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Sulfinimine-Mediated Asymmetric Synthesis of 1,3-Disubstituted Tetrahydroisoquinolines: A Stereoselective Synthesis of *cis*- and *trans*-6,8-Dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline

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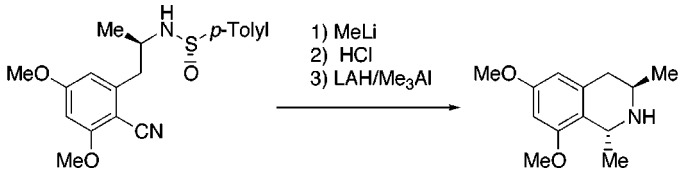
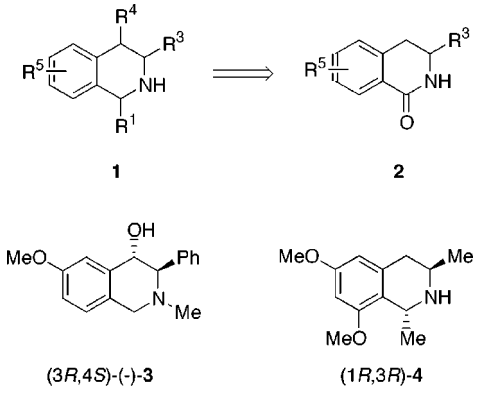
ABSTRACT



The highly diastereoselective addition of lateral lithiated *o*-tolunitriles to sulfinimines followed by treatment of the resulting sulfinamide with MeLi, hydrolysis, and reduction represents a concise new methodology for the asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines.

We recently introduced methodology for the asymmetric synthesis of 3-substituted 1(2*H*)-isoquinolones **2** and suggested that they may be useful chiral building blocks for the construction of tetrahydroisoquinolines **1** (Scheme 1). In this context, a highly stereoselective asymmetric synthesis of (3*R*,4*S*)-(−)-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**3**) was reported.[1] Isoquinolones **2** were prepared by condensing lateral lithiated amides[2] with enantiopure sulfinimines (*N*-sulfinyl imines).[3] This methodology avoids many of the limitations of the Bischler−Napieralski and Pictet−Spengler protocols as well as providing isoquinolines with substitution patterns not readily accessible by other means.

Scheme 1



To extend the utility of **2**, it is necessary to devise procedures for the stereoselective replacement of the 1-oxo group with other substituents (R^1). Described here are studies aimed at the asymmetric synthesis of 6,8-dimethoxy-1,3-

(1) Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627.
(2) For a reviews on lateral lithiation reactions, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 5.
(3) For reviews on the chemistry of sulfinimines, see: (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (b) Hua, D. H.; Chen, Y.; Millward, G. S. *Sulfur Rep.* **1999**, *21*, 211. (c) Zhou, P.; Chen, B.-C.; Davis, F. A. Syntheses and Reactions of Sulfinimines. In *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAL Press: 2000; Vol 2, pp 249−282.

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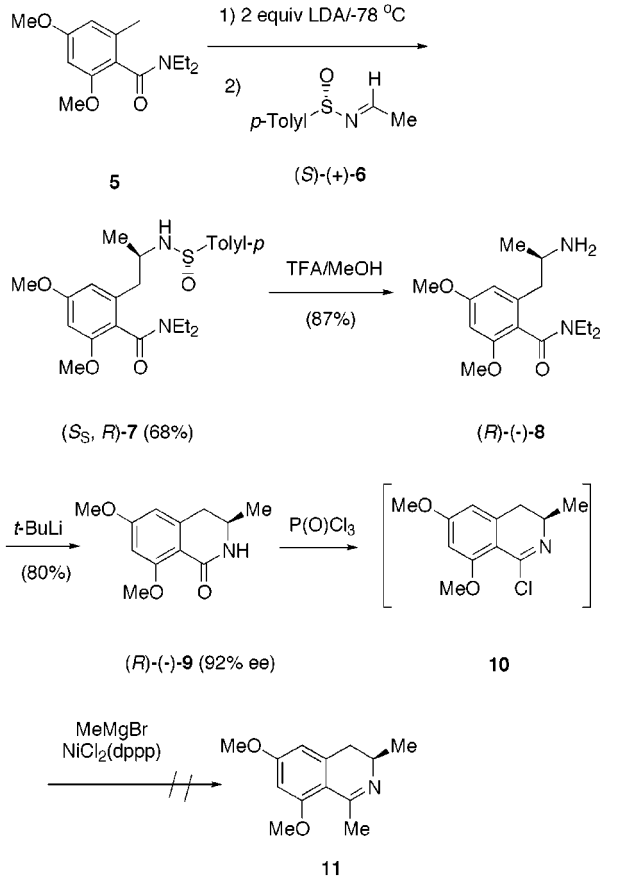
dimethyl-1,2,3,4-tetrahydroisoquinoline (**4**),[4] the isoquinoline segment of the anti-HIV michellamines.[5] These studies revealed for the enantioselective synthesis of 1,3-disubstituted isoquinolines that the addition of lateral lithiated *o*-tolunitriles to sulfinimines is superior to the use of lateral lithiated amides.

Our first attempt at the construction of **4** is outlined in Scheme 2 and involves generating the lateral lithiated amide

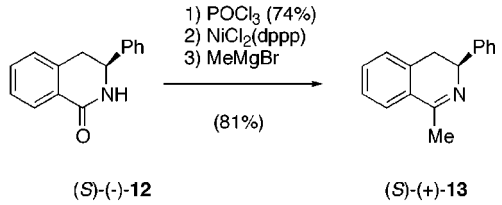
Scheme 2



of *N*,*N*-diethyl-2,4-dimethoxy-6-methylbenzamide (**5**)[6,7] by treatment with 2.0 equiv of LDA followed by addition of (*S*)-(+)-(acetylidene)-*p*-toluenesulfinamide (**6**).[8] The sulfinamide **7** was isolated in 68% yield by flash chromatography and is assumed to have the (*R*)-configuration at the new stereogenic center based on an empirical model developed in our synthesis of **3** (see also below).[1] The ^{1}H NMR spectra of **7** was complex because diastereomeric atropisomers were formed due to restricted rotation about the amide C−N and C−aryl bonds. Heating the NMR sample to ca. 90 °C failed to resolve the spectra, so it was not possible to establish the diastereoselectivity by this method. For the same reason, analysis by HPLC also proved unsuccessful. Selective removal of the sulfinyl group with TFA/MeOH gave amine **8** in 87% yield following flash chromatography. Attempts to determine the enantiomeric purity of **8** by chiral HPLC, using chiral shift reagents, and by making the Mosher amide were also unsuccessful. However, chiral HPLC analysis of **9** (ChiralCel OD) indicated that the ee was 92%. Isoquinolone **9** was prepared in 80% yield by cyclization of **8** with *tert*-butyllithium at −78 °C.

With isoquinolone **9** in hand, our thought was to convert it into the imidoyl chloride **10** followed by metal-catalyzed coupling with methylmagnesium bromide to give dihydroisoquinoline **11**.[9] Stereoselective reduction of **11** would then afford the target **4**. Compound **9** was heated at reflux in benzene with phosphorus oxychloride for 1.5 h, and purification by alumina chromatography gave a 50% yield of the hydrolytically unstable chloride **10** as indicated by the disappearance of the amide proton. The catalyst [1,3-bis(diphenylphosphino)propane]dichloronickel(II) [$NiCl_2$(dppp)][9a] was employed for coupling of **10** with methylmagnesium bromide. Unfortunately, decomposition occurred on addition of the Grignard reagent and none of the desired product could be detected. It is interesting to note that in a model study the imidoyl chloride of 3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one (**12**)[1] gave an 81% yield of **13** under similar conditions (Scheme 3). The presence of the 8-methoxy group may sterically inhibit the addition of the Grignard reagent and/or may provide an unproductive site for coordination of the catalyst.

Scheme 3



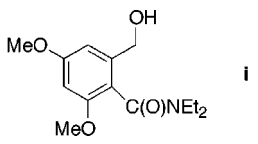
Even if we had been successful in coupling the Grignard reagent to the imidoyl chloride **10**, the lateral lithiated amide

(4) For studies related to the synthesis of this isoquinoline and its epimers, see: (a) Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 913. (b) Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877 (c) Upender, V.; Pollart, D. J.; Liu, J.; Hobbs, P. D.; Olsen, C.; Chao, W.-R.; Boden, B.; Crase, J. L.; Thomas, D. W.; Padey, A.; Lawson, J. A.; Dawson, M. I. *J. Heterocycl. Chem.* **1996**, *33*, 1371. (d) Hoye, T. R.; Chen, M. *Tetrahedron Lett.* **1996**, *37*, 3099. (e) Hoye, T. R.; Chen, M.; Hoang, B.; Mi, L.; Priest, O. P. *J. Org. Chem.* **1999**, *64*, 7184.

(5) For a review, see: Bringmann, G.; Pokorny, F. The Naphthylisoquinoline Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 46, p 127.

(6) Froyen, P. *Synth. Commun.* **1995**, *25*, 959.

(7) Despite using normal precautions to exclude moisture and oxygen, with an argon atmosphere about 10−15% *N*,*N*-diethyl-2-hydroxymethyl-4,6-dimethoxybenzamide (**i**) was formed on generation of the lateral lithiated amide of **5**.



i

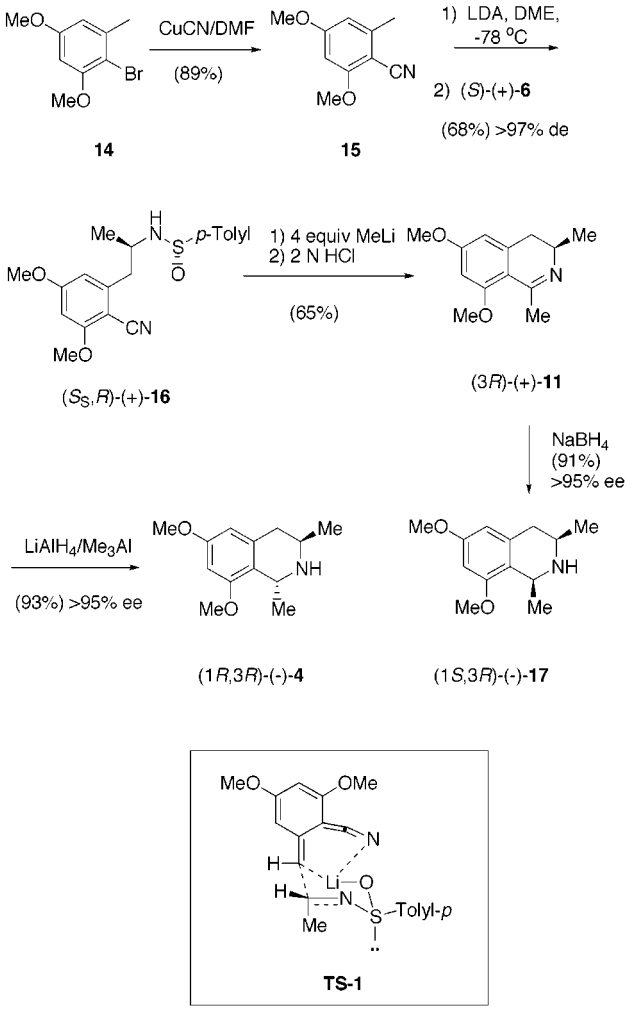
(8) (a) Davis, F. A.; Zhang, Y. Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1043. (b) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50.

protocol for the synthesis of 1,3-disubstituted tetrahydroisoquinolines was still problematic (Scheme 2). The problem is the difficulty in determining the diastereoselectivity in the key addition step because of the formation of atropodiastereoisomers. The presence of these rotamers makes it nearly impossible to improve the stereoselectivity and to obtain a diastereomerically pure product. To overcome this limitation, an anionic species is needed that, on addition to the sulfinimine, does not produce rotamers while still retaining the necessary functionality for elaboration to the target. The lateral lithiated species generated from a substituted *o*-tolunitrile[2,10] would appear to meet these requirements since rotamer formation would be unlikely and the nitrile can be considered to be a masked carbonyl for further elaboration. However, *o*-tolunitrile anions are reported to dimerize[2] and the presence of the methoxy group could present problems similar to those encountered in our first approach (Scheme 2).

2-Bromo-1,5-dimethoxy-3-methylbenzene (**14**)[11] was heated with copper(I) cyanide in DMF to give 2,4-dimethoxy-6-methylbenzonitrile (**15**) in 89% yield (Scheme 4). The nitrile was reacted with 2 equiv of LDA in THF at −78 °C to give the dark-red lateral lithiated species, which was treated with (*S*)-(+)-**6** to afford the sulfinamide **16** in 45% yield. Use of diglyme improved the yield to 68%. The diastereoselectivity of the addition was >97% and was easily determined by integration of the methyl protons in **16**. This selectivity confirms the absence of atropodiastereoisomers. On treatment with 4 equiv of MeLi, **16** was directly converted into cyclic imine (3*R*)-(+)-**11** on acidification. This accomplished three operations in one-pot: (i) removal of the sulfinyl auxiliary, (ii) installation of the 1-methyl group, and (iii) cyclization to the imine. Although the sequence of steps leading from **16** to **11** is not known with certainty, it is reasonable to propose that deprotonation of the acidic sulfinamide proton occurs first followed by addition of MeLi to the cyano group with formation of the methyllithium ketimine. Hydrolysis removes the sulfinyl group, to afford the free amine, which then intramolecularly cyclizes to **11**.

Imine **11** was converted into (1*R*,3*R*)-(−)-**4** in 93% yield and >95% ee by reduction with $LiAlH_4/Me_3Al$, as described by Bringmann,[4a,b] to assign the stereochemistry of the stereogenic center. Reduction of **11** with $NaBH_4$ gave the cis isomer (1*S*,3*R*)-(−)-**17** in 91% yield, which means that the stereochemistry of the initially formed stereogenic centers in **7** and **16** is (*R*). These results support the chiral-recognition model developed earlier for the addition of lateral lithiated amides to sulfinimines.[1] In this representation, the *o*-quinonedimethane structure derived from the nitrile anion is chelated through the lithium cation to the sulfinyl oxygen and approaches the *Si*-face of the sulfinimine via a six-membered chair-like transition state, **TS-1**.

Scheme 4



In summary, new methodology is presented for the asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines from lateral lithiated nitriles and chiral sulfinimines. This new protocol is illustrated in the concise, highly stereoselective four-step asymmetric synthesis of *cis*- and *trans*-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinolines **17** and **4** from (*S*)-(+)-**6** in 40−41% overall yield.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For examples of metal-catalyzed Grignard coupling with imidoyl chlorides, see: (a) Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, K. *Tetrahedron* **1982**, *38*, 3354. (b) Lin, S.-Y.; Sheng, H.-Y.; Haung, Y.-Z. *Synthesis* **1991**, 235. (c) Faust, R.; Gobelt, B. *Tetrahedron Lett.* **1997**, *38*, 8071.

(10) (a) Kobayashi, K.; Uneda, T.; Takada, K.; Tanaka, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *J. Org. Chem.* **1997**, *62*, 664. (b) Beaton, H.; Hamley, P.; Tinker, A. C. *Tetrahedron Lett.* **1998**, *39*, 1227. (c) Bunce, R. A.; Johnson, L. B. *Org. Prep. Proc. Int.* **1999**, *31*, 407.

(11) Srebnik, M.; Mechoulan, R.; Yona, I. *J. Chem. Soc.* **1957**, 1946.