the present study we have approached the topic of enantioselective sulffimidation by using a yet unexplored catalytically active metal (silver). Even more importantly, we combined the metal with a ligand that pre-coordinates to lactam substrates III by hydrogen bonding and thus displays one of the two enantiotopic lone pairs to the reactive nitrogen center. As a result, products of type IV have become readily available in high optical purity. The scope and the mechanism of the reaction have been studied and the results of our experiments are presented in this research article.

Results and Discussion

Ligand synthesis and preliminary studies. The development of chiral ligands with a lactam hydrogen bonding site continues to be a research focus of our group.[9] The goal is to achieve not only an improved site-selectivity in a given transition-metal catalyzed reaction[10] but also to induce a significant enantioselectivity. In a recent contribution,[11] we prepared chiral phenanthroline ligands 1 which are based on the readily available octahydro-1H-4,7-methanoisoindol-1-one skeleton.[12] Their synthesis can be achieved by Sonogashira cross-coupling of known alkyne 2[13] with the respective bromo-substituted phenanthroline (Scheme 2). Ligand 1a was successfully employed in an enantioselective Ag-catalyzed amination of C–H bonds which was assumed to occur by an enantioselective nitrene insertion[14] at the hydrogen-bonded substrate. Although silver catalysis has shown to be a viable approach for the amination[15,16] and aziridination[17,18] of organic substrates it has not been extensively applied to sulfides. Bolm and co-workers found that silver nitrate acts in combination with an achiral terpyridine ligand as a catalyst to mediate the imidation of sulfoxides to generate sulfoximines.[18,19] Two sulfimides were obtained in high yields (77% and 83%) albeit in racemic form.

Our initial experiments aimed to identify the ligand best suited for a defined prochiral sulfide. Although pre-coordination by a given lactam to any of the three ligands 1 can be assumed, the trajectory of the nitrene transfer was expected to be different resulting in varying reactivity and enantioselectivity. We employed Ag(PF₆)₃ as the source of the catalytically active metal center (10 mol %) and added 1,10-phenanthroline (10 mol %) as an achiral ligand. The chiral ligand was used in 12 mol % and N-(p-nitrophenylsulfonyl)iminophenylidionane (PhI=NNs) was employed as the nitrene precursor and dichloromethane as the solvent. The first set of reactions (Scheme 3) was performed with 3-phenylthio-2-quino lone (3a). While all ligands 1 facilitated a complete conversion within 16 hours and yields varied only marginally (92–98%), the enantioselectivity in the formation of sulfimide 4a was most pronounced with catalysts 1a (97% ee) and 1c (96% ee). Although we had anticipated the reaction to be enantioselective, the high selectivity achieved in the reaction came as a very pleasant surprise. In the amination reactions,[11] enantioselectivities exceeding 90% ee could only be achieved with cyclic substrates in which free rotations were completely restricted.

With 3-phenylthio-2-pyridone (5a) a reactivity difference was notable for the three ligands and the yields of the respective sulfimide 6a were only moderate when ligands 1b and 1c were used. The by far best result was recorded for ligand 1a. Not only did the ligand provide the highest yield (70%), but it also facilitated the formation of product 6a with the highest enantioselectivity (92% ee). Also, for the 2-pyridones the degree of selectivity was remarkable given the flexibility of the substrate (see the Supporting Information for further details and other substrates).

Before applying the imidation by a nosyl-protected nitro- gen to a larger array of substrates two other iminophenylidionanes were probed as reagents for a possible nitrene transfer. The related para-tolueneusulfonyl (tosyl, Ts) reagent gave product 7 in a much lower enantioselectivity of only...
The electronically different trichlorothioxysulfonyl (Tces)-substituted reagent, however, displayed a similar degree of reactivity and selectivity as the nosyl-based reagent. Product 8 was obtained in 94% yield and with 90% ee. The latter result bears some synthetic relevance since removal of the Tces group can be performed under conditions that are orthogonal to those employed for the Nos group.[20]

Scope and site-selectivity. The imidation of 3-thiosubstituted 2-quinolone 3a suggested that various sulfides with a similar structure could be converted into the respective sulfimides irrespective of the nature of the thio substituent. Accordingly, 2-quinolones 3 were prepared and subjected to a nitrone transfer reaction, both racemic[21] and enantioselective. Several aryl groups were introduced as group R in substrates 3 and the reaction turned out to be robust towards the electronic (products 4b–4f) and the steric situation (products 4g–4i). If the opposite enantiomer ent-1a of ligand 1a was employed in the reactions, the ee remained identical but the opposite sulfimide enantiomer was produced. The reactions of 3a in the presence of ent-1a for example delivered ent-4a on a scale of 0.4 mmol. For reasons of availability the absolute configuration of the sulfimides was representatively determined for dextrorotatory product ent-4a. Comparison of experimental and calculated vibrational circular dichroism (VCD) spectra allowed the assignment with high fidelity (see the SI for details).[22,23] The (R)-configuration was assigned to compound ent-4a, its enantiomer 4a is (S)-configured. The assignment of the configuration for all other products which were obtained with 1a and which were consistently levorotatory was based on analogy.

As mentioned in the introduction, the most remarkable feature of the present Ag-catalyzed sulfimidation is the fact that it is applicable to diaryl sulfides irrespective of the relative size of the two substituents. As seen for the aryl-substituted products 4a–4i the results fully met the expectations (Scheme 5). Interestingly, also a methyl group could be used as group R and 3-methylthio-2-quinolone (3j) gave sulfimide 4j in 98% yield and 96% ee. However, if the size of the alkyl group increases, the enantioselectivity drops. With R = isopropyl (substrate 3k) and R = cyclohexyl (substrate 3l) the enantioselectivity remained moderate (70–73% ee).

In a second set of experiments, the scope of the sulfimidation was explored with 3-thiosubstituted 2-pyridones 5 (Scheme 6). The conditions remained unchanged as compared to 3 and a clean transfer of the nitrogen fragment from PhI=NNs to the sulfides was observed. If there was no additional substituent X in the pyridones, the enantioselectivities were in all cases higher than 83% ee (products 6a–6g). There is a weak correlation between the selectivity and the reactivity. The most reactive substrate 5e (vide supra) delivered most side products and the lowest ee. The high ee for ortho-tolyl-substituted product 6g was unexpected given that this substituent had led in the quinolone case (product 4h) to a decreased enantioselectivity. For substrate 5h (X = methyl), the enantioselectivity of the sulfimidation was high but the yield suffered, for substrate 5i (X = trifluoromethyl) the opposite scenario—high yield, diminished ee—applied.

The observed enantiotopos differentiation in the Ag-catalyzed sulfimidation were in agreement with the previous hypothesis that the heteroleptic complex 9 was the catalytically competent species (Figure 1).[11] Upon transfer of the protected nitrogen fragment from iminophenyldiiodane to the metal center, pre-coordination of a given substrate, for example, 3a, would allow in the reactive complex 10 only to display the pro-S electron pair towards the reactive nitrone
Sulfimides

This issue was addressed with formed from the silver electron pair at the sulfur atom of substrate observed. n = 15 and 3m 10 (Figure 1) should = . Despite the fact was formed as the racemate (of the iminophenyliodinane the enantioselec- 9 m or the (Scheme 7). The s ulfimidation led to a product which was completely racemic (product rac-12).

An interesting consequence of the hydrogen bond-mediated sulfimidation relates to the fact that the reaction should not only proceed with high enantioselectivity but also with exquisite site-selectivity.\textsuperscript{[24]} This issue was addressed with substrate 3m that contains two potentially reactive sulfur center. The reaction would consequently lead to the (S)-configured sulfimides as observed.

The constraints for a nitrene transfer as postulated in complex 10 stimulated further experiments which aimed to verify and to exploit the pre-coordination by hydrogen bonds. A straightforward experiment along these lines involves the reaction of an N-alkylated substrate that is not competent to form two hydrogen bonds to complex 9. The experiment was performed with 2-quinolone 11, the N-methylated derivative of substrate 3a (Scheme 7). The sulfimidation led to a product which was completely racemic (product rac-12).

An interesting consequence of the hydrogen bond-mediated sulfimidation relates to the fact that the reaction should not only proceed with high enantioselectivity but also with exquisite site-selectivity.\textsuperscript{[24]} This issue was addressed with substrate 3m that contains two potentially reactive sulfur atoms (Scheme 8). All reactions with this substrate were performed with a stoichiometric amount of the imidation reagent to avoid a two-fold imidation. Achiral conditions which allowed for a relatively clean reaction included use of 20 mol% Ag(PF\textsubscript{6})\textsubscript{−} and 60 mol% of 1,10-phenanthroline. After 24 h the conversion was 60% and sulfimidation had occurred with notable selectivity at the methylthio group in the periphery of the molecule. The site-selectivity was determined as r.r. (regioisomeric ratio) = rac-13/rac-4m = 84/16 by \textsuperscript{1}H NMR spectroscopic analysis of the crude product. The enantiomeric resolution was performed with ligand 1a and the standard catalyst loading was strikingly different. Product 13 could not be detected, and the reaction exclusively occurred at the internal sulfur atom that is located at position C3 of the quinolone. The only product was sulfimide 4m which was isolated in 53% yield (58% conversion) with 97% ee.

The fact that a bound substrate can only display a distinct lone pair to the catalytically active center (cf. Figure 1) should result for any substrate with a single reactive center in a kinetic resolution. Sulfoxides are like sulfimides chiral and carry a lone pair at the sulfur atom. If subjected to the conditions of the enantioselective sulfimidation, one sulfoxide enantiomer should be preferentially processed as its stereogenic sulfur atom is properly configured to match the chirality of the active site within the catalytically active silver complex. We probed this hypothesis with sulfoxide rac-14 which was treated with the imidation reagent and the optimized catalyst mixture (Scheme 9). The resulting sulfoximine 15 was obtained in enantiomerically enriched form while the recovered sulfoxide also showed some optical purity. Depending on the equivalents n of the iminophenyldiodane the enantioselectivity could be optimized for the sulfoximine or the sulfoxide. Although we did not prove the absolute configuration in this case, it is highly likely that the (R)-enantiomer of sulfoxide 14 is preferentially processed leaving the (S)-enantiomer behind. Sulfoximine 15 should thus be (R)-configured as shown.

Mechanistic experiments and discussion. Despite the fact that the synthetic experiments delivered circumstantial evidence (see the SI for further details) for the postulated mechanism of the enantioselective sulfimidation we attempted to obtain further data to substantiate the proposed reaction pathway. A hint for the formation of the postulated heteroleptic complex 9 was obtained by high resolution electrospray ion mass spectrometric (ESI-MS) analysis.
Under conditions that mimicked the composition of the catalytically active mixture, a sample was subjected to ESI-MS in the positive detection mode (detection of cationic species). It was clearly evident from the exact mass analysis (Figure 2) that the most intense peak at \( m/z = 640.1254 \) (\( m/z \) calcd = 640.1261) corresponds to the heteroleptic complex 9 with the formula C\(_{35}\)H\(_{27}\)AgN\(_5\)O\(^+\) formed from one equivalent AgPF\(_6\), 1,10-phenanthroline and ligand 1a (see the SI for further details). Likewise, the other two signals at \( m/z = 467.0411 \) (\( m/z \) calcd = 467.0420) and \( m/z = 813.2081 \) (\( m/z \) calcd = 813.2102) could be matched with the formula C\(_{24}\)H\(_{16}\)AgN\(_4\)+ and C\(_{46}\)H\(_{38}\)AgN\(_6\)O\(_2\)+. The former mass correlates to the homoleptic silver complex 16 with two 1,10-phenanthroline ligands while the latter mass can be assigned to the homoleptic complex 17 of silver and two chiral phenanthroline ligands 1a.

Diffusion Ordered Spectroscopy (DOSY) experiments\[25\] were performed with AgPF\(_6\), and 1,10-phenanthroline in CD\(_2\)Cl\(_2\) solution and corroborated the existence of homoleptic complex 16. Likewise, the homoleptic complex 17 could be identified when studying AgPF\(_6\) and ligand 1a. Experiments with AgPF\(_6\), phen, and ligand 1a, remained somewhat inconclusive, however. \(^1\)H-NMR chemical shift data suggest its formation but the increase in the apparent volume as measured by the DOSY experiment was lower than expected (see the SI for further details).

In order to evaluate a possible transition state that would be accessible for heteroleptic complex 9 and substrate 3a upon conversion of 9 to a nitrene complex, we turned to DFT calculations (M06L\[26\]-D3\[27\] def2-TZVP(D)\[28\] for further details see SI). Assuming triplet multiplicity, two transition states leading to product 4a and its enantiomer (ent-4a) were identified. The former is approx. 26 kJ mol\(^{-1}\) more favorable in Gibbs free energy, in agreement with the experimental findings. The associated barrier of activation is 83 kJ mol\(^{-1}\), which is also in line with a reaction at room temperature.

The more favorable transition state is shown in Figure 3. It features N···S and Ag···N distances of 1.91 and 2.23 Å, respectively, and the substrate is also clearly bound via a two-point hydrogen bonding motif (with O···H distances of 1.86 and 1.90 Å). Each phenanthroline ligand is coordinated to the Ag center via a shorter bond (2.22 and 2.25 Å) and a somewhat longer bond (2.34 and 2.55 Å). The C3-S single bond adapts an s-trans orientation.
that is, the phenyl group points away from the site of hydrogen bonding (cf. structure 10 in Figure 1). In addition, the sulfur center to be sulfimidated carries a noticeable positive charge of +0.98 according to an NBO analysis. The less favorable transition state (leading to *ent*-4a) shares several structural similarities with the more favorable one, for example, with respect to the hydrogen bonding motif and the orientation of the phenanthroline ligands (see the SI for further information). However, the C3-S single bond is *s-cis* oriented and the phenyl group points towards the binding site. The transition state is overall somewhat later on the reaction coordinate, with a shorter N···S (1.89 Å) and a longer Ag···N (2.27 Å) distance. Apart from this, the two most striking differences are the already mentioned CO-C3-S-C6 interacts with the already mentioned CO-C3-S-C6, cisdihedral angle (−44° vs. −148°) and a narrower Ag-N-S angle (105° vs. 121°).

The DFT calculation suggests that the sulfur atom carries a partial positive charge in the transition state. A Hammett analysis of the sulfimidation reaction was performed in order to interrogate the stereoelectronic situation at the sulfur atom and to potentially confirm the predicted positive charge increase (Figure 4). To this end, the six *para*-substituted 3-(phenylthio)quinolones 3b–3f were studied and the relative rates of the sulfimidation were determined in comparison with the parent compound 3a. Depending on the substituent X we see a rate increase for electron donating substituent and a rate decrease for electron withdrawing groups. The decadic logarithm of the relative rates log(κo/κH) reveals a good relation with the tabulated ρ values[33] of the substituents X. The slope of the linear function was determined as ρ = −0.52 (see the SI for more details) in agreement with a positive charge to be developed at the reactive center.[32,33]

![Figure 4: Hammett analysis performed for substrates 3a–3f. Conditions: Competing reactions were performed under typical catalytic conditions with 1 equiv of the respective *para*-substituted 3-(phenylthio)quinolone 3 and 1 equiv of 3a at ambient temperature (2 equiv PhI=NNs). The reaction was stopped after two hours (<25% conversion) and the relative ratio of the products 4 was determined by 1H NMR spectroscopy.](image)

**Conclusion**

In summary, our study has revealed that the directing power of hydrogen bonding ligands is not only operative in defined metal complexes but also in an equilibrium scenario with reversible coordination of chiral and achiral ligands at a cationic metal center. The observed site- and enantioselectivity makes several heterocyclic sulfimides available which would be difficult to access in enantioselective form by known methods of asymmetric catalysis. The suggested reaction mechanism of the nitrene transfer which had been previously proposed to occur via a nitrene-silver complex with distorted trigonal bipyramidal coordination[11] has been further corroborated and offers a useful model for the design of related phenanthroline ligands with which more remote positions of a given substrate can be aminated.

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**Conflict of interest**

The authors declare no conflict of interest.

**Stichwörter:** asymmetric catalysis · enantioselectivity · hydrogen bonds · ligand design · silver

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