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Improved and Efficient Synthesis of Chiral N,P-Ligands via Cyclic Sulfamidates for Asymmetric Addition of Butyllithium to Benzaldehyde

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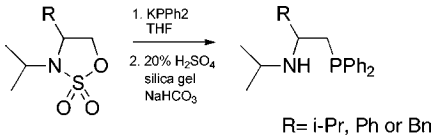
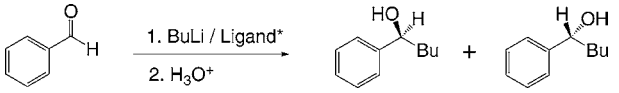
ABSTRACT



A robust and scaleable route to chiral 1-isopropylamino-2-(diphenylphosphino)ethanes is described via the ring-opening of chiral, cyclic sulfamidates with potassium diphenylphosphide ($KPPh_2$). The novel protocol offers a robust access to gram quantities of chiral amino phosphinoethanes in high yields. The Li-amides of the chiral aminophosphines were evaluated as chiral ligands in the asymmetric addition of *n*-butyllithium (BuLi) to benzaldehyde, yielding 1-phenylpentanol up to 98% ee.

The 1,2-addition of organolithium compounds to aldehydes or ketones is one of the most straightforward ways for carbon−carbon bond formation, and the development of asymmetric versions of the reaction is of fundamental interest.[1] Ever since the first reports nearly 40 years ago,[2] chiral complexing agents have been used to control the enantiofacial selectivity of the addition reaction (Scheme 1).

Scheme 1. Chiral Ligand-Mediated Asymmetric Butylation of Benzaldehyde



The chiral complexing agents that have been evaluated in the asymmetric addition of, e.g., *n*-butyllithium (BuLi) to benzaldehyde, have historically been based on "hard" chelates such as sp^3 nitrogen and/or oxygen donor groups.[3] Some representative examples are depicted in Figure 1. However, recent studies from our laboratory have shown that the presence of a soft chelate may sometimes lead to greatly improved enantioselectivities. A series of chiral lithium amides bearing a chelating thioether (Scheme 1) were found to give exceptionally high levels of enantioselectivity (typically

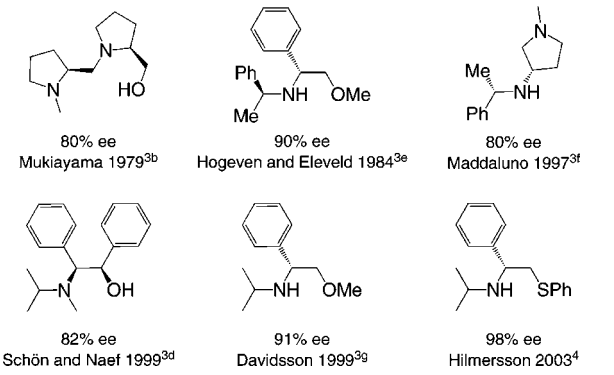


Figure 1. Examples of chiral ligands used to induce asymmetry in the addition of BuLi to benzaldehyde.

(1) *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Springer: Heidelberg, 2003; Vol. 5.

(2) (a) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *38*, 4097−4098. (b) Seebach, D.; Dörr, H.; Bastani, B.; Ehrig, V. *Angew. Chem.* **1969**, *81*, 1002−1003.

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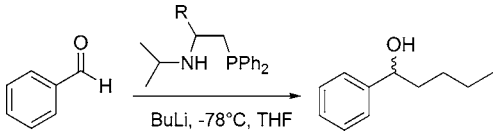
around 95% ee) in the 1,2-addition of organolithiums to aldehydes.[4]

Intrigued by these observations, which are still far from well understood, we wanted to further explore the influence of sulfur and other soft donor groups, e.g., phosphines. Furthermore, for our ongoing program of using ^{6}Li NMR to study the structure and reactivity of chiral lithium amides, the investigation of P−Li interactions could add new and valuable insights to the nature of the reaction and potentially to the concept of hard and soft Lewis basicity.

Herein, we present our initial studies, including a novel, scaleable route to chiral 1-isopropylamino-2-(diphenylphosphino)ethanes (N,P ligands) and their application in the asymmetric addition of BuLi to benzaldehyde (Scheme 2).

Scheme 2. Asymmetric Addition of BuLi to Benzaldehyde in the Presence of Chiral Aminophosphinoethanes



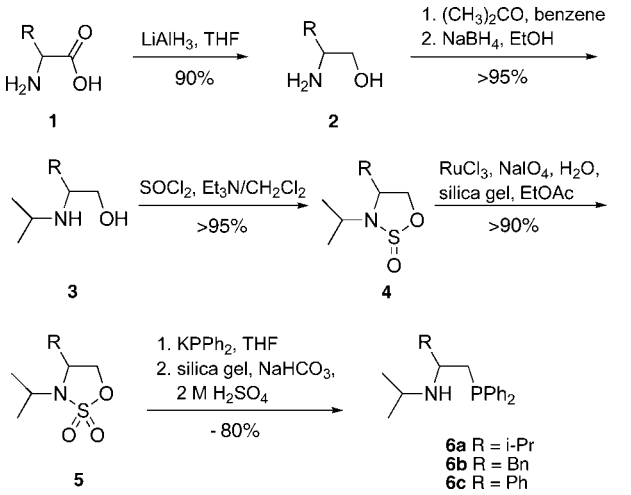
The preparation of chiral *N*-monoalkyl-1,2-aminophosphinoethanes from α-amino acid precursors is less than trivial. To the best of our knowledge, the very few examples have all been prepared via the reductive *N*-alkylation of the primary NH_2-aminophosphinoethane precursor[5,6] and thus involve multiple synthetic steps and purification of potentially oxygen-sensitive phosphine intermediates. Moreover, the introduction of the phosphorus should be considered a challenge in its own right, which has been accomplished by adding, under strict temperature control at −35 °C, the free diphenylphosphide ion[7] or its BH_3 complex,[6] to a suitably *N*-protected and *O*-activated aminoalcohol derivative. Many classes of N,P-ligands have been synthesized in this way,[7] but there are also several reports on problems with formation of byproducts and difficulties in purification, even after rigorous attempts to control and optimize the reaction conditions.[6,7b]

Due to the sensitive nature of the phosphination, we considered an alternative synthesis via the nucleophilic ring opening of chiral cyclic sulfamidates.

Cyclic sulfamidates are versatile electrophilic intermediates that may undergo S_N2-type ring-opening in the presence of suitable nucleophiles.[8] Compared to the existing preparations of *N*-monoalkyl-1-amino-2-phosphinoethanes, an approach via cyclic sulfamidates would offer a number of advantages, e.g.: (i) Introduction of the phosphorus in the last sequence minimizes the handling of oxidation-sensitive material. (ii) The overall number of steps are reduced because the sulfamidate acts simultaneously as *N*-protection and *O*-activation. (iii) The possibility for aziridine formation in the phosphination step is therefore effectively eliminated because the nitrogen is locked by the N−S−O bridge in the sulfamidate.[9] Furthermore, because the ring opening of cyclic sulfamidates has been reported to be compatible with a variety of substituents at nitrogen,[8] the method may prove to be general and flexible.

Three amino alcohol precursors were chosen for our investigation, namely (*S*)-phenylalaninol, (*R*)-phenylglycinol, and (*S*)-valinol, each of which were reductively alkylated[10] using acetone and $NaBH_4$ (Scheme 3). Treatment of the

Scheme 3. Our Route to the Chiral N,P Ligands



N-isopropylamino alcohols with thionyl chloride afforded the cyclic sulfamidites in high yields. The literature protocols for the oxidation into sulfamidate, using catalytic $RuCl_3$ with $NaIO_4$ as reoxidant in biphasic (H_2O/EtOAc) media,[11] gave good results on small scale, but the yields dropped considerably on gram scales, presumably due to insufficient magnetic stirring. Inspired by studies using wet silica as a means of improving aqueous/organic mass transfer, we attempted to replace the free aqueous phase by silica gel which had been coated with an aqueous mixture of the RuO_4/$NaIO_4$ oxidant based on the method developed by Ali and co-workers.[12]

To our delight, these reactions proceeded cleanly in the presence of wet silica gel and could be reproducibly scaled

(3) (a) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455−1460. (b) Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K. A.; Bollinger, A. M.; Grosz, A. L.; Mani, V. *Tetrahedron* **1994**, *50*, 6109−6116. (c) Schön, M.; Naef, R. *Tetrahedron: Asymmetry* **1999**, *10*, 169−176. (d) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187−5190. (e) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266−8275. (f) Arvidsson, P. I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527−534.

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(6) Anderson, C.; Cubbon, R. J.; Harling, J. D. *Tetrahedron: Asymmetry* **2001**, *12*, 923.

(7) (a) Saitoh, A.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3567−3570. (b) Saitoh, A.; Uda, T.; Morimoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4501J. (b) Quirmbach, M.; Holz, J.; Tararov, V. I.; Börner, A. *Tetrahedron* **2000**, *56*, 775.

(8) (a) Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, 766. (b) Melendez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581.

(9) Aziridine formation has been observed the treatment of chiral 1-*N*-Boc-2-*O*-tosylates with $KPPh_2$. See, e.g., ref 6.

(10) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2003**, *59*, 4717.

(11) Alker, D.; Doyle, K. J.; Harwood, L. M.; McGregor, A. *Tetrahedron*: *Asymmetry* **1990**, *1*, 877.

up to above 10 mmol. After the reaction, the oxidant/catalyst/silica mixture is simply removed by filtration through a short pad of water-free silica. Furthermore, the reactions were found to perform equally well when run using the unpurified mixtures of sulfamidites as produced in the previous step.

For the phosphination step, the cyclic sulfamidates **5** were treated with $KPPh_2$ at −78 °C, which led to a rapid consumption of the starting material indicated by TLC. For the acidic hydrolysis of the initial sulfamate product, we first employed literature procedures,[8] typically involving evaporation of the THF followed by prolonged stirring with a solvent biphasic mixture of, e.g., CH_2Cl_2 and aqueous HCl or H_2SO_4. These methods, however, gave large amounts of undesired phosphine oxide byproduct, as indicated by TLC. In our efforts to accelerate the sulfamate hydrolysis and minimize the exposure to oxygen and water, we found that the hydrolysis was much cleaner and faster in the presence of wet, acidic silica (0.4 mL of 2.0 M H_2SO_4 per gram of SiO_2). Using the acidic silica method, the sulfamate intermediate could be hydrolyzed in situ at room temperature, to yield the desired N,P-ligands in high yields after neutralization, filtration and column chromatography. The purified products showed no detectable oxidation at P (^{31}P NMR), and the reactions could be scaled up to 15 mmol without loss in yield or purity. In our hands, the novel protocol offers a rapid, robust, operationally simple, and potentially general route to *N*-monoalkylaminophosphines from commercially available amino alcohols.

Next, our N,P ligands were evaluated in the asymmetric addition of BuLi to benzaldehyde at −116 °C and were found to give clean and high-yielding reactions, with ee's higher or comparable with those reported with the corresponding ether ligand (**8c**) and thioether ligands (**7a**, **7b**, and **7c**, Figure 2 and Table 1, respectively).[13] Clearly, the use of soft chelates

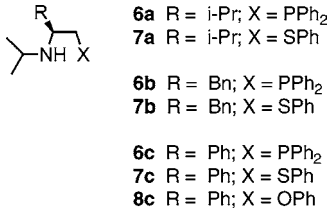

Figure 2. Chiral amines used in the asymmtric alkylation reactions, Table 1.

is compatible with the asymmetric 1,2-addition of organolithiums to carbonyls and offers a highly interesting entry for further synthetic and mechanistic studies.

In conlusion, we have developed a new method for the efficient synthesis of chiral N,P ligands. The key to the success of the phosphination is the use of the cyclic sulfamidate, avoiding aziridine formation, as well as a rapid, clean, and in situ hydrolysis of the sulfamic acid intermediate in the presence of wet acidic silica gel. The Ru-catalyzed oxidation of cyclic sulfamidites **4** into sulfamidates **5** was also carried out in the presence of wet silica gel instead of

Table 1. **Li−6−8** Mediated Asymmetric 1,2-Addition of BuLi to PhCHO[a]

entry	chiral amine	X =	R =	conversion (%)	enantiomeric excess (%)
1	**6a**	PPh_2	*i*-Pr	82	93
2	**7a**	SPh	*i*-Pr	87	68
3	**6b**	PPh_2	Bn	93	82
4	**7b**	SPh	Bn	87	68
5	**6c**	PPh_2	Ph	71	98
6	**7b**	SPh	Ph	82	98
7	**8c**	OPh	Ph	96	96

[a] BuLi (0.30 mmol), PhCHO (0.05 mmol), **Li−6−8** (0.20 mmol), THF/Et_2O (1:1), −116 °C.

a solvent biphasic media, which leads to greatly improved scaleability and reproducibility of the process. In the asymmetric addition of BuLi to benzaldehyde, the N,P analogues gave significantly higher ee's than the corresponding N,S analogues for the chiral ligands **6** and **7**, derived from the natural (*S*)-valine and (*S*)-phenylalanine, respectively. In analogy with previous observations for the highly selective phenylglycine derivatives **7c** and **8c**, the corresponding N,P analogue **6c** (98% ee) was indeed found to give the highest enantioselectivity within the N,P series of ligands as well. These observations indicate that phosphines and soft donor groups may be beneficial in organolithium and Li-amide chemistry, which has traditionally focused on the use of hard chelating groups. We are currently studying the synthetic potential of these and other aminophosphines, as well as investigating the solution structure and dynamics of these N,P lithium amides by NMR. In parallel, we are pursuing the cyclic sulfamidate chemistry with other than P-nucleophiles, as a common and improved synthetic entry to a wide range of novel chelates and the fine-tuning of steric and electronic properties in each of the N,O-, N,S-, and N,P-families of ligands.

Acknowledgment. Financial support from the Swedish research council is gratefully acknowledged. We thank Dr. A. Dahlén and AstraZeneca for R&D for HRMS analysis. Prof P.-O. Norrby is gratefully acknowledged for iluminating discussions, particularly on the use of cyclic sulfamidates. We also thank Prof. Mohammed H. Ali (Southeast Missouri State University) for generously sharing his findings and basic procedure for the silica-supported Ru/periodate oxidation.

Supporting Information Available: Experimental procedures and analytical data for compounds **4−6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Ali, M. H.; Stricklin, S. *Synth. Commun.* **2006**, *36*, 1779. (b) Ali, Mohammed H.; Wencewicz, Timothy A. *Catalytic Oxidation of Sulfides to Sulfones with Silica Gel Supported $RuCl_3$/$NaIO_4$ in Non-Aqueous Media*, poster presented at the 57th Southeast/61st Southwest Joint Regional Meeting of the American Chemical Society, Memphis, TN, 2005.

(13) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021.