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SULFINIMINE MEDIATED ASYMMETRIC SYNTHESIS OF 3-SUBSTITUTED -1(2*H*)-ISOQUINOLONES: (3*R*,4S)-(-)-4-HYDROXY-3-PHENYLTETRAHYDROISOQUINOLINE

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Summary: A general approach to enantiomerically pure 3-substituted-1(2H)-isoquinolones is illustrated by the addition of lateral lithiated amide 7 to sulfinimine 5. Isoquinolone 8 is readily transformed into (3R,4S)-(-)-4-hydroxy-3-phenyltetrahydroisoquinoline 15 via hydroxylation and reduction. © 1998 Elsevier Science Ltd. All rights reserved.

The 3-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids **3**, although not as common as their 1substituted analogs, are of considerable importance because of their unique structure and biological activity. Examples include naphthylisoquinoline,¹ protoberberine² and amaryllidaceae³ families of alkaloids which exhibit a wide range of biological activity; e.g. antimalarial. antitumor and anti-viral activity. The traditional approach to this skeleton has been the cyclization of 1-arylethylamino derivatives using Bishler-Napieralski (B-N) or Pictet-Spengler (P-S) protocols. However, with these procedures the regio- and stereoselective formation of the isoquinoline ring is often an issue.⁴ and side reactions resulting from the nitrilium ion intermediate can be a problem.⁵ In this regard a modified procedure has been introduced.⁶ The enantioselective synthesis of the 1-arylethylamino derivatives and their compatibility with the sometimes harsh B-N and P-S conditions are also problematic.

A potentially important method for the enantioselective synthesis of 3-substituted 1,2,3,4tetrahydroisoquinoline 3, illustrated in Scheme 1, is the condensation of lateral lithiated amides 1^7 with chiral imines. This approach, developed by Clark et. al.⁸ with racemic imines,⁹ has the potentiality of preparing tetrahydroisoquinolines with substitution patterns not easily accessible by other means because the 3,4dihydro-1(2*H*)-isoquinolones 2 can be readily manipulated and substituents introduced at the 1- and 4positions. What has undoubtedly prevented the general application of this method to the asymmetric synthesis of 3 is the unreactivity of imines, the propensity of aliphatic examples to undergo α -deprotonation rather than addition and the lack of suitable chiral examples. Sulfinimines (thiooxime S-oxides, ArS(O)N=CHR) developed in our laboratory offer a solution to this problem.^{10,11} The chiral sulfinyl group in sulfinimines is a superior auxiliary in that it activates the imine toward addition to such an extent that α -deprotonation is not

Scheme 1



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an important issue. It is highly stereodirecting and easy to remove. Furthermore, sulfinimines are prepared in "one pot" from commercially available (1R,2S,5R)-(-)-menthyl (S)-p-toluenesulfinate or (1S,2R,5S)-(+)-menthyl (R)-p-toluenesulfinate (Andersen reagent) and aromatic or aliphatic aldehydes.¹⁰ Here we illustrate the application of sulfinimines to the asymmetric synthesis of 3,4-dihydro-1(2H)-isoquinolones 2 and tetrahydroisoquinolines 3 in the highly diastereoselective synthesis of (3R,4S)-(-)-6-hydroxy-3-phenyltetetrahydroisoquinoline (15). This isoquinoline is a precursor of the 13-hydroxyprotoberberines,¹² and its enantiomer was recently prepared in 7 steps starting from an enzymatically resolved cyanohydrin by Domingues and co-workers.¹³

4-Methoxy-*N*,*N*-diethyl-*o*-toluamide (4),¹⁴ [6.0 mmol] was treated with a slight excess of LDA at -78 °C in THF to generate the intensely burgundy colored solution of the lateral lithiated amide (Scheme 2). After a few min, 0.5 equiv of (S)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (5)¹⁰ was added and after 15 min. the solution was quenched with sat. NH₄Cl solution. Flash column chromatography afforded (S_S ,S)-(+)-*N*-[1-phenyl-2-*N*,*N*-diethylbenzamido)ethyl]-*p*-toluenesulfinamide (6) in 70% yield as a single diastereoisomer as analyzed by NMR spectroscopy. Attempts to cyclize this material directly to (3*S*)-(-)-3-phenyl-3,4-dihydro1(2*H*)-isoquinolone (8) by treatment with excess LDA failed, undoubtedly due to the stability of the N-sulfinyl amine anion. Removal of the sulfinyl auxiliary in 6 was easily accomplished by treatment with 5 equiv of TFA in MeOH to give the amine (-)-7 in nearly quantitative yield. Preparation of the Mosher amide of 7 with (*S*)-MTPS-Cl indicated that the enantiomeric purity of the amine was >97% ee. At this point it was not possible to establish the configuration of the initially formed chiral center in 6, subsequently shown to have the (*S*)-configuration (*vide infra*), because suitable crystals for X-ray analysis could not be obtained. Cyclization of 7 to the isoquinolone 8 was easily effected by treatment with 3 equiv of *tert*-butyllithium to give 8 in 90% yield.

Scheme 2



After N-methylation of the amide nitrogen in 8 with NaH/MeI, we next turned our attention to the introduction of the 4-hydroxyl group into 9 (Scheme 3). This was readily accomplished by the stereoselective

oxaziridine mediated hydroxylation¹⁵ of the anion of 9, generated by treatment of 8 with 3 equivalents of LDA at -78 °C. Thus reaction of the anion of 9 with 1.5 equivalents of 2-(phenylsulfonyl)-3-phenyloxaziridine (10) or (camphorylsulfonyl)oxaziridine (11) affords 12 in 56 and 85% yield, respectively. As previously reported, much higher yields with fewer side reactions are observed for carbanion and enolate hydroxylations with 11.^{15a} In each case only a single diastereoisomer of (3R,4S)-12 was detected. The *trans* selectivity is consistent with our earlier findings that demonstrated that the hydroxylation stereochemistry is governed by nonbonded steric interactions in the transition state such that 10 or 11 approach from the sterically least hindered direction.^{15a} In full agreement with this assignment is the small 3,4-coupling constant (2.1 Hz) in 12.¹⁶ Silylation with TBDPS-Cl/imidazole, reduction with BH₃:DMS and desilylation with tetrabutylammonium fluoride (TBAF) afforded (3*R*,4*S*)-(-)-4-hydroxy-3-phenyl-6-methoxy-tetrahydroisoquinoline (15) in >95% ee (determined using Eu(hfc)₃) and in 78% overall yield for the three steps. This establishes that the initially formed stereocenter in 6 has the (*S*)-configuration and results from approach of the lateral lithiated amide anion, thought to exist as an *o*-quinodimethane,⁷ at the sterically least congested face of sulfinimine C-N double bond; e.g. TS-1.





In summary, new methodology is introduced for the enantioselective synthesis of 3-substituted-1(2H)isoquinolines via the highly diastereoselective addition of lateral lithiated amides to sulfinimines. The efficient stereoselective conversion of 8 into (3R,4S)-(-)-4-hydroxy-3-phenyltetrahydroisoquinoline 15 was demonstrated. The application of this protocol in the asymmetric synthesis of 3-substituted 1,2,3,4tetrahydroisoquinoline alkaloids is under vigorous investigation.

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