LATVIJAS UNIVERSITĀTE

Hirālu 1,2,3,4-tetrahidroizohinolīnu sintēze un izmantošana asimetriskajā protonēšanā

Promocijas darbs doktora grāda iegūšanai ķīmijas nozarē organiskās ķīmijas apakšnozarē

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Chiral 1,2,3,4-Tetrahydroisoquinolines
Synthesis and Use in Enantioselective Protonation

by

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Contents

Introduction.

Creation of a stereogenic center in a planned manner has been a challenge for chemists since the stereoisomerism of organic molecules was discovered. Development of new methodologies for the preparation of stereoisomers is among the most important topics in modern organic synthesis. One of the most direct ways to form an asymmetric center is selective proton delivery from a chiral proton source to either side of a planar enolate (*enantioselective protonation*). Since the enolate is generated from a racemic material, the method is also known as *deracemization*. Racemic ketones, esters and amides can be deracemized in one step by an enolization, enantioselective protonation sequence. In contrast to traditional resolution *via* a diastereomer pair that would give a maximum of 50% chemical yield of a chiral product, the deracemization affords nearly quantitative recovery of enantioenriched material. In the most practical examples, a simple extractive procedure is sufficient to separate the chiral proton source from the desired non-racemic product. Furthermore, there is a clear advantage in the use of sub-stoichiometric quantities of expensive chiral proton donor and a catalytic version of several stoichiometric protonations has been developed recently.

Potentially being a powerful and attractive method for the synthesis of enantioenriched carbonyl compounds, asymmetric protonation of enolates has not yet developed into a convenient synthetic tool. The best protonation examples have required extensive optimization of a chiral proton donor and deracemization conditions. Very little is known about the design of a chiral proton source. The acidic proton obviously must be in a sufficiently chirotopic environment for effective enantioselection, but the importance of the pKa relationship between a proton donor and enolate is less well understood.

Optically active 1-anilino-1,2,3,4-tetrahydroisoquinoline CAPTIQ is a highly efficient "chiral acid" in deracemization of various amide enolates. Our main objective was to extend the scope of deracemization to other carbonyl compounds, such as esters and amino acid derivatives. A series of isosteric chiral CAPTIQ analogs that vary in acidity would allow the investigation of the enantioselectivity relationship with the pKa difference between the enolate and a proton donor. The details of these studies are highlighted in **Chapter C**.

Despite the fact that isoquinoline is a principal constituent of many alkaloids and medicines, there is a lack of a general and convenient method for the asymmetric synthesis of 1-aryl-1,2,3,4-tetrahydroisoquinoline. Chiral auxiliary mediated asymmetric synthesis usually affords optically enriched isoquinolines. The purity of diastereomers has to be further increased to >99% de by chromatography or crystallization technique. Important disadvantages of covalently bonded chiral auxiliaries are the cost of a chiral reagent and the additional steps needed to attach and cleave the auxiliary. More convenient is resolution of inexpensive racemic isoquinolines by crystallization of diastereomeric salts. In this transformation the resolving agent can be easily recovered by a simple acid-base extractive work-up. The approach was examined in **Chapter A**.

Catalytic asymmetric synthesis is an important alternative to all the above mentioned techniques, because a large quantity of the chiral material can be produced using a small amount of a chiral catalyst. The most direct route to non-racemic 1-aryl-1,2,3,4-tetrahydroisoquinolines would be the asymmetric reduction of corresponding 3,4-dihydroisoquinolines. Recent report on highly efficient enantioselective transfer hydrogenation of 1-phenyl-3,4-dihydroisoquinoline using a chiral ruthenium catalyst encouraged us to apply this method for the synthesis of various CAPTIQ analogs. **Chapter B** summarizes the scope and limitations of the Ru-catalyzed asymmetric transfer hydrogenation as well as illustrates a practical application of the method for the synthesis of chiral tetrahydroisoquinolines with aniline subunit.

Chapter A

Preparation of chiral anilino-isoquinolines by diastereomeric pairs crystallization technique

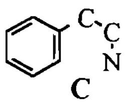
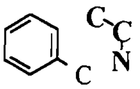
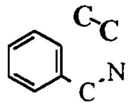
Racemates resolution *via* diastereomer pairs crystallization technique is the most straightforward route to optically active amines.[1] In this type of reaction, substrate (racemic amine) is treated with one enantiomer of a chiral substance (the resolving agent, chiral acid). Diastereomer pairs usually are ionic (diastereomeric salts) or covalent. The method is fairly inexpensive because the chiral reagent can be recovered by a simple acid-base extractive work-up. On the other hand, resolution success often requires extensive screening of various chiral acids as well as careful adjustment of crystallization conditions. The synthetic problem, however, becomes technically easier in the cases when resolution of structurally related substrates has already been reported.

Since tetrahydroisoquinoline is a principal constituent of various alkaloids and drugs, a number of chiral reagents have been applied for the resolution of racemates. Among them, tartaric acid and its O-substituted analogues as well as diacetone-2-keto-*L*-gulonic acid are most frequently used[1b] for preparation of diastereomeric salts. For example, chiral isoquinoline CAPTIQ, so far the best chiral proton donor for deracemization of various amides,[2] is commercially available as a salt with L(+) tartaric acid (Aldrich). Use of tartaric acid for resolution of other 1-anilino-1,2,3,4-tetrahydroisoquinolines[3] stimulated us to employ this technique for the preparation of various CAPTIQ analogues as potential asymmetric proton donors.

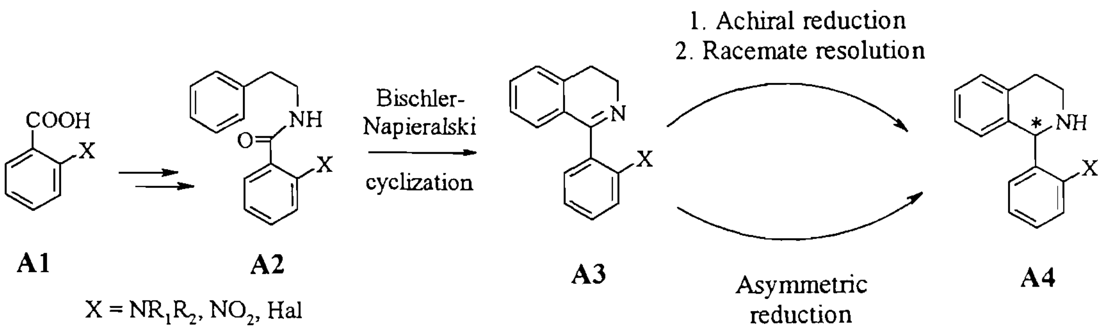
1. Synthesis of racemic 1-anilino-1,2,3,4-tetrahydroisoquinolines. Optimization of Bischler-Napieralski cyclization.

There are a number of methods for isoquinoline ring construction[4] and the most frequently used processes are summarized in Table A1.

Table A1. General methods for isoquinoline ring construction.

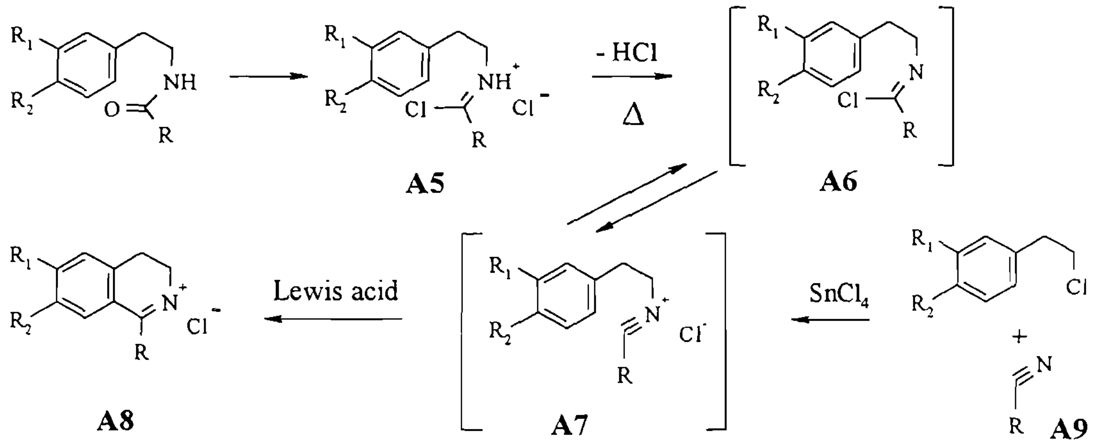
"Disonnection approach"	Reaction	Products
	Bischler-Napieralski	**3,4-dihydroisoquinolines**
	Pictet-Spengler	**1,2,3,4-tetrahydroisoquinolines**
	Pomeranz-Fritsch	**isoquinolines**
	Schlittler-Muller	**isoquinolines**

Bischler-Napieralski cyclization is somewhat more attractive compared to the alternatives because it employs relatively easily available substituted benzoic acids **A1** as the starting material. Moreover, the cyclization affords C=N double bond containing 3,4-dihydroisoquinolines **A3**, that potentially can be reduced in an asymmetric way yielding chiral or enantiomerically enriched products **A4**.



Bischler-Napieralski cyclization proceeds *via* initial formation of hydrochloric salts of imidoyl chloride **A5** using $POCl_3$, PCl_5 or $SOCl_2$ as a reagent. Subsequent loss of hydrogen chloride generates imidoyl chloride species **A6** which is in equilibrium with the corresponding nitrilium salt **A7**.[5] In the presence of Lewis acids, such as $SnCl_4$, $ZnCl_2$ or $POCl_3$, PCl_5 and $SOCl_2$, nitrilium salt undergoes cyclization affording 3,4-dihydroisoquinolines **A8**.

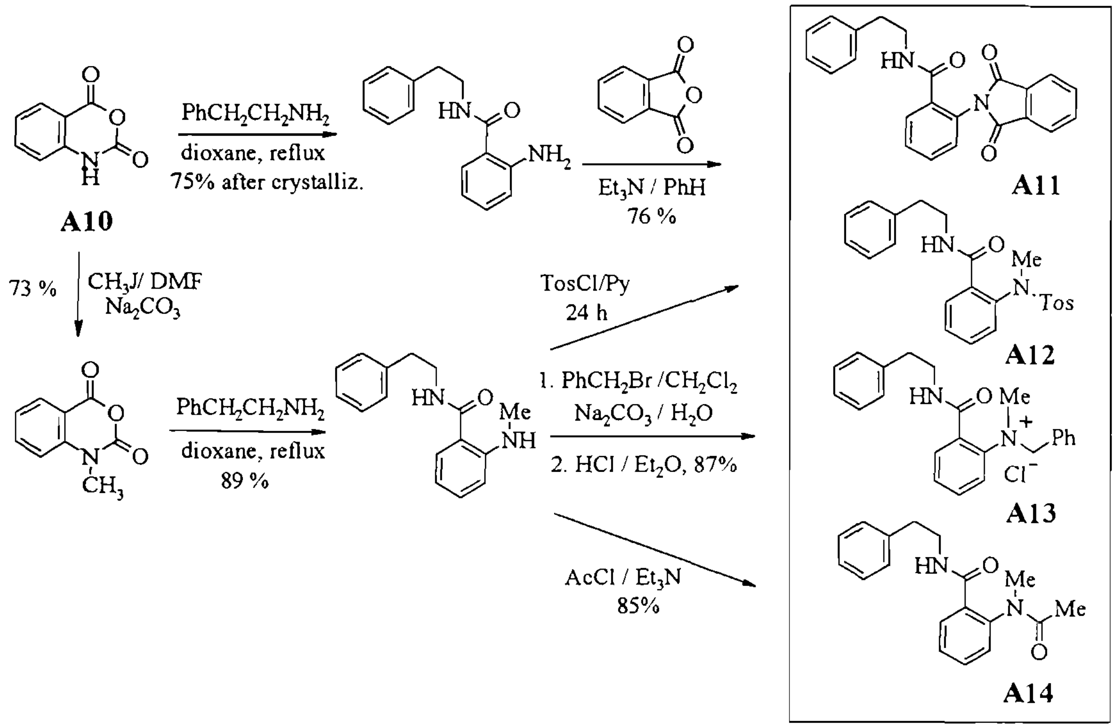
Scheme A1.



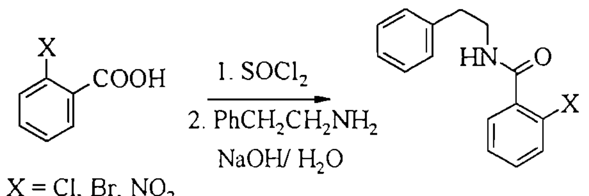
It was also shown that related nitrilium salts **A7** prepared by direct alkylation of the corresponding nitriles **A9** yield 3,4-dihydroisoquinolines **A8** in the presence of various Lewis acids ($SnCl_4$, $ZnCl_2$).[6] Employing P_2O_5 and polyphosphoric acid esters as dehydrating agents resulted in the formation of corresponding imidoyl phosphates as the intermediates.

Since our objective was the synthesis of various 1-anilino-1,2,3,4-tetrahydroisoquinolines **A4** (X=NR_1R_2), choice of the proper N-protecting group in β-phenethylamides **A2** (X=NR_1R_2) was critical, because unprotected aniline NH_2 group obviously does not survive harsh Bischler-Napieralski cyclization conditions. Moreover, it was reported that even cyclization of mono-N-protected anilino-β-phenethylamides (N-acetyl and N-tosyl) failed to give the desired 3,4-dihydroisoquinolines.[3a] A family of various N-*bis*-protected β-phenethylamides **A11-A14** was therefore readily prepared from isatoic anhydride **A10** in order to determine the best protecting group for the cyclization.

Scheme A2.



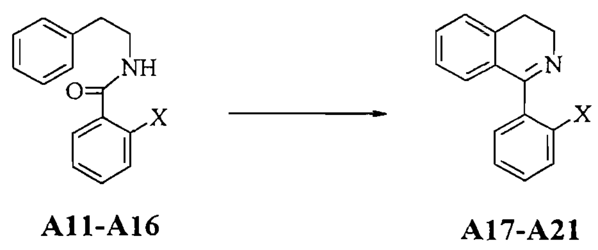
Electron-withdrawing N-protecting groups were chosen assuming that an electron-deficient 1-aryl substituent could polarize an amide carbonyl group, thus facilitating formation of the corresponding imidoyl chloride **A6** and, consequently, the nitrilium intermediate **A7** (Scheme A1). An alternative approach to aniline protection is the use of appropriate functionality that is resistant to cyclization conditions and can afterwards be easily converted to anilino group. A suitable candidate is a nitro group that can be selectively reduced to aniline[7] in the presence of 3,4-dihydroisoquinoline C=N bond as well as halogen, that can be replaced by various amines under miscellaneous conditions.[8] Both nitro and halogen-substituted β-phenethylamides **A15** and **A16** were easily prepared from the corresponding benzoic acids.



A15 (X=NO_2)
A16 (X=Cl, Br)

β-Phenethylamides **A11-A16** were subjected to Bischler-Napieralski cyclization and the results are summarized in Table A2.

Table A2. Bischler-Napieralski cyclization of various β-phenethylamides **A11-A16**.



Entry	Substrate	X	Dehydrating agent	Conditions[a]	Product	Yield (%)
1	**A13**	$N(CH_3)CH_2Ph \cdot HCl$	P_2O_5	6h	**A17**[b]	16
2	**A14**	$N(CH_3)Ac$	P_2O_5	24h	-	0
3	**A12**	$N(CH_3)Tos$	P_2O_5 or $POCl_3$	20h	**A18**	30
4	**A11**	N-phthalyl	P_2O_5	24h	**A19**	20
5	**A11**	N-phthalyl	PCl_5	30 min. reflux, $CHCl_3$, then $SnCl_4$, 4h	**A19**	73
6	**A15**	NO_2	P_2O_5	5h	**A20**	72
7	**A16**	Cl, Br	P_2O_5	20h	**A21**	70

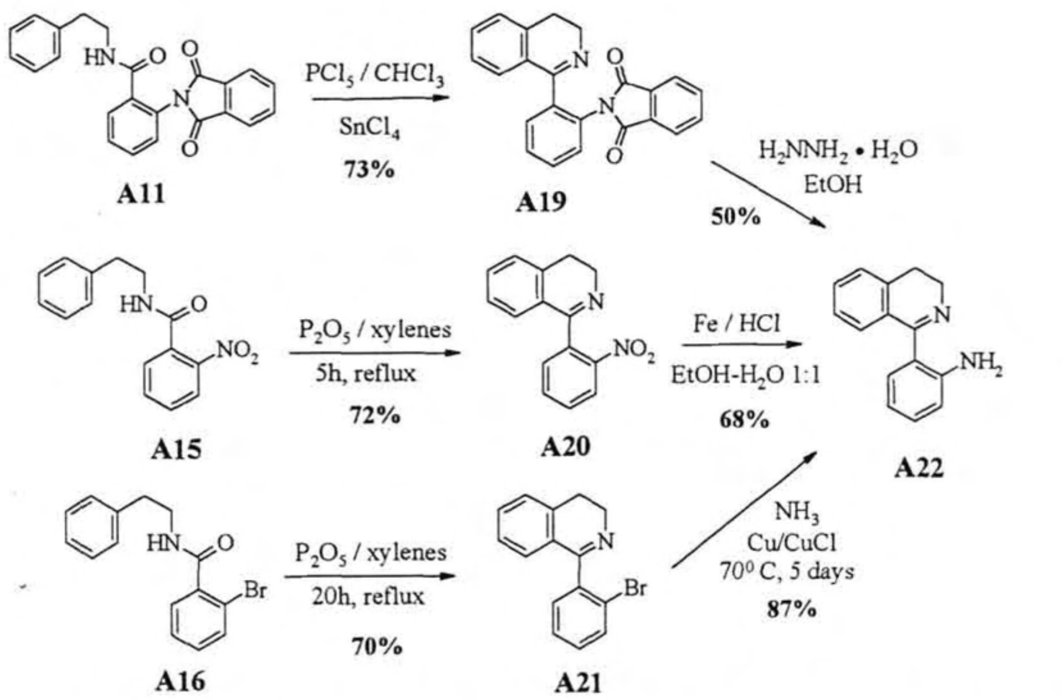
(a) Unless indicated otherwise, all cyclizations were performed in xylenes under reflux. (b) N-debenzylated product **A17** ($X=NHCH_3$) was isolated.

Initially, N-benzyl group was employed for N-methyl aniline protection (entry 1). The tertiary amine was converted to hydrochloric salt **A13** (See Scheme A2), making the aryl group electron-deficient and thus favoring imidoyl phosphate **A6** formation (see Scheme A1). Also, it was expected that ammonium salt would be less prone to various side-reactions with an excess of phosphorylating agent. Surprisingly, instead of the anticipated N-methyl-N-benzylaniline from the oily dark red reaction mixture, the N-debenzylated product **A17** was obtained in a low 16% yield. Isolation of deprotected product **A17** suggested that phosphorylation side-reaction and subsequent phosphono-anilide degradation is responsible for the low chemical outcome. Consequently, N-benzyl group can not be employed for aniline protection in Bischler-Napieralski cyclization. It was also found that the N-acetyl protected substrate **A14** (entry 2) is unreactive under standard conditions, while N-tosyl analog **A12** afforded the desired isoquinoline **A18** in a low 30% yield (entry 3). Similarly, N-phthalyl aniline **A11** gave only 20% of the desired isoquinoline **A19** under standard conditions (entry 4), however, the yield was significantly increased employing modified reaction conditions (entry 5). Thus, treatment of β-phenethylamide **A11** with excess PCl_5 in boiling $CHCl_3$ for 30 min. resulted in the formation of a yellow precipitate, which upon addition of Lewis acid ($SnCl_4$) turned brick-red. Color change indicates the formation of cyclized product **A19**, because 3,4-dihydroisoquinolines usually are intensely red-colored in acidic media. The reaction was refluxed for an additional 4 hours to complete cyclization and the desired N-phthalyl-isoquinoline **A19** was isolated in 73% yield. The cyclization was readily scaled-up to 85 g without a drop in yield and consequently, the N-phthalyl protecting group combined with modified Bischler-Napieralski cyclization conditions can be employed for preparative scale synthesis of 1-anilino-3,4-dihydroisoquinoline.

In contrast to N-*bis*-protected anilines (entries 1-4), cyclization of nitrobenzene **A15** does not suffer from side-reactions and proceeds relatively fast, evidently because of a strong electron-withdrawing nitro group effect. The desired nitro-isoquinoline **A20** was obtained in 72% yield after 5h under standard conditions (entry 6). The same level of conversion (ca. 70%) for bromo- and chloro-substituted β-phenethylamides **A16** was achieved after a considerably longer reaction time (20h, entry 7). 3,4-Dihydroisoquinolines **A21** (X=Cl, Br) are especially useful because a number of methods for direct aryl halogen displacement by various amines have been reported.[3a,8]

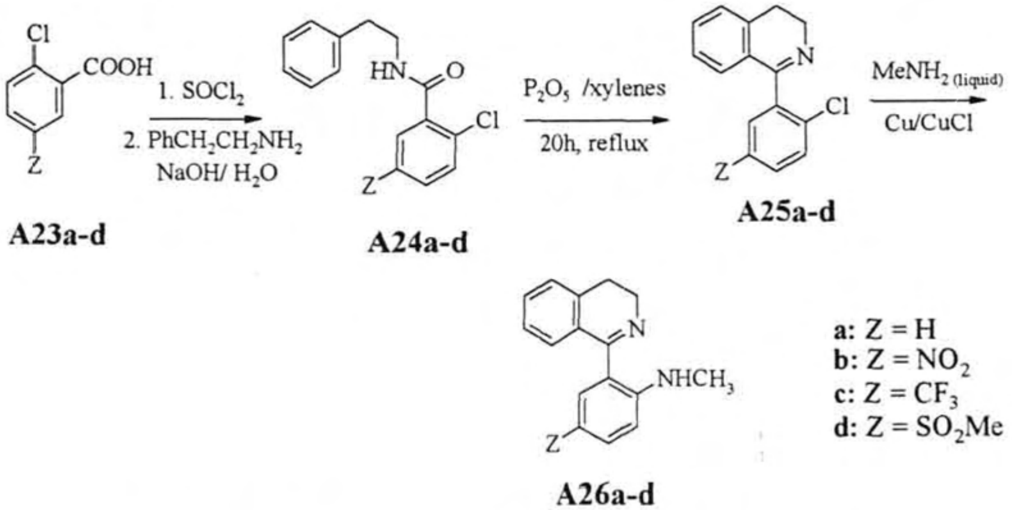
Since β-phenethylamides **A11**, **A15** and **A16** are almost equally good Bischler-Napieralski cyclization substrates, overall reaction sequence to 1-anilino-3,4-dihydroisoquinoline **A22** was examined for each amide **A11**, **A15** and **A16** in order to evaluate the most efficient route to the product (see Scheme A3). Thus, cyclization of N-phthalyl-aniline **A11**, followed by hydrazine hydrate mediated protecting group cleavage,[9] afforded the desired 3,4-dihydroisoquinoline **A22** in <u>37% overall yield</u>. Higher <u>overall yield (ca. 50%)</u> was achieved using the nitro-substituted β-phenethylamide **A15** (see Scheme A3). In this sequence, the nitro group was selectively reduced in the presence of C=N double bond in 68% yield. The most efficient route to 1-anilino-3,4-dihydroisoquinoline **A22** turned out to be the Bischler-Napieralski cyclization of 2-chloro(or bromo)phenyl-β-phenethylamides **A16**, followed by halogen displacement with liquid ammonia or lower alkylamines[3a] affording the desired heterocycle **A22** in <u>61% overall yield</u>.

Scheme A3.



The reaction sequence **A16→A22** technically is fairly simple and was easily scaled-up (25 g amide **A16** loading) without drop in chemical yields. The method was also employed for the synthesis of various substituted N-methylanilines **A26a-d** from the corresponding *ortho*-chlorobenzoic acids **A23a-d** (Scheme A4).

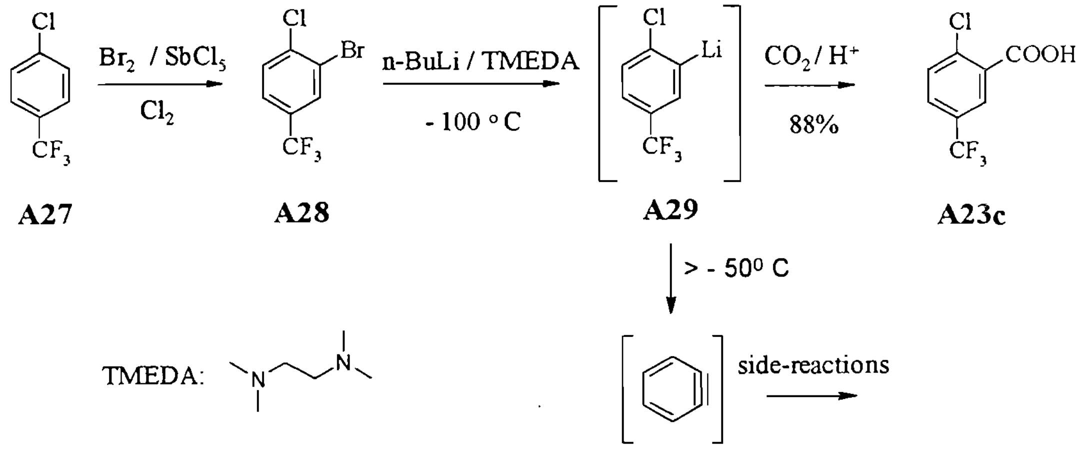
Scheme A4.



Benzoic acids **A23a-c** are commercially available, however, trifluoromethyl-benzoic acid **A23c** is relatively expensive for use as a starting material.[A] Therefore, it was prepared in 2 steps from chlorobenzene **A27** (Scheme A5).

(A) Aldrich, 18 DM/g

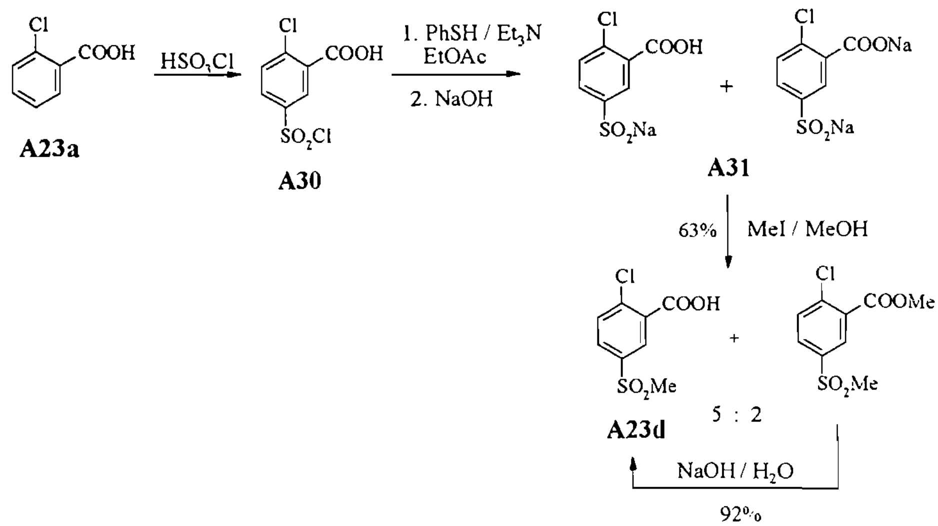
Scheme A5.



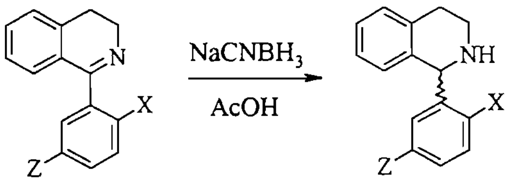
Bromination was performed according to the literature procedure[10] followed by selective lithium-bromine exchange in **A28**.[11] Low temperature (-100 ^{0}C) is crucial to achieve chemoselectivity in the metalation reaction as well as to avoid side-reactions *via* dehydrobenzene, which are dominant at temperatures above –50 ^{0}C. Additional stabilization of the intermediate **A29** can be achieved by using bidentate ligand TMEDA, frequently used as a complexing agent for various organolithium derivatives.[12] Finally, carboxylate was introduced by treatment of the aryllithium intermediate **A29** with CO_2 (dry ice), yielding the desired benzoic acid **A23c** in 52% overall yield.

Methylsulfonyl-benzoic acid **A23d** was prepared in 3 steps from *ortho*-chlorobenzoic acid **A23a** *via* formal reduction[13] of chlorosulfonylbenzene **A30**[14] to the corresponding sulfinic acid **A31**, followed by alkylation of "soft" nucleophilic sulfur by MeI.[15]

Scheme A6.



All substituted 1-anilino-3,4-dihydroisoquinolines **A20**, **A22** and **A26a-d** were conveniently transformed to the desired racemic 1,2,3,4-tetrahydroisoquinolines employing reduction with $NaCNBH_3$ in acetic acid[16] (70-85% yield).



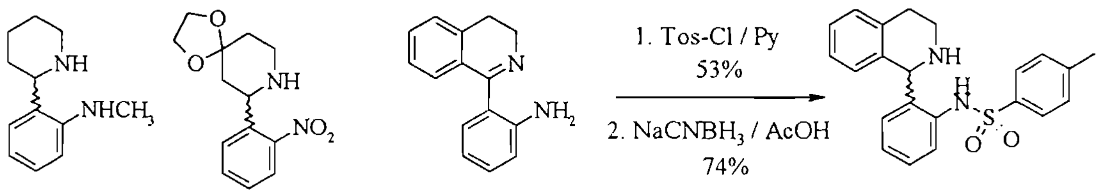
A20, A22, A26a-d

A31: X = NO_2, Z = H
A32: X = NH_2, Z = H
A33a: X = $NHCH_3$, Z = H
A33b: X = $NHCH_3$, Z = NO_2
A33c: X = $NHCH_3$, Z = CF_3
A33d: X = $NHCH_3$, Z = SO_2Me

2. Racemates resolution by crystallization of diastereomeric tartrates.

Tartaric acid was chosen for the resolution because preparation of structurally similar, optically pure 1-(5-chloro-2-methylamino)phenyl-1,2,3,4-tetrahydroiso-quinoline (CAPTIQ) *via* crystallization of diastereomeric tartrates has already been reported.[3a] Moreover, tartaric acid mediated racemate resolution succeeded also in the case of N-unsubstituted diamine **A32**.[3b]

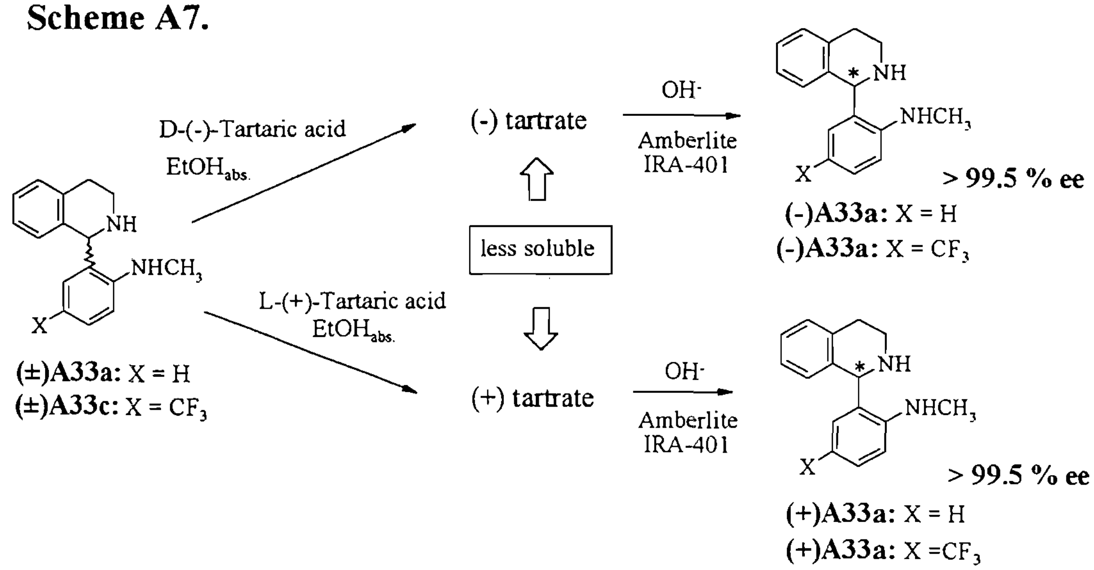
Contrary to reported successful resolution of diamine **A32**, we were unable to achieve even smallest enantiomerical enrichment by the crystallization of tartrates from ethyl alcohol and other solvents (methanol, acetone, EtOAc etc.). Moreover, all attempts to prepare chiral diamine **A32** using O,O-dibenzoyl tartaric acid, successfully applied for racemic piperidine **A34** resolution,[17] as well as *D*-(+)-camphorsulfonic acid (efficient in case of amine **A35**)[17] in various solvents, failed. Evidently, the difference in diastereomeric salt solubility is too small for the separation by selective crystallization. Neither was any diastereomer separation observed in the case of nitro-isoquinoline **A31** and N-tosylanilide **A36** employing tartaric, O,O-dibenzoyltartaric and camphorsulfonic acids in various solvents.



A34 **A35** **A22** **A36**

In contrast, crystallization of diastereomeric tartrates derived from N-methylanilino-1,2,3,4-tetrahydroisoquinolines **A33**, was effective for resolution of unsubstituted and CF_3-substituted diamines **A33a** and **A33c**, respectively. Thus, two crystallizations of corresponding tartrate salts from ethyl alcohol, after workup, afforded single enantiomers of potential chiral proton donors with > 99.5% enantiomerical purity according to HPLC on the chiral stationary phase (CSP).

Scheme A7.



No difference in the solubility of diastereomeric tartrates, however, was observed in the case of poorly soluble nitro-isoquinoline **A33b** and, as a consequence, all precipitate crops, according to HPLC on CSP, contained 1:1 mixture of diastereomeric tartrates. Similarly, methylsulfonyl-isoquinoline **A33d** was not resolved using various chiral acids and different solvents. Lack of separation in this case is hard to explain in view of the easy resolution of CF_3-substituted and unsubstituted analogs **A33a** and **A33c**.

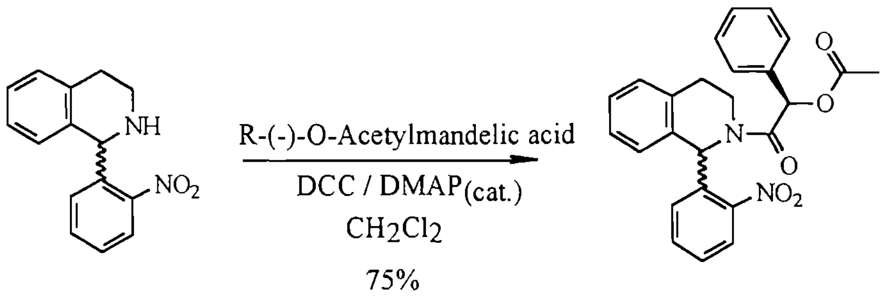
Thus, only moderate success has been achieved in the preparation of chiral diamines by diastereomeric salt crystallization. Moreover, it was clearly shown that the process is highly substrate-dependent and even small changes in substrate structure affect the efficiency of resolution. Consequently, racemates resolution by crystallization technique can not be employed in the design of a general method for the synthesis of chiral 1,2,3,4-tetrahydroisoquinolines.

3. Chiral diamine preparation *via* (*R*)-O-acetylmandelic acid amides.

Potential solution of the problem could be synthesis of a key intermediate by the resolution method and subsequent chemical transformations of optically pure material. The most appropriate candidates for the key structure are nitro- and aminophenyl-1,2,3,4-tetrahydroisoquinolines **A31** and **A32**. Because all attempts to resolve these substrates by diastereomeric salts crystallization technique have failed so far, it was decided to employ an alternative resolution method. Thus, another approach frequently used for racemates resolution is the introduction of a covalently bonded chiral auxiliary, separation of diastereomers by chromatography or crystallization technique and, finally, the removal of the chiral auxiliary.

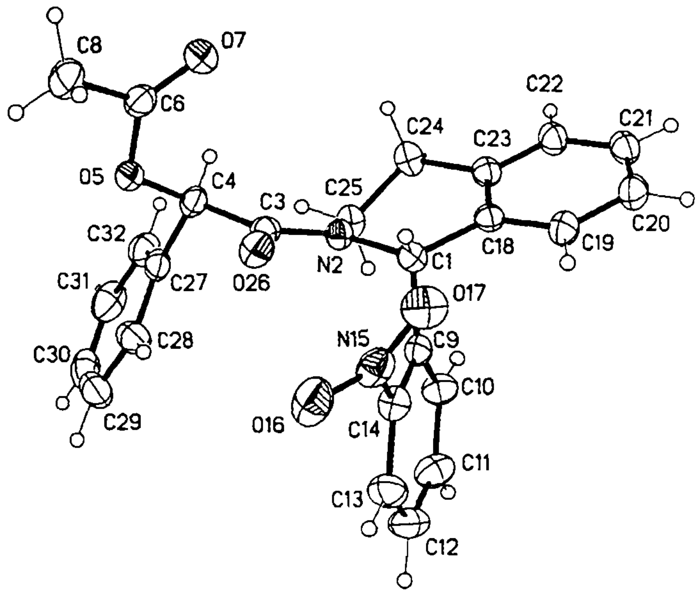
It has been recognized that multiple interactions between the resolution substrate and resolving agent are essential for successful resolution. Consequently, chiral acid should possess an aromatic ring and an additional functional group besides the acid functionality.[1c] A promising candidate is mandelic acid and its O-Me and O-Ac substituted analogs, that have been widely used for racemic amines resolution.[18] Moreover, successful application of (*R*)-O-acetylmandelic acid as a chiral auxiliary for HPLC separation of 1-phenyl-1,2,3,4-tetrahydroisoquinolines[19] urged us to examine this commercially available resolving agent for the resolution of key intermediates **A31** and **A32**.

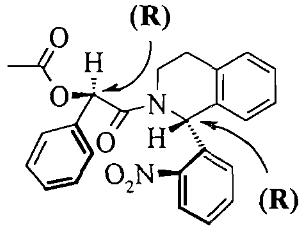
Treatment of nitro-isoquinoline **A31** with commercially available (*R*)-O-acetylmandelic acid in the presence of dicyclohexylcarbodiimide gave amide **A37** as a 1:1 mixture of diastereomers:



A31 **A37**

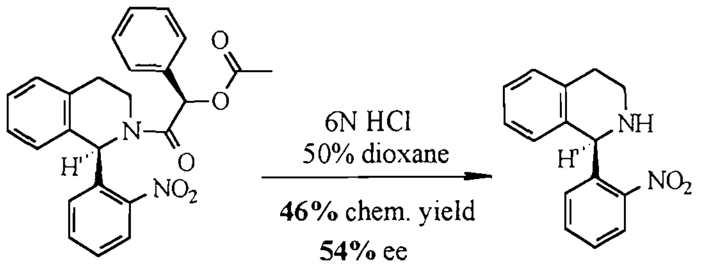
All attempts to separate **A37** diastereomers by flash chromatography on silica gel failed. As amide **A37** is solid, crystallization was applied in the hope that diastereomers have difference in solubility. Indeed, two crystallizations from ethyl acetate - hexanes gave a single amide **A37** diastereomer in 31% yield with (*R*,*R*) absolute configuration according to X-ray analysis.





(R,R)-A37

With the single diastereomer **(*R*,*R*)-A37** in hand, the racemization-free removal of the chiral auxiliary became a crucial issue. Initially, hydrolytic methods were employed to remove the O-acetylmandelic auxiliary. Thus, amide **(*R*,*R*)-A37** was heated under reflux in 6 N hydrochloric acid for 1 hour and the isolated desired isoquinoline **(*R*)-A38** was partially racemized.[B]



(R,R)-A37 **(R)-A38**

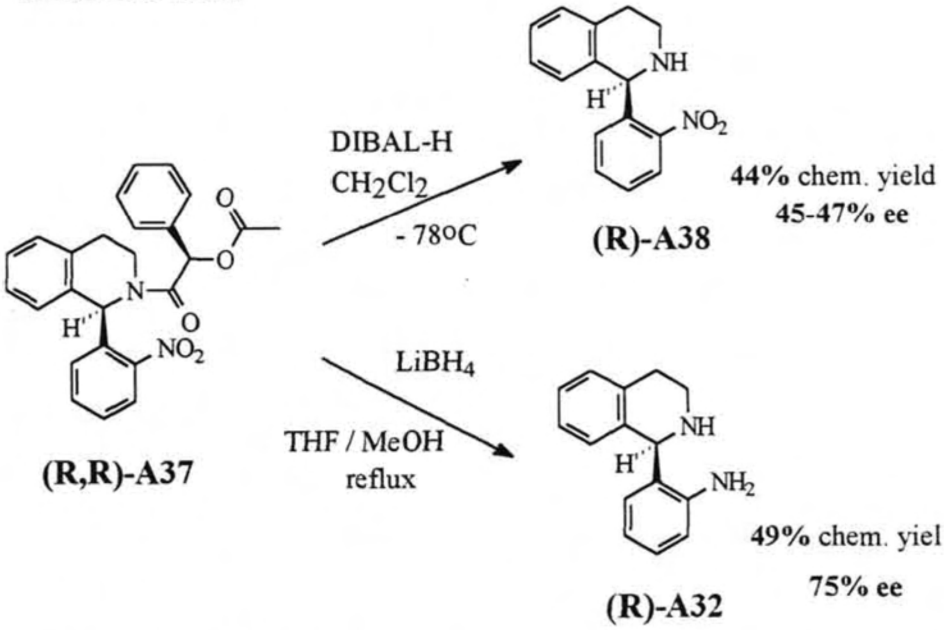
Although use of less concentrated hydrochloric acid (1N) resulted in a lower degree of racemization (67% ee), the chemical yield was too poor (10%) to utilize this method on a preparative scale.

Racemization apparently took place *via* an isoquinoline ring opening-ring closure sequence in strongly acidic media, however, no attempts were made to study the process in detail. Instead, the amide bond reductive cleavage to the corresponding amine and aldehyde (alcohol) was examined.[20] It should be noted that the scope of potentially useful reducing agents for amide bond cleavage was diminished by low

(B) The optical purity of products was determined by HPLC on CSP.

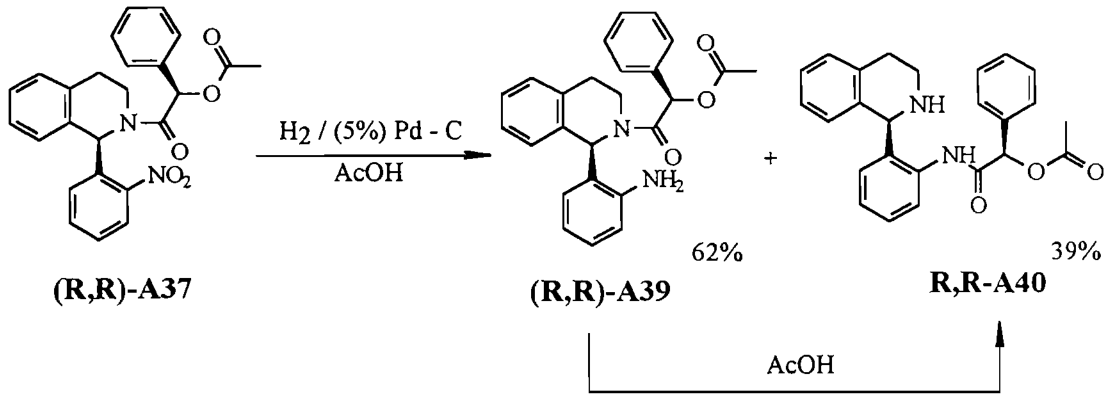
substrate solubility in common solvents such as THF, ether and toluene. The solubility of ***(R,R)*-A37** in CH_2Cl_2 allowed to perform the reduction with DIBAL-H (Scheme A8).[21]

Scheme A8.

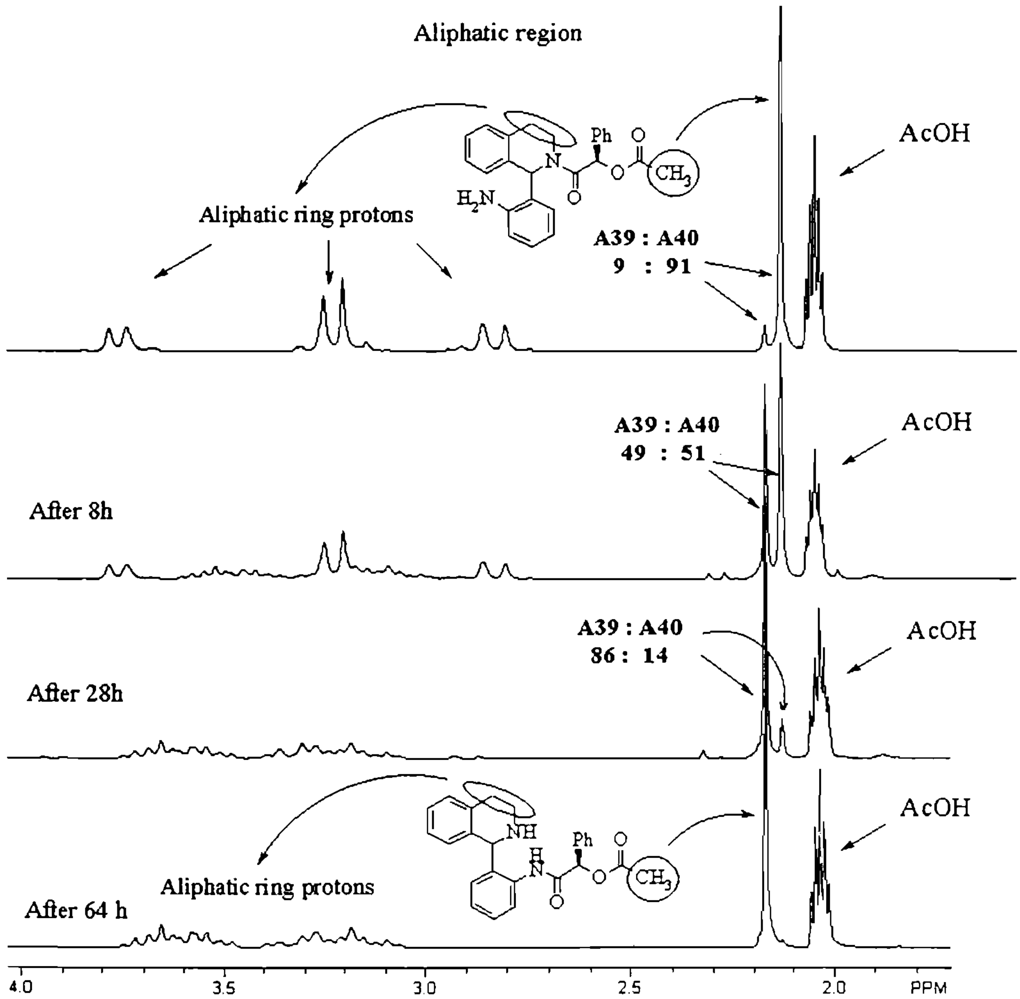


Surprisingly, product isoquinoline **A38** isolated in 44% yield, was again partially racemized. Optical yield did not improve even when the reaction was performed at −100 ^{0}C (by DIBAL-H addition to a melting surface of the reaction mixture). As expected, nitro group was left unaffected. Partial racemization (75% ee) was also observed using $LiBH_4$ in refluxing THF-methyl alcohol mixture.[22] In this case, nitro group was reduced and anticipated diamine **A32** was obtained in 49% chemical yield (Scheme A8).

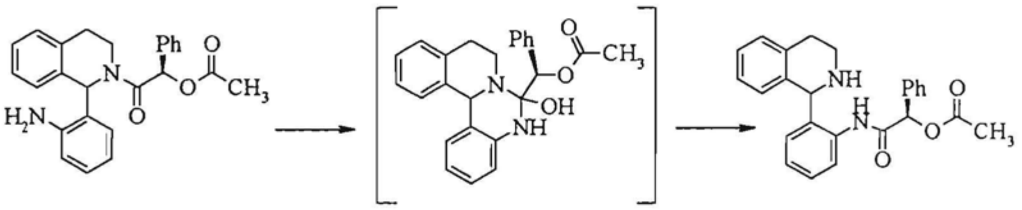
Since use of other reducing agents ($LiAlH_4$, LiAlH(*t*-BuO)$_3$, Red-Al)[20] was limited by the poor solubility of the amide **A37**, it was expected that the conversion of nitro group to amino could solve the solubility issue. Nitro group hydrogenation was performed in acetic acid and resulted in the formation of anticipated aniline **A39** accompanied by an unexpected product of acyl group migration **A40**.



[1]H-NMR experiments in acetic acid-d_4 showed that 50% of aniline **A39** has been already rearranged to isoquinoline **A40** after 8h at 20 ^{0}C, while complete acyl group migration was observed after 64 h at room temperature (ca. 4% of starting material **A39**).



Anilide **A40** formation was rather unexpected because O-acetylmandelyl group migrates from the basic isoquinoline nitrogen to the much less basic aniline. It can be rationalized either by sterical factors or by assumption that the driving force for this rearrangement is protonation of isoquinoline as the more basic amine in acidic media. It is believed that rearrangement occurs *via* a cyclic tetrahedral transition state **A41**:



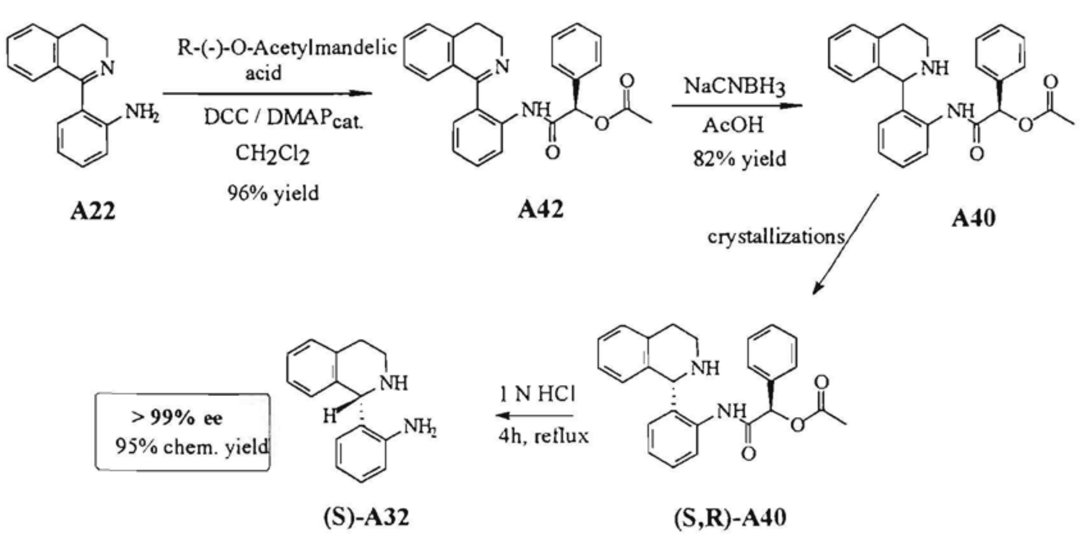
A39 **A41** **A40**

Lack of O-acetylmandelyl group migration product **A40** in acetonitrile-d_3 (polar aprotic solvent) and methanol-d_4 (polar protic solvent) after 18h at 70 ^{0}C followed by 72h at 20 ^{0}C suggests that acidic media is crucial for the rearrangement. This supports the assumption that the process driving force is protonation of the more basic isoquinoline nitrogen.

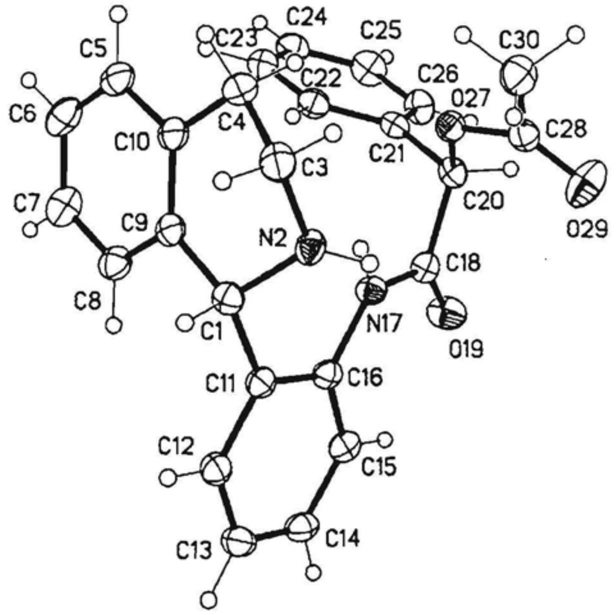
Absolute configuration of amide **A40** isoquinoline carbon was not determined with independent methods; nevertheless, retention of *R*-configuration was assumed because the rearrangement does not involve the chiral center.

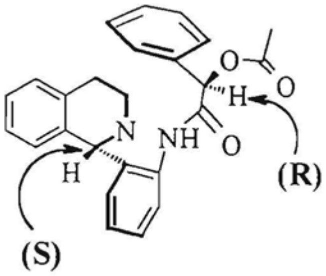
To verify the structure of the amide **A40**, it was decided to prepare it using an alternative pathway (Scheme A9). Besides, in the case of successful amide **A40** diastereomers separation, cleavage of the O-acetylmandelic auxiliary would cause fewer concerns because chiral N-unsubstituted isoquinolines do not racemize in acidic media.

Scheme A9.



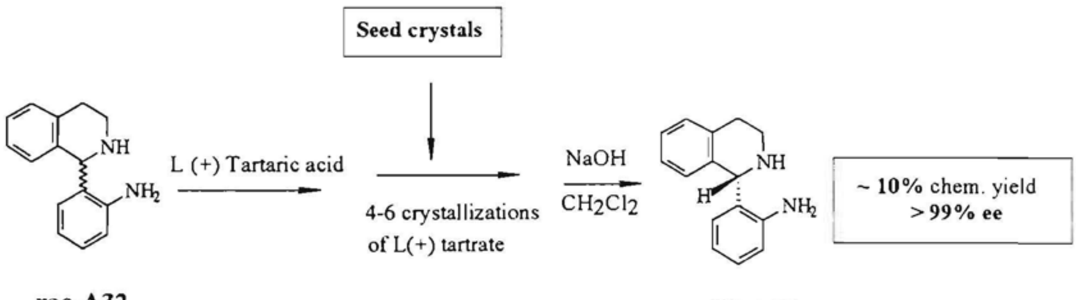
Since single diastereomer of nitro-amide **A37** could be obtained by crystallization technique, this approach was also applied to optical purification of **A40**. Two crystallizations afforded a single diastereomer with (*S,R*) absolute configuration according to X-rays analysis:





(S,R)-A40

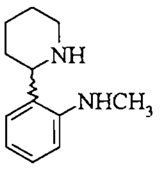
Hydrolytic cleavage of O-acetylmandelic auxiliary in refluxing 1N HCl for 4 hours proceeded without the complications encountered in the case of amide **(*R,R*)-A37**, and desired optically pure diamine **(*S*)-A32** was isolated in 95% yield (see Scheme A9). Thus, O-acetylmandelic acid turned out to be highly efficient chiral auxiliary for resolution of racemic anilino-isoquinoline **A32**. From the other hand the chiral reagent is too expensive[C] to be employed for preparative scale synthesis. This shortage was overcome by combination of chiral auxiliary mediated racemates resolution with diastereomeric salts crystallization technique. Thus, optically pure (*S*)-diamine **A32** was treated with *L*(+) tartaric acid and the resulting salt used as the seed in crystallization of racemic diamine **A32** salt with L(+)-tartaric acid.



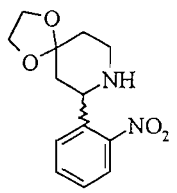
rac-A32 **(S)-A32**

(C) Aldrich, 21.66 DM / g.

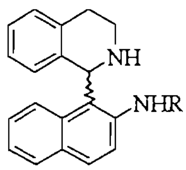
Usually 4 to 6 crystallizations with seed crystals were required to obtain enantiomerically pure diamine **A32** in ca. 10% overall chemical yield. The method is relatively inexpensive because once the seed crystals are generated they can be retrieved after a successful prep-scale crystallization routine. Moreover, both chiral tartaric acid and diamine can be recovered by a simple acid-base extractive workup. At the same time, the procedure is fairly laborious and since diastereoselective crystallization is a relatively slow process, it takes 2-3 weeks to complete the whole crystallization cycle from racemate to pure single enantiomer. Another important drawback is that the method gives access only to optically active N-unsubstituted anilino-3,4-dihydroisoquinoline **A32** and various derivatives that could be prepared from this chiral diamine. Meanwhile, analogues such as 1-aryl-piperidines **A34**, **A35**, as well as various 1-naphthyl-isoquinolines **A43**, apparently would require development of different resolution conditions, which is, as mentioned above, a laborious and time consuming process.



A34



A35



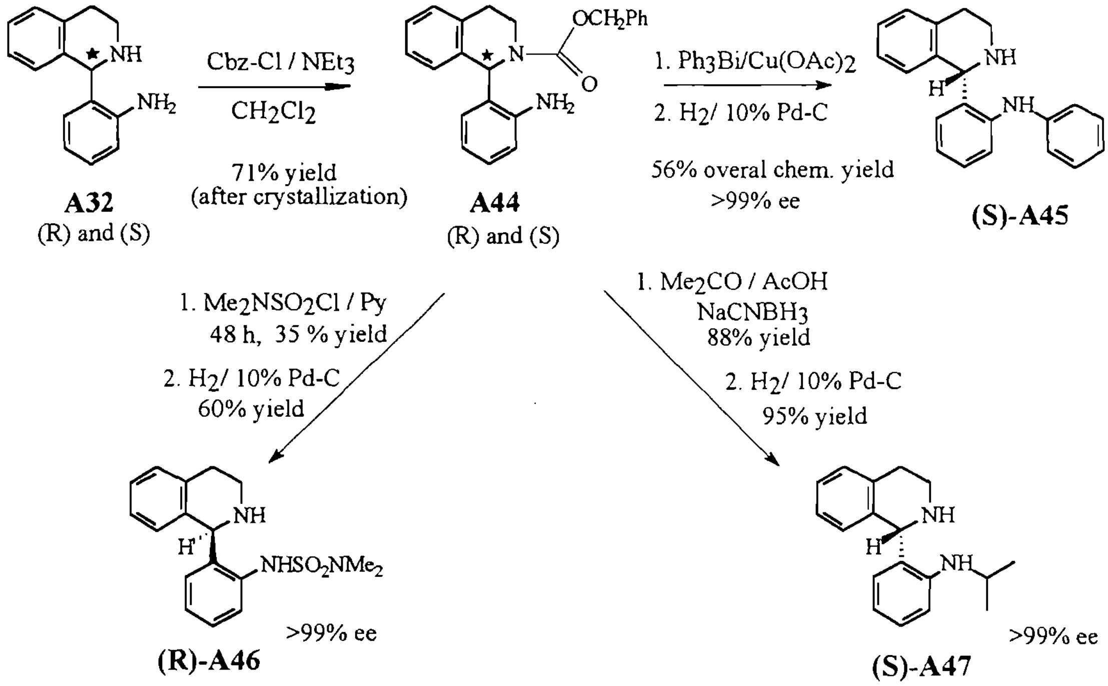
A43

Although it is not an ideal route to the desired chiral 1-anilino-isoquinolines, seed crystals mediated diastereomeric salts crystallization technique afforded a reasonable quantity of chiral starting material **A32** for synthesis of various derivatives.

4. Synthesis of chiral 1,2,3,4-tetrahydroisoquinolines as asymmetric proton donors.

Protection of the more reactive benzylic nitrogen as O-benzylcarbamate **A44** allowed to prepare various chiral diamine **A32** analogs (Scheme A10).

Scheme A10.



Thus, N-phenylation according to the Barton procedure[23] with Ph_3Bi and $Cu(OAc)_2$, followed by the N-protecting group hydrogenolysis, afforded chiral N-phenylaniline **(*S*)-A45** in 56% overall yield with > 99% ee (Scheme A10).[D] N-isopropyl-diamine **(*S*)-A47** was readily obtained by reductive alkylation procedure. Sulfamoylamide **(*R*)-46** was synthesized in a low 21% overall yield, and the critical step (35% yield) was N,N-dimethylsulfamoyl group introduction in aniline **A44**. Side-reactions in this transformation will be discussed in Chapter B.

All optically active diamines **A32**, **A33a,** **A33c** and **A45-A47** were examined as asymmetric proton donors in deracemization of various lithium enolates derived from amides and esters (for results and discussion see Chapter C).

(D) It is noteworthy to mention that all attempts to resolve racemic diphenylamine **A45** with various chiral acids in different solvents were completely unsuccessful.

5. Summary.

1. N-phthalyl group is the best protection for aniline in Bischler-Napieralski reaction. Nitro-substituted β-phenethylamide is superior to N-protected analogues. Cyclization of *ortho*-bromo(or chloro)benzoyl-β-phenethylamides and halogen displacement by liquid ammonia or lower alkylamines is the method of choice for the synthesis of 1-anilino-3,4-dihydroisoquinolines.

2. Resolution of racemic tetrahydroisoquinolines by diastereomeric salts crystallization technique requires an extensive series of trial-and-error procedures for every particular substrate. Moreover, the method was efficient only for resolution of N-methylanilines **A33a** and **A33c**.

3. Chiral O-acetylmandelic acid is an excellent resolving agent for isoquinolines with nitrobenzene and aniline subunit **A38** and **A32**. Complications with chiral auxiliary removal after resolution of nitro-amide ***(R,R)*-A37**, however, preclude its practical application. In contrast, the O-acetylmandelyl group was successfully cleaved in mandelyl-diamine ***(S,R)*-A43**, affording an optically pure (> 99% ee) desired key compound ***(S)*-A32**. The relatively high cost of the chiral reagent makes the method too expensive for preparative scale synthesis.

4. The combining of (*R*)-O-acetylmandelic acid mediated racemic diamine **A32** resolution as a method for seed crystals preparation with diastereomeric tartrates crystallization technique gave access to a reasonable amount of non-racemic diamine ***(S)*-A32**. The chiral material was further employed for the synthesis of various analogs as asymmetric proton donors.

6. References.

1. (a) Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates and Resolutions*; Krieger Publishing Company: Florida, 1994. (b) Newmann, P. *Optical Resolution Procedures for Chemical Compounds; Amines and Related Compounds*; Riverdale, N.Y.: Optical Resolution Information Center, 1984. (c) "Chemical Separation of Enantiomers *via* Diastereomers" Eliel, E.L.; Wilen, S.H. in *Stereochemistry of Organic Compounds;* Wiley&Sons, New York, 1994; pp 322-381.

2. (a) "Deracemization via Highly Enantioselective Enolate Protonation Using a Chiral Aniline as the "Acid" " Vedejs, E.; Lee, N.; Sakata, S.T. *J. Am. Chem. Soc.* **1994**, *116*, 2175. (b) "Catalytic Asymmetric Protonation of Amide Enolates: Optimization of Kinetic Acidity in the Catalytic Cycle" Vedejs, E.; Kruger, A.W. *J. Org.Chem.* **1998**, *63*, 2792.

3. (a) "Tetrahydroisoquinolino[2,1-*d*][1,4]benzodiazepines. Synthesis and Neuropharmacological Activity" Ott, H.; Hardtmann, G.; Denzer, M.; Frey, A.- J.; Gogerty, J. H.; Leslie, G. H.; Trapold, J. H. *J. Med. Chem.* **1968**, *11*, 777. (b) "6-Amino-8,9-dihydro-13bH-isoquinolo[2,1-c]quinazolines and intermediates thereof" Ott, H. *U.S.Patent 3,297,696,* **10 Jan 1967**, 9 pp.; *Chem.Abstr.* **1967**, *66:* 65505a.

4. (a) Bischler-Napieralski cyclization: "The Preparation of 3,4-Dihydroisoquinolines and related compounds by the Bischler-Napieralski reaction" Whaley, M.; Govindachari, T.R. *Org. Reactions* **1951**, *6*, 74. (b) For Pictet-Spengler see "The Pictet-Spengler Synthesis of Tetrahydroisoquinolines and Related Compounds" Whaley, W.M.; Govindachari, T.R. *Org. Reactions* **1951**, *6*, 151. (c) Pomeranz-Fritsch reaction: "The Synthesis of Isoquinolines by the Pomeranz-Fritsch Reaction" Gensler, W.J. *Org. Reactions* **1951**, *6*, 191. (d) Schlittler-Muller cyclization: Norman, R.O.C.; Coxon, J.M. in *Principles of Organic Synthesis,* 3rd ed, Blackie Academic & Professional, London,1993, p.708.

5. (a) "The Mechanism of the Bischler-Napieralski Reaction" Nagubandi, S.; Fodor, G. *J.Heterocycl.Chem.* **1980**, *17*, 1457. (b) "Correlation of the von Braun, Ritter, Bischler-Napieralski, Beckmann and Schmidt Reactions via Nitrilium Salt Intermediates" Nagubandi, S.; Fodor, G. *Tetrahedron,* **1980**, *36*, 1279. (c) "Abnormal Products in the Bischler-Napieralski Isoquinoline Synthesis" Doi S.; Shirai N.; Sato, Y. *J.Chem.Soc.Perkin Trans.1* **1997**, 2217.

6. "Derivate des 3,4-Dihydro-isochinolins" Lora-Tamayo, M.; Madroñero, R.; Muñoz, G.G. *Chem.Ber.* **1959**, *93*, 289.

7. "2,4-Diaminotoluene" Mahood, S.A.; Schaffner, P.V.L. *Org.Synth. Coll.Vol. II* **1943**, 160.

8. (a) "Copper Assisted Nucleophilic Substitution of Aryl Halogen" Lindley, J. *Tetrahedron*, **1984**, *40*, 1433. (b) "Aryllead Triacetates: Regioselective Reagents for N-Arylation of Amines" Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.-P.; Guiry, P.J. *J.Chem.Soc. Perkin Trans. 1* **1991**, 2095. (c) for a recent rewievs on Pd- and Ni-catalyzed aromatic amination see: "Rational Development of Practical Catalysts for Aromatic Carbon-Nitrogen Bond Formation" Wolfe, J.P.; Wagaw, S.; Marcoux, J.-F.;

Buchwald, S. L. *Acc.Chem.Res.* **1998**, *31*, 805. "Carbon-Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides" Hartwig, J.F. *Acc.Chem.Res.* **1998**, *31*, 852.

9. "Convenient Synthesis of Some Purine 8,5'-Imino Cyclonucleosides" Sasaki, T.; Minamoto, K.; Itoh, H. *J.Org.Chem.* **1978**, *43*, 2320.

10. "Bromination of Trifluoromethylbenzenes" McBee, E.T.; Sanford, R.A. *J.Am.Chem.Soc.* **1950**, *72*, 1651.

11. "The Synthesis of 2-Chlorophenyl Derivatives of Group V" Al-Jabar, N.A.; Massey, A.G. *J.Organomet.Chem.* **1985**, *288*, 145.

12. "Is N,N,N'N'-Tetramethylethylenediamine a Good Ligand for Lithium?" Collum, D.B. *Acc.Chem.Res.* **1992**, *25*, 448.

13. "Sulfinic Acids and Related Compounds 23. Preparation of Sulfinic Acids by the Reaction of Sulfonyl Halides with Thiols" Lee, C.; Field, L. *Synthesis* **1990**, 391.

14. "*p*-Acetaminobenzenesulfonyl Chloride" Smiles, S.; Stewart, J. *Org.Synth. Coll. Vol. I*, **1941**, 8.

15. "O and S Methylation of the Ambident *p*-Toluenesulfinate Anion" Meek, J.S.; Fowler, J.S. *J.Org.Chem.* **1968**, *33*, 3422.

16. "Reactions of Sodium Borohydride in Acidic Media; III. Reduction and Alkylation of Quinoline and Isoquinoline with Carboxylic Acids" Gribble, G.W.; Heald, P.W. *Synthesis*, **1975**, 650.

17. Dr. Hong-Wei, Y. private communication.

18. (a) For a use of mandelic acid see: "Resolution and Use in α-Amino Acid Synthesis of Imidazolidinone Glycine Derivatives" Fitzi, R.; Seebach, D. *Tetrahedron*, **1988**, *44*, 5277. "A New C_2 Chiral Secondary Amine" Whitesell, J.K.; Minton, M.A.; Chen, K.-M. *J. Org. Chem.* **1988**, *53*, 5388. "Design of Resolving Reagents: *p*-Substituted Mandelic Acids as Resolving Reagents for 1-Arylalkylamines" Kinbara, K.; Sakai, K.; Hashimoto, Y.; Nohira, H.; Saigo, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1539. (b) Amine resolution *via* crystallization of O-Ac madelates: "A Stable and Easily Prepared Catalyst for the Enantioselective Reduction of Ketones. Applications to Multistep Syntheses" Corey, E.J.; Bakshi, R.K.; Shibata, S.; Chen, C.-P., Singh, V.K. *J.Am.Chem.Soc.* **1987**, *107*, 7925. (c) HPLC resolution of O-Me mandelylamides: "Resolution of 1-Methyl-2-propynylamine via Chromatographic Separation of its Diastereomeric *O*-Methylmandelic Amides" Nilsson, B.M.; Hacksell, U. *Acta Chem. Scand., Ser. B* **1988**, *B42*, 55.

19. (a) Dr. Daugulis, O. private communication. (b) for a related succesful HPLC separation of O-Ac-mandelylamide diastereomers see "Isothiocyanate-Substituted κ-Selective Opioid Receptor Ligands Derived form *N*-Methyl-*N*-[(1*S*)-1-phenyl-2-(1-

pyrrolidinyl)ethyl]phenylacetamide" Weerawarna, S.A.; Davis, R.D.; Nelson, W.L. *J.Med.Chem.* **1994**, *37*, 2856.

20. (a) March, J. in *Advanced Organic Chemistry*, 4th ed.; Wiley&Sons: New-York, 1992; pp 448-449. (b) "Reduction of Amides" Hollingworth, G.J. in *Comprehensive Organic Functional Group Transformations, vol.3,* Katritzky, A.R.; Meth-Cohn, O.; Rees, C. W., Ed.; Pergamon, 1995; pp. 85-86. (c) for a use of $LiAlH_4$ see "Asymmetric Synthesis and Enantioselectivity of Binding of 1-Aryl-1,2,3,4-tetrahydroisoquinolines at the PCP Site of the NMDA Receptor Complex" Wanner, K.T.; Beer, H.; Höfner, G.; Ludwig, M. *Eur.J.Org.Chem.* **1998**, 2019.

21. "Asymmetric Synthesis of the Benzoquinoid Ansamycin Antitumor Antibiotics: Total Synthesis of (+)-Macbecin" Evans, D.A.; Miller, S.J.; Ennis, M.D. *J.Org.Chem.* **1993**, *58*, 471.

22. "Mixed Solvents Containing Methanol as Useful Reaction Media for Unique Chemoselective Reductions with Lithium Borohydride" Soai, K.; Ookawa, A. *J.Org.Chem.* **1986**, *51*, 4000.

23. "Copper Salts Catalysis of N-Phenylation of Amines by Trivalent Organobismuth Compounds" Barton, D.H.R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1987**, *28*, 887.

Chapter B

Synthesis of Chiral Proton Donors via Catalytic Asymmetric Transfer Hydrogenation

1. Introduction to the catalytic enantioselective reduction of cyclic imines.

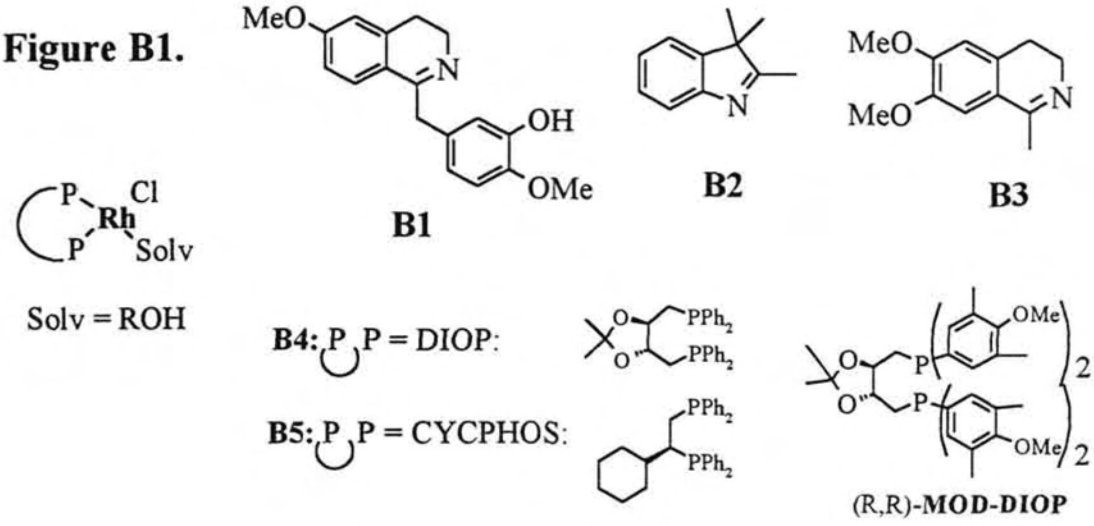
The most direct route to chiral isoquinolines is the resolution of racemates using diastereomeric salts crystallization technique.[1] Although chiral acids used for amines resolution can be quantitatively recovered, the process is highly substrate dependent and success often relies on chemist's fortune (see Chapter A). Both asymmetric synthesis of optically active isoquinolines[2] and diastereoselective reduction of dihydroisoquinolines[3] usually employs *stoichiometric* amount of chiral building blocks, auxiliaries or chiral reagents. Since chiral auxiliaries and reducing agents can not be recovered, overall asymmetric synthesis process usually is expensive. *Catalytic* enantioselective reduction is an important alternative to these techniques, because a large quantity of the chiral compound can be produced using a small amount of a chiral catalyst.

In contrary to catalytic asymmetric carbonyl group reduction, corresponding reaction for imines is much more less developed.[3] The subsequent literature review covers the most important examples of catalytic enantioselective reduction of cyclic imines. Particular attention will be paid to 1-aryl substituted cyclic imines as well as 3,4-dihydroisoquinolines because the main purpose is to find the most suitable and efficient method for asymmetric synthesis of chiral tetrahydroisoquinolines with an aniline subunit.

1.1. Rhodium and iridium catalyzed asymmetric hydrogenation and hydrosilylation.

Rhodium (I) chloride modified with various chiral bidentate phosphorous ligands was the first transition metal catalyst applied for asymmetric C=N bond hydrogenation. In contrast to high enantioselectivities observed in hydrogenation of various acyclic substrates (up to 95% ee for acyclic imines and 97% ee for hydrazones),[4] only very limited success has been achieved in the case of cyclic imines.[5] While reduction of dihydroisoquinoline **B1** with *in situ* prepared Rh(I)-DIOP catalyst **B4** afforded amine "optically pure or very nearly so after recrystallization of the hydrochloride salt",[5a] hydrogenation of imine **B2** was completely non-selective.[5b] Isoquinoline **B3** in the presence of modified Rh(I) catalyst **B5** also yielded racemic product.[5c]

Figure B1.



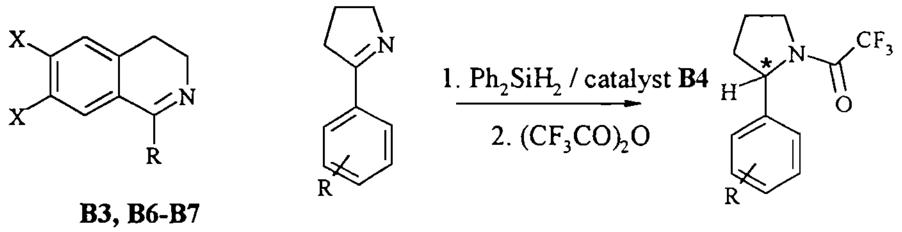
The replacement of Rh (I) with the corresponding Ir (I) catalyst completely changed the reduction course. Hydrogenation of imine **B2** with Ir(I) analogue of catalyst **B4** afforded optically enriched amine with 66% ee.[5b] Enantiocontrol was even higher employing modified ligand - MOD-DIOP (see Figure B1):

Table B1. Comparison of catalytic asymmetric imine **B2** hydrogenation in the presence of Rh(I) and Ir(I) catalysts.

Entry	Metal	Ligand	Conversion (%)	ee (%)
1	Rh(I)	DIOP	95	**0**
2	Ir(I)	DIOP	100	**66**
3	Rh(I)	MOD-DIOP	60	**0**
4	Ir(I)	MOD-DIOP	100	**81**

Somewhat more promising method for reduction of cyclic imines is rhodium (I) catalyzed asymmetric hydrosilylation procedure.[6] In 1975 *Kagan*[6a] obtained several enantiomerically enriched tetrahydroisoquinolines **B3, B6-B7**, while *Brunner and Wiegrebe* reported hydrosilylation of various 2-phenyl-3,4-dihydropyrrole derivatives[6b] **B8-B11**:

Scheme B1.



B3, B6-B7

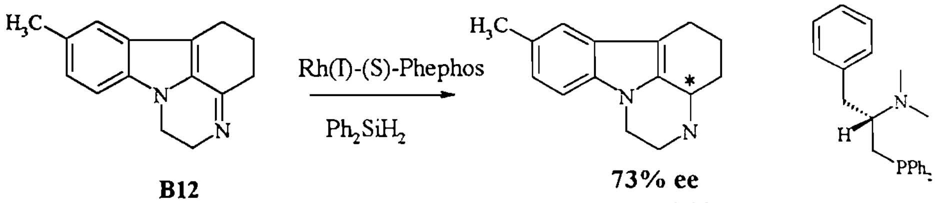
B8-B11

Pyrrolines were separated from the unreacted starting imines **B8-B11** *via* distillation of *in situ* prepared N-trifluoroacetamides. Reductions were run in toluene, however the best ee is achieved in the absence of solvent (entry 4, Table B2):

Table B2. Asymmetric hydrosilylation of various cyclic imines employing Ph_2SiH_2 and 2 mol% of *in situ* generated [RhCl]-DIOP **B4**.

Entry	Imine	R	X	Conversion (%)	ee (%)
1	**B6**	CH_2Ph	H	78	**23**
2	**B3**	CH_3	OCH_3	93	**6**
3	**B7**	CH_2Ph	OCH_3	98	**39**
4	**B8**	H	-	84	**64**
5	**B9**	2-OCH_3	-	85	**31**
6	**B10**	3,4,5-$(OCH_3)_3$	-	81	**31**
7	**B11**	4-Br	-	82	**60**

Drop in optical induction for MeO substituted substrates (entries 5-6 vs. entries 4 and 7, Table B2) was attributed to intermolecular coordination of MeO-groups to Rh. Rh(I)-Phephos catalyzed hydrosilylation procedure was also applied for the reduction of cyclic structure **B12** yielding enantiomer of the antidepressant "Pyrazidole" with 73% enantioselectivity:[6c]



B12

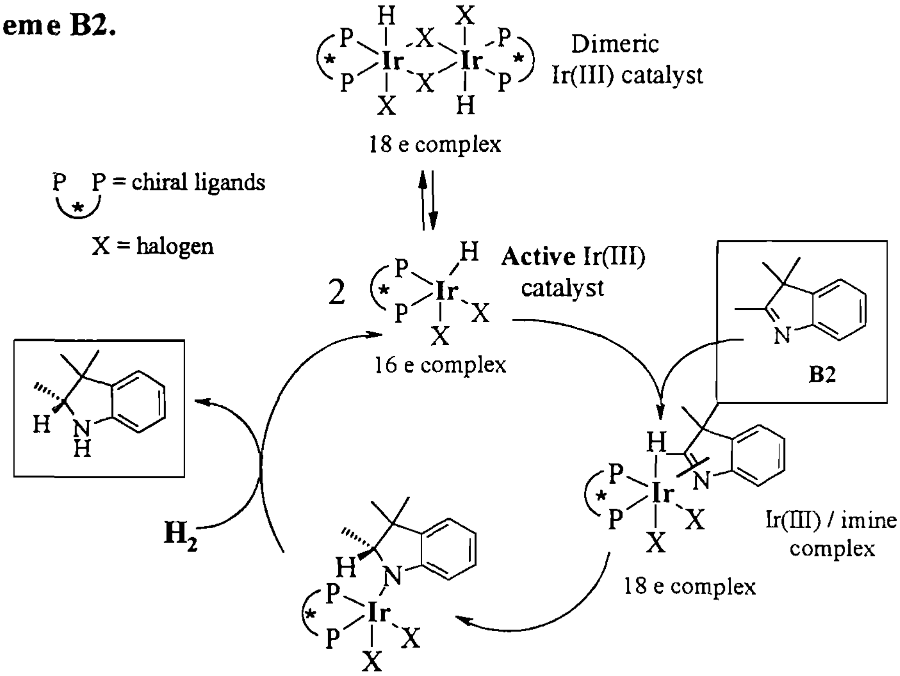
73% ee
69% yield

(S)-Phepho

In general, Rh(I)-catalyzed asymmetric reductions afford cyclic amines with moderate enantioselectivities, lower than observed using other transition metal catalysts (see also Table B1). Evidently, this is the reason why further development of asymmetric catalytic reduction methods has been based on transition metals other that Rh, such as Ir, Ru and Ti.

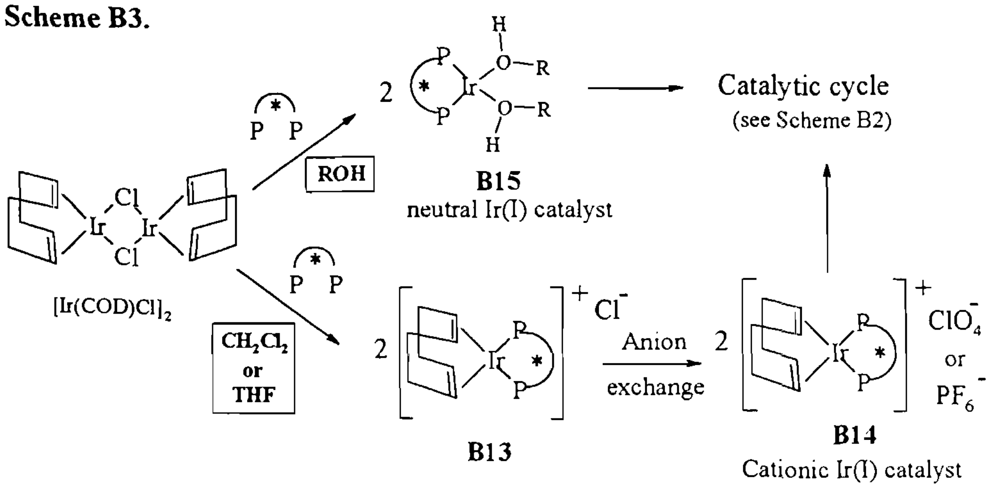
Chiral neutral Ir(III),[7] Ir(I)[8] and cationic Ir(I)[9] catalysts have been widely used in asymmetric hydrogenation of various imines. Ir(III) catalyst exists as stable and easy-handled dimer that was successfully introduced and explored by *Osborn.*[7] In the reaction mixture dimeric species equilibrate with monomers which was proposed to be the active catalyst:

Scheme B2.



In contrary, neutral as well as cationic iridium (I) catalysts usually are prepared *in situ* from commercially available chloro(1,5-cyclooctadiene)iridium (I) or chloro-(norbornadienyl)iridium (I) dimers and an appropriate chiral diphosphine ligand:

Scheme B3.



Cationic Ir(I) complex **B13** forms if catalyst preparation is carried out in CH_2Cl_2 or THF. Chlorine replacement by non-nucleophilic coordinating anion such as ClO_4^- or PF_6^- affords cationic Ir(I) catalysts **B14**, which are stable enough to be isolated and purified by recrystallization. In the presence of alcohol, however, formation of neutral complex **B15** is proposed. Catalysts **B15** usually are prepared *in situ* within minutes before hydrogenation is carried out and utilized without isolation.

Iridium catalysts of different oxidation states (Ir(I) and Ir(III)) as well as neutral and cationic Ir(I) species have been used for reduction of structurally distinct cyclic imines, so it is difficult to compare the reactivity and selectivity of catalysts. Fortunately, there are several common substrates for all catalysts - imines **B2** and **B16** and rough selectivity comparison can be made.

Figure B2.

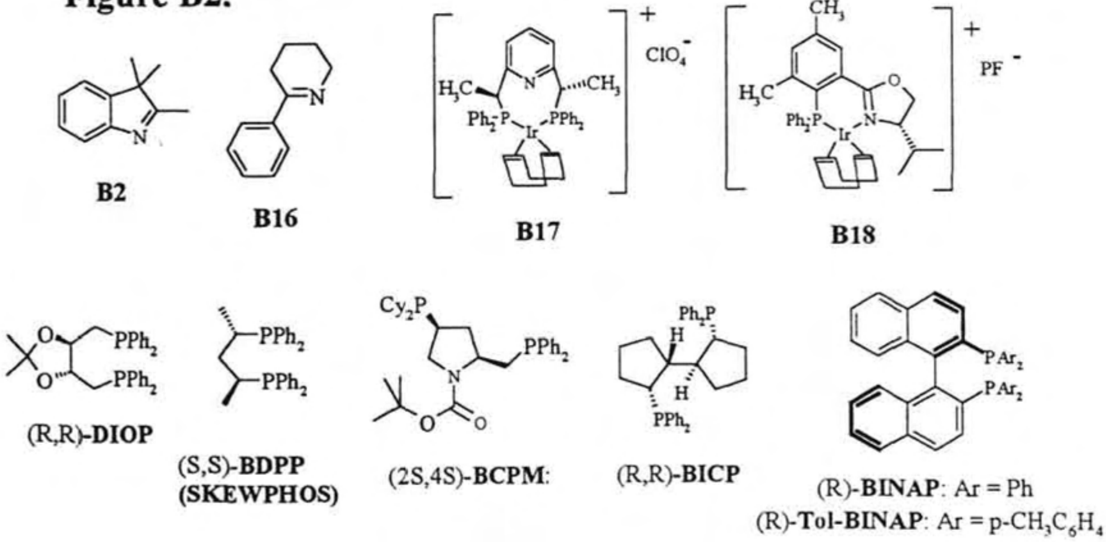


Table B3. Asymmetric hydrogenation of cyclic imines **B2** and **B16** with different iridium catalysts (see Figure B2 for ligands structure):

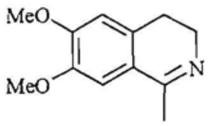
Entry	Catalyst[a]	Ligand	Imine	Pressure (atm)	Yield (%)	ee (%)	Lit. ref.
1	Ir (III)	BDPP	**B2**	40	99	**80**	7a
2	Ir (III)	DIOP	**B2**	28	99	**51**	7a
3[b]	Ir (I)	DIOP	**B2**	100	99	**66**	5b
4[b]	Ir (I)	BCPM	**B2**	100	32	**28**	8a
5[c]	Ir (I)	BCPM	**B2**	100	99	**66**	8a
6[d]	Ir (I)	BICP	**B2**	68	99	**78**	8b
7	Cationic Ir (I) **B17**		**B2**	80	99	**8**	9a
8[d]	Ir (I)	BICP	**B16**	68	99	**65**	8b
9	Ir (I)	Tol-BINAP	**B16**	60	99	**23**	8c
10	Ir (I)	Tol-BINAP	**B16**	60	46	**89**	8c
11	Cationic Ir (I) **B18**		**B16**	100	-	**64**	9b

(a) 0.2 Mol% Ir(III), 1mol% Ir(I) and 0.2 mol% catalyst **B17**. (b) Hydrogenation was carried in the presence of 2mol% $Bu_4N^+I^-$ as additive. (c) Additive: 2 mol% BiI_3. (d) Hydrogenation in the presence of 4mol% phthalimide$^-$ as additive.

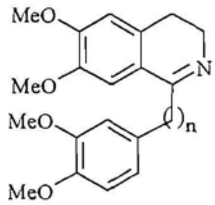
Although DIOP-modified Ir (I) catalyst is more selective than the corresponding Ir (III) species (entry 3 vs. 2), simple DIOP ligand replacement by BDPP (entry 1) makes Ir (III) catalyst enantioselectivity similar to the best Ir (I) example (entry 6; see also Table B1, entry 4). Cationic catalyst **B17** is significantly less selective than the neutral one (entry 7 vs. 6), however deactivation of the catalyst **B17** during hydrogenation is reported. In contrary, cationic Ir (I) catalyst **B18** is comparable to Ir(I)-BICP (entries 8 and 11). Thus, Table B3 shows that there is no decrease in selectivity comparing *in situ* prepared catalysts with isolated neutral Ir (III) and cationic ones. Obviously, iridium oxidation state and type of catalyst complex is a minor issue compared to chiral ligand structure that has to be optimized for each particular substrate. Additives, solvents and hydrogenation temperature are additional variables of great importance. For example, replacement of $Bu_4N^+I^-$ for BiI_3 as additive results in more than twofold enantioselectivity improvement (from 28% to 66% ee, entries 4-5), while hydrogenation temperature lowering by 50 ^{0}C (to -30^0) resulted in further increase in enantioselectivity to 91% ee. Finally, hydrogenation selectivity is sensitive also to the solvent used. Thus, hydrogenation of cyclic imine **B16** in methanol yields corresponding amine with 23% ee, while in benzene 89% ee was observed (entry 9 and 10).

Because hydrogenation success depends on many variables that have to be carefully adjusted for each particular substrate, further literature analysis will be focused mainly on asymmetric transfer hydrogenation of various isoquinolines.[10]

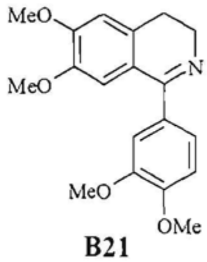
Table B4. Effects of additives, solvents and reduction temperature on Ir(I)-BCPM catalyzed asymmetric hydrogenation of 3,4-dihydroisoquinolines.[a]



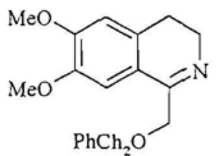
B3



B19: n=1
B20: n=2



B21



B22

Entry	Imine	Additive	Solvent	T (^{0}C)	Conv. (%)	ee (%)	Lit. ref.
1	**B3**	none	PhH-MeOH	20	90	**18**	10a
2	**B3**	BiI_3	PhH-MeOH	-	92	**12**	10a
3	**B3**	1,8-naphthalimide	PhH-MeOH	-	66	**3**	10a
4	**B3**	phthalimide	PhH-MeOH	-	96	**44**	10a
5	**B3**	phthalimide	THF	20	95	**41**	10a
6	**B3**	phthalimide	CH_2Cl_2	-	94	**70**	10a
7	**B3**	phthalimide	toluene	20	94	**79**	10a
8	**B3**	phthalimide	toluene	2-5	95	**85-93**	10a,b
9	**B19**	F_4-phthalimide	toluene	5	84	**88**	10b
10	**B20**	phthalimide	toluene	2	75	**87**	10b
11[b]	**B21**	phthalimide	PhH-MeOH	5	50	**31**	10b
12[c]	**B22**	F_4-phthalimide	toluene-MeOH	2-5	85	**86**	10c

(a) Under 100 atm hydrogen pressure and with 1 mol% of the catalyst. (b) 0.5 Mol% Ir(I)-BINAP catalyst was used. (c) In the presence of 2 mol% Ir(I)-BINAP.

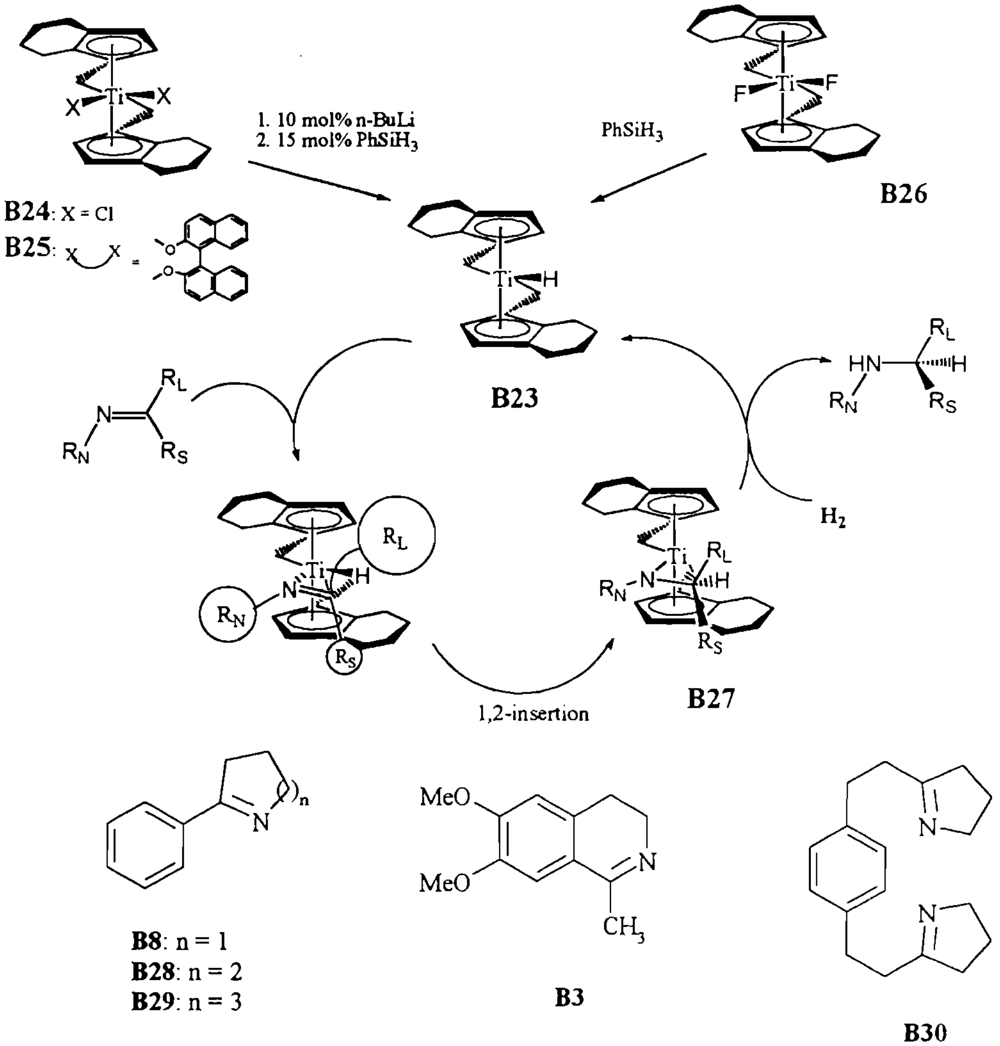
If no additive is present or an iodide such as BiI_3 and $Bu_4N^+I^-$ is added as a co-catalyst, enantioselectivities are lower than 20% ee (entries 1-2). Six-membered imides are ineffective, while five-membered imides improve ee's (entry 3 vs. 4). Clear solvents effect is observed: in less polar solvents higher selectivities are obtained (entries 4-7). The lowering of hydrogenation temperature further improves ee's (entry 8 vs. 7). Optimized conditions (entry 8) were applied for hydrogenation of various isoquinolines **B19-B22** affording chiral alkaloids or their precursors in reasonable optical purity (86-88% ee).

Enantiocontrol achieved with Ir-catalysts is relatively high (up to 93 % ee).[10a,b] Moreover, Ir-catalyst system tolerates presence of various functional groups such as nitro-group, ketones esters and nitriles.[7b] On the other hand, disadvantages of Ir-catalyzed procedure (relatively high hydrogen pressure (28-100 atm), sensitivity to temperature and solvents used) combined with need for empirical adjustment of ligand structure and additives for each particular substrate make it less attractive compared to alternative Ti and Ru catalyst systems.

1.2. Hydrogenation and hydrosilylation catalyzed by chiral titanocene catalysts.

Buchwald achieved excellent enantioselectivities and chemical yields in asymmetric hydrogenation[11] and hydrosilylation[12] of various cyclic and acyclic imines employing a chiral *ansa*-titanocene catalyst. Based on extensive mechanistic studies, *ansa*-titanocene (III) hydride **B23** was proposed to be the active hydrogenation catalyst. Because catalyst **B23** is highly reactive and air-sensitive it is generated *in situ* from air-stable chiral precatalysts **B24-B26.** Treatment of chiral *ansa*-titanocene dichloride **B24** and 1,1'-binaphth-2,2'-diolate **B25** with n-BuLi and phenylsilane under hydrogen atmosphere generates green colored solution of active catalyst **B23**. In the presence of 5 mol% catalyst reduction of various cyclic imines **B28-B30** proceeds with excellent enantiocontrol (95-99% ee) and high yields.

Scheme B4.

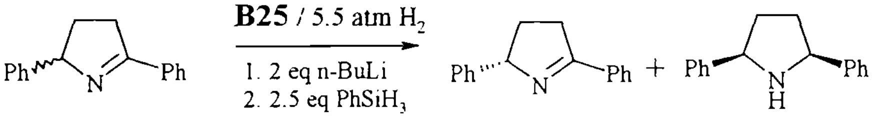


The first step of the proposed catalytic cycle is reaction of titanium (III) hydride **B23** with an imine via 1,2-insertion reaction to form titanium amide **B27**.[11c] Reduction enantioselectivity is controlled at the stage of amide **B27** formation and depends on sterical interaction between catalyst ligands and imine substituents, particularly at imine nitrogen (R_N) (Scheme B4). According to the proposed model[11c] *syn*-imine should give (*S*)-isomer of amine while *anti*-imine should afford opposite product enantiomer (*R*)-isomer. Experimental observations supported stereochemistry predicted by models (Table B5, entries 1-2, *anti*-imine vs. entries 5-6, *syn*-imine). The second step in catalytic cycle is the hydrogenolysis of amide **B27** via σ-bond metathesis process to form amine enantiomer and regenerate the titanium hydride **B23**.

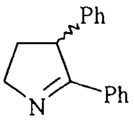
Table B5. Catalytic asymmetric hydrogenation[11a-c] (entries 1-7) and hydrosilylation[12a] (entries 8-9) of cyclic imines using chiral titanocene catalyst.

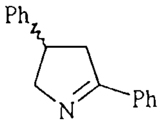
Entry	Imine	Catalyst mol%	Pressure (atm)	T (^{0} C)	Yield (%)	ee (%) (config)
1	**B8**	5	34	21	86	99 (*R*)
2	**B8**	5	5.4	65	83	99 (*R*)
3	**B28**	5	34	65	78	98
4	**B29**	5	34	45	71	98
5	**B3**	5	136	65	82	98 (*S*)
6	**B3**	5	5.4	65	79	95 (*S*)
7	**B31**	5	5.4	65	72	99
8	**B8**	0.1	-	35	96	98
9	**B30**	2	-	r.t.	64	98

Ansa-titanocene catalyzed hydrogenation was applied also for kinetic resolution of various 2,3, 2,4 and 2,5-disubstituted pyrrolines.[13] The best result was obtained in reduction of *rac*-2,5-diphenylpyrroline **B32**. The reaction was allowed to proceed to 50% conversion and enantioselectivity measured for reduction product - *cis*-2,5-pyrrolidine **B33** was 99% ee (34% yield). Unreacted enantiomer of starting material **B32** (99% optically pure) was recovered in 37% yield.



rac-**B32** (S)-**B32** 99% ee *cis*-**B33** 99% ee





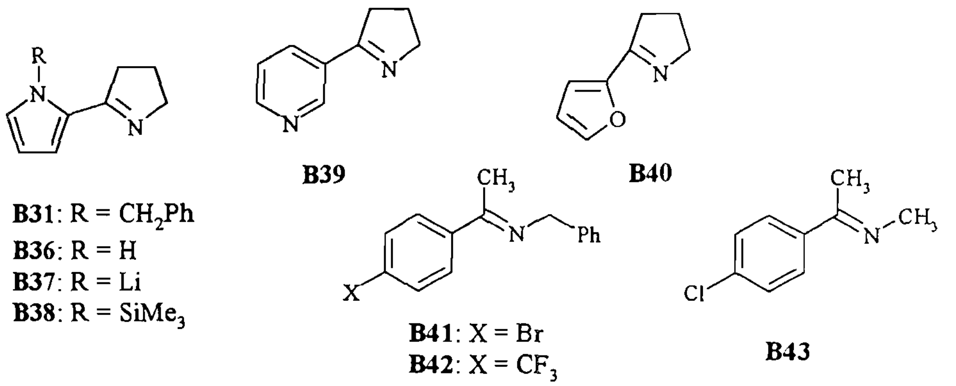
B34 **B35**

Modest result, however, was achieved for 2,3-diphenylpyrroline **B34** (75% ee for unreacted starting material), while 2,4-diphenylpyrroline **B35** showed relatively poor selectivity (49% ee for unreacted **B35**).

Although various cyclic imines are reduced with excellent enantiocontrol, relatively high hydrogen pressure (5.4-136 atm) and highly demanding (air and moisture-free) reduction conditions combined with necessity of the catalyst preactivation are important drawbacks of *Buchwald*'s hydrogenation procedure.

Even more important disadvantage is poor catalyst compatibility with various functional groups.[11b] While N-benzyl pyrrolylimine **B31** is reduced with 99% ee and in 72% chemical yield (Table B5, entry 7), free pyrrole **B36** is reported to destruct catalyst, but N-lithio and N-TMS derivatives (**B37** and **B38**, resp.) failed to react at all. Pyridyl substituted imine **B39** also failed to react, but reduction of 2-furyl-2-pyrroline **B40** could not be forced to completion even under harsh conditions, possibly due to catalyst inhibition by binding of the amine to the metal in a bidentate fashion:

Figure B3.



B31: R = CH_2Ph
B36: R = H
B37: R = Li
B38: R = $SiMe_3$

B39 **B40**

B41: X = Br
B42: X = CF_3

B43

It was also found that an imine containing an aromatic bromide **B41** deactivates the catalyst and ca. 5% debrominated product was detected. Besides, imine **B42** containing trifluoromethyl group was found to destroy catalyst. On the other hand, titanium catalyst tolerates presence of oxygenated functional groups, such as acetals, silyl ethers and alcohols (alcohols are silylated *in situ*).

More convenient precatalyst **B26** activation as well as simpler experimental procedure was achieved using hydrosilylation procedure.[12a] *Ansa*-difluoro titanocene **B26** was *in situ* converted to the active catalyst **B23** by reaction with $PhSiH_3$ (Si-F bond formation is proposed to be driving force for this reaction). Hydrosilylation proceeded at room temperature in argon atmosphere with lower catalyst loading (0.1-2 mol%) and cyclic chiral imines **B8** and **B30** were reduced with 98-99% ee and in substantially higher chemical yields (96-97%; silylamines were never isolated due to their lability) than in hydrogenation experiments (77-86%). Chiral substituted pyrrolidines were obtained with the same absolute configuration as in the case of titanium-catalyzed hydrogenation. Hydrosilylation is proposed to proceed by a catalytic cycle similar to that for hydrogenation (Scheme B4). It was also found that reaction tolerates presence of an aromatic chloride **B43**.

Recently, polymethylhydrosilane (PMHS) in the presence of *i*-$BuNH_2$ was employed as more convenient and inexpensive hydride source for the reduction of acyclic imines.[12b]

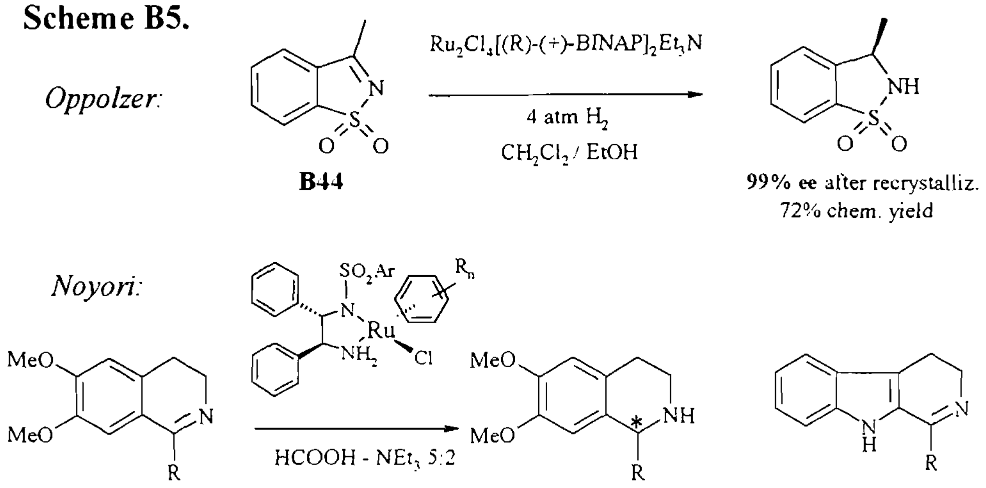
Finally, hydrosilylation procedure was successfully employed in asymmetric total synthesis of piperidine alkaloids (*S*)-Coniine and (2*R*,6*R*)-*trans*-Solenopsin A.[14]

Conclusion. Titanocene catalyzed asymmetric hydrogenation and hydrosilylation affords cyclic amines with excellent enantioselectivities (97-99% ee) and in high yields. However, due to low titanium catalyst compatibility with various functional groups at current level of development it can not be employed for synthesis of chiral anilino-isoquinolines.

1.3. Ruthenium(II) catalyzed asymmetric reduction of cyclic imines.

Although the first highly selective ruthenium catalyzed imine **B44** asymmetric hydrogenation was reported by *Oppolzer* in 1990,[15] (see Scheme B5), this remained the only attempt to employ Ru(II) catalysts for reduction of cyclic imines until 1996 when *Noyori* applied Ru(II)-catalyzed asymmetric transfer hydrogenation protocol to reduction of various cyclic imines[16] **B3**, **B19-B21** and **B45-B47**:

Scheme B5.

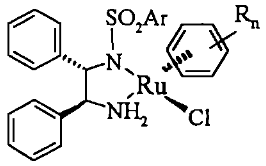


B3: R = CH_3
B19: R = 3,4-$(MeO)_2C_6H_3CH_2$
B20: R = 3,4-$(MeO)_2C_6H_3(CH_2)_2$
B21: R = 3,4-$(MeO)_2C_6H_3$
B45: R = Ph

B46: R = CH_3
B47: R = Ph

Due to excellent optical yields, operational simplicity and functional groups compatibility and selectivity Noyori procedure is regarded as breakthrough in development of methods for catalytic asymmetric isoquinolines reduction. The catalytic method is particularly useful for transfer hydrogenation of cyclic imines with ee values ranging from 90% to 97% ee:

Table B6. Asymmetric Transfer Hydrogenation of Imines by Chiral Ru(II) complexes **B48-B50**:

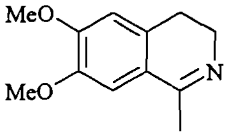


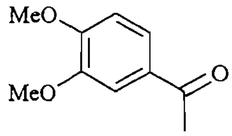
B48: η^6(arene) = *p*-cymene; Ar = 4-$CH_3C_6H_4$
B49: η^6(arene) = *p*-cymene; Ar = 2,3,4-$(CH_3)_3C_6H_4$
B50: η^6(arene) = benzene; Ar = 1-naphthyl

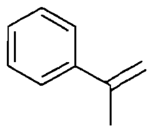
Entry	Imine	Catalyst	S/C	Time (h)	Yield (%)	ee (%)
1	**B3**	**B48**	200	3	99	**95**
2	**B3**	**B48**	1000	12	97	**94**
3	**B19**	**B49**	200	7	90	**95**
4	**B20**	**B49**	200	12	99	**92**
5	**B21**	**B50**	100	12	99	**84**
6	**B45**	**B50**	200	8	99	**84**
7	**B46**	**B48**	200	5	86	**97**
8	**B46**	**B48**	1000	12	89	**93**
9	**B47**	**B48**	200	5	83	**96**

Reduction of 1-methyl-3,4-dihydroisoquinoline **B3** proceeds with enantioselectivity comparable to that obtained using *ansa*-titanocene catalyst. The experiment simplicity, however, makes this method more attractive than *Buchwald's* procedure (compare Table B6, entries 1-2 and Table B5, entry 4). Substituted 1-aryl (entries 5-6, Table B6) and 1-arylalkyl-3,4-dihydroisoquinolines (entries 3-4) are reduced in higher optical and chemical yields compared also to Ir(I)-catalyst[10b] (Table B4, entries 9-11). Asymmetric reduction is successfully extended to the synthesis of optically active indoles from the corresponding imines **B46-B47** (entries 7-9).

Transfer hydrogenation is reported to proceed smoothly in various aprotic polar solvents such as DMF, DMSO, MeCN and CH_2Cl_2, using inexpensive, stable and easy-handled formic acid-triethylamine 5:2 azeotropic mixture as a hydrogen source. Generally, Ru catalyst is prepared from $[RuCl_2(\eta^6\text{-arene})_2]_2$ and N-sulfonylated 1,2-diphenylethylenediamine, however, the same result can be obtained using catalyst formed *in situ*. The C=N/C=O chemoselectivity is superior to that observed in the stoichiometric reduction using $NaCNBH_3$ and imine **B3** can be reduced even in acetone. A competitive experiments show that imine **B3** is >1000 times more reactive than structurally related acetophenone **B51** or α-methylstirene **B52**.



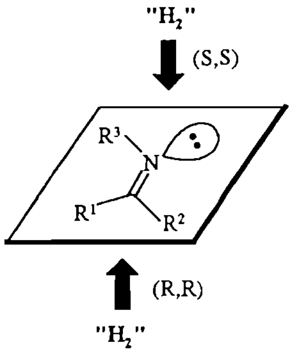


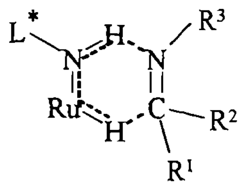


B3 **B51** **B52**

The hydrogenation rate and enantioselectivity is influenced by Ru catalyst (η^6-arene and arylsulfonyl group in catalyst ligand) as well as by the solvent and reduction temperature used.[16c] The general sense of asymmetric induction with Ru(II)-catalyst **B48-B50** system is illustrated in Figure B4. In the stereodetermining hydrogen-transfer step, Ru catalyst discriminates between the enantiofaces at the sp^2 nitrogen atom of the imine, generating a stereogenic sp^3 carbon.

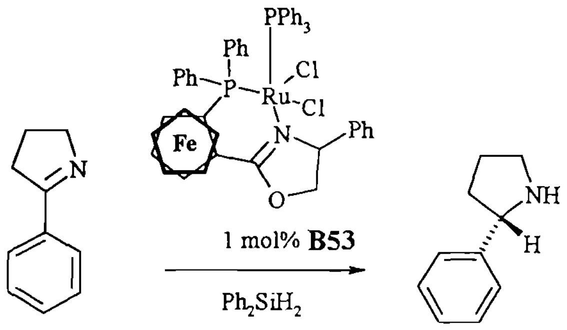
Figure B4.





Hydride transfer from active catalyst - Ru-hydride species to an imine requires out-of-plane interaction between the Ru-H moiety and C=N bond. *Noyori*[16b] suggests that N-H linkage in Ru catalyst **B48-B50** can stabilize a transition state through hydrogen bonding with imine nitrogen (see Figure B4).

Recently, chiral Ru-(oxazolinylferrocenyl)phosphine catalyst **B53** has been employed in asymmetric hydrosilylation of 2-aryl-3,4-dihydropyrrole **B8**.[17]



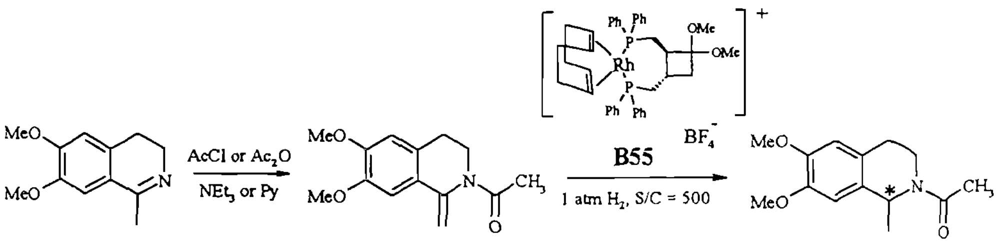
B8

Corresponding (*S*)-amine was isolated with 88% ee and in 60% yield. Analogous Rh(I) catalyst showed considerably lower selectivity (34% ee) (see also Table B2, entry 4).

Conclusion. Ru(II) catalyzed transfer hydrogenation of cyclic imines affords the highest enantioselectivities for almost all substrates tested. In combination with operational simplicity it is the method of choice for the synthesis of chiral isoquinolines containing an aniline subunit.

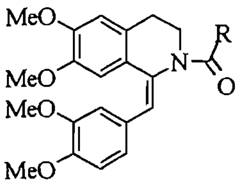
1.4. Asymmetric hydrogenation of cyclic enamides.[18]

Being closely related to olefins hydrogenation, asymmetric reduction of cyclic enamides is one of the most efficient tool for highly enantioselective synthesis of 1-alkyl and 1-arylalkyl substituted isoquinolines.[19] Initially, chiral Rh(I)-complexes[19a,b] such as **B55** were employed affording N-acetyl-1-methyl-1,2,3,4-tetrahydroisoquinoline with reasonable enantioselectivities (81% ee in the best case): **Scheme B6.**

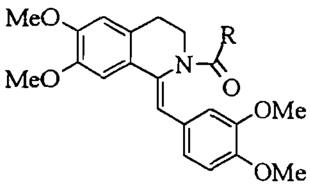


B3 **B54** **81% ee** 99% conversion

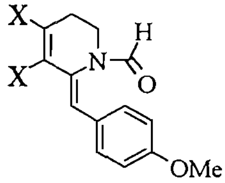
The method became synthetically important after *Noyori* had shown[19c,d] that various N-acylated 1-alkylidene and 1-benzylidene isoquinolines can be hydrogenated in the presence of Ru(II)-BINAP catalyst with excellent enantioselectivities (up to 100% ee, see Table B7).



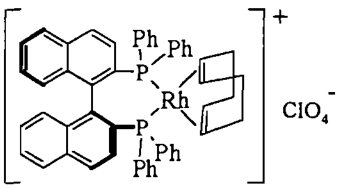
(E)-B56



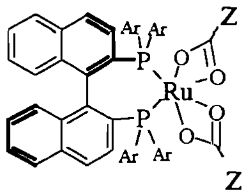
(Z)-B56



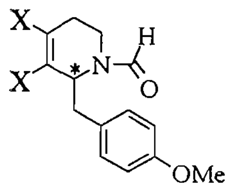
(Z)-**B57**: X = CH_3
(Z)-**B58**: X = $(CH_2)_4$



(S)-**B61**



(R)-**B62**: Z=CH_3; Ar=Ph
(R)-**B63**: Z=CF_3; Ar=4-$CH_3C_6H_4$



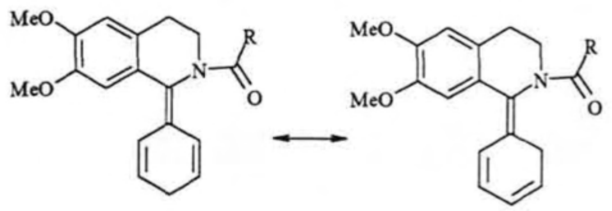
B59: X = CH_3
B60: X = $(CH_2)_4$

Table B7. Asymmetric hydrogenation of 2-acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines **B54, B56-B58**.

Entry	Substrate	Catalyst	S/C	Pressure (atm)	T (^{0}C)	Yield (%)	ee (%)
1	(Z)-**B56** (R=CH_3)	(S)-**B61**	100	4	30	95	75
2	**B54**	(S)-**B62**	50-200	4	-	100	**96**
3	(Z)-**B56** (R=H)	(R)-**B62**	200	1	30	100	**>99.5**
4	(Z)-**B56** (R=H)	(R)-**B62**	200	100	30	100	**96**
5	(Z)-**B56** (R=H)	(R)-**B62**	200	4	0	0	-
6	(Z)-**B56** (R=H)	(R)-**B62**	200	100	60	98	**91**
7	(Z)-**B56** (R=CH_3)	(R)-**B62**	200	4	24	100	**>99.5**
8	(E)-**B56** (R=CH_3)	(R)-**B62**	200	4	24	<3	-
9	(Z)-**B56** (R=CF_3)	(R)-**B62**	200	4	24	10	-
10	(Z)-**B56** (R=tBu)	(R)-**B62**	200	4	24	100	**50**
11	(Z)-**B57**	(R)-**B63**	50-200	100	-	99	**96**
12	(Z)-**B58**	(R)-**B63**	50-200	100	-	98	**98**

The comparison of catalysts clearly shows that Ru-complex is superior to cationic Rh(I)-catalyst (entry 7 vs. 1 and entry 2 vs. Scheme B6). Extensive studies revealed that N-acyl group is crucial for the reaction because it acts as a binding tether to the catalytic metal center. Z-olefin geometry is important for high reactivity and enantioselectivity.[19d] E-olefin could not be reduced under standard conditions (entry 8 vs. 7). Hydrogenation occurs regioselectively at the enamide part leaving tetra-substituted olefinic linkage intact (entry 11-12, product amines **B59-B60**). Both N-formyl and N-acetyl amides can be used (entries 3 and 7), but the strongly electron-withdrawing CF_3CO-group and bulky pivaloyl group decreases reactivity and/or enantioselectivity (entries 9-10 vs. 3 and 7). The reaction usually is run under 1-4 atm of hydrogen at 30^0C. Increased temperature and pressure results in lower enantioselectivity (entry 4 and 6 vs. 3), while diminishing the temperature to 0 ^{0}C causes inhibition of the reaction (entry 5 vs. 3).

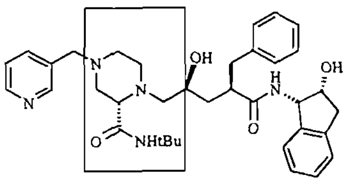
Despite the excellent enantioselectivities achieved for a variety of isoquinolines, hydrogenation can not be employed for reduction of 1-aryl substituted substrates (formation of the corresponding enamide would require non-aromatic, unstable quinone-type structure **B64**):



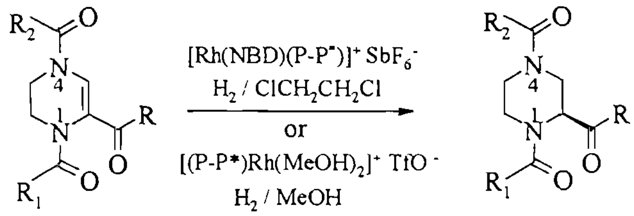
B64

Asymmetric hydrogenation has been successfully employed for large-scale synthesis of piperazine-2-carboxamide **B66**,[20] building block of *Merck* HIV protease inhibitor *Indinavir®*.

Scheme B7.

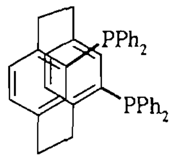


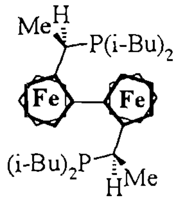
Indinavir®



B65 **B66**

a: R = NHtBu, R_1 = BnO, R_2 = t-BuO
b: R = OMe, R_1 = Me, R_2 = t-BuO
c: R = NHtBu, R_1 = H, R_2 = t-BuO
d: R = NHtBu,R_1 = t-BuO, R_2 = PhO

P-P* : [2,2]-Phanephos = 

P-P* : i-BuTRAP = 

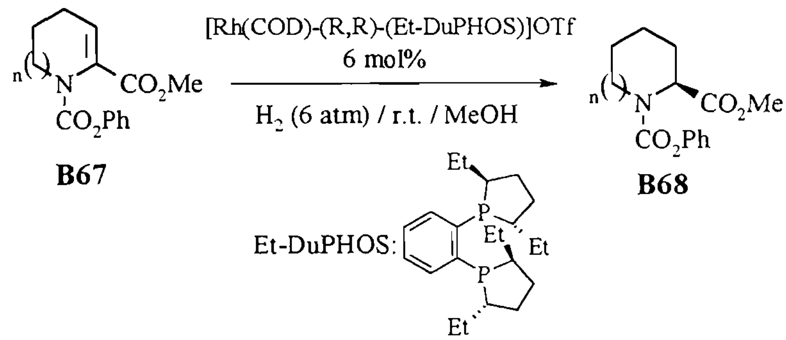
The enantioselectivity of reduction was found to depend on electronic character of olefinic double bond, which can be regulated by N-protecting groups, particularly at nitrogen in 4th position. N^4-Boc group was found to be the best. Careful optimization of reduction conditions for each particular substrate combined with extensive screening of diphosphine ligands resulted in highly enantioselective large-scale synthesis of chiral piperazine **B66**.

Table B8. Optimized conditions for asymmetric hydrogenation of cyclic enamide **B65** in the presence of Rh(I) catalysts.

Entry	Enamide	Ligand (P-P*)	Catalyst mol%	T (^{0}C)	Pressure (atm)	Yield (%)	**ee (%)**	Lit. ref.
1	**B65a**	BINAP	2	40	70	96	**99**	16a
2	**B65b**	[2,2]-Phanephos	-	-40	1.5	>99	**86**	16b
3	**B65c**	BINAP	7	40	100	>99	**97**	16c
4	**B65d**	i-BuTRAP	1	50	1	85	**96**	16d

The hydrogenation of enamides has been recently extended also to the synthesis of cyclic amino acids **B67** and **B68** with various ring size.[21a]

Scheme B8.



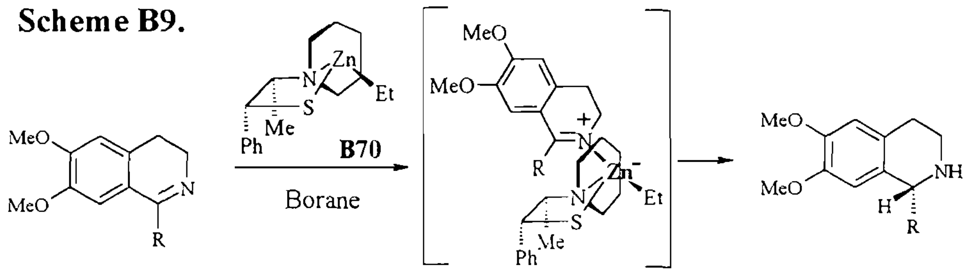
	Size	Chem(%)	ee(%)
a:	n=0	84	**0**
b:	n=1	95	**27**
c:	n=2	96	**95**
d:	n=3	96	**97**
e:	n=4	97	**95**
f:	n=8	96	**91**
g:	n=11	86	**86**

Excellent enantioselectivities were achieved in the case of medium **B68c-e** and large ring size **B68f-g** while 5- and 6-membered cyclic enamides **B68a-b** were obtained either racemic or with low ee's. In contrary, *Comins* was able to reduce enamide **B67b** with reasonable 80%ee employing [(*S*)-BINAP]Ru catalyst.[21b]

1.5. Catalytic enantioselective imines reduction by borane.

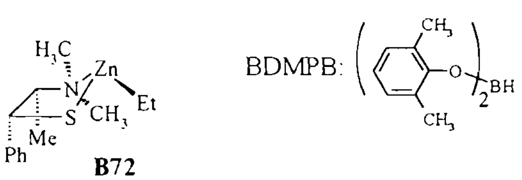
Despite to the very few reports on successful borane-mediated catalytic asymmetric reduction of imines, potentially it is an alternative to transition metals catalyzed hydrogenation, especially because there is no need of high-pressure equipment. Various chiral boranes have been used as catalysts and chiral Lewis acid complexation to nitrogen lone pair allowed to discriminate imine enantiofaces by a non-chiral hydride source, usually borane (BH_3-THF, BH_3-SMe_2 *etc.*). Enantioselective catalytic reduction has been applied mainly for acyclic imines and only recently *Kang* reported enantioselective reduction of cyclic imines - 3,4-dihydroisoquinolines in the presence of 20 mol% chiral thiazazincolidine catalyst **B70**:[22]

Scheme B9.



B71

B3: R = CH_3
B19: R = 3,4-$(MeO)_2C_6H_3CH_2$
B21: R = 3,4-$(MeO)_2C_6H_3$
B73: R = 3,4,5-$(MeO)_3C_6H_2CH_2$



B72

The reduction is assumed to proceed *via* formation of enantioface-selective complex **B71** between chiral Lewis acid **B70** or **B72** and isoquinoline nitrogen lone pair and the complex geometry controls the reaction stereoselectivity. Borane-THF is the best reducing agent for all substrates (entries 1-3, Table B9), except of 1-aryl-3,4-dihydroisoquinoline **B21**, where BDMPB is superior (entry 5 vs. 4):

Table B9 Reduction of 3,4-dihydroisoquinolines with 20 mol% thiazazincolidine catalyst in toluene at -5 ^{0}C:

Entry	Imine	Catalyst	Borane	Yield (%)	**ee (%)**
1	**B3**	**B70**	BH_3-THF	65	**86**
2	**B19**	**B70**	BH_3-THF	83	**78**
3	**B73**	**B70**	BH_3-THF	25	**76**
4	**B21**	**B70**	BH_3-THF	92	**24**
5	**B21**	**B72**	BDMPB	69	**56**

1.6. Summary.

Literature analysis was carried out to reveal the most suitable method for catalytic asymmetric synthesis of chiral isoquinolines with aniline subunit. The following conclusions can be made:

1. Rh(I) and Ir(I) catalyzed asymmetric hydrogenation and hydrosilylation procedure requires a careful optimization of catalyst, additives and reduction conditions and in the best case affords chiral isoquinolines with lower enantioselectivity than the corresponding titanocene and Ru(II) catalyzed processes.

2. Despite to excellent enantiocontrol, several limitations in the case of *ansa*-titanocene catalyst, namely, relatively high hydrogen pressure (5.4-136 atm), highly demanding (air and moisture-free) reduction conditions combined with the necessity to activate titanocene catalyst prior to use is an important drawback of *Buchwald*'s hydrogenation procedure. Moreover, *ansa*-titanocene catalyst shows low tolerance toward various functional groups, such as unprotected imine N-H and aryl halogens.

3. Asymmetric hydrogenation of 3,4-dihydroisoquinoline-derived enamides is questionable in the case of 1-aryl substituted substrate since it requires formation of potentially unstable quinone-type structure.

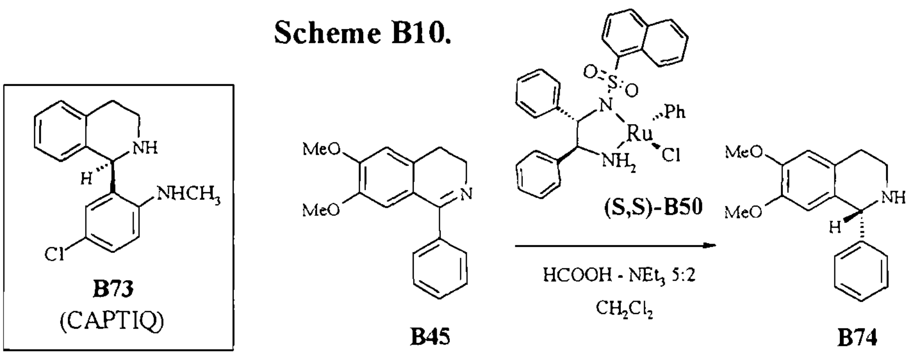
4. Ru(II) catalyzed transfer hydrogenation of various 3,4-dihydroisoquinolines proceeds with excellent enantioselectivity and chemical yield. Operational simplicity (reduction can be preformed in open reaction vessel with *in situ* prepared catalyst) makes *Noyori* procedure the method of choice for the synthesis of various chiral 1-aryl substituted isoquinolines.

2. Asymmetric reduction studies.

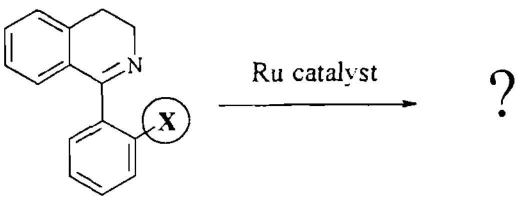
Because the chiral environment in commercially available diamine **B73** (CAPTIQ) (see Scheme B10) has been demonstrated to be highly effective in the protonation of amide enolates,[23] our goal was to utilize the same scaffold for the generation of chiral acids with enhanced acidity, useful for protonation of more acidic enolates, derived from esters or lactones.

Review on catalytic asymmetric hydrogenation shows that *Noyori*'s procedure is superior to alternative reduction techniques because of experimental simplicity and promising enantioselectivities. Thus, 1-phenyl-3,4-dihydroisoquinoline **B45** is quantitatively reduced to chiral amine **B74** with 84% ee.[16a]

Scheme B10.



Our objective was to apply *Noyori* method for synthesis of CAPTIQ and its analogs - chiral 1-anilino-1,2,3,4-tetrahydroisoquinolines. The initial goal was to find the optimum catalyst and reduction conditions as well as to test various functional groups tolerance to Ru(II)-catalyzed transfer hydrogenation. Another goal was to establish how ortho-substituents in phenyl ring influence the reduction process.



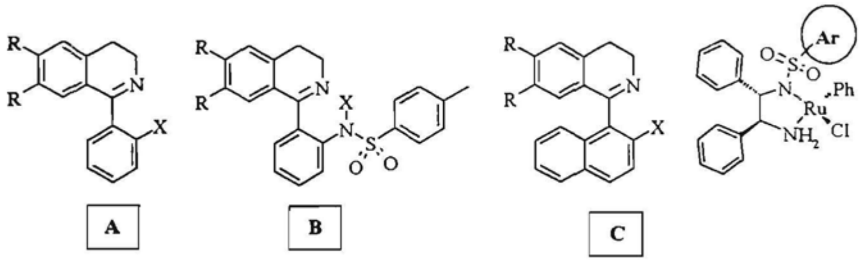
X = Hal, NHR, etc.

Precise understanding of *Noyori* procedure's scope and limitations would allow creating a general and convenient method for asymmetric synthesis of various chiral 1-anilino-1,2,3,4-tetrahydroisoquinolines as potential asymmetric proton donors.

2.1. Experimental results.

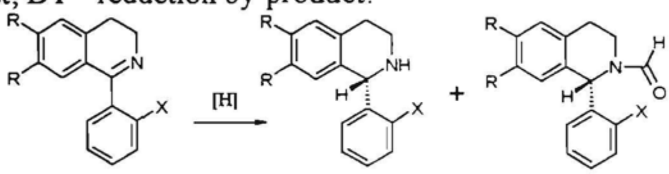
Asymmetric reduction experiments are summarized in Table 10.

Table B10. Asymmetric reduction of 3,4-dihydroisoquinolines using different chiral Ru catalysts.[a]



Entry	Substrate[b]			Catalyst (mol-%) [Time] (h)	Catalyst					
					Ar = 1-naphthyl		Ar = 4-methylphenyl		Ar = 4-fluorophenyl	
	Type	R	X		PR:SM:BY[c] (%)	ee (%)	PR:SM:BY[c] (%)	ee (%)	PR:SM:BY[c] (%)	ee (%)
1	A	H	H	1[13]	68:16[d,e]	**44(50)[f]**	87:8[e]	**28**	84:4[e]	**33**
2	A	MeO	H	1[13]	97:1:2	**63(88)[f]**	96:1:3	**58**	93:1:6	**67**
3	A	H	NH_2	2[16]	48:44[e]	**78**	66:23[e]	**85**	66:26[e]	**79**
4	A	MeO	NH_2	2[16]	75:10:8	**71(83)[f]**	74:6:15	**43**	71:6:11	**56**
5	A	H	$NHCH_3$	2[16]	54:44[e]	**85**	79:14[e]	**91**	82:11[e]	**86**
6	A	H	Cl	1[13]	56:36[e]	**86**	66:28[e]	**90**	57:35[e]	**91**
7	A	H	Br	1[13]	59:36:4	**94**	41:51:7	**94**	55:35:9	**95**
8	A	MeO	Br	0.67[13]	71:23:4	**98.3**	67:29:3	**98.7**	69:26:4	**97.8**
9	A	H	NO_2	1[13]	-	-	0:99	-	-	-
10	A	MeO	NO_2	1[13]	-	-	20:80:<1	**97.1**	-	-
11	B	MeO	H	2[16]	-	-	0:99[d]	-		
12	B	MeO	H	7.5[72][g]	-	-	11:87	**96-98[h]**	-	-
13	B	H	Me	2[16]	-	-	34:61	**93**		
14	B	MeO	CH_2Ph	7.5[72]	-	-	76:19	**98-99[h]**		
15	C	MeO	H	1[13]	82:9:8	**98.1**	82:9:8	**98.5**	88:4:7	**98.7**
16	C	MeO	OCH_2Ph	1[13]	-	-	0:99	-	-	-

(a) All the reductions were performed in 0.5 mM scale, HCO_2H:substrate molar ratio 6:1; if not otherwise noted, both chemical yields and enantioselectivities (ee) were determined by HPLC on CSP (using separately prepared standards) for a crude reaction mixture and represent average of at least two reactions (two HPLC runs for each reaction). (b) Unless indicated otherwise, one and the same substrate batch was used for all reductions in the corresponding entry. (c) SM - starting material; PR - reduction product; BY - reduction by-product:



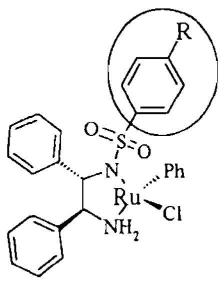
SM **PR** **BY**

(d) Isolated yield after purification on preparative TLC plate. (e) Yields of BY (and other minor by-products) was not determined either due to inadequate HPLC assay or lack of standards. (f) Yields in brackets correspond to runs with different sample of catalyst (see Table B11 and following discussion). (g) HCO_2H:substrate molar ratio 55:1. (h) Approximate value is shown; exact ee's could not be determined due to lack of proper HPLC assay (peak of starting material traces overlapped with minor enantiomer peak).

2.2. Discussion. Factors controlling asymmetric reduction process.

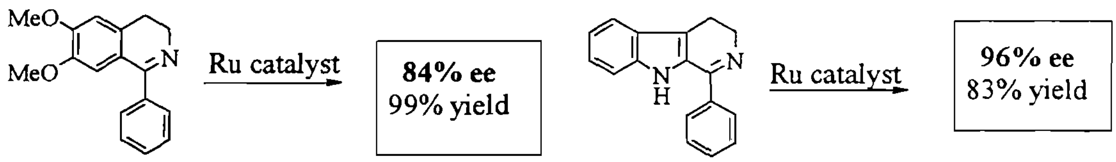
2.2.1. Substrate influence.

The original *Noyori* procedure[16a] employs 6,7-dimethoxy substituted isoquinolines as hydrogenation substrates (Scheme B10). It was decided to apply the reduction to 6,7-unsubstituted-3,4-dihydroisoquinolines, analogues of commercially available diamine (CAPTIQ) **B73**. It was found, however, that substrates having methoxy groups generally show higher chemical and optical yields (compare entry 2 vs. 1, 8 vs. 7 and 10 vs. 9). This is not always the case (entries 3-4) and although preliminary experiments supported higher enantioselectivity also for MeO-substituted anilines, further experiments reversed this pattern for these particular substrates (see Table 13, entries 3-4; this will be discussed later). Higher chemical outcome and enantioselectivity for MeO substrates could be attributed to electronic factors, namely, increasing C=N double bond electronic density due to electron-releasing effect of methoxy groups. This would make stronger Ru catalyst - substrate complex and, thus, improve enantioselectivity. To support this assumption both electronic rich (*tolyl*) and poor (*4-fluorophenyl*) groups containing Ru catalysts **B76** and **B77** were utilized, anticipating that electronic poor ligand in Ru catalyst would stronger interact with electronic rich substrate due to π system interaction ("π-stacking").[24]



B76: R = CH_3
B77: R = F

It turned out, however, that generally there is no difference between these two catalysts. Obviously, electronic factors are less important than sterical preferences. Possibly methoxy groups expand isoquinoline system thus improving C=N enantiofacial discrimination by Ru(II) catalyst. Observation that indolyl-imine **B78** was reduced with higher enantioselectivity than dimethoxyisoquinoline **B45** supports this assumption.[A]



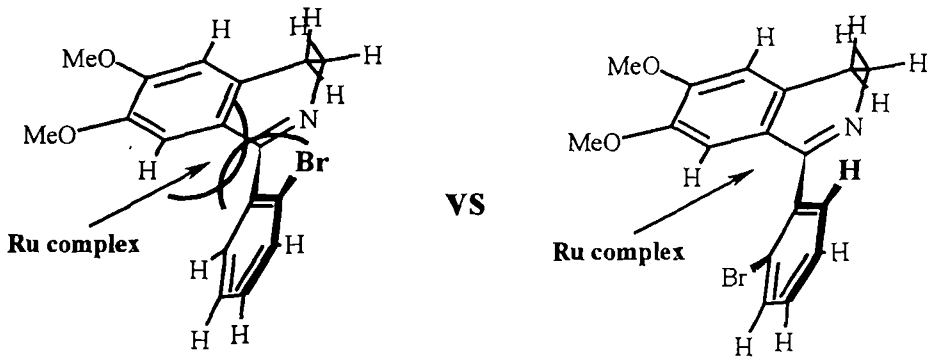
B45 **B78**

Even more considerable turned out sterical demands of ortho-substituents in 1-phenyl ring. Increasing bulk of ortho-group (compare entries 1, 3, 5, 6, 7, and 10, Table B10), enhances reduction enantioselectivities:

$$\mathbf{H < NH_2 < NHCH_3 \sim Cl < NO_2 \sim Br}$$

Obviously, ortho-substituent helps to hinder one C=N enantioface, thus favoring a specific rotamer in one of competing diastereomeric transition states during substrate - Ru catalyst complex formation.

Figure B5. Formation of competing diastereomeric substrate-Ru catalyst complexes.



A sterically demanding *ortho*-substituent efficiently hinders Ru(II) catalyst approach to one imine enantioface resulting in enhanced enantioselectivity. For example, the *o*-bromophenyl group provides sufficient control in the asymmetric hydrogenation step so that useful ee levels can be achieved with or without the methoxy substituents.

Unprotected N-tosylamide (entries 11-12) and, especially, N-substituted tosylamides (entries 13-14) also are bulky enough to help ruthenium catalyst efficiently discriminate between C=N enantiofaces resulting in high optical yields

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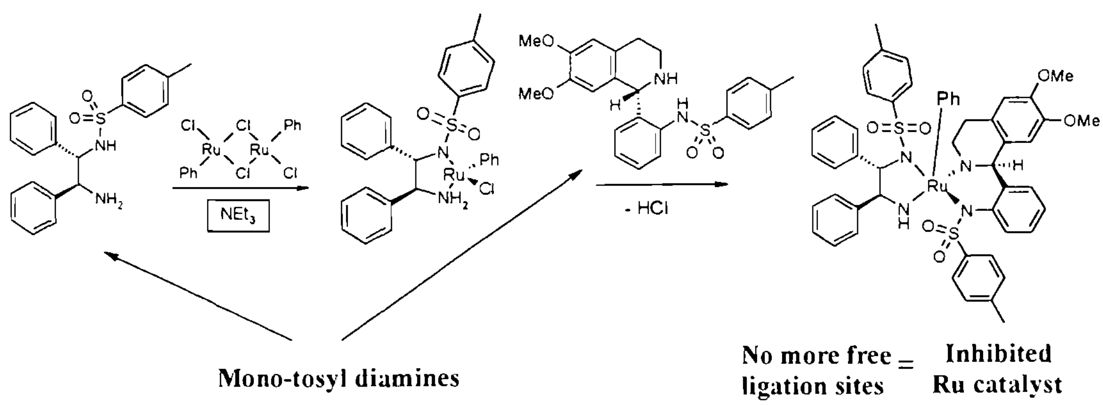
(A) It should be noted that Ru catalysts with different ligands were used for substrates **B45** and **B78**.

(92-99% ee) for all tested substrates. Substrate with condensed benzene ring instead of ortho-substituent (entry 15, Table 10) behaves similarly. Furthermore, if there is both condensed benzene ring from the one side and bulky substituent from the other in the 1-phenyl ring (entry 16), the reduction does not take place at all (in standard conditions). Evidently, access to either side of planar C=N system in this case is hindered.

Dihydroisoquinolines with less sterically demanding ortho-substituents (H, NH_2) (entries 1-4) show lower optical yields. In these substrates methoxy groups play a role in enantiofaces discrimination (entries 1-2). Surprisingly, ortho-aminophenyl substituted isoquinolines do not match general pattern (entries 2 and 3) and, unexpectedly, MeO presence lowers ee's. The influence of MeO groups on the enantioselectivity of reduction of sterically demanding substrates is low (compare entry 7 and 8).

Chemical yields in general are higher for MeO-substituted isoquinolines (entry 2 vs. 1, 4 vs. 3, 8 vs. 7 and 10 vs. 9). N-Sulfonylanilines afforded reduction products in significantly lower yields compared to halogen and amino substituted substrates, thus requiring substantially higher catalyst loading and prolonged reaction time. For instance, reduction of N-tosyl-3,4-dihydroisoquinoline under standard conditions used for amino substituted isoquinolines yielded 99% recovered starting material with no reduction product (entry 11 vs. entries 3-5). Even increased catalyst loading and prolonged reaction time gave chiral tetrahydroisoquinoline in only 11% yield (entry 12). Low chemical yields can be attributed to fact that reduced 1,2,3,4-tetrahydroisoquinolines, being mono-sulfonylated diamines are structurally related to the ruthenium catalyst ligand. Eventual strong complexation with the reduction product can strongly (depending on the complex dissociation rates) inhibit the catalyst.



Increased ruthenium catalyst loading (7.5 mol% and more) makes asymmetric reduction of N-sulfonyl-3,4-dihydroisoquinolines too expensive, especially on a preparative scale. Alternative approach is to diminish complexation ability of the reduction products by inactivation of a diamine ligation site. Indeed, sulfonamide N-H replacement by methyl group significantly increased chemical yields (entry 13 vs. 11; note that only 2 mol% catalyst and 16 h was used compared to entry 12). Unfortunately, it is almost impossible to remove methyl group after reduction and therefore it is useless as a protecting group. N-Benzyl protection was tested instead of N-methyl and chemical yield was reasonably higher accompanied with excellent enantioselectivity (entry 14 vs. 12). Nevertheless, at least 7.5 mol% Ru(II) catalyst loading was crucial also for N-benzylsulfonamide reduction. This is a reasonably higher loading than in the case of N-unsubstituted 1-anilino-3,4-dihydroisoquinolines. Consequently, more "reduction fuel" - HCOOH-NEt_3 (5:2 azeotropic mixture) was also used.

It should be noted that reaction conditions used for all experiments in Table B10 are by no means optimal - the main principle was to provide equal reduction conditions to compare relative reactivity of various substrates.

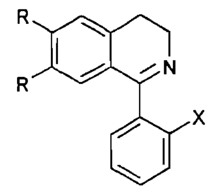
2.2.2. Catalyst effect.

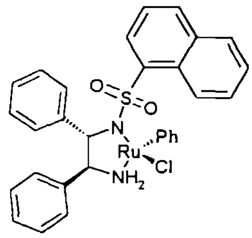
Ruthenium catalyst dominates in favoring one of competing diastereomeric transition states in the case of *ortho*-unsubstituted substrates and substrates with small sterical demands. Bulky sulfonyl group (1-naphthylsulfonyl) in catalyst ligand increase optical yields (entries 1,2 and 4) compared to smaller tosyl and 4-fluorophenylsulfonyl group. The catalyst effect, however, disappears as substrates with strong sterical preferences (bulky ortho-groups) are subjected to the reduction (entries 5-8). In this case *ortho*-substituent dominates in preferring one of the competing transition state.

2.2.3. Substrate and catalyst quality.

As mentioned above, ortho-aminophenyl substituted 3,4-dihydroisoquinolines fall out of general pattern regarding to methoxy group influence on reduction enantioselectivity. While in preliminary experiments naphthyl-Ru catalyst (batch #2, see Table B11) reduced diMeO-ortho-aminophenyl isoquinoline **B80** in higher optical yield than observed for unsubstituted substrate,[B] consistent results could not be obtained employing different catalyst batch (#3) (entry 4 vs. 3, Table B11). Because identical reduction conditions were constantly used there are only two variables that could provoke substantial fluctuation of results, namely - purity of substrate and catalyst. It is believed that substrate impurities reduce chemical outcome while optical yields are under control of catalyst.

Table B11. Differences in asymmetric reduction enantioselectivities depending on employed naphthyl-Ru catalyst **B50** batches.[a]





B50

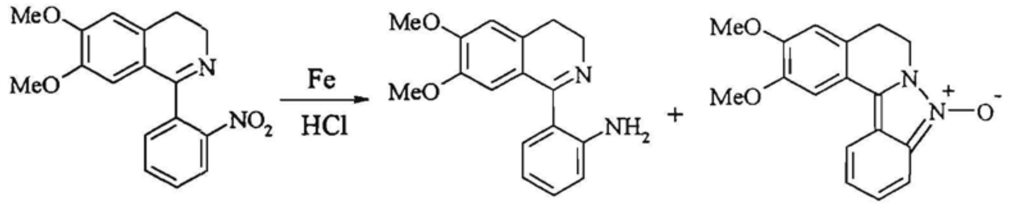
Entry	Substrate		Naphthyl-Ru catalyst batches.					
	R	X	Batch #1[b]		Batch #2		Batch #3	
			ee(%)	chem (%)	ee(%)	chem (%)	ee(%)	chem (%)[f]
1	H	H	44[c]	68[d]	50[e]	76[d]	-	-
2	MeO	H	84[g]	99[g]	88	70[d]	63	97
3[h]	H	NH_2	-	-	48	46[d]	78	48
4[h]	MeO	NH_2	-	-	83	10-20[f]	71[i]	75

(a) If not otherwise noted, one and the same substrate batch was used for all reductions in the corresponding entry. (b) We thank Prof. R. Noyori for providing this sample of naphthyl-Ru(II) catalyst. (c) Average of 2 reactions (43.5 and 44.9% ee resp.). (d) Isolated yields. (e) Represents 2 reactions (both shows 50% ee). (f) Chemical yields determined by HPLC using standards. (g) Published result from *Noyori* group.[16a] (h) Different substrate portions were used for catalyst batch #2 and #3 (i) Average of 2 reactions (70.1 and 71.8% ee resp.)

The variation of chemical yields in reduction of anilino-imine **B80** (Table B11, entry 4, batch #2 vs. batch #3) can be attributed to the fact that substrate was contaminated to various extent with an impurity. 1-Anilino-3,4-dihydroisoquinoline **B80** was prepared from the corresponding nitro-imine **B79** by reduction with Fe/HCl.[25] It was found that the product aniline contained intensely yellow impurity

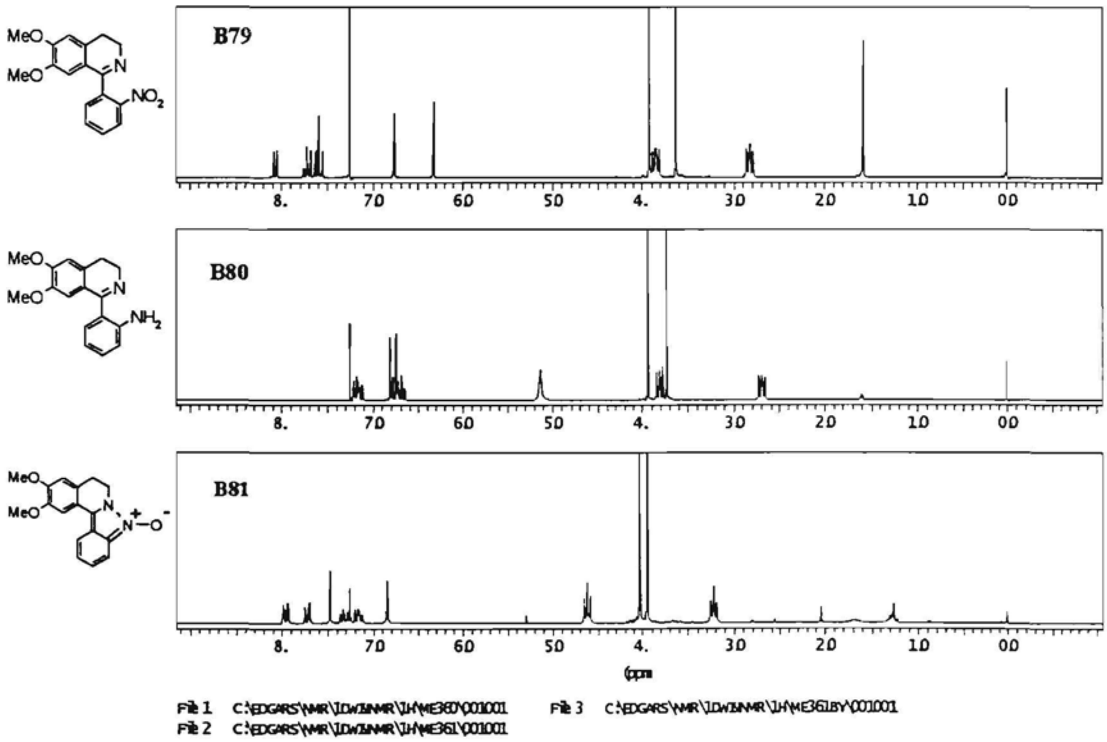
(B) These results agree with the general trend for higher yields in the case of dimethoxy substituted substrates; see Table B10.

that could not be removed by flash chromatography.



B79 **B80** **B81**

The yellow contaminant could not be separated well enough to give satisfactory analysis or spectra, but one small sample was obtained having a 3:2 ratio of oxygen:nitrogen according to elemental analysis. 200 MHz ^{1}H-NMR spectrum shows similar signal pattern to that of aniline **B80** with all aliphatic isoquinoline ring protons shifted downfield by approximately 0.4-0.8 ppm:



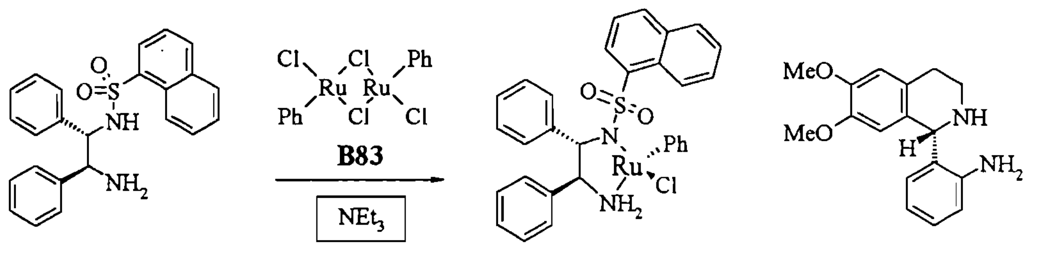
Taking as a basis NMR spectra and elemental analysis, structure **B81** was assigned for yellow contaminant. Analogous indazole N-oxides are reported as yellow solids.[26]

With impurity levels near 20%, transfer hydrogenation did not occur within 16 h at 20 °C suggesting that contaminant inhibits the catalyst. Repeated crystallizations reduced the amount of the contaminant to 2%, but with considerable material loss. When **B80** containing ca. 2% of the impurity was treated with 1 mol% of the naphthyl-Ru catalyst (batch #3), transfer hydrogenation proceeded in 75% yield (compare entry 4, Table B11) and with 71% ee.

In another attempt using catalyst batch #2, enantioselectivity mysteriously increased to 83% ee, and similar inconsistencies were encountered in attempts to hydrogenate *Noyori* substrate **B45** and its 6,7-unsubstituted analog (entries 1-2, Table B10). No substantial difference between the two batches of catalyst could be detected using NMR methods, but the limited solubility of both naphthyl-Ru(II) catalyst and its precursor $(C_6H_6)_2RuCl_2$[27] complicates catalyst assay using spectroscopy. Furthermore, having identical NMR spectra, naphthyl-Ru catalyst batch #2 reduced *ortho*-unsubstituted dimethoxy isoquinoline **B45**[C] in higher ee's than both sample received from *Noyori* lab (batch #1) and batch #3 (entries 1-2, Table 11).

A possible problem in catalyst preparation could be incomplete conversion of $[RuCl_2(\eta^6\text{-benzene})]$ **B83** and ligand **B82** to catalyst **B50**.

Scheme B11.



B82 **B50** **B84**

Unreacted ruthenium source **B83** can in principle serve as non-chiral hydrogenation catalyst thus lowering optical yields. Simple recrystallization could in principle solve contaminant issue, however, catalyst is reported to decompose upon attempted purification.[16a] On the other hand, employing Ru catalyst formed *in situ* from $[RuCl_2(\eta^6\text{-benzene})]$ **B83** and mono-N-sulfonyl diamine **B82** in triethylamine *Noyori* was able to achieve results similar to the ones obtained in reduction employing isolated catalyst.[16]

Ligand exchange in Ru(II) catalyst (N-sulfonyl-ethylenediamine **B82** replacement by reduction product amino-isoquinoline **B84**, see scheme B11) could be an alternative interpretation of scattered ee's values, however in recent paper *Noyori* has shown that structurally related $[(BINAP)Ru]Cl_2$ complex irreversibly interacts with ethylenediamine ligand, similar to **B82**. Resulting Ru(II)-ethylene diamine complex was found to be resistant toward competing diamine ligands.[28]

(C) One and the same isoquinoline batch was used for all reduction experiments.

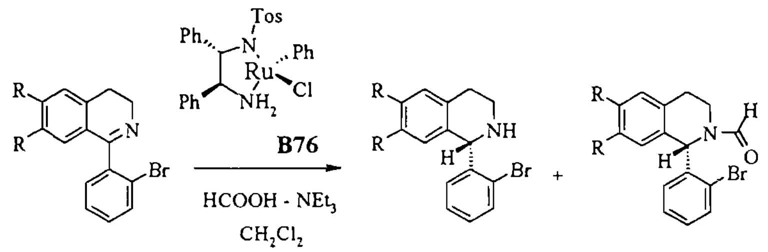
Most likely the problems arise from improper Ru(II) catalyst preparation procedure. No attempts were made to define the source of the problem in catalyst preparation because relatively consistent results were obtained with modified *Noyori* catalysts **B76**[16c] and **B77** (see entries 3-4, Table B10).

2.3. Optimization of the reduction conditions.

Early hydrogenation attempts gave <25% conversion using a 6,7-unsubstituted analog of *Noyori* substrate **B45**, but this difficulty was overcome simply by arranging an outlet for the reaction vessel. Evidently, it is important to provide an exit for the gases (H_2 + CO_2) produced by decomposition of the HCO_2H/Et_3N reducing reagent as the hydrogenation proceeds. This, however, is a minor problem compared to the examples above where reduction products or impurities acted as catalyst inhibitors.

As already mentioned, asymmetric reduction conditions used for all experiments (Table B10) are not optimal and were chosen to provide equal reduction conditions in order to compare relative reactivity of various substrates. There are several potential ways to improve reduction rate - larger catalyst loading, longer reaction time, higher temperature as well as use of different substrate concentration and change of solvent.

Table B12. Optimization of asymmetric transfer hydrogenation.



B85 **B86** **B87**

a: R = H
b: R = OMe

Entry	R	Solvent	T (°C)	Catalyst (mol%)	Rxn time (h)	ee (%)	HPLC yield (%)		
							B86	**B85**	**B87**
1[a]	*MeO*	*CH_2Cl_2*	*20*[b]	*0.67*	*13*	*98.7*	*68*	*30*	*3*
2	MeO	CH_2Cl_2	20[b]	**1**	13	98.6	84	8	8
3	MeO	CH_2Cl_2	20[b]	0.67	**24**	98.6	78	3	19
4[a]	*H*	*CH_2Cl_2*	*20*[b]	*1*	*13*	*94*	*41*	*51*	*7*
5	H	**CH_3CN**	20[b]	1	13	85	53	45	2
6	H	CH_2Cl_2	**reflux**	1	13	90	45	49	5
7	H	CH_2Cl_2	**reflux, then 20° C**	1	13+24	90	43	47	10

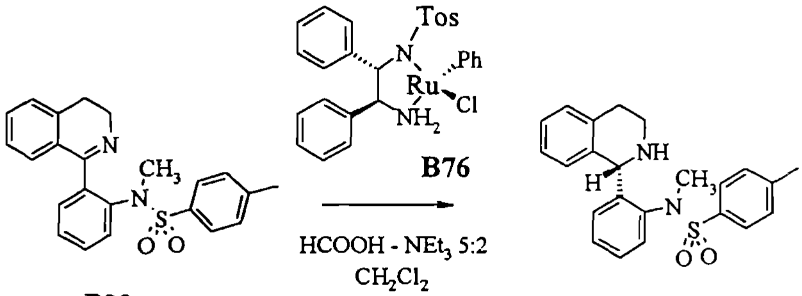
(a) Standard conditions (see Table B10). (b) Approximate room temperature.

Prolonged reaction time (entry 3) increased both the amount of product **B86b** and by-product **B87b**, while larger catalyst loading resulted mostly in higher product yield (entries 1-3, Table B12). Formation of by-product (N-formamide) was encountered to varying degrees in all of the hydrogenations, increasingly so for the slower reductions (see also Table B10). Evidently, formamide formation by HCOOH-NEt_3 reagent increases with time (entry 3 vs. 1, Table B12). Consequently, additional loading of "reduction fuel" - HCOOH-NEt_3 (5:2 azeotropic mixture) also increased formamide **B87b** formation.

Bromoisoquinoline **B85a** reduction in acetonitrile[D] occurs with lower enantioselectivity and in slightly higher chemical yield (entry 5 vs. 4). Temperature increase does not affect reaction course (entry 6 and 4).

Different substrate concentrations as an additional variable were examined in the case of N-toluenesulfonamides reduction experiments.[E]

Table B13. Asymmetric reduction yields depending on substrate concentration.[a]



B88 **B89**

Entry	Substrate concentration (mM/mL)	Yields[b] (%) B88:B89	ee
1	0.09	21:72	**92**
2	0.2	34:61	**92**
3	0.4	57:39	**93**

(a) Asymmetric reductions were carried out in 0.5 mM scale (within 16 hours and employing 2 mol% tosyl-Ru catalyst **B76**); see also Table B10. (b) Both chemical yields and enantioselectivities (ee) were determined by HPLC (using separately prepared standards) for a crude reaction mixture.

(D) Another alternative solvent - DMF was not examined.

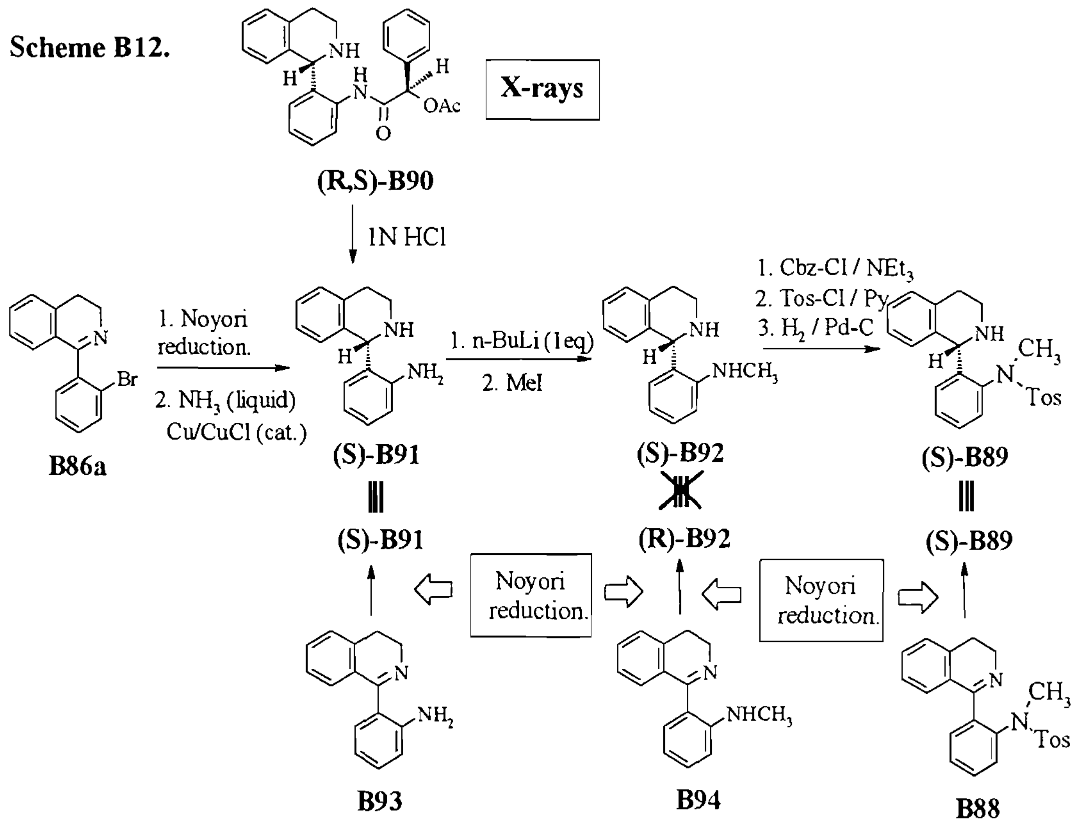
(E) In all previous asymmetric reduction experiments (Tables B10-B12) components concentration was equal to that used in the original *Noyori* paper (0.4 mM/mL).

As shown in Table B13 higher dilution lowers chemical yields, however it is believed that concentration issue has comparatively smaller influence than other factors discussed above.

2.4. Absolute stereochemistry of the reduction products.

Absolute configuration in 6,7-unsubstituted diamines series was assigned by comparison of transfer hydrogenation products chiral HPLC behavior with that of standards prepared from diamine with known (*S*)-absolute configuration, unambiguously assigned by X-ray analysis for corresponding (*R*,*S*)-O-acetylmandelic acid anilide **B90** (see Chapter A).

Scheme B12.

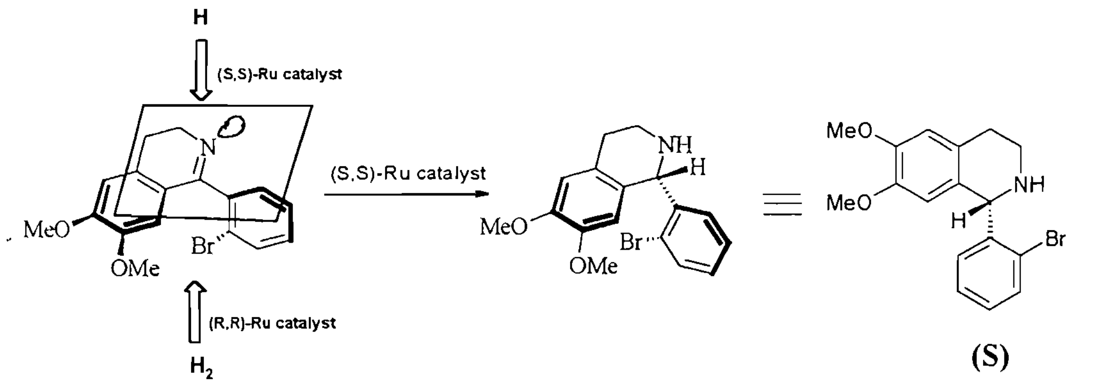


Chiral auxiliary cleavage in (*R*,*S*)-amide **B90** and asymmetric transfer hydrogenation of bromo-imine **B86a** with subsequent bromine displacement by ammonia both yielded (*S*)-enantiomer of anilino-isoquinoline **B91**. Consequently, *Noyori* reduction of bromo-imine **B86a** affords corresponding (*S*)-bromo-isoquinoline. Asymmetric hydrogenation of anilino-imine **B93** also yielded (*S*)-diamine **B91** (Scheme B12).

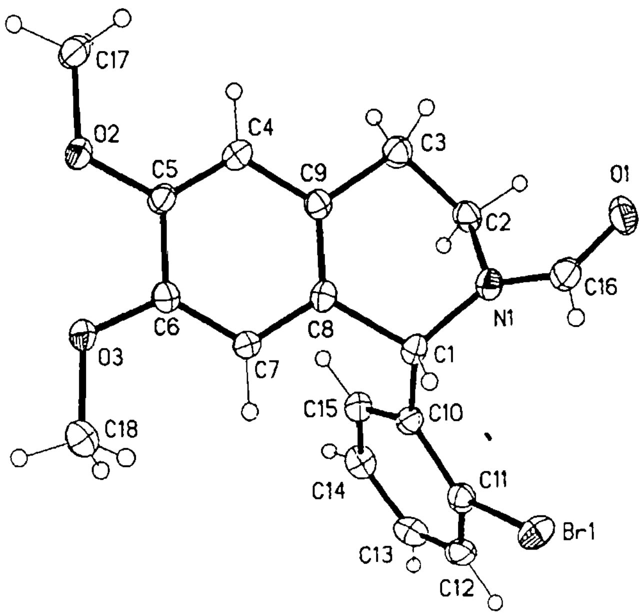
Regioselective alkylation of N-lithio-anilide with MeI gave (*S*)-N-methyldiamine **B92**. Surprisingly, asymmetric hydrogenation of corresponding imine **B94** afforded opposite enantiomer - (*R*)-isomer, according to chiral HPLC comparison with standard **(*S*)-B92**, respectively (see Scheme B12). In contrast, transfer hydrogenation of N-tosylamide **B88** yielded the anticipated (*S*)-enantiomer of **B89**.

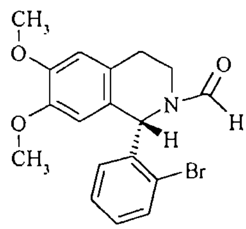
Thus, asymmetric transfer hydrogenation of imines **B86a**, **B88** and **B93** employing (*S,S*)-Ru(II) catalyst afforded (*S*)-isomer as the major enantiomer. These results are in accordance with the general sense of asymmetric induction introduced by *Noyori*:[16a,b]

Figure B7. Noyori scheme for the general sense of asymmetric induction



Reversed enantioselectivity in the case of N-methylaniline **B94** falls out of general pattern and remains unexplained, especially because transfer hydrogenation enantioselectivity in 6,7-dimethoxy series also supports *Noyori*'s asymmetric induction model (Figure B7). Thus, the absolute configuration of 6,7-dimethoxy-bromobenzene **B86b** was confirmed to be (*S*) by X-ray crystallography in the case of crystalline N-formyl by-product **B87b** (anomalous dispersion method).

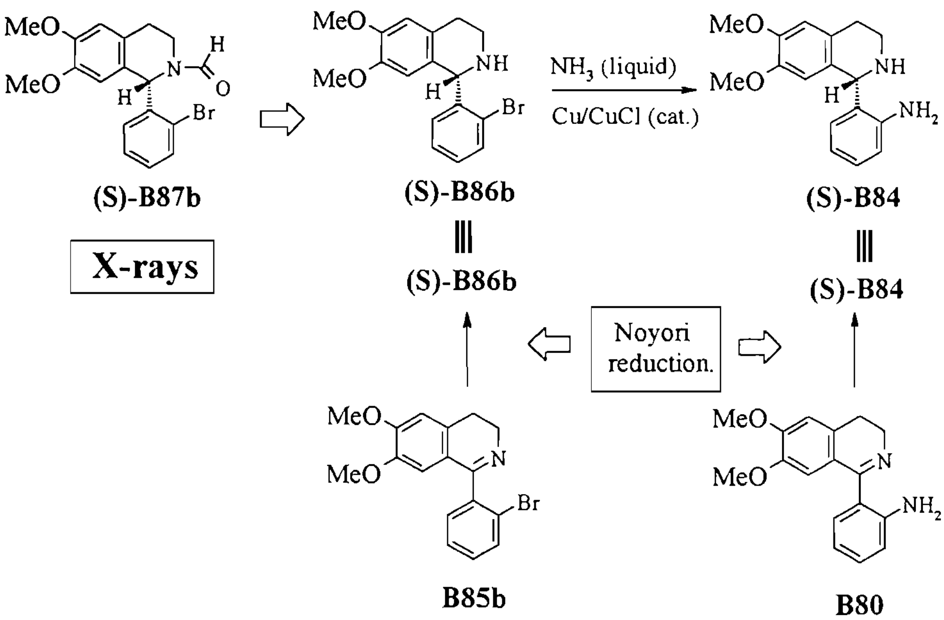




B87b

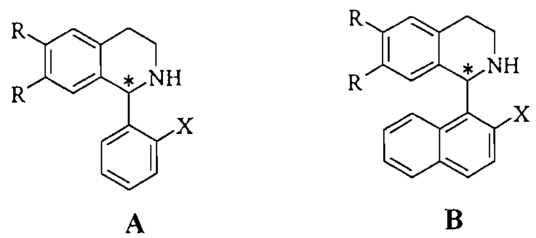
Employing bromo-isoquinoline **B86b** as a standard, absolute configuration was assigned for several asymmetric reduction products in 6,7-dimethoxy series:

Scheme B13.



Thus, all the hydrogenations with the exception of N-methyl substrate **B94** correspond to *Noyori* model for asymmetric induction[16a,b] (Figure B7). Table B14 summarizes all confirmed absolute configurations as well as those assigned on the basis of chiral HPLC behavior of structurally related products:

Table B14. Absolute configuration of major enantiomer of asymmetric reduction products:[a]



Entry	Substrate			*Absolute configuration*
	Type	R	X	
1	A	H	H	*R*[b,c]
2	A	MeO	H	*R*[c,d]
3	A	H	NH_2	*S*
4	A	MeO	NH_2	*S*
5	A	H	$NHCH_3$	*R*
6	A	H	Cl	*S*[b]
7	A	H	Br	*S*
8	A	MeO	Br	*S*
9	B	MeO	H	*S*[b]

(a) Unless indicated otherwise, absolute configurations were confirmed by chemical correlation with diamine (*S*)-**B91** or bromo-isoquinoline (*S*)-**B86b**. (b) Assigned by comparison of chiral HPLC behavior of structurally related products. (c) Absolute configuration is (*R*) because of different substituents priority order; (*R*) configuration still corresponds to *Noyori* model for asymmetric induction (Figure B7). (d) Absolute configuration determined by *Noyori* group[16a] (X-ray crystallography).

2.5. Summary.

1. Ruthenium(II) catalyzed asymmetric transfer hydrogenation is directed mainly by sterical factors. **Substrates** with bulky ortho-substituents influence the reduction enantioselectivity by favoring specific rotamer in one of competing diastereomeric transition states for hydrogenation. Ruthenium **catalyst** influence dominates in the case of sterically less demanding isoquinolines. Dihydroisoquinolines with methoxy groups yield reduction products with higher optical and chemical outcome. Relative strength of factors controlling the reduction course can be arranged in a following order:

Ortho-substituent > isoquinoline methoxy groups > Ru catalyst ligand

2. Ruthenium catalysts modified by *tosyl* and *para-fluorophenylsulfonyl* group in general show similar selectivity toward tested substrates. *1-Naphthylsulfonyl* ruthenium catalyst demonstrates higher enantiodifferentiation ability toward substrates with low sterical demands.

3. To achieve high reduction yields substrates must be especially pure. Small amount of contaminant can cause a serious drop in chemical outcome and enantioselectivity.

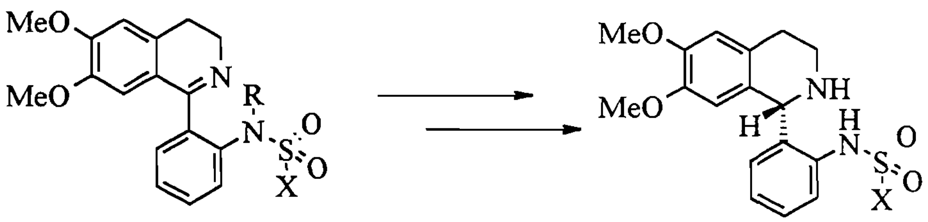
4. Absolute configuration can be established using *Noyori*'s model for asymmetric induction.

3. Practical application of the Noyori reduction.

3.1. Synthesis of chiral sulfonamides by direct transfer hydrogenation of the corresponding imines.

Moderate enantioselectivities (70-85% ee) and high purity levels required for anilino-imine **B80** due to catalyst inhibition by contaminant indazole N-oxide **B81** make direct Noyori hydrogenation unattractive for the synthesis of desired chiral diamines **B84** and **B91**. In contrary, excellent ee values (93-99%) observed in reduction of N-tosylanilides are encouraging despite the high Ru(II) catalyst loading needed. Because several methods for mild N-sulfonyl group cleavage[29] have been reported this approach could be an alternative route to chiral diamines **B84** and **B91**. Furthermore, chiral N-sulfonyldiamines themselves are asymmetric proton donor with enhanced N-H acidity, potentially useful for protonation of ester and amino acid enolates.

Additional advantage is that all necessary substituents are introduced in racemic 3,4-dihydroisoquinoline prior to the asymmetric reduction. This allows creating a chiral center at the end of reaction sequence, thus avoiding further multi-step chemical manipulations with optically active reduction product. We hoped to diminish catalyst loading and to increase chemical yields by finding an appropriate protecting group for sulfonamide N-H. Proposed approach was employed for synthesis of chiral N-sulfonyl-isoquinolines.

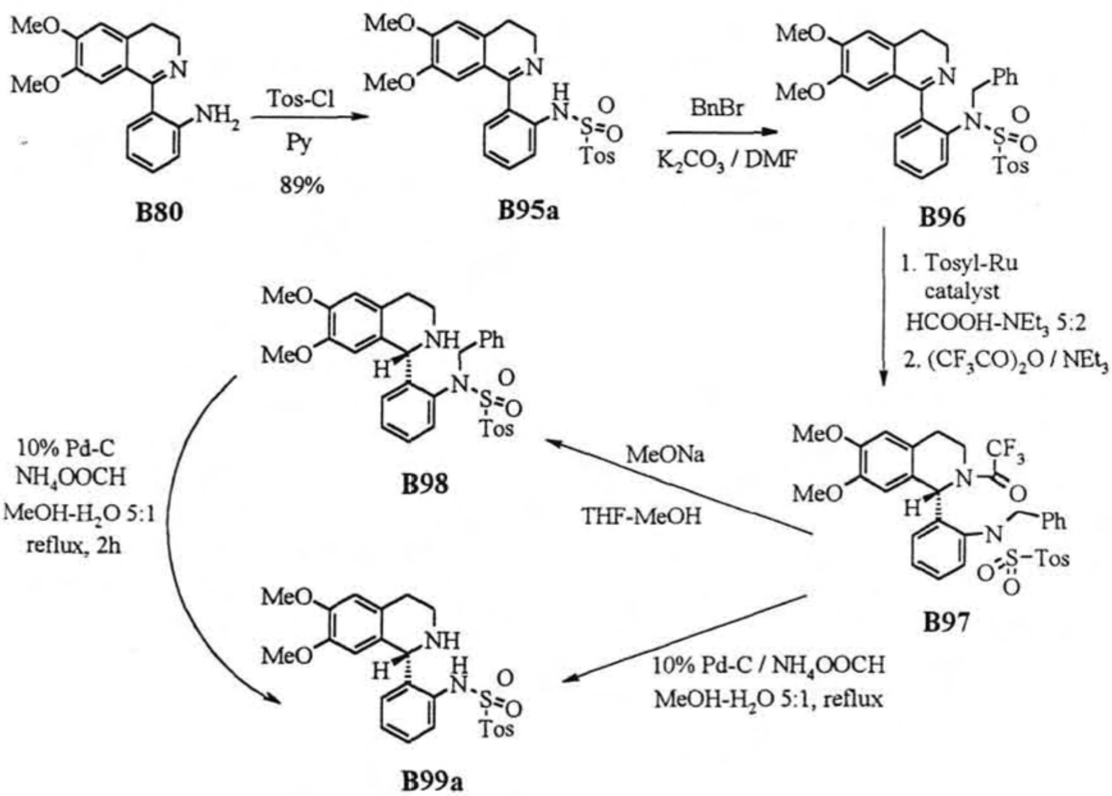


X = p-tolyl, CH_3, 1-naphthyl, 2-naphthyl
R = H, CH_2Ph, methoxymethyl

3.1.1. Chiral sulfonamides *via* asymmetric reduction of N-benzyl protected 3,4-dihydroisoquinolines. Racemization problems.

As follows from Table B10, reduction of N-protected sulfonyl-3,4-dihydroisoquinolines resulted in higher chemical outcome and consumed less catalyst compared to N-unsubstituted sulfonamides (entries 13-14 vs. 11-12). Initially, N-benzyl group was chosen as the protecting group for prep-scale synthesis of chiral tosylamide **B99**.

Scheme B14



N-Benzyl protected sulfonamide **B96** was prepared in 68% yield from tosylamide **B95a**. Asymmetric reduction (2.5 mM scale) was carried out using 6.3 mol-% tosyl-Ru catalyst. After quench the mixture contained reduced chiral isoquinoline **B98** together with unreacted starting material **B96**. Because preparative scale separation by flash chromatography was complicated due to close R_f values and unsuitable elution order (product comes out of column after starting material) the reduction product **B98** was not isolated,[F] but *in situ* converted to N-trifluoroacetanilide **B97**. This transformation reversed elution order and allowed an efficient separation of product **B98** (in form of CF_3-amide **B97**) from starting dihydroisoquinoline **B96**. Besides, N-trifluoroacetamide **B97** was readily crystallized from ethyl alcohol thus further increasing both chemical and optical purity.[G]

N-trifluoroacetyl and N-benzyl protecting group cleavage turned out to be critical step in the reaction sequence. Only method suitable for racemization-free removal of trifluoroacetyl group was treatment with methanolic MeONa in THF for 72 h at room temperature. Chiral isoquinoline **B98** (99% ee) was obtained in almost quantitative yield (98%). The following alternative methods were unsuccessful:[30]

(a)K_2CO_3 in MeOH-H_2O 4:1, 120 h, room temperature failed to give deprotected isoquinoline **B98**;

(b)$PhCH_2N^+Me_3$ OH^- in absolute MeOH led to incomplete conversion after 120 h at room temperature (product <20%);

(c)$NaBH_4$ in MeOH-THF 1:1 (5 h reflux) caused partial racemization (>95% chem. yield and 93 % ee).

Treatment of CF_3-amide **B97** with 10% Pd-C under transfer hydrogenation conditions (NH_4OOCH, MeOH-H_2O 5:1, 5 h reflux) cleaved both N-trifluoroacetamide and N-benzyl groups (75% yield of deprotected sulfonamide), however product N-tosylanilide **B99** was partially racemized (87% ee). Surprisingly, stopping reaction prior to completion (2h reflux, ca. 60% conversion) yielded N-tosyl diamine **B99** racemized to a smaller extent (96% ee). The same degree of racemization (87% ee) was observed upon N-benzyl group cleavage in isoquinoline **B98** under transfer hydrogenation conditions (72% isolated yield). Furthermore, when catalytic hydrogenation[H] was employed to remove N-benzyl group, desired diamine **B99** obtained was still partially racemized (96% ee). These results indicate that unsubstituted 1,2,3,4-tetrahydroisoquinolines **B98** and **B99** are apt to partial racemization in the presence of Pd catalyst and hydrogen source, however mechanism

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(F) Aliquot was taken from the mixture to determine reduction enantioselectivity (99% ee) and chemical yields (63% together with 25% recovery of starting material).

(G) Initially Cbz-group was employed instead of trifluoroacetyl. However, the corresponding carbamate could not be made crystalline after purification by flash chromatography.

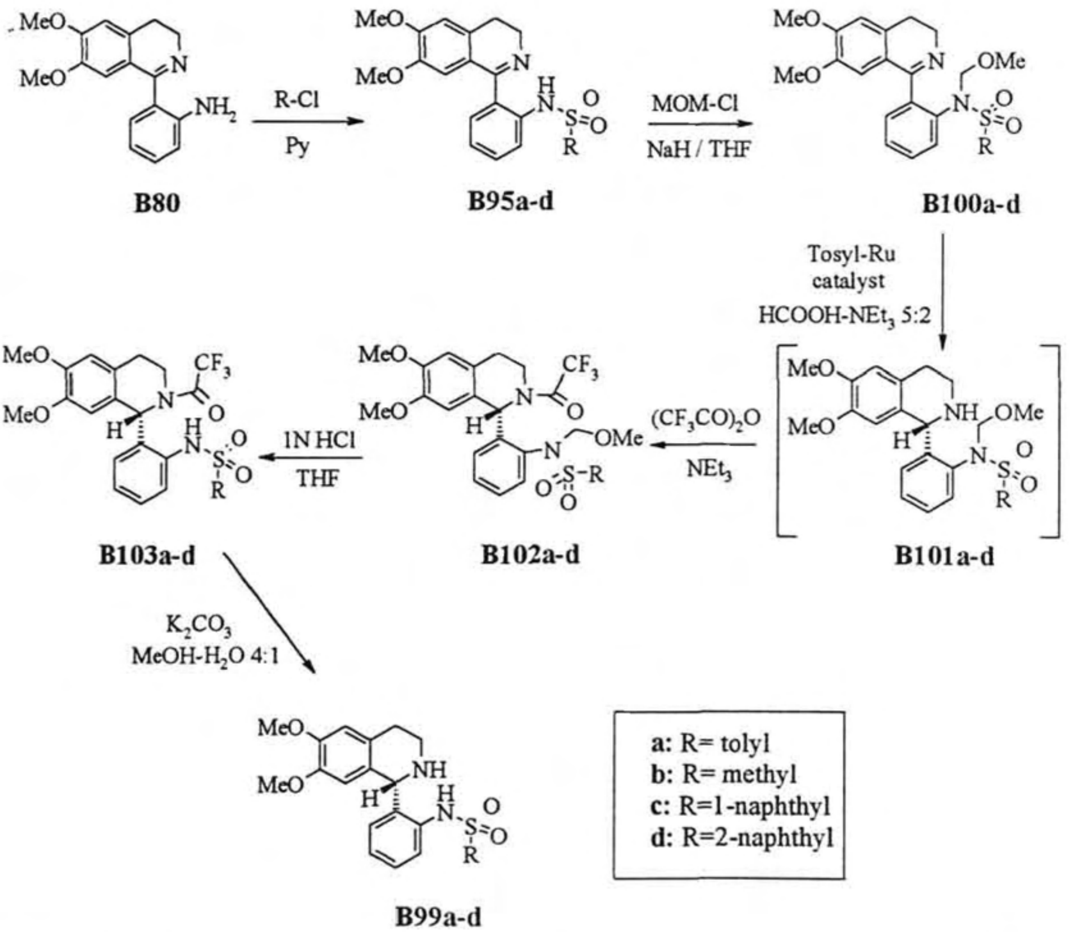
(H) Successfully used to remove N-Cbz group without racemization in synthesis of various chiral N-substituted anilino-isoquinolines, for example tosylamide **B89** (Scheme B12).

is not clear. It should be pointed out that optical purity of both compounds **B98** and **B99** can be increased by crystallization. Besides, N-benzyl protecting group cleavage is as a matter of optimization. Meanwhile, lack of available racemization-free method for the removal of N-benzyl protecting group forced us to investigate alternative ways for the synthesis of chiral N-sulfonyldiamines.

3.1.2. Practical scheme for N-sulfonyldiamines synthesis. Methoxymethyl protecting group.

To avoid N-benzyl group cleavage problems more labile N-methoxymethyl (MOM) protecting group was employed.[I]

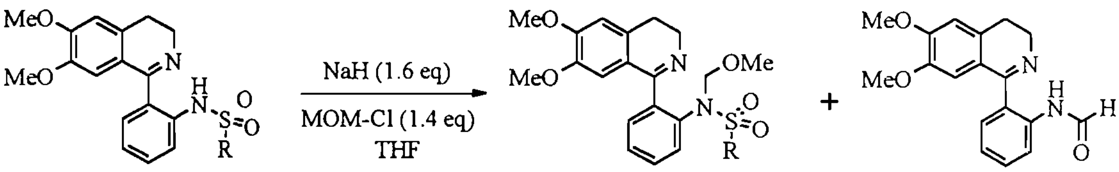
Scheme B15.



Sulfonamides **B95a-d**, prepared by treatment of aniline **B80** with the corresponding sulfonylchloride in pyridine, were converted to sodium salts by NaH in THF and alkylated with MOM-Cl. Protected isoquinolines **B100a-d** were isolated in 56-72%

(I) In our case N-MOM group is stabilized by electron withdrawing substituent at nitrogen.

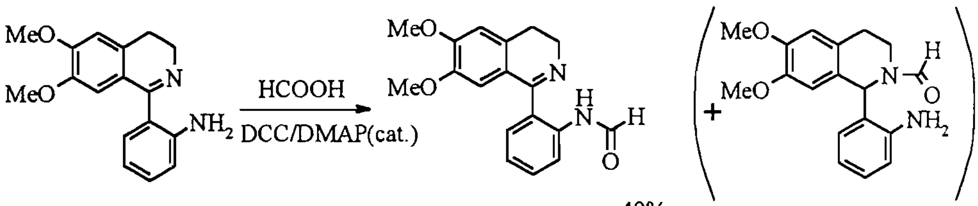
yield, accompanied with a byproduct. Taking as a basis NMR spectra and elemental analysis, by-product was identified as N-formyl-3,4-dihydroisoquinoline **B104**:



B95a-d **B100a-d** **B104**

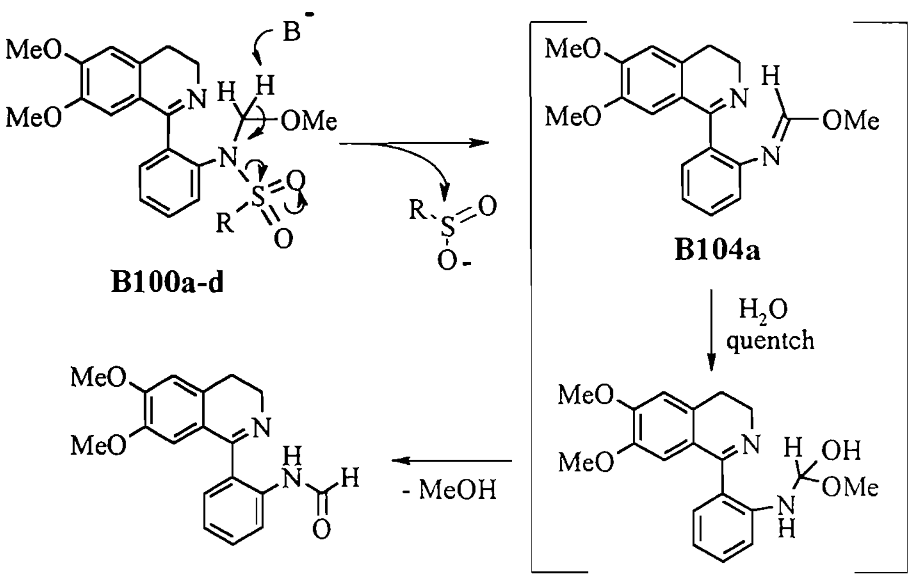
If R = 2-naphthyl, **B100d** : **B104** = 62 : 12 (%)

The structure of formamide **B104** was verified by synthesis from anilino-3,4-dihydroisoquinoline **B80**.



B80 **B104** 40% 60%

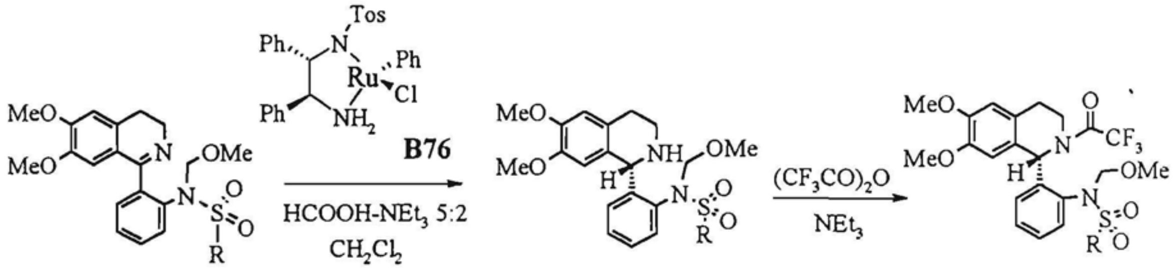
Although byproduct was isolated and characterized particularly in synthesis of MOM-protected tosyl and 2-naphthylsulfonamides, it was observed in all the MOM-protection reactions. The formation of byproduct **B104** from sulfonamides **B100a-d** could in principle proceed *via* imine **B104a** in the presence of an excess of base, however no attempts were made to prove the mechanism:



B104

Asymmetric reduction of MOM-protected substrates **B100a-d** yielded chiral 1,2,3,4-tetrahydroisoquinolines in excellent enantioselectivities and good chemical yields (Table B15).

Table B15. Asymmetric reduction of MOM-protected N-sulfonyl-3,4-dihydroisoquinolines **B100a-d**[a].



B100a-d **B101a-d** **B102a-d**

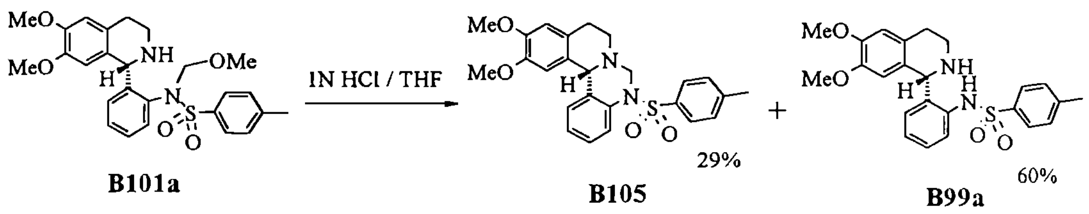
Entry	R	ee (%)	Isolated yield (%)	
			B101	**B100**
a	tolyl	**99**	58	30
b	methyl	**93**[b]	18[b]	-
c	1-naphthyl	**97**	53	40
d	2-naphthyl	**97**	73	22

(a) In the presence of 7.5 mol% **B76**, HCO_2H:substrate molar ratio 55:1, reaction time - 84h. (b) Determined for the corresponding crystalline N-trifluoroacetamide **B102b**.

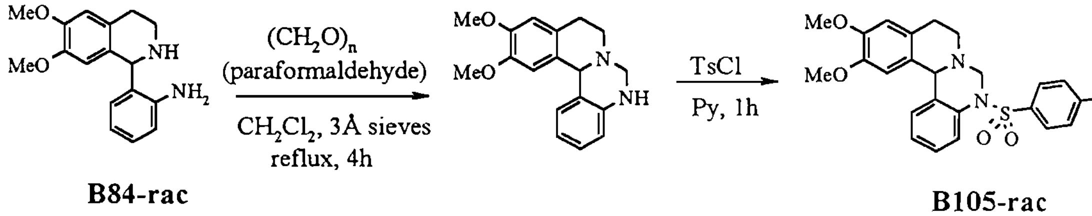
After quench the reduction mixture contained products **B101a-d** together with unreacted starting material **B100a-d**. For the same experimental reasons as in the case of N-benzyl substituted sulfonamide **B98** the reduction products were not isolated[J] and converted *in situ* to N-trifluoroacetanilides **B102a-d**.

It should be pointed out that the cleavage order of N-trifluoroacetyl and N-methoxymethyl protecting groups is crucial. Preliminary N-MOM group cleavage experiments with tosylamide **B101a** showed that anticipated isoquinoline **B99a** forms in 29% yield after 3 h reflux in 1N HCl, while the undesired cyclization product **B105** was formed in 60% yield.

(J) Aliquots were taken from the reduction mixtures to determine hydrogenation enantioselectivity and chemical yields for **B101a** and **B101c-d**.



Heterocycle **B105** chemical structure[K] was verified by synthesis from racemic diamine **B84-rac**.



To avoid the formation of heterocycle **B105** it was decided to cleave N-MOM group prior to N-trifluoromethyl protection removal. Thus, N-methoxymethyl group was hydrolyzed in boiling 1N HCl (18 h) to give sulfonamides **B103a-d** (Scheme B15) in 87-93% yield without affecting N-trifluoroacetyl group. The latter was then hydrolyzed by K_2CO_3 in wet methyl alcohol (36h at 20 ^{0}C) to give the desired chiral sulfonyldiamines **B99a-d**.

The reaction sequence (Scheme B15) allowed to prepare a family of potentially useful, chiral aniline derivatives **B99a-d** having enhanced N-H acidity, from the corresponding imines **B100a-d** with high enantiomeric purity (>99% ee after crystallization). However, the number of steps required due to the problems with catalyst inhibition, as well as the complications with the protecting group chemistry, make this approach laborious, especially for preparative scale synthesis of various CAPTIQ analogs.

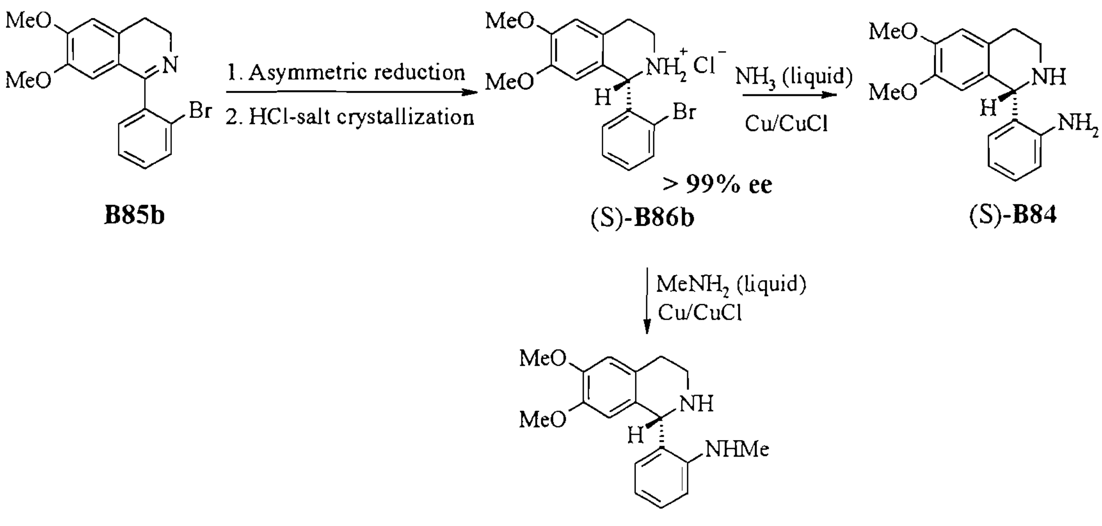
3.2. Preparative scale synthesis of (*S*)-1-anilino-1,2,3,4-tetrahydroisoquinoline. Reinvestigation the hydrogenation stereochemistry of N-sulfonamides.

While direct reduction of unsubstituted anilino-3,4-dihydroisoquinolines **B80** and **B93** occurs with moderate enantioselectivity and requires high substrates purity levels, hydrogenation of suitably N-protected analogs **B95**, **B96** and **B100** is fairly

(K) Optical purity of **B105** was not determined.

laborious and demands high catalyst loading (7.5 mol%). Alternative and more direct route to desired chiral diamines **B84** and **B91** would have to involve asymmetric hydrogenation of imines with substituent that can be converted into nitrogen functionality. Suitable candidates are bromo-isoquinolines **B85a-b** because a number of methods for aromatic halogen replacement by amines have been reported.[31] Moreover, asymmetric hydrogenation of *ortho*-bromo imines **B85a-b** employing 0.67 or 1 mol% catalyst proceeded without any of the complications encountered with the various ortho-amino derivatives and afforded products with excellent enantioselectivities (94-99% ee, see Table B12).

Scheme B16.



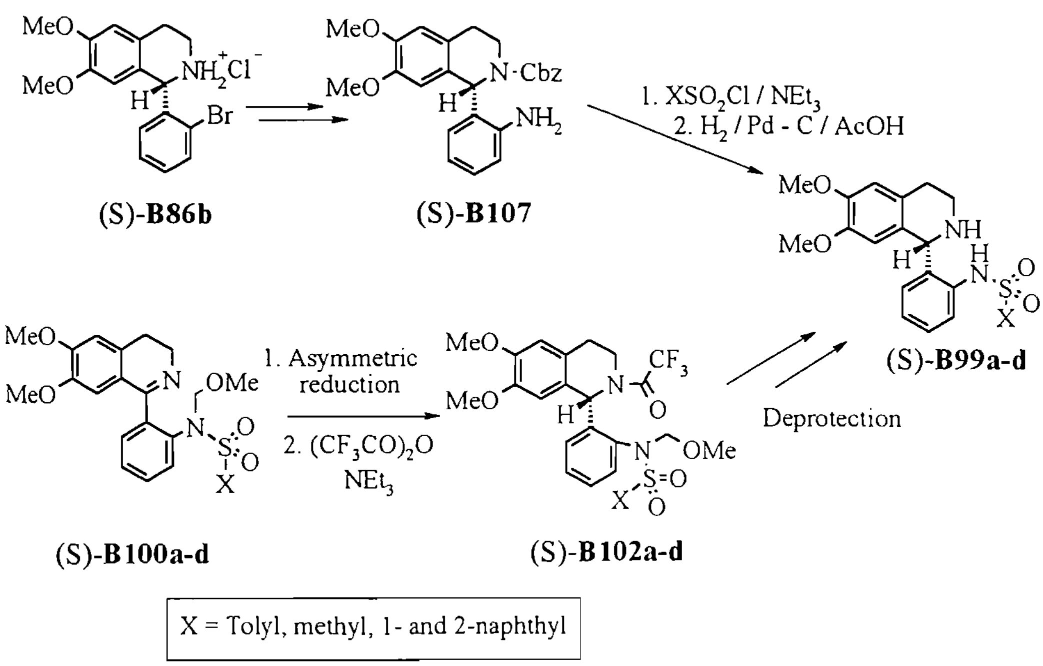
(S)-**B106**

As the reaction mixture contained hydrogenation product (S)-**B86b**, accompanied with byproduct N-formamide (up to 19%) and unreacted starting material **B85b**, product isolation from the reaction mixture was critical, especially for prep-scale hydrogenation. It was found that the reduction product can be conveniently isolated and purified as a hydrochloride salt. Furthermore, when **B86b** was released from the hydrochloride with aqueous base, >99% ee was measured for the recrystallized material. Thus, the asymmetric hydrogenation and subsequent crystallization provides material with excellent enantiomeric purity and in reasonable yield. Scaling up to 18 g afforded product in 62% yield and with 10% loss in chemical yield compared to 0.5 mM scale.

With practical access to >99% enantiomerically pure (*S*)-**B86b**, the problem of replacing bromide by an amino group was investigated. This proved to be relatively easy by an adaptation of the method published in 1968 by *Ott et al.*[31a] Thus, aryl-bromide (*S*)-**B86b** was treated with liquid NH_3 in the presence of copper powder and CuCl in a Parr reactor at 70 °C for 5 days. The product (*S*)-**B84** was obtained in 82% yield after crystallization (99% ee). In a similar process, (*S*)-**B86b** reacted with CH_3NH_2/Cu/CuCl to afford (*S*)-**B106**, 80% isolated yield after crystallization, 99% ee. Bromine displacement in the presence of catalytic Cu/CuCl is Ullmann-type reaction. The reaction readily occurs with simplest liquid amines[31a,b] (reactivity order: dimethylamine > methylamine > ammonia) and can be easily scaled-up. Higher boiling amines such as N,N-dimethylethylenediamine gave lower yields (30%) under the usual conditions.

The asymmetric hydrogenation - amination sequence provided sufficient amount of (*S*)-**B84** to allow the reinvestigation of the sulfonamide derivatives. After protecting secondary amine nitrogen as the Cbz derivative (*S*)-**B107**, N-sulfonylation could be carried out without complications, and deprotection (H_2/Pd-C) gave sulfonamides **B99a-d**. The absolute configuration of chiral sulfonamides **B99a-d** prepared from (*S*)-bromophenyl-1,2,3,4-tetrahydroisoquinoline (*S*)-**B86b** was the same as for material prepared by asymmetric reduction of protected N-sulfonylamino-3,4-dihydroisoquinolines **B100a-d** (Scheme B17).[L]

Scheme B17.

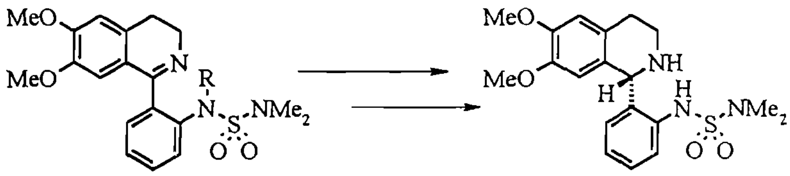


(L) Verified by the HPLC on CSP.

Thus, asymmetric reduction of various N-sulfonylamino-3,4-dihydroisoquinolines (*S*)-**B100a-d** follows the Noyori's asymmetric induction model[16a] and affords chiral isoquinolines with *S* absolute configuration.

3.3. Synthesis of N,N-(dimethylsulfamoyl)anilino-isoquinoline.

As our objective was synthesis of various acidic CAPTIQ **B73** analogs, N,N-dimethylsulfamoyl-anilide **B108** (pK_a(DMSO) ~ 12-14)[32] was chosen as synthetic target. Initially, direct asymmetric hydrogenation of suitably protected sulfamoylanilide **B107** was tested.

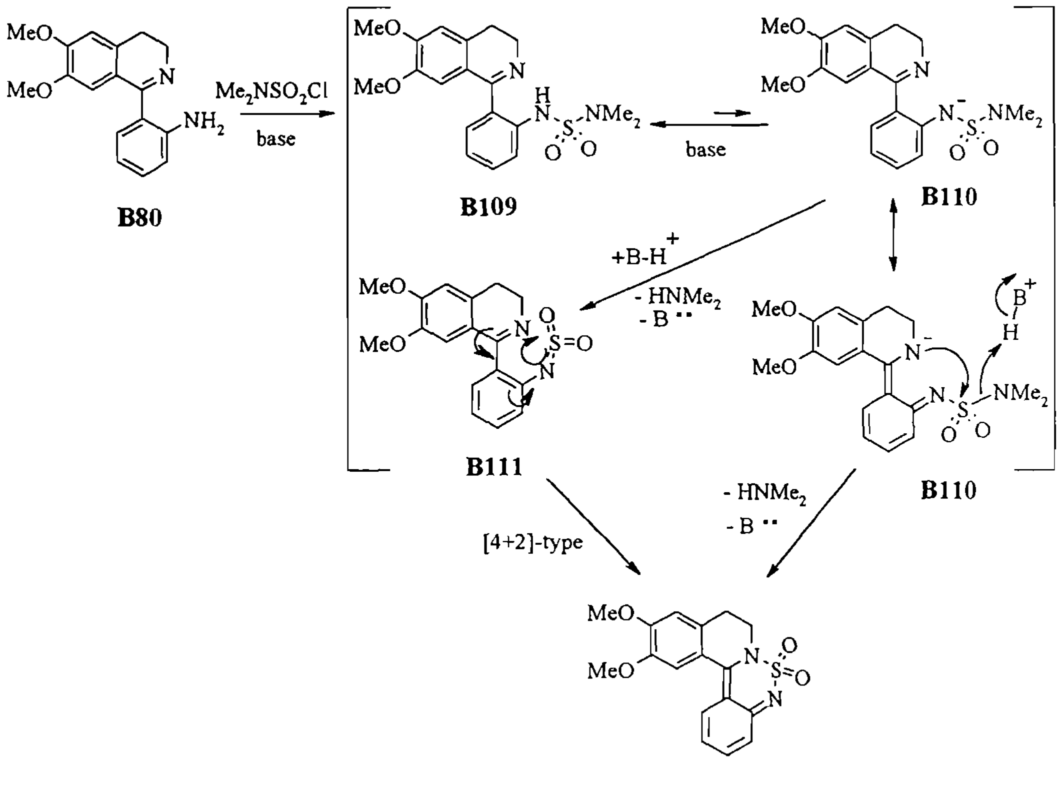


B107: R = benzyl or methoxymethyl (MOM)

B108

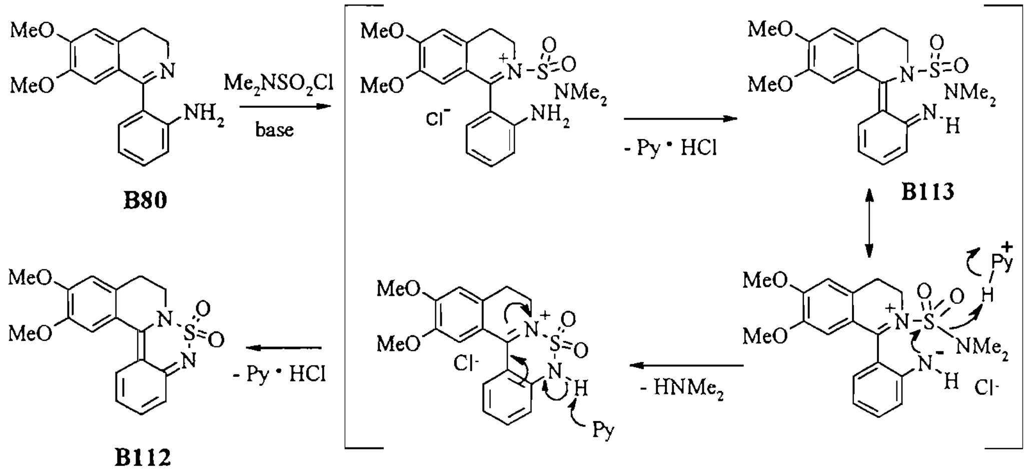
Serious problems, however, were encountered upon attempts to synthesize sulfonamide **B107**. Thus, treatment of aniline **B80** with N,N-dimethylsulfamoyl chloride in pyridine gave unexpected cyclic sulfonamide **B112** (Scheme B18).

Scheme B18.

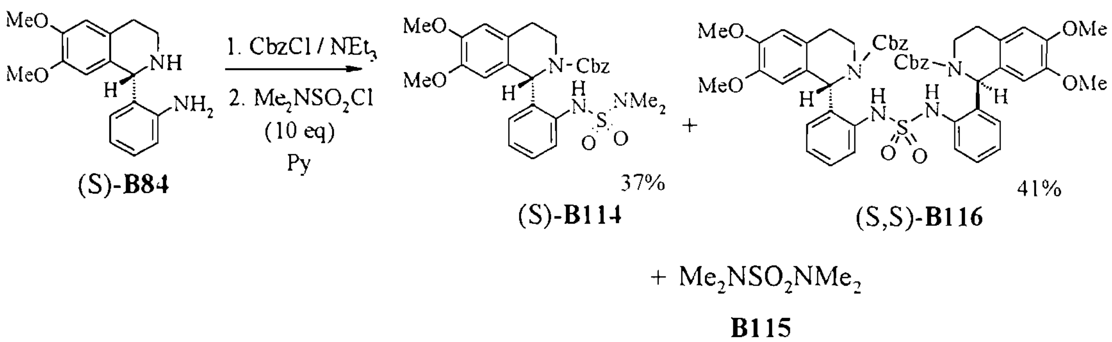


It is believed that upon formation, the desired sulfonamide **B109** in the presence of base equilibrates with the deprotonated anilide **B110,** showed as 2 resonance forms. Because there is no nucleophile in the reaction media (except of unreacted aniline **B80**) intramolecular attack by nucleophilic isoquinoline nitrogen on sulfur could in principle take place with formation of 6-membered ring. Alternatively, formation of cyclic sulfonamide **B112** proceeds *via* sulfonylamine **B111** followed by intramolecular [4+2]-type cycloaddition.[33] According to another possible pathway reaction proceeds *via* ring alkylated sulfamoylamide **B113** (Scheme B19).

Scheme B19.

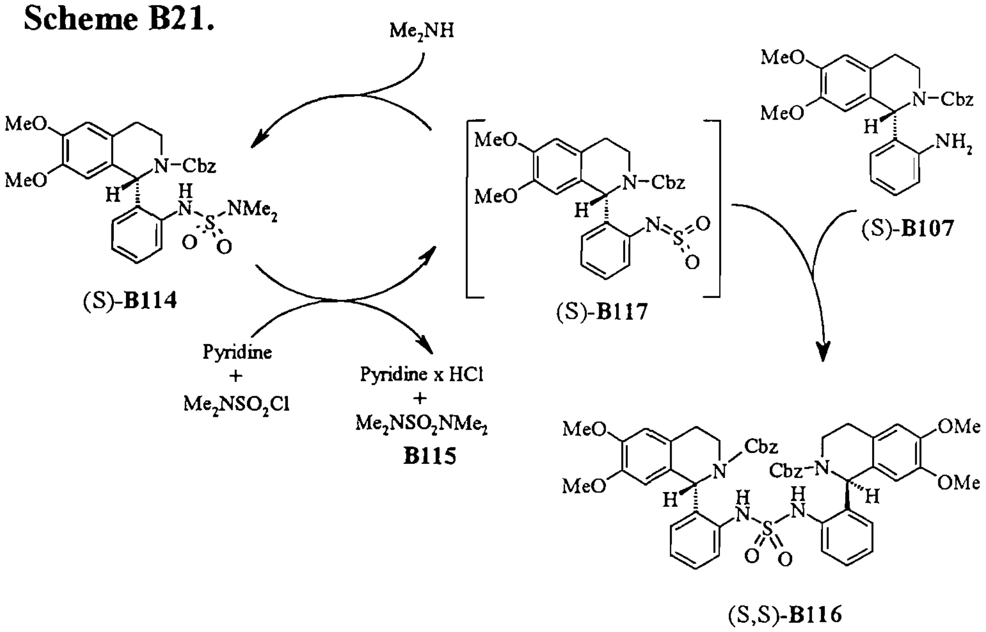


Because of unexpected difficulties in the synthesis of sulfamoylamide **B107** an alternative route to desired product **B108** was employed starting from chiral aniline (*S*)-**B84**. Isoquinoline nitrogen in diamine (*S*)-**B84** was selectively protected by Cbz group and subjected to reaction with 10-fold excess of N,N-dimethylsulfamoylchloride for 48 hours at room temperature. Flash column chromatography gave mixture of desired N-sulfamoyl derivative **B114** (37% yield) and starting material (*S*)-**B84** (22% recovery) accompanied by dimer **B116** (41% yield) and tetramethylsulfamylamide **B115**.

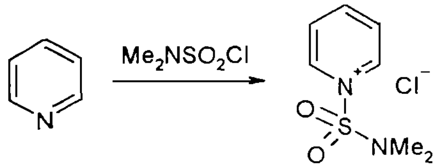


Large excess of sulfamoylchloride was employed to increase sulfamoylation rate and to diminish amount of unreacted Cbz-isoquinoline, thus avoiding the formation of dimeric product **B116**.

Scheme B21.



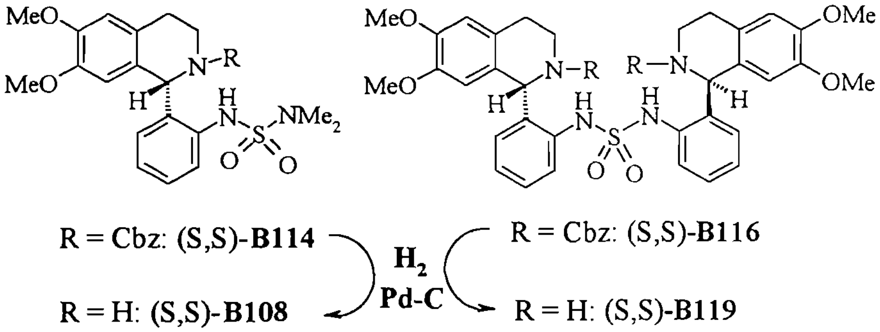
The formation of sulfonylamines from the corresponding sulfamoylchlorides or sulfamoylphthalimides in the presence of base traditionally has been used to generate substrates for cycloaddition reactions.[33] To avoid sulfamoylamine (*S*)-**B117** formation, Cbz-aniline (*S*)-**B107** was treated with N,N-dimethylsulfamoyl chloride in the presence of only 1.5 eq of NEt_3 in THF. No product was observed after refluxing for 8 h. Obviously pyridine is necessary because it acts not only as HCl scavenger but also as sulfamoylation catalyst, forming activated amide **B118**.



B118

To exclude presence of any base sulfamoyl pyridinium chloride **B118** was prepared separately and added (4 eq) to Cbz-aniline (S)-**B107** solution in MeCN. Surprisingly, no product (*S*)-**B114** was detected after 18 h stirring at room temperature. Thus, the reaction in pyridine so far is the only applicable method for preparation of sulfonamide (*S*)-**B114**.

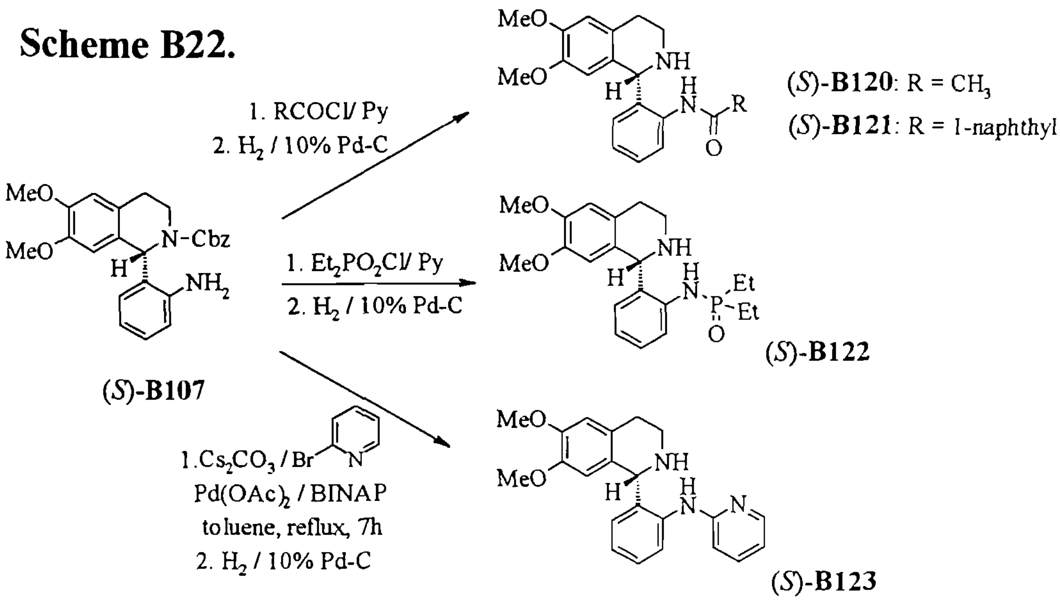
Cbz group removal by catalytic hydrogenation in the presence of 10% Pd-C failed in EtOAc, but succeeded in glacial AcOH to give the desired chiral isoquinoline (*S*)-**B108** in 91% yield. In a similar manner protecting group was removed in *bis*-product (*S,S*)-**B116** to give bis-sulfonamide (*S,S*)-**B119** (Scheme B22).



3.4. Preparation of various CAPTIQ analogs with increased N-H acidity.

To avoid complications with synthesis of Noyori hydrogenation substrates, optically active Cbz-protected anilino-isoquinoline (*S*)-**B107** was employed as a starting material for the preparation of various CAPTIQ analogues. N-Acyl, N-phosphinyl and N-2-pyridyl groups were introduced in a straightforward manner followed by Cbz protective group cleavage to afford chiral anilines **B120-B123**.

Scheme B22.



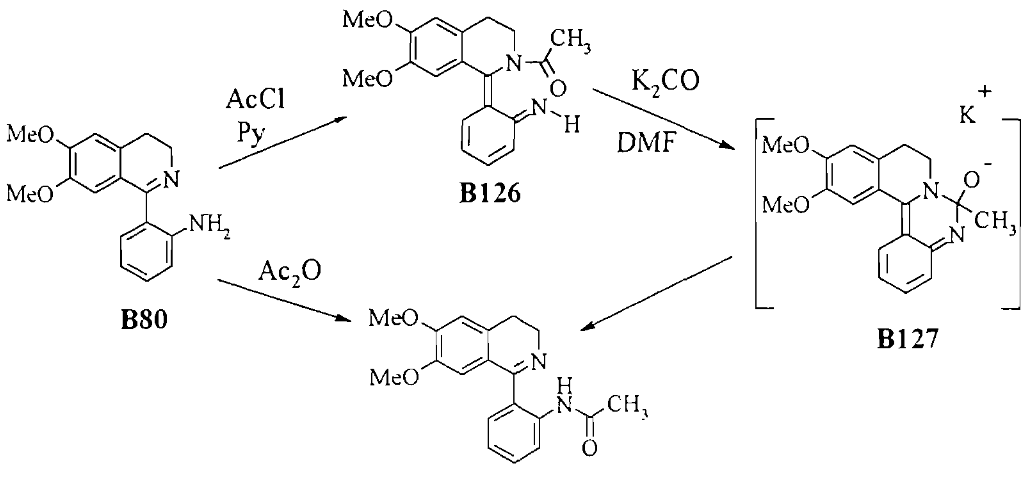
Slightly modified Buchwald's procedure[34] was employed for 2-pyridyl group introduction in aniline (*S*)-**B107**. Triamine (*S*)-**B123** is potentially a promising chiral proton donor because tridentate ligand has an increased ability to coordinate lithium.

3.5. Specific properties of N-anilino-3,4-dihydroisoquinoline system. Acetyl group migration.

Initially the preparation of N-acetanilide **B120** was attempted *via* transfer hydrogenation of (N-benzyl-N-acetyl)anilino-3,4-dihydroisoquinoline **B124**. Complications encountered in the synthesis of the reduction substrate **B124** forced to pursue alternative routes and desired N-acetyl substituted chiral diamine (S)-**B120** was later prepared from chiral starting material (see above). Attempts to synthesize N-acetyl 3,4-dihydroisoquinoline **B124**, however, revealed specific properties of 1-anilino-3,4-dihydroisoquinoline system that are worth to be mentioned in brief.

Reaction of aniline **B80** with AcCl in pyridine (standard procedure used for N-sulfonamides **B95a-d**) caused the precipitation of a yellow material almost immediately after acid chloride was added. Alternatively, aniline **B80** was treated with neat acetic anhydride. Major products isolated from both reactions were identical according to elemental analysis and matched the calculated values for the corresponding N-acetylaniline. Surprisingly, ^{1}H-NMR spectra showed that both products have similar set of signals, arranged, however, in a different pattern. Careful NMR spectra interpretation allowed to assign major product structures for each reaction. Thus, anticipated N-acetanilide **B125** was formed in the reaction of aniline **B80** with neat Ac_2O without added base, while treatment with AcCl in pyridine afforded a surprisingly stable *ortho*-quinone imine **B126**.

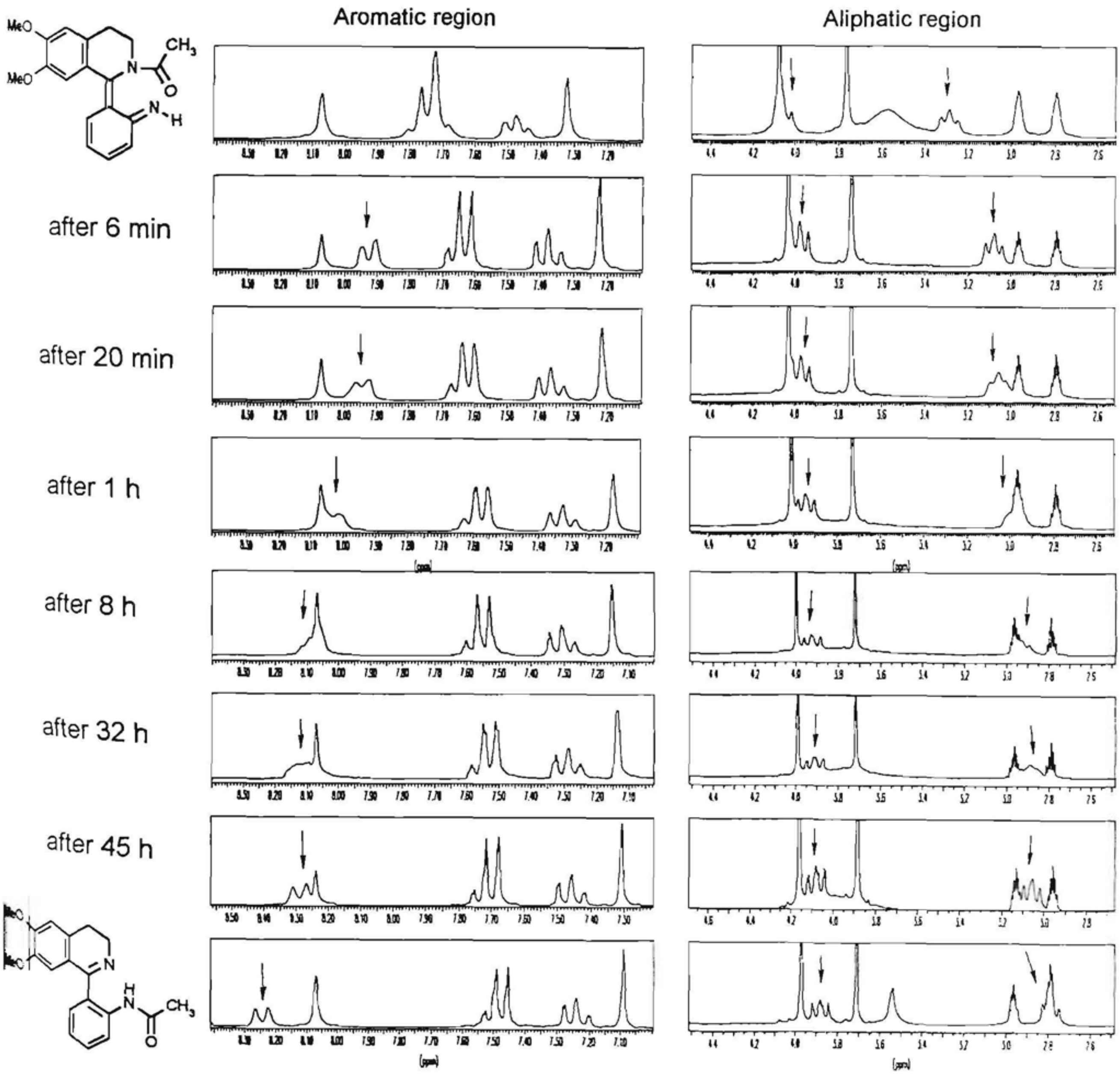
Scheme B23.



Ortho-quinone imines or aza-*ortho*-xylylenes generally are unstable and usually have been generated *in situ* for various cycloaddition reactions.[35] Structurally related 1-

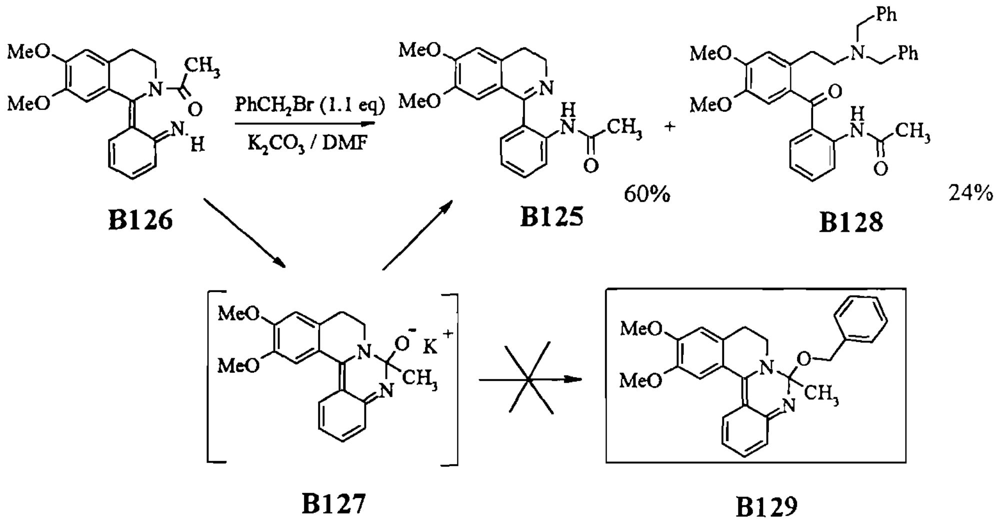
alkyl-3,4-dihydroisoquinoline derived N-acyl enamides were prepared by acylation in pyridine.[19d,36]

Even more intriguing is the rearrangement of quinone imine **B126** to N-acetanilide **B125** in the presence of base. Acetyl group migration (rearrangement) to aniline nitrogen in DMF in the presence of NaH occurs in less than 30 minutes (first aliquot taken from the reaction mixture after 30 min. showed that reaction is already completed). Although considerably slower, rearrangement takes place even in the presence of dry K_2CO_3 in DMF-d_7 and the process can be observed by ^{1}H-NMR.



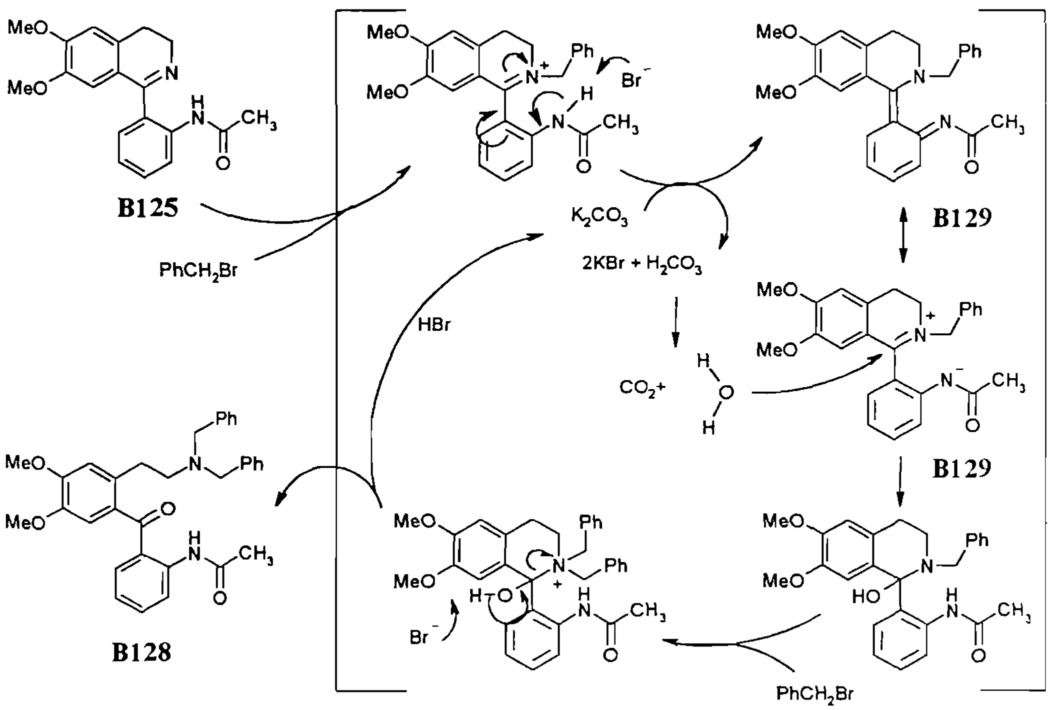
It is believed that rearrangement can proceed *via* a six-membered intermediate **B127**. Several attempts to trap the possible intermediate **B127** were made. Initially, benzyl bromide in DMF and dry K_2CO_3 was employed and instead of anticipated O-benzyl ether **B129** rearranged acetanilide **B125** was isolated as the major product, accompanied with benzophenone **B128**:

Scheme B24.



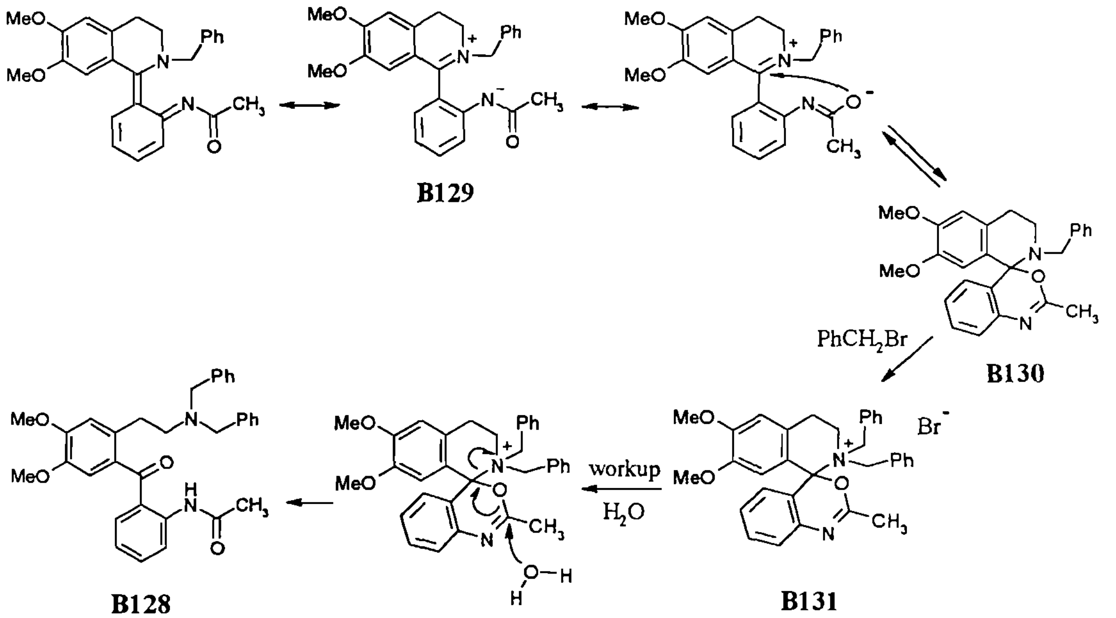
The formation of ring-opening product **B128** is assumed to occur *via* alkylation of rearranged isoquinoline **B125** nitrogen with a strong alkylating agent - benzyl bromide.

Scheme B25.



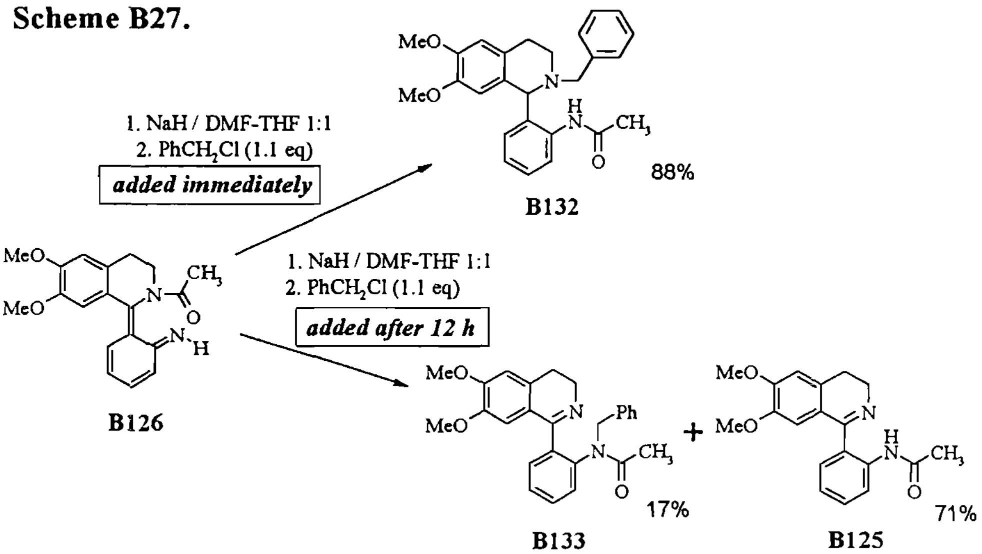
One equivalent of water necessary for the formation of benzophenone **B128** formally can be generated from K_2CO_3 and 2 eq. of HBr (formed upon alkylation with BnBr). Alternatively, ring-alkylated product **B129** can undergo intramolecular cyclization to **B130**. Subsequent alkylation with another molecule of BnBr results in a charged structure **B131** that generates benzophenone **B128** upon aqueous workup (Scheme B26):

Scheme B26.



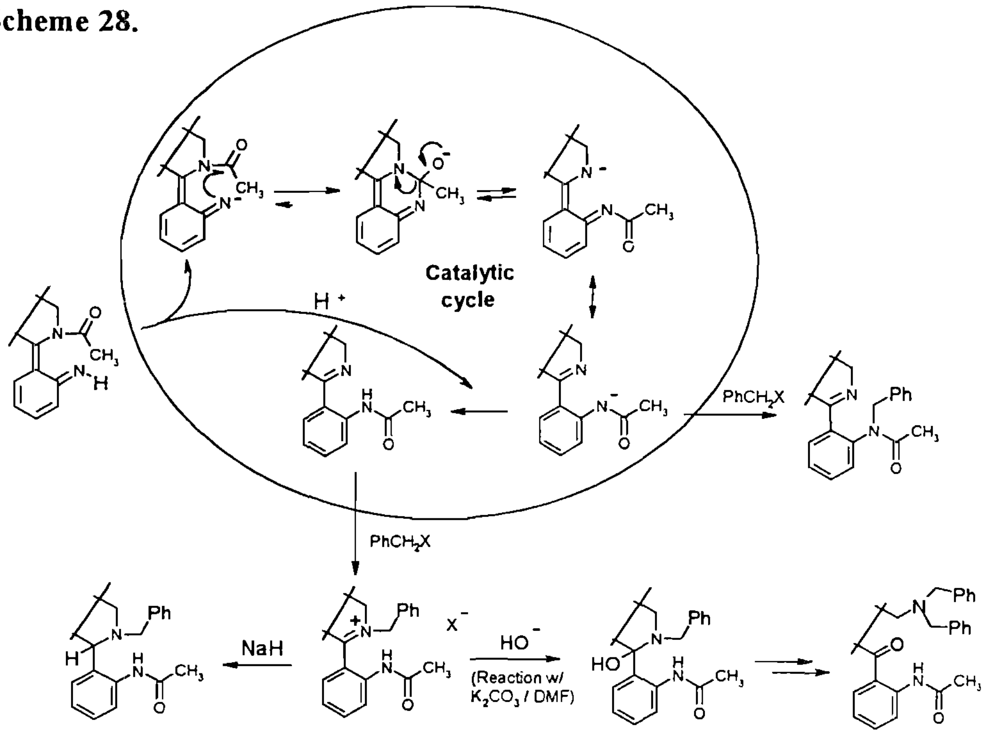
To avoid the formation of ring opening product **B129** a weaker electrophile - benzyl chloride as well as cooling to 0^0 C was employed. Quinone imine **B126** was added to NaH (1.3 eq) suspension in DMF *immediately* followed by benzyl chloride (5 eq). After stirring for 6 h reduced N-benzyl isoquinoline **B132** was isolated as the main product in 88% yield (Scheme B27). Evidently, benzyl chloride alkylated the rearranged product and the resulting isoquinolinium salt was reduced by NaH. In contrary, if benzyl chloride is added to the mixture of NaH and substrate **B126** *beforehand stirred for 12 h*, N-benzyl acetanilide **B133** was isolated as minor product (17%) together with unreacted acetyl migration product **B125**.

Scheme B27.



Similar results were obtained employing DMSO as a solvent. Such a diverse outcome can be understood assuming that acetyl group migration occurs in the presence of a catalytic amount of base. When benzyl chloride is added immediately after NaH, acetyl group has already migrated, whereas the resulting N-acetanilide **B125** is not yet deprotonated, because NaH is insoluble in DMF and forms a heterogenous system. As a result, alkylation occurs on isoquinoline nitrogen. On the other hand, after 12 hours rearranged acetanilide **B125** is completely deprotonated and added benzyl chloride alkylates amide nitrogen yielding the desired amide **B133**. Summary of the above reactions is given in Scheme B28.

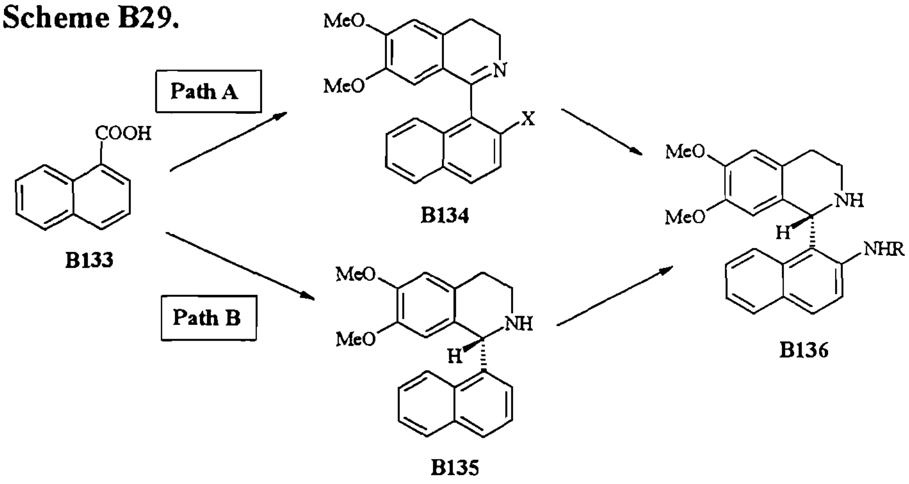
Scheme 28.



3.6. Toward 1-naphthyl diamine.

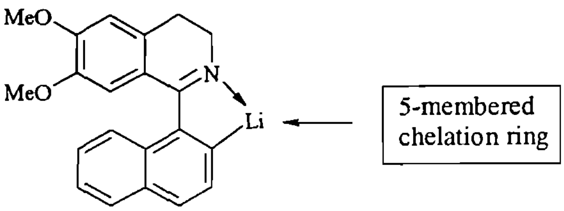
Naphthyl tetrahydroisoquinolines **B136** are of special interest as potential asymmetric proton donors. Because of limited access to suitably substituted naphthalenecarboxylic acids two general ways to the desired compounds were chosen. Path A provides introduction of appropriate substituents in 3,4-dihydroisoquinoline **B134** and subsequent creation of chiral center while path B includes modification after asymmetric reduction of unsubstituted substrate **B135**.

Scheme B29.



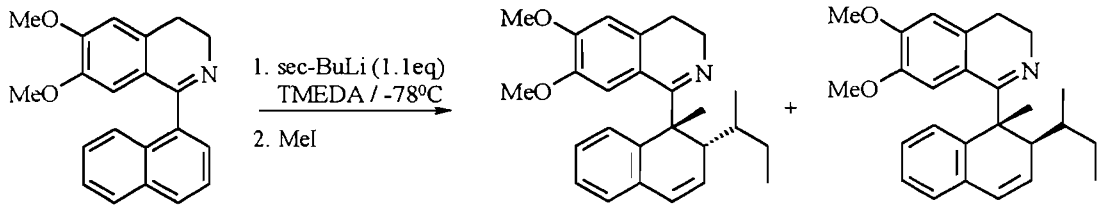
Examination of Path A.

3,4-Dihydroisoquinoline **B134** (X=H) was prepared in 3 steps from commercially available naphthalene-1-carboxylic acid **B133** *via* Bischler-Napieralski cyclization of corresponding β-phenethylamide in 58% overall yield. Initially *ortho*-lithiation was employed for the introduction of substituents in β-position of naphthalene ring in **B134**, with the hope that lithiated naphthalene **B134** (X=Li) is stabilized *via* chelation by isoquinoline nitrogen:[37]



B134 (X=Li)

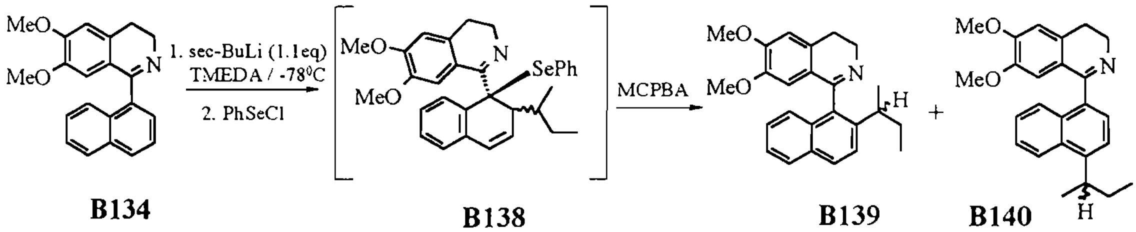
sec-Butyllithium was employed for lithiation and instead of anticipated ortho-methyl product after quench with MeI 1,4-Michael-type addition products *syn*-**B137** and *anti*-**B137** were isolated in a 1:4 ratio (determined by NMR).



B135 *anti*-**B137** 1 : 4 *syn*-**B137**

71% after recrystall.

Similar 1,4-type Michael addition of various lithium amides to naphthyloxazolines have been studied by *Meyers* group.[38] They observed competitive 1,6-type versus 1,4-conjugated addition and found that sterical factors are responsible for addition regioselectivity.[38b] We decided to exploit 1,4-Michael type addition for the introduction of amino group in naphthylisoquinolines. Both in *Meyer*'s studies and our experiment with *sec*-BuLi aza-enolate formed after conjugated addition of nucleophile was trapped by MeI thus interrupting aromatic system. To regenerate aromatic naphthalene it was necessary to use electrophile that could be subsequently removed. Phenylselenyl chloride was chosen as an aza-enolate quenching agent because it can be oxidatively eliminated[39] with regeneration of naphthalene aromatic system.

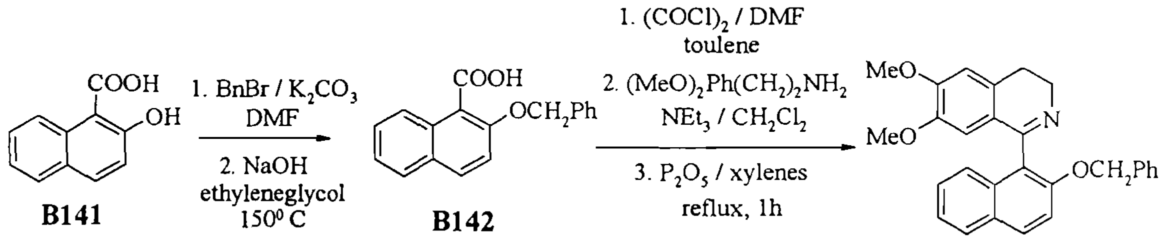


B134 **B138** **B139** **B140**

The addition product **B138** was not isolated; however, it had similar TLC behavior to the adduct **B137**. Treatment with m-chloroperoxybenzoic acid (MCPBA) yielded 2:1 mixture of two isomers according to NMR. It has been impossible to determine whether they are two regioisomers **B139** and **B140**[40] or two diastereomers of **B139**.[M] Nevertheless, our approach was successful and it potentially can be employed for the introduction of substituents at the *ortho*-position of various 1-substituted naphthalenes. With efficient synthetic approach in hand model studies were necessary to simplify NMR spectra interpretation and to test further crucial asymmetric transformations.

(M) It is possible that isoquinoline **B139** exists as mixture of atropoisomers and each of them has a chiral center in *sec*-Bu group.

Ortho-substituted naphthyl-3,4-dihydroisoquinoline as a model compound for NMR and asymmetric hydrogenation studies was prepared from commercially available 2-hydroxy-1-naphtoic acid **B141**.



B143

The reaction of naphthoic acid **B141** with excess BnBr gave bis-benzylated derivative. Benzyl ester hydrolysis failed with 50% NaOH in DMF and with NaOH in DMSO at 100°C. Carboxylic acid **B142** was prepared only by employing more harsh hydrolysis conditions - solid NaOH in boiling ethyleneglycol. Conversion to acid chloride, followed by reaction with β-phenethylamine and cyclization afforded the desired isoquinoline in 61% yield (from acid **B142**). Debenzylated isoquinoline was detected as a cyclization byproduct. As anticipated, 3,4-dihydroisoquinoline **B143** exists as a mixture of atropoisomers.[N]

Further synthetic strategy required either the resolution of racemate **B143** into atropoisomers with subsequent *asymmetric* reduction of a pure enantiomer or *achiral* reduction followed by the resolution of racemic product. Surprisingly, no reduction product was observed by applying Noyori asymmetric transfer hydrogenation conditions (7.5 mol% tosyl-Ru catalyst) to isoquinoline **B143** (see also Table B10). Moreover, preliminary experiments showed that even $NaCNBH_3$ reagent in glacial acetic acid[41] does not reduce 3,4-dihydroisoquinoline **B143** under standard conditions. Evidently, access to either side of planar C=N system for 2-substituted naphthyl isoquinoline is hindered. In contrary, unsubstituted analog **B134** (X=H) can be hydrogenated with excellent enantioselectivity (98.1-98.7 % ee) and in high yield (82-88%, see Table B10, entry 15 vs. 16).

Consequently, synthetic strategy based on the reduction of 2-substituted naphthyl isoquinoline (Path A, Scheme B29) turned out to be unsuccessful. Further attempts will be directed towards the modification of chiral unsubstituted 1-naphthyl-1,2,3,4-tetrahydroisoquinoline **B135** (Scheme B29).

(N) Two peaks were observed on HPLC on CSP for **B143**.

3.7. Summary.

1. Noyori asymmetric transfer hydrogenation using tosyl-Ru catalyst **B76** is effective for the enantioselective hydrogenation of imines **B96** and **B100a-d**, having fully substituted nitrogen groups. On the other hand, number of steps required because of the problems with catalyst inhibition and complications with the protecting group chemistry, combined with high catalyst loading (7.5 mol%) make this approach relatively laborious and expensive.

2. N-Unsubstituted 1-anilino-3,4-dihydroisoquinolines **B80** and **B93** can be hydrogenated with moderate enantioselectivity (71-85% ee), but required impractical purity levels for the substrate.

3. The best hydrogenation results were obtained with the bromophenyl imine **B85**. In the case of **B85b**, the product (*S*)-**B86b** was formed with 98.7% ee, and the material could be upgraded to >99% ee by the crystallization of the hydrochloride salt. Scale-up to 18 g was carried out with a 10% loss in yield without encountering other complications.

4. Reaction of (*S*)-bromophenyl-isoquinoline **B86b** with liquid NH_3 in the presence of Cu/CuCl gave the desired chiral aniline (*S*)-**B84**. Chiral diamine (*S*)-**B84** was successfully employed as a chiral starting material for the synthesis of various N-substituted anilino-tetrahydroisoquinolines as potential asymmetric proton donors. Thus, asymmetric hydrogenation of bromo imine **B85b** combined with the copper-catalyzed amination currently is the method of choice for the synthesis of CAPTIQ analogues.

3.8. References.

1. (a) Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates and Resolutions*; Krieger Publishing Company: Florida, 1994. (b) Newmann, P. *Optical Resolution Procedures for Chemical Compounds; Amines and Related Compounds*; Riverdale, N.Y.; Optical Resolution Information Center, 1984.

2. (a) "Recent Progress in the Enantioselective Synthesis of Isoquinoline Alkaloids" Rozwadowska, M.D. *Heterocycles* **1994**, *39*, 903. (b) for a recent selected examples see "A Novel Route to Chiral, Nonracemic 1-Alkyl and 1-Aryl-Substituted Tetrahydroisoquinolines. Synthesis of (-)-Salsolidine and (+)-Cryptostyline II" Munchhof, M.J.; Meyers, A.I. *J.Org.Chem.* **1995**, *60*, 7086. "Asymmetric Synthesis and Enantioselectivity of Binding of 1-Aryl-1,2,3,4-tetrahydroisoquinolines at the PCP Site of the NMDA Receptor Complex" Wanner, K.T.; Beer, H.; Höfner, G.; Ludwig, M. *Eur.J.Org.Chem.* **1998**, 2019. "Diastereoselective Addition of Chiral (2-Lithiophenyl)acetaldehyde Acetals to Various Imines as Key Step in the Asymmetric Synthesis of 1-Aryltetrahydroisoquinolines, Part 4" Wünsch, B.; Nerdinger, S. *Eur.J.Org.Chem.* **1999**, 503.

3. (a) "Asymmetric Reductions of Carbon-Nitrogen Double Bonds. A Review", Zhu, Qi-Cong; Hutchins, O.; Hutchins, M.K. *Org.Prep.Proc.Int.* **1994**, *26*, 193. (b) "Reduction of Imino Groups (C=N)" Martens, J. in *Methods of Organic Chemistry (Houben-Weyl), Stereoselective Synthesis, vol.7*, Helmchen, G.; Hoffmann, R.W.; Mulzer, J.; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1996; pp 4199-4236. (c) "Stereoselective Reduction of Endocyclic Carbon-Nitrogen Double Bond: Application to the Synthesis of Biomolecules" Yurovskaya, M.A.; Karchava, A.V. *Tetrahedron: Asymmetry*, **1998**, *9*, 3331.

4. "Enantioselective Hydrogenation of the C=N Group: A Catalytic Asymmetric Reductive Amination Procedure" Burk, M.J.; Feaster, J.E. *J.Am.Chem.Soc.* **1992**, *114*, 6266 and references cited therein.

5. (a) "Synthesis of Chiral 1-Benzyl-1,2,3,4-Tetrahydroisoquinolines by Asymmetric Reduction" Rice, K.C. *U.S.Patent 4,727,146*, **23 Feb 1988**, 8 pp.; *Chem.Abstr.* **1986**, *105:* 226387e. (b) "Efficient Asymmetric Hydrogenation of Imines Catalyzed by a Neutral Iridium(I) Complex of (4R,5R)-MOD-DIOP" Morimoto, T.; Nakajima, N.; Achiwa, K. *Chem.Pharm.Bull.*, **1994**, *42*, 1951. (c) "Catalytic Asymmetric Hydrogenation of Imines. Use of Rhodium(I)/ Phosphine Complexes and Characterization of Rhodium(I)/Imine Complexes" Becalski, A.G.; Cullen, W.R.; Fryzuk, M.D.; James, B.R.; Kang, G.J.; Rettig, S.J. *Inorg.Chem.* **1991**, *30*, 5002.

6. (a) "Synthese D'amines Chirales au Moyen D'un Complexe de Rhodium et D'isopropylidene Dihydroxy-2.3-bis(diphenylphospino)-1,4 Butane (DIOP)" Kagan, H.B.; Langlois, N.; Dang, T.P. *J.Organometallic Chem.* **1975**, *90*, 353. (b) "Enantioselective Hydrosilylation of Prochiral 3,4-Dihydro-2*H*-pyrrole Derivatives" Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew.Chem.Int.Ed.Engl.* **1985**, *24*, 995. (c) Жоров, Е. Ю.; Павлов, В. А.; Федотова, О. А.; Шведов, В. И.; Мистрюков, Э. А.; Платонов, Д. Н.; Горшкова, Л, С.; Клабуновский, Е. И. *Изв. АН СССР, сер.хим.* **1991**, 865. *Chem.Abstr.* **1992**, *118*, 217541.

7. (a) "Iridium (III) Hydride Complexes for the Catalytic Enantioselective Hydrogenation of Imines" Chan, Y.N.C.; Osborn, J.A. *J.Am.Chem.Soc.* **1990**, *112*, 9400. (b) "Chemoselective Hydrogenation of Imines Catalysed by Ir^{III} Complexes" Chan, Y.N.C.; Meyer, D.; Osborn, J.A. *J.Chem.Soc.Chem.Commun.* **1990**, 869. (c) "Asymmetric Hydrogenation of Imines Catalysed by Carboxylato(diphosphine)-iridium(III) Complexes" Sablong, R.; Osborn, J.A. *Tetrahedron: Asymmetry* **1996**, *7*, 3059.

8. (a) "Asymmetric Hydrogention of Cyclic Ketimines Catalyzed by Iridium(I)-Complexes of BCPM and Its Analog" Morimoto, T.; Nakajima, N.; Achiwa, K. *Synlett*, **1995**, 748. (b) "Additive effects in Ir-BICP catalyzed asymmetric hydrogenation of imines" Zhu, G.; Zhang, X. *Tetrahedron: Asymmetry*, **1998**, *9*, 2415. (c) "Iridium(I)-Catalyzed Asymmetric Hydrogenation of Prochiral Imines; Protic Amines as Catalyst Improvers" Tani, K.; Onouchi, J.; Yamagata, T.; Kataoka, Y. *Chem.Lett.* **1995**, 955.

9. (a) "The Asymmetric Hydrogenation of Imines Using Tridentate C_2 Diphosphine Complexes of Iridium(I) and Rhodium(I)" Sablong, R.; Osborn, J. *Tetrahedron Lett.* **1996**, *37*, 4937. (b) "Enantioselective Hydrogenation of Imines with Chiral (Phosphanodihydrooxazole)iridium Catalysts" Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F.M.; Krueger, C.; Phaltz, A. *Chem.Eur.J.* **1997**, *3*, 887.

10. (a) "An Improved Diphosphine-Iridium(I) Catalyst System for the Asymmetric Hydrogenation of Cyclic Imines: Phthalimide as an Efficient Co-catalyst" Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry*, **1995**, *6*, 2661. (b) "Asymmmetric Synthesis of (S)-Norlaudanosine and (S)-Tetrahydrohomopapaverine by Catalytic Asymmetric Hydrogenation with Chiral Diphosphine-Iridium(I)-Phthalimide Complex Catalysts" Morimoto, T.; Suzuki, N.; Achiwa, K. *Heterocycles*, **1996**, *43*, 2557. (c) "Enantioselective Synthesis of (S)-Calycotomine Employing Catalytic Asymmetric Hydrogenation with an Iridium(I)-(R)-BINAP-Phthalimide Complex" Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry*, **1998**, *9*, 183.

11. (a) "Synthesis of Highly Enantiomerically Enriched Cyclic Amines by the Catalytic Asymmetric Hydrogenation of Cyclic Imines" Willoughby, C.A.; Buchwald, S.L. *J.Org.Chem.* **1993**, *58*, 7627. (b) "Catalytic Asymmetric Hydrogenation of Imines with a Chiral Titanocene Catalyst: Scope and Limitations" Willoughby, C.A.; Buchwald, S.L. *J.Am.Chem.Soc.* **1994**, *116*, 8952. (c) "Catalytic Asymmetric Hydrogenation of Imines with a Chiral Titanocene Catalyst: Kinetic and Mechanistic Investigations" Willoughby, C.A.; Buchwald, S.L. *J.Am.Chem.Soc.* **1994**, *116*, 11703.

12. (a) "Highly Enantioselective Imine Hydrosilylation Using (S,S)-Ethylenebis(η^5-tetrahydroindenyl)- titanium Difluoride" Verdaguer, X.; Lange, U.E.W.; Reding, M.T.; Buchwald, S.L. *J.Am.Chem.Soc.* **1996**, *118*, 6784. (b) "Amine Additives Greatly Expand the Scope of Asymmetric Hydrosilylation of Imines" Verdaguer, X.; Lange, U.E.W.; Buchwald, S.L. *Angew.Chem.Int.Ed.Engl.* **1998**, *37*, 1103.

13. "Kinetic Resolution of Racemic Disubstituted 1-Pyrrolines *via* Asymmetric Reduction with a Chiral Titanocene Catalyst" Viso, A.; Lee, N.E.; Buchwald, S.L. *J.Am.Chem.Soc.* **1994**, *116*, 9373.

14. "Short Enantioselective Total Synthesis of the Piperidine Alkaloids (S)-Coniine and (2R,6R)-*trans*-Solenopsin A via Catalytic Asymmetric Imine Hydrosilylation" Reding, M.T.; Buchwald, S.L. *J.Org.Chem.* **1998**, *63*, 6344.

15. "Chiral Toluene-2,α-Sultam Auxiliaries: Preparation and Structure of Enantiomerically Pure (R)- ans (S)-Ethyl-2,1'-Sultam" Oppolzer, W.; Wills, M. Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117.

16. (a) "Asymmetric Transfer Hydrogenation of Imines" Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J.Am.Chem.Soc.* **1996**, *118*, 4916. (b) "Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes" Noyori, R.; Hashiguchi, S. *Acc.Chem.Res.*, **1997**, *30*, 97. (c) Personal communication: Hashiguchi, S.; Ikariya, T.

17. "Ruthenium-Catalyzed Asymmetric Hydrosilylation of Ketones and Imine" Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics*, **1998**, *17*, 3420.

18. For a recent review see "Enantioselective Hydrogenations and Isomerizations" Pfaltz, A.; Brown, J.M. in *Methods of Organic Chemistry (Houben-Weyl), Stereoselective Synthesis, vol.7*, Helmchen, G.; Hoffmann, R.W.; Mulzer, J.; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1996; pp 4334-4359.

19. (a) "Catalytic Asymmetric Synthesis of (S)- and (R)-Salsolidine" Achiwa, K. *Heterocycles* **1977**, *8*, 247. (b) "Synthesis of a New Chiral Bisphosphine Ligand, MOCBP, and Its Use in Rhodium(I)-Catalyzed Asymmetric Hydrogenation of a Cyclic Enamide" Morimoto, T.; Nakajima, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 75. (c) "Asymmetric Synthesis of Isoquinoline Alkaloids by Homogeneous Catalysis" Noyori, R.; Ohta, M.; Hsiao Yi; Kitamura, M.; Ohta, T.; Takaya, H. *J.Am.Chem.Soc.* **1986,** *108*, 7117. (d) "General Asymmetric Synthesis of Isoquinoline Alkaloids. Enantioselective Hydrogenation of Enamides Catalyzed by BINAP-Ruthenium(II) Complexes" Kitamura, M.; Hsiao Yi; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J.Org.Chem.* **1994**, *59*, 297.

20. (a) "Asymmetric Hydrogenation of Tetrahydropyrazines: Synthesis of (S)-Piperazine-2-tert-butylcarboxamide, an Intermediate in the Preparation of the HIV Protease Inhibitor Indinavir" Rossen, K.; Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 6419. (b) " An Efficient Asymmetric Hydrogenation Approach to the Synthesis of the Crixivan® Piperazine Intermediate", Rossen, K.; Pye, P.J.; DiMichele, L.M.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* **1998**, *39*, 6823. (c) "Asymmetric Hydrogenation of 1,4,5,6-Tetrahydropyrazine-2-(N-*tert*-butyl)carboxamide Catalyzed by Trans-Chelating Chiral Diphosphine-Rhodium Complexes" Kuwano, R.; Ito, Y. *J.Org.Chem.* **1999**, *64*, 1232.

21. (a) "Synthesis and Reactions of α-(Trifluromethanesulfonyloxy) Enecarbamates Prepared from N-Acyllactams" Foti, C.J.; Comins, D.L. *J.Org.Chem.* **1995**, *60*, 2656. (b) "An Efficient Asymmetric Synthesis of (R)-3-Amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one" Armstrong, III, J.D.; Eng, K.K.; Keller, J.L.; Purick, R.M.; Hartner, F.W.; Choi, W.B.; Askin, D.; Volante, R.P. *Tetrahedron Lett.* **1994**, *35*, 3239.

22. "Enantioselective Catalytic Reduction of Dihydroisoquinoline Derivatives" Kang, J.; Kim, J.B.; Cho, K.H.; Cho, B.T. *Tetrahedron: Asymmetry*, **1997**, *8*, 657.

23. (a) "Deracemization via Highly Enantioselective Enolate Protonation Using a Chiral Aniline as the "Acid" " Vedejs, E.; Lee, N.; Sakata, S.T. *J. Am. Chem. Soc.* **1994**, *116*, 2175. (b) "Catalytic Asymmetric Protonation of Amide Enolates: Optimization of Kinetic Acidity in the Catalytic Cycle" Vedejs, E.; Kruger, A.W. *J. Org.Chem.* **1998**, *63*, 2792.

24. "π Stacking Effects in Asymmetric Synthesis" Jones, G.B.; Chapman, B.J. *Synthesis* **1995**, 475.

25. "2,4-Diaminotoluene" Mahood, S.A.; Schaffner, P.V.L. *Org.Synth. Coll.Vol. II* **1943**, 160.

26. (a) "Position Isomerism in the Azoxybenzenes" Behr, L. C. *J. Am. Chem. Soc.* **1954**, *76*, 3672. (b) "The m-Nitroazoxybenzenes" Behr, L. C.; Alley, E. G.; Levand, O. *J. Org. Chem.* **1962**, *27*, 65.

27. "Arene Ruthenium(II) Complexes formed by Dehydrogenation of Cyclohexadienes with Ruthenium (III) Trichloride" Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans. 1* **1974**, 233.

28. "Asymmetric Activation of Racemic Ruthenium(II) Complexes for Enantioselective Hydrogenation" Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J.Am.Chem.Soc.* **1998**, *120*, 1086.

29. (a) "Desulfonylation of Amides Using Samarium Iodide" Knowles, H.; Parsons, A.F.; Pettifer, R.M. *Synlett*, **1997**, 271. (b) "Deprotection of Arenesulfonamides with Samarium Iodide" Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.

30. Greene, T.W.; Wuts, P.G.M. in *Protective groups in Organic Synthesis*, 2nd ed.; Wiley&Sons: New-York, 1991; pp. 353-354.

31. (a) Ott, H.; Hardtmann, G.; Denzer, M.; Frey, A. J.; Gogerty, J. H.; Leslie, G. H.; Trapold, J. H. *J. Med. Chem.* **1968**, *11*, 777. (b) "Copper Assisted Nucleophilic Substitution of Aryl Halogen" Lindley, J. *Tetrahedron*, **1984**, *40*, 1433.(c) "Aryllead Triacetates: Regioselective Reagents for N-Arylation of Amines" Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.-P.; Guiry, P.J. *J.Chem.Soc. Perkin Trans. 1* **1991**, 2095. (d) for a recent rewievs on Pd- and Ni-catalyzed aromatic amination see: "Rational Development of Practical Catalysts for Aromatic Carbon-Nitrogen Bond Formation" Wolfe, J.P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc.Chem.Res.* **1998**, *31*,

805. "Carbon-Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides" Hartwig, J.F. *Acc.Chem.Res.* **1998**, *31*, 852.

32. "Equilibrium Acidities in Dimethyl Sulfoxide Solution" Bordwell, F.G. *Acc.Chem.Res.* **1988**, *21*, 456. "Effects of Sulfenyl, Sulfinyl and Sulfonyl Groups on Acidities and Homolytic Bond Dissociation Energies of Adjacent C-H and N-H Bonds" Bordwell, F.G.; Liu, W.-Z. *J.Phys.Org.Chem.* **1998**, *11*, 397.

33. "Novel Applications of N-Sulfonyl-alkylamines in [2+4] Cycloadditions" Tornus, I.; Schaumann, E. *Tetrahedron,* **1996**, *52*, 725.

34. (a) Singer, R.A.; Sadighi, J.P.; Buchwald, S.L.; Wagaw, S. *J.Am.Chem.Soc.* **1998**, *120*, 213. (b) "Improved Functional Group Compatibility in the Palladium-Catalyzed Amination of Aryl Bromides" Buchwald, S.L.; Wolfe, J.P. *Tetrahedron Lett.* **1997**, *38*, 6359.

35. Recent examples: (a) "Diels-Alder Reactions of N-sulfonyl Substituted Aza-*ortho*-xylylenes Generated from the Corresponding 1,4-Dihydro-2*H*-3,1-benzoxazin-2-one Derivatives" Consonni, R.; Croce, P.D.; Ferraccioli, R.; La Rosa, C. *J.Chem.Soc. Perkin Trans. 1* **1996**, 1809. (b) "Synthesis of Fullerotetrahydroquinolines by Cycloaddition Reaction of C_{60} with Aza-*ortho*-xylylenes" Ohno, M.; Sato, H.; Eguchi, S. *Synlett* **1999**, 207.

36. "Diastereoselective Reduction of Derivatives of 3,4-Dihydro-1-methylidene-2-tartaroylisoquinoline" Czarnocky, Z.; MacLean, D.B.; Szarek, W.A. *Heterocycles,* **1992**, *34*, 943.

37. "Directed Ortho Metalation. Tertiary Amide and O-Carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics" Snieckus, V. *Chem.Rev.* **1990**, *90*, 879.

38. (a) "Asymmetric Diastereoselective Conjugate Additions of Lithium Amides to Chiral Naphthyloxazolines Leading to Novel β-Amino Acids" Meyers, A.I.; Shimano, M. *J.Org.Chem.* **1995**, *60*, 7445. (b) "Diastereoselective 1,6-Additions of Lithium Amides to Naphthyloxazolines. A Route to Novel δ-Amino Acid Derivatives" Meyers, A.I.; Shimano, M. *J.Org.Chem.* **1996**, *61*, 5714.

39. "Functional Group Manipulation Using Organoselenium Reagents" Reich, H.J. *Acc.Chem.Res.* **1979**, *12*, 22.

40. "Conjugate Addition of Lithium Enolates to Aromatic Carbonyl Compounds Complexed with Aluminum Tris(2,6-diphenylphenoxide) (ATPH)" Saito, S.; Sone, T.; Shimada, K.; Yamamoto, H. *Synlett,* **1999**, 81.

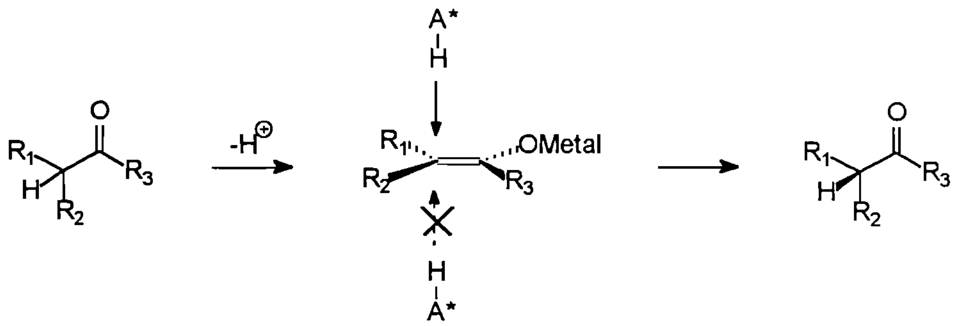
41. Standard system used for isoquinolines reduction: "Reactions of Sodium Borohydride in Acidic Media; III. Reduction and Alkylation of Quinoline and Isoquinoline with Carboxylic Acids" Gribble, G.W.; Heald, P.W. *Synthesis,* **1975**, 650.

Chapter C

Asymmetric Protonation of Lithium Enolates

1. Literature review.

The enantioselective proton transfer from a chiral proton source to enolate is a powerful and attractive method for the synthesis of enantioenriched carbonyl compounds, because there is no need to use classical resolution or a covalently bonded auxiliary, which introduce additional steps. Racemic ketones, esters and amides can be deracemized in one step by an enolization - enantioselective protonation sequence.[1] In the most practical examples, a simple extractive procedure is sufficient to separate the chiral acid from the desired carbonyl compounds.



Despite the conceptual simplicity, proton transfer is a complicated process and enantioselectivity depends on a number of variables.

1) <u>pK_a relationship between a proton source and enolate</u>.

A chiral acid H-A* must discriminate between the prochiral faces of the planar enolate and as small as ~ 5.3 kcal/mol[A] difference in free energies of activation[2] ($\Delta\Delta G^{\neq}$) between diastereomeric transition states accounts for proton transfer selectivity. Consequently, enantioselective protonations are kinetically controlled reactions and under thermodinamic control racemic products are obtained. If pK_a difference between enolate and proton donor is insufficient, the rates of enolate protonation (forward reaction) and reverse reaction (deprotonation) are comparable. This results in equilibrium between protonated substrate and enolate (thermodynamic process) and after quench racemized substrate is obtained. Large pK_a difference decreases reverse reaction (deprotonation) to the minimum value and makes proton transfer irreversible. However, there is a risk of the excessively rapid and therefore less selective enolate quenching if pK_a difference is too large. Therefore, the choice of a chiral proton donor of appropriate acidity is essential and low temperatures as well as short reaction times enhance the chances of success. Evidently, it is impossible to

(A) Calculated for 99% enantiomeric excess (see refs. 2).

design a universal proton donor that could be used for a range of enolates varying from ketones to amides, because of substantial difference in enolate basicity. Instead, better understanding of pK_a relationships between enolate and chiral acid would in principle allow to create a certain set of proton donors that could be practically used for deracemization of various carbonyl compounds. Despite a large number of reports on enantioselective kinetic protonations, no systematic invesigations of the pKa relationship between chiral acids and enolates have been made up to date.

2) Enolate geometry.

E- and *Z*-enolates exhibit different enantiofacial selectivities, because two diastereomeric transition states for the protonation of the *E*-enolate are different from those for the *Z*-enolate. It is therefore important to minimize the amount of that enolate isomer which leads to lower, possibly reversed asymmetric induction.

3) Enolate-proton donor complex properties. Aggregation and complexation.

Lack of precise information concerning transition state structures complicates design of effective proton donors. It is generally accepted, however, that the preferred trajectory for the C-protonation of enolates is a vertical approach of the "proton" to the enolate π-system plane, with a preferential colinear arrangement between donor atom, proton and acceptor atom. Optimally, the transferred proton should be located near the stereogenic center (within the "chiral environment").

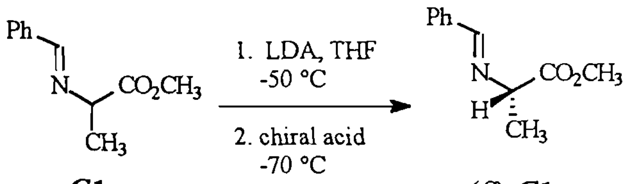
Considering the enolate-chiral acid complex formation as the first step in deracemization reaction, it can be assumed that protonation enantioselectivity is controlled at the stage of the mixed aggregate formation. Efficient chiral proton donors generally have electron-rich groups capable to chelate or coordinate enolate counterion, usually lithium, thus enhancing conformational rigidity in the transition state. The best lithium coordinating agents are various nitrogen and/or oxygen containing bi- and tridentate ligands.[3]

Additional variables that influence the structure, aggregation and reactivity of metal enolates complexes are Lewis basicity of solvent and the concentration of metal salts.[3a] These variables presumably affect also the transition state for proton transfer from a chiral acid to an enolate. The following literature examples will highlight the most important of these effects.

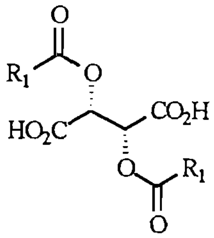
Duhamel was the first to achieve practical results by protonation of an enolate (Scheme C1).[4a] By appropriate selection of the ester group in the diacyl tartrate C2-

C5, the product (*S*)-**C1** could be obtained in up to 54 % ee. Methyl esters **C2** gave essentially racemic product, but increasing the ester steric bulk resulted in higher ee. In the best case, the di-adamantyl ester **C5** gave 54% ee.

Scheme C1.

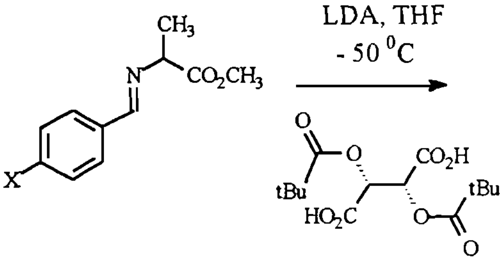


C1 (*S*)-**C1**



chiral acid	R	ee (%)
C2	Me	**3**
C3	*i*-Pr	**12**
C4	*t*-Bu	**50**
C5	adamantyl	**54**

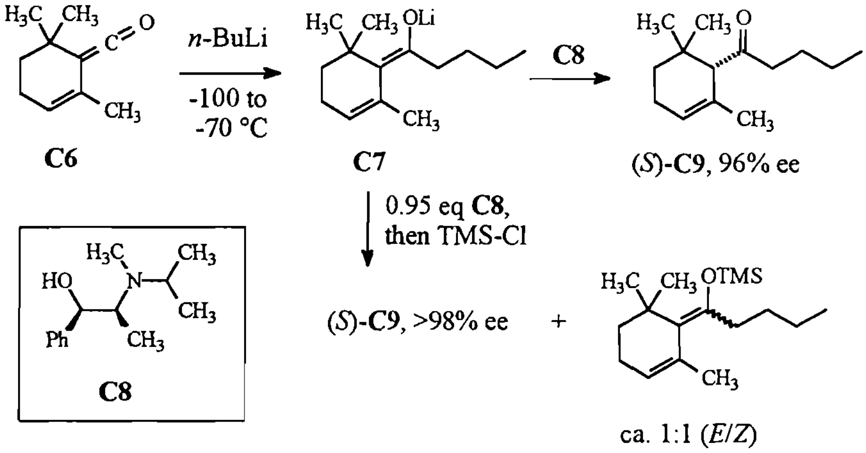
It was also found that substituents on the aromatic ring had an effect on the enantioselectivity.[4b] Increasing enolate **C1** basicity by electron donating groups in the benzylidine group enhanced ee up to 61% in the case of the *p*-dimethylamino group. In contrast, decreasing basicity relative to the unsubstituted benzaldehyde by electron withdrawing groups diminished the ee to 12% in the case of the *p*-cyano group.



X	ee (%)
CN	12
H	50
CH_3	55
OCH_3	57
$N(CH_3)_2$	61

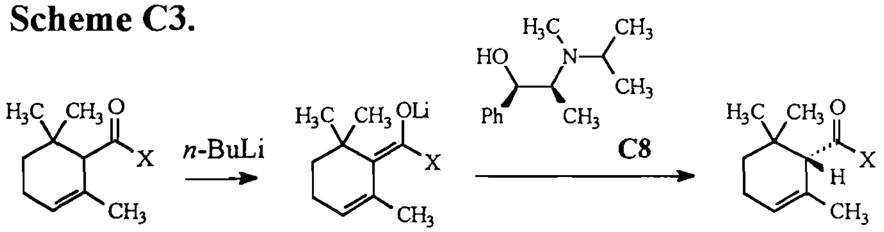
Based on these pioneering studies more practical levels of enantiocontrol were achieved by Fehr and Galindo.[5] The addition of *n*-BuLi at -110 °C to the ketene **C6** affords a 97:3 (E:Z) ratio of ketone enolate **C7** isomers. Protonation of this enolate mixture with excess **C8** afforded product (S)-**C9** with an impressive 96% ee (Scheme C2). However, if the enolate was quenched with only 0.95 equiv. of **C8** and the residual enolate trapped with TMS-Cl, then (*S*)-**C9** was recovered in greater than 98% ee along with a ca. 1:1 (*E*:*Z*) ratio of enol silane isomers. Enolate that is protonated at a lower rate and with lower selectivity (*Z*) is trapped by TMS-Cl, along with some unreacted (*E*) isomer (Scheme C2). These results indicate that the major enolate isomer (*E*) has a large kinetic advantage in the protonation step.

Scheme C2.



Using the same chiral acid **C8**, Fehr extended the scope of the protonation reaction to thioester enolates and reported the highest level of enantiocontrol for a proton transfer reaction to date.[5b] Various α-cyclogeranate ester derivatives **C10** were deprotonated with *n*-BuLi at -100 ^{0}C. Quenching the enolate **C12** with chiral alcohol **C8** revealed a large effect of the ester substituent on proton transfer enantioselectivity (Scheme C3). Simple esters (**C10**, X=OMe) were protonated with modest selectivity (36% ee). The analogous phenyl ester improved the ee (77% ee), but a dramatic increase in ee was observed with the aryl-thiol esters, achieving 99% ee.

Scheme C3.



C10 C11 C12

X	ee (%)
OCH_3	36
OPh	77
SPh	99

Fehr suggested that the protonation of the simple esters suffered from insufficient OLi/OMe differentiation and from faster, less selective proton transfer due to the higher pKa of the ester enolate compared to the thioester.

In a similar, highly sterically differentiated enolate system, Takeuchi has also proposed that the enolate geometry is important issue.[6] The samarium enolates **C14** were prepared by SmI_2 catalyzed allyl group addition to the ketene **C13** by allyl iodide. Enolate **C14** quench with chiral diol **C15** affords the enantioenriched product **C16**. The similarity between the ee's and the (*E*/*Z*) ratio of the enolate **C14** suggested that the (*E*) and (*Z*) enolate are each protonated with high stereocontrol, but with opposite enantiofacial attack (Scheme C4).

Scheme C4.

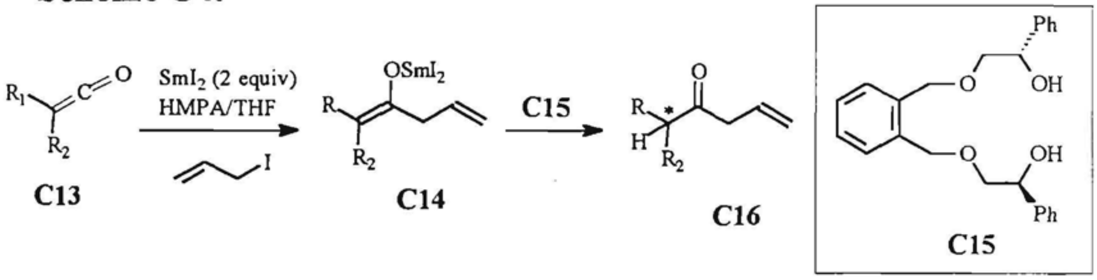
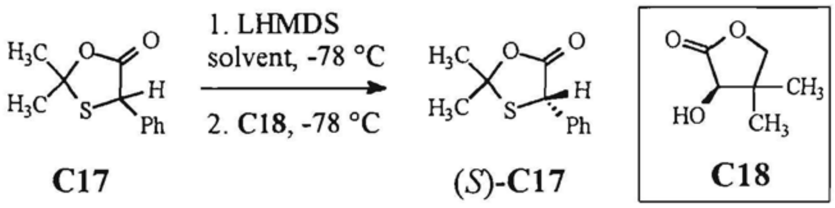


Table C1. Correlation between samarium enolate geometry and protonation enantioselectivity.

R_1	R_2	Enolate **C14** geometry (%, *E* or *Z*)	ee (%)
Ph	Et	85 (*Z*)	84 (*R*)
Ph	Me	92 (*Z*)	91 (*R*)
$PhCMe_3$	Me	> 98 (*Z*)	97 (*R*)
n-$BuCMe_3$	Me	> 98 (*Z*)	91 (*R*)
$PhCH_2$	Et	29 (*E*)	29 (*S*)

A report from Hünig illustrates the large role that *solvent* can play in determining the enantioselectivity of proton transfer from a chiral acid to enolate (Scheme C5).[7] Deprotonation of heterocycle **C17** by LHMDS forms the enolate. After quenching with chiral alcohol **C18**, low ee's were observed when THF or ether was the solvent. However, small amounts of THF in ether were found to dramatically improve the ee of the product. The best solvent ratio was 9:1 ether/THF, which afforded enantioenriched lactone (S)-**C17** with 72% ee.

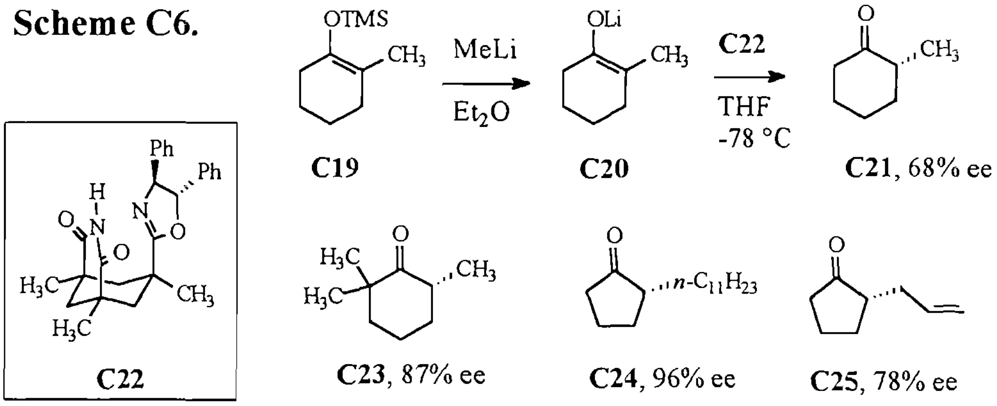
Scheme C5.



solvent	ee (%)
THF	44
ether	27
9:1 ether:THF	72

Yamamoto has reported the protonation of some simple cyclic ketone **C19** and **C23-25** enolates with a chiral proton donor **C22** derived from Kemp's triacid (Scheme C6).[8]

Scheme C6.



The enolate **C20** was prepared from the silyl enol ether **C19** by reaction with MeLi. Enantioselective proton delivery from imide **C22** afforded the enantioenriched ketone **C21** in 68% ee. Other enolates examined in a similar manner showed that bulk near the reaction site increases the ee (**C23**, 87% ee). Interesting that change to the cyclopentanone **C24** caused an increase in enantioselectivity (96% ee) compared to cyclohexanones. However, the stereoselectivity in the cyclopentanone series proved to be very sensitive to the α-substituent and **C25** was obtained with only 78% ee.

Yamamoto's system also illustrates the strong protonation results dependence on *lithium salts* and *counterions.*[8b]

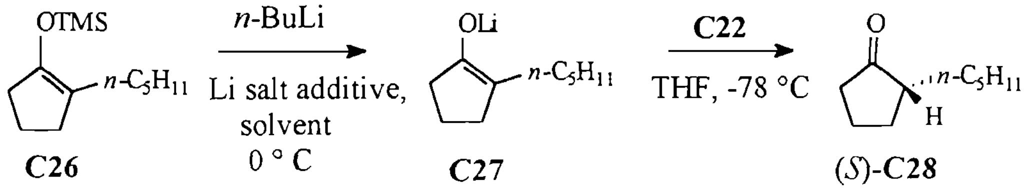


Table C2. Lithium salt and solvent influence on enolate **C27** protonation enantioselectivity.

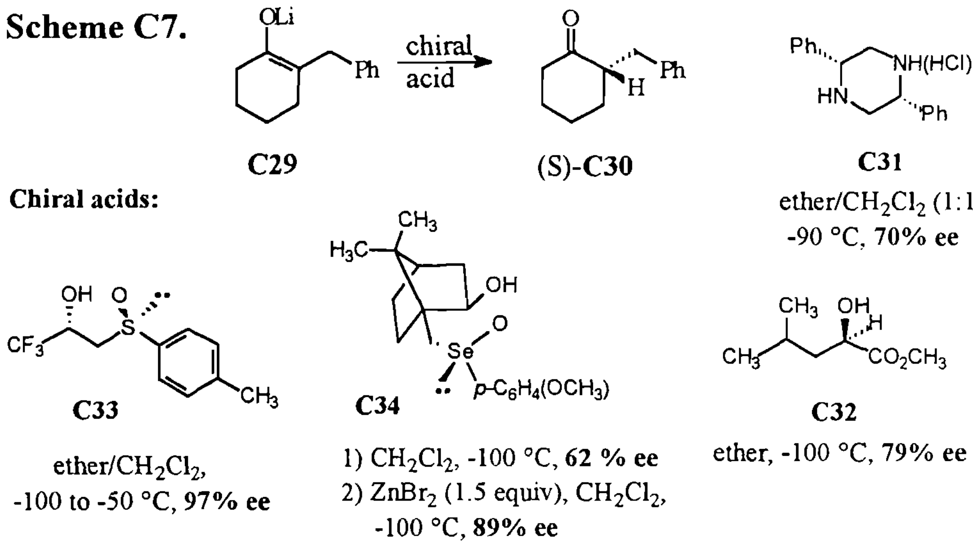
Entry	Additive (eq)	Solvent	ee (%)
1	-	Et_2O	**74**
2	LiBr (1)	Et_2O	**83**
3	LiBr (5)	Et_2O	**90**
4	LiCl (5)	Et_2O	**77**
5	$LiClO_4$ (5)	Et_2O	**72**
6	-	THF	**63**
7	LiBr (1)	THF	**79**
8	LiBr (5)	THF	**77**

Addition of an equimolar quantity of LiBr to silyl enol ether **C26** improved protonation enantioselectivity from 74 to 83% in Et_2O (entry 2 vs. 1). Further increasing the lithium concentration to 5 equiv. resulted in higher ee's (90%, entry 3). The source of the lithium ion is also a factor, because 5 equiv. of LiCl or $LiClO_4$ instead of LiBr lowered enantioselectivity (from 90% to 77%, entries 4-5). Noteworthy, the increase of enantioselectivity due to the presence of lithium salts is less pronounced in the more Lewis basic THF. Thus, one equivalent of LiBr in THF solvent raised the ee from 63 to 79% (entries 6-7), but no further increase in the ee was observed upon addition of more lithium salt (entry 8).

Similarly, Asensio also observed that LiBr is superior to other salts as an additive. Moreover, highest protonation enantioselectivities were observed when LiBr was present in reaction mixture during enolate generation.[9] This was rationalized by change in enolate structure due to mixed aggregate formation with extra lithium cation.[3]

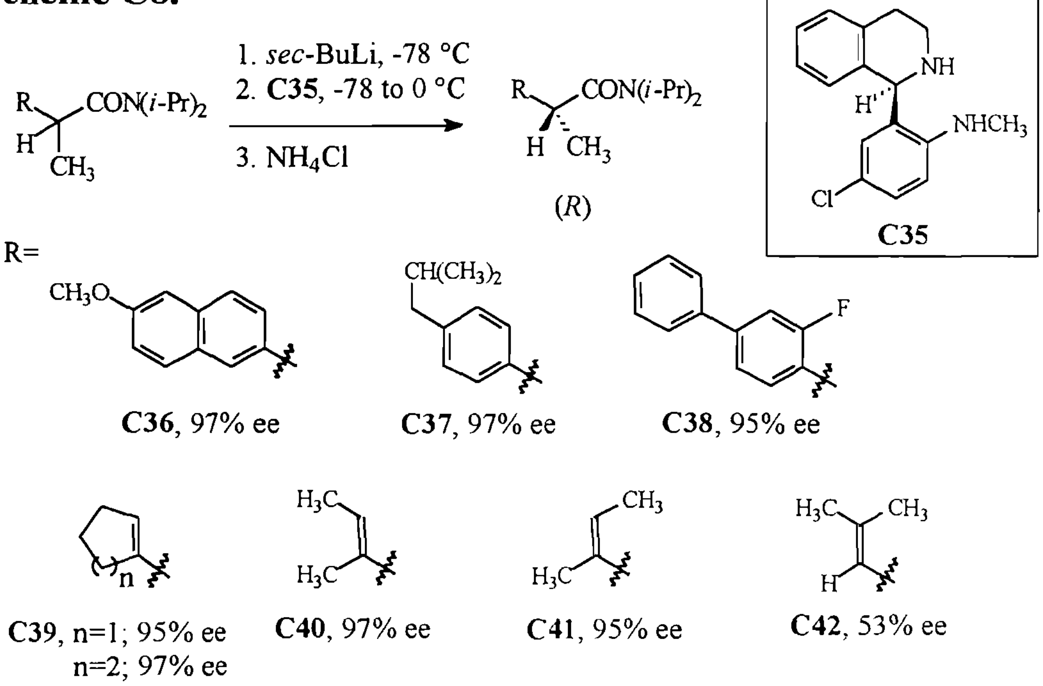
Several groups have succeeded preparing 2-benzyl cyclohexanone **C30** in enantiomerically enriched form using a chiral acid to protonate the corresponding lithium enolate **C29** (Scheme C7).[10] Fuji used the chiral piperazine hydrochloride salt **C31** and achieved up to 70% ee.[10a] Ohta found that higher enantiocontrol could be accomplished by **C32** as the chiral acid.[10b] The highest enantiocontrol has been observed using sulfoxide **C33** and selenoxide **C34**. Kosugi reported that β-hydroxy sulfoxide **C33** reacted with the same enolate **C29** with excellent enantiocontrol (97% ee).[10c] The chelating ability of the sulfoxide group presumably plays a large role upon formation of enolate-chiral acid complex. Finally, Koizumi has used the hydroxy-selenoxide **C34** to deracemize ketone **C30** in 62% ee.[10d] The addition of $ZnBr_2$ prior to quenching of the enolate with **C34** improves the ee (89%).

Scheme C7.



Important to the current work is the report by Vedejs, Lee and Sakata that amide enolates are protonated by a chiral diamine with high enantiocontrol (Scheme C8).[11] In contrast to the enolate protonations already discussed, **C35** has a high tolerance toward enolate structural modifications. Both α-aryl **C36-C37** and α-alkenyl **C38-C41** propionamides are deracemized in >90% ee. However, branching at the β-position affects enantioselectivity as evidenced by modest ee's in the case of **C42**. In most cases, protonation occurred exclusively at the α-position, but in **C39** and **C41**, γ-protonation was competitive which afforded α,β-unsaturated amides as by-products.

Scheme C8.



The protonation results suggest that the pKa relationship between chiral acid **C35** and enolate is important. Excellent enantiocontrol (97% ee) achieved in proton transfer between the amide enolate **C36** (pK_a(DMSO)= 31) and proton donor **C35** (pK_a(DMSO)= 27.7)[11] indicates that ΔpKa of 3-4 is optimal (pKa match). This ΔpKa corresponds to reaction that is exothermic enough to make reverse proton transfer (deprotonation) slow under the reaction conditions, and in the same time sufficiently slow in the forward direction to allow adequate discrimination between diastereomeric transition states.

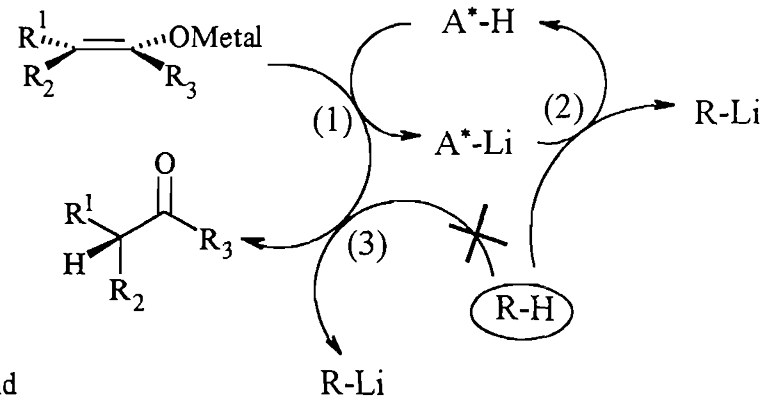
Although highly enantioenriched β,γ-unsaturated amides **C36-C42** have became available by the reaction of diamine **C35** with the corresponding amide enolates, the direct protonation of analogous ester enolates with **C35** does not go to completion. Evidently, chiral acid **C35** is not acidic enough to irreversibly protonate ester enolate and mixed enolate-diamine complex has been destroyed upon quench yielding racemic or poorly enantioenriched substrate[B]. To promote irreversible proton transfer *prior* to quench, various Lewis acid such as BF_3·OEt has been used. The added Lewis acid interacts with chiral amine **C35** nitrogen lone pairs, thus increasing N-H bond acidity what results in rapid C-protonation through an "*internal proton return*" (IPR) mechanism.[12] Important weakness of the IPR technique is that the enantioselectivity is strongly influenced by solvent and temperature, stoichiometry, order of mixing and choice of Lewis acid as well as external quenching agent. In contrast, if exothermic proton transfer occurs between a chiral acid and an enolate ("direct protonation"), the ee of the product is not affected by the quenching agent. Thus, to achieve the direct proton transfer to ester enolates, chiral acids with enhanced acidity compared to **C35** are required.

In many of discussed examples simple aqueous workup allows efficient recovery and reuse of the chiral acid. There are clear advantages, however, in use of sub-stoichiometric quantities of expensive chiral proton donor and catalytic variants of previously reported stoichiometric protonations have been recently developed. Utilization of a catalytic amount of chiral acid **A*-H** requires an additive **R-H** that can serve as stoichiometric proton source. In addition to pK_a matching requirement between the chiral acid **A*-H** and enolate (equation 1, Figure C1), *kinetic acidity* of

(B) External quenching agents such as H_2O or various acids destroy enolate-diamine mixed aggregate *prior* to proton transfer within complex.

achiral proton source **R-H** became a crucial issue.[13] Non-chiral acid **R-H** must efficiently discriminate between an enolate (carbon base) and lithiated chiral proton donor **A*-Li** (heteroatom base, lithiated amines or alkoxides) respectively, equation 2 should be dominant over equation 3 (see Figure C1):

Figure C1.

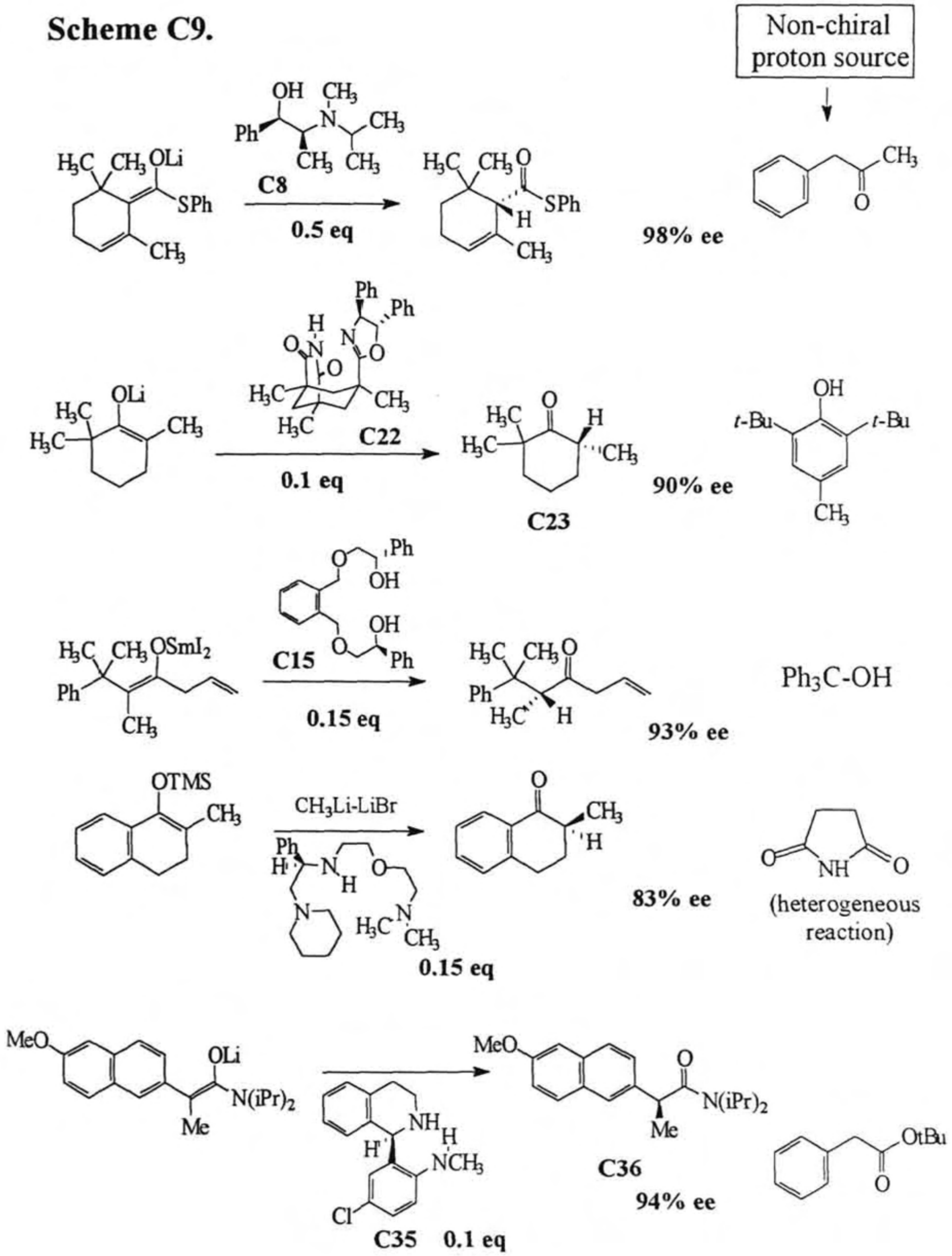


A*- H: Chiral acid

R - H: Non-chiral proton source

It has been observed that proton transfer between a heteroatom base and a carbon acid is essentially much faster than transfer involving a carbon acid and a carbon base.[12] In other words, *rates* at which proton is transferred to a base are different, respectively, *kinetic* acidities are different. Therefore the requirements for pK_a matching (*thermodynamic* acidity) between stoichiometric chiral acid **R-H** and protonated enolate are considerably less demanding than for enolate and a chiral proton donor **A*-H**. Despite great efforts toward understanding of proton transfer processes, the practical choice of both chiral acid **A*-H** and non-chiral proton source **R-H** still is a matter of trial-and-error procedure. The most successful catalytic asymmetric protonation examples are summarized in Scheme C9.

Scheme C9.



Non-chiral proton source
C8
0.5 eq
98% ee
C22
0.1 eq
C23
90% ee
C15
0.15 eq
93% ee
Ph3C-OH
CH3Li-LiBr
0.15 eq
83% ee
(heterogeneous reaction)
C35 0.1 eq
C36
94% ee

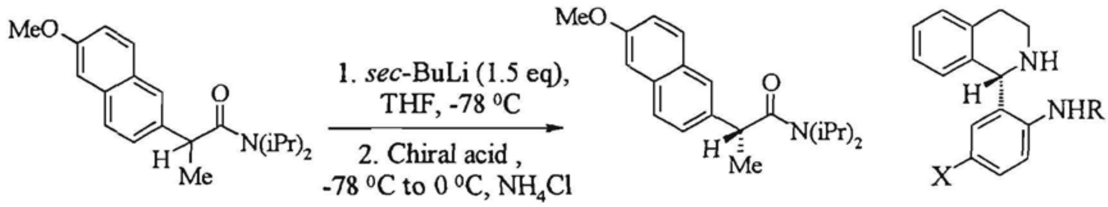
2. Asymmetric protonation experiments. Methods and objectives.

Literature background clearly shows that each successful deracemization is a result of a careful and laborious adjustment of protonation conditions, additives and solvents. Generally, deracemization is highly substrate sensitive and even small changes in enolate structure are responsible for a significant drop in enantiocontrol. The obvious reason for the dominating trial-and-error approach to deracemization is lack of comprehensive understanding of main issues responsible for enantioselective proton transfer, such as lithium enolate-chiral acid complex geometry as well as pKa relationships between a proton donor and substrate.

It has been demonstrated that commercially available chiral diamine CAPTIQ **C35** is highly effective for protonation of a range of amide enolates.[11] Based on these results it was also proposed that pKa difference of 3-4 units between a chiral acid and enolate is optimal to achieve high enantiocontrol. Our objective was to examine pKa and enantioselectivity relationship. Because the chiral acid environment in commercially available diamine **C35** has been demonstrated to be highly effective in the protonation of amide enolates, the goal was to utilize the same scaffold generating proton donors with different acidity. Besides, better understanding of deracemization process would allow to design a chiral acid for deracemization of various synthetically important enolates of amino acids and esters.

2.1. Asymmetric protonation of naproxen-N,N-diisopropylamide.

Various chiral isoquinolines (see Chapters A and B for the synthesis) were compared in their ability to protonate amide enolates that are optimized substrates for commercially available chiral acid CAPTIQ **C35**. Treatment of the amide at -78 ^{0}C with 1.75 equivalents of *sec*-BuLi formed the orange colored enolate. After 15 minutes 2 equivalents of a chiral proton source was added (within 5 minutes), the reaction mixture was kept at -78°C for 30 min and then slowly warmed to 0°C. Quenching with saturated NH_4Cl solution afforded **C46** in >90% yield. Acid/base extraction routinely returned the chiral acid in >85% yield. Deracemization results are summarized in Table C3.



rac-C46 **(R)-C46** Chiral acid

Table C3. Deracemization of naproxen-*N,N*-diisopropylamide.

Entry	Chiral acid	R	X	pK_a(DMSO)^a	ee (%)^b
1	(S)-**C47**	i-Pr	H	~29-30	**4** (S)
2^c	(S)-**C48**	Me	H	29.0	**90** (R)
3	(R)-**C49**	H	H	~28-29	**19** (S)
4^d	*(R)-C35*	*Me*	*Cl*	*27.7*	*97 (R)*
5^c	(R)-**C50**	Me	CF_3	25.3	**93** (R)
6	(S)-**C51**	Ph	H	23.2	**10** (?)
7	(R)-**C52**	SO_2NMe_2	H	11.7	**53** (R)

(a) Unless otherwise noted pKa (DMSO) values are estimated as described below, using pKa values of parent anilines(see reference 14c) (b) Absolute configuration of deracemized amide **C46** was determined by chiral HPLC behavior on Pirkle(S,S)-β-GEM-1 and comparison with the product from entry 4. (c) We wish to thank Dr. A. Kruger for testing chiral acids **C48** and **C50** as asymmetric proton donors. (d) Entry form reference 11.

Not surprisingly, the previously optimized CAPTIQ **C35** gave the best enantioselectivity[11] (entry 4). Trifluoromethyl-aniline **C50** afforded slightly reduced ee's (entry 5), however, this is the best result of all tested CAPTIQ analogs. The dechloro-analog **C48** (entry 2) turned out to be somewhat less selective, while N-unsubstituted aniline **C49** and N-phenyl analog **C51** showed a sharp reduction in ee to 19% and 10%, respectively. N-Isopropyl aniline **C47** gave essentially racemic product (entry 1), while sulfonamide **C52** afforded unexpectedly high deracemization enantiocontrol (entry 7).

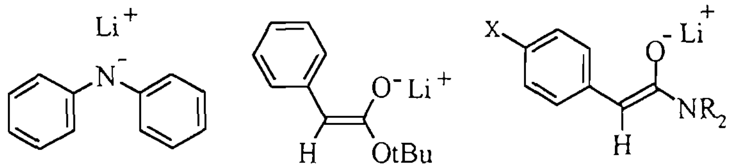
2.2. Discussion.

2.2.1. pKa relationship between a chiral acid and enolate.

Serious problem with a detailed pKa analysis is that the exact pKa(THF) values of the chiral acid **C35** as well as amide and ester enolates are not known. Most pKa values for organic compounds are measured in DMSO as the solvent.[14] Polar aprotic solvent DMSO promotes formation of solvent separated ion pairs by strong solvation of the cation and disfavors aggregation of ions. In contrast, THF is a relatively non-polar aprotic solvent and ion pairing in THF is common in order to reduce charge separation. Moreover, alkyllithium reagents and enolates in THF solutions are stabilized by aggregation into dimers, tetramers and higher order structures.[3a] On the other hand, solvate properties (monomer vs. aggregate equilibrium as well as contact vs. solvent-separated ion pairs) strongly depend on the degree of carbanion delocalization.[15b] For instance, highly delocalized carbanions tend to form monomeric solvent-separated ion pairs with lithium as a counter-ion.

Due to the differences in ion pairing and aggregation effects it is difficult to compare pKa values in DMSO versus THF. Studies of Streitwieser,[15] however, enable raw extrapolations between these solvents. In general, the pKa in THF is lower than the pKa(DMSO) because of stabilization due to ion pair formation and aggregation. For example, the pKa(DMSO) of diphenylamine **C53** is 24.95 and the lithium ion pair pKa in THF is 19.05[15a] (Figure C2). Similarly, the pKa of *t*-butyl phenylacetate **C54** is 23.6 in DMSO[14b] and 19.6 in THF.[15b] Surprisingly, pKa difference of ~3 units between ester **C54** and amide **C55** (R=Me) enolates observed in DMSO is substantially diminished in THF. Thus, ester enolate **C54** and structurally similar amide **C56** (R=Me) enolate[C] show comparable lithium ion-pairs acidity[D] of 19.6-19.8 pKa[15c] in THF as a solvent.

Figure C2.

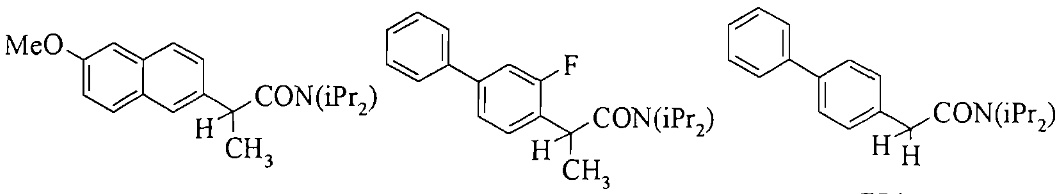


	C53	C54	C55 (X=H) C56 (X=Ph)
DMSO (solvent separated ion pairs)	$pK_a = 24.95$	$pK_a = 23.6$	**C55:** $pK_a = 26.6$ (R=Me)
THF (contact ion pairs)	$pK_a = 19.05$	$pK_a = 19.6$	**C56:** $pK_a = 19.77$ (R=Me) **C56:** $pK_a = 20.36$ (R=Et)

(C) Although differently substituted amide enolates **C55** (R=Me) and **C56** (R=Me) were used for pKa measurements in DMSO and THF, biphenylamide **C56** (R=Me) is expected be more acidic in THF than *para*-unsubstituted phenylacetamide **C55** (R=Me) because of higher anion delocalization in biphenylamide.

(D) It should be noted that ester enolate **C54** lithium ion pairs acidities were measured against the 9-phenylfluorene (pKa=18.49) as indicator, while in the case of amide enolate **C56** (R=Me) pKa value was assigned relatively to 3,4-benzofluorene (pKa=19.29).

Because of steric hindrance to conjugation in the anion,[15c] *N,N*-dimethylamide **C56** (R=Me) is found to be more acidic by ~0.6 pKa(THF) units than *N,N*-diethyl analog **C56** (R=Et). Further basicity increase (pKa(THF) ~ 21) could be anticipated for the corresponding *N,N*-diisopropyl amide **C56** (R=iPr). Interestingly, that Vedejs[11] achieved excellent enantiocontrol (97% ee) in deracemization of structurally related *N,N*-diisopropylamides **C36** and **C38** by CAPTIQ (**C35**) (see Scheme C8):



C36 (97% ee) **C38** (95% ee) **C56** pKa(THF) ~ 21

Thus, pK_a(THF) of lithium amide **C53** and enolates **C54-C56** are 4 to 6 units below the corresponding pK_a(DMSO) values. This allows to use known pK_a(DMSO) in the parent aniline system, directly measured in DMSO by Bordwell.[14] The evaluation has been made easier by measuring the pKa of CAPTIQ **C36** (pKa(DMSO)=27.7).[11] Equilibrium acidity of parent *p*-chloroaniline is 29.4 and the 1.7 pKa unit increase for diamine **C36** compared to *p*-chloroaniline could be attributed to stabilization of the conjugate base (the anion) through an intramolecular hydrogen bond.[16] This evidently surpasses destabilization of lithium anilide by N-methyl group. Thus, to estimate the pKa of the chiral acids, the 1.7 pKa unit correction factor was subtracted from the parent aniline derivatives.

pK_a(DMSO) values of CF_3-aniline **C50** (protonation of amide **C46** enolate afforded 93% ee) and *para*-unsubstituted analogue **C48** (amide **C46** was obtained with 90% ee; see Table C3, entries 2 and 5) span the crucial ~ 3-4 pKa units below equilibrium acidity of naproxenamide (pKa(DMSO)=30-31)[E] Surprisingly, N-unsubstituted aniline **C49** having the optimal pKa value (see Table C3, entry 3) displays unexpectedly low enantiocontrol (19% ee). Similarly, N-phenyl analog **C51** (Table C3, entry 6), being only 2.3 pKa units more acidic than CF_3-aniline shows a large drop in enantioselectivity (10% vs. 93% ee, resp.). Obviously, it is impossible to rationalize these results only by pKa issue. Furthermore, sulfonamide **C52** (Table C3, entry 7) affords enantioenriched naproxenamide with 53% ee despite the fact that it is

(E) pKa difference of 3 units was proposed to be optimal for high enantiocontrol (ref. 11).

much more acidic than all previously described chiral acids and pKa difference between enolate **C46** and **C52** is larger than 15 pKa units.

One important experimental observation should be pointed out. Chiral acid CAPTIQ changes the orange enolate color to yellow when reactants are combined in THF at -78°C. Similar color changes were observed for proton donors **C49** and **C51**. Color shift evidently indicates formation of a new aggregate – chiral acid-enolate complex. Upon warming yellow color faded suggesting the proton transfer is completed.[11] In the case of N-isopropylaniline **C47**, however, orange enolate color turned to "Soviet" red which is a color of N-deprotonated aniline. Within the next ca. 10 minutes intense red color slightly turned back to orange and did not changed further. Evidently, proton transfer equilibrium between enolate and diamine was established and quenching at 0°C afforded racemic naproxenamide (entry 1, Table C3). Similar equilibrium acidities calculated for amide enolate **C46** and estimated for the chiral acid **C47** (pKa(DMSO)=30-31) supports this observation. Consequently, to achieve essentially irreversible proton transfer, the chiral acid must have DMSO pKa ≥ 3 units below that of protonated substrate ("*upper pKa level*"). This so far is in agreement with the pKa match principle.[11]

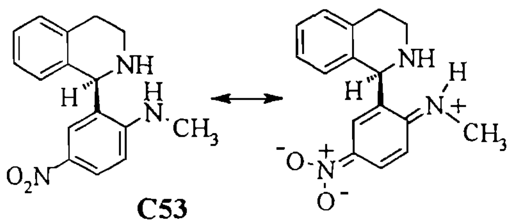
Completely different picture was observed in the case of sulfonamide **C52**. Orange enolate color disappeared already upon addition of the chiral acid **C52** and colorless mixture formed at –78 °C. This observation suggests a fast exothermic proton transfer upon addition of the chiral acid. It was believed that a rapid proton transfer should result in enantioselectivity drop, because in this case transition state becomes progressively earlier and with a larger intermolecular distance. The increased distance should reduce the specific interactions in the competing diastereomeric transition states.[17a] Relatively high enantiocontrol achieved by sulfonamide **C52** (53% ee at ΔpKa >15 units) suggests that strong complexation and aggregation ability of a chiral acid could compensate diffuse early transition state. Compared to a family of chiral anilines **C35** and **C47-50** *N,N*-dimethylsulfamoylaniline **C52** has additional groups capable to complex lithium, thus favoring stronger aggregates formation. Consequently, it appears that "*lower pKa level*", respectively, ultimate acidity of a chiral proton source below the crucial ΔpKa of 3 units is less important for high enantiocontrol if a chiral acid possesses functional groups with good lithium chelating ability.

2.2.2. Structural features of a chiral acid.

Considering that the enolate-chiral acid complex formation is the first step in deracemization reaction, it can be assumed that protonation enantiocontrol is largely influenced by conformational rigidity and stability of the complex. The mixed aggregate stability in turn depends on the strength of coordination of the chiral proton donor to lithium,[F] what evidently matches optimum in the case of N-methyl anilines **C35**, **C48** and **C50** (table C3, entries 2,4 and 5, respectively). CAPTIQ and its analogs as diamines with C3 bridge between nitrogens structurally are similar to TMEDA, a frequently used bidentate ligand for lithium. It is known, however, that TMEDA-lithium interaction is strong in the sterically least demanding lithium derivatives and weak in sterically congested environments.[3b] Moreover, steric effects in diamine can significantly affect its Lewis basicity.[16] In our case it would mean that more sterically demanding substituents at aniline nitrogen (i-Pr and Ph vs. Me) could decrease strength and conformational rigidity of a mixed aggregate that results in enantioselectivity drop (compare entries 1,6 and 4, Table C3).

Furthermore, because aniline transfers its acidic N-H proton to enolate, introduction of substituents with different electronical and sterical demands at aniline nitrogen could modify bond angles, thus changing position of the N-H proton in the chiral pocket. Although there is no information about the actual structure of mixed chiral aniline-enolate complex, high enantiocontrol achieved by CAPTIQ suggests that there is optimum position of transferable hydrogen in N-methyl aniline series. On the other hand, Kruger[17a] compared X-ray structures for CAPTIQ **C35** and nitro-analog **C53** and found that in CAPTIQ the dihedral angle between the N-CH_3 bond and the plane of the aniline is 13.6^0, while in **C53** it is only 1.3^0. Evidently, nitro group rehybridizes the crucial aniline nitrogen resulting in complete lost of enantiocontrol.[17a]

Figure C3.



Deracemization of naproxenamide **C46**

	pK_a(DMSO)	ee (%)
C35 (CAPTIQ):	27.7	97
C53:	19.2	0

Most likely, sharp drop in enantioselectivity upon aniline N-CH_3 substitution by N-Ph group (entry 6, Table C3) can be rationalized by unfavorable bond angles in crucial aniline nitrogen environment. Similar effect is assumed to dominate for N-unsubstituted aniline **C49** (entry 3, Table C3). Moreover, chiral acid **C49** has two potentially transferable protons.

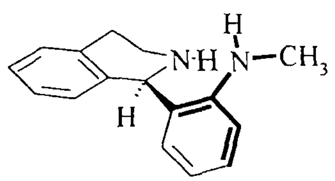
Thus, one should be very careful introducing various acidifying groups both at aniline nitrogen and at anilino aryl group in order to diminish pKa of a chiral acid. On the other hand, unfavorable change of transferable proton location in a chiral environment eventually could be compensated by introduction of additional lithium coordinating groups into a chiral acid. This conceptual approach is demonstrated to be effective in case of *N,N*-dimethylsulfamoyl-aniline **C52** (53% ee; see entry 7, Table C3).

2.2.3. Enolate geometry.

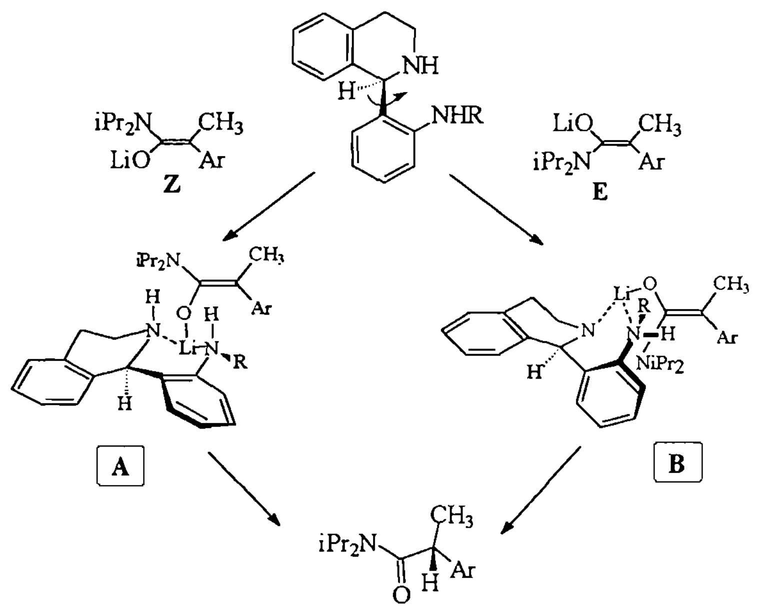
Under protonation conditions naproxenamide enolate exists a 14:1 ratio of *Z*:*E* isomers. Such ratio of isomers could give a maximum empirical ee of 87% if 100% enolate face selectivity for the protonation is assumed for each enolate isomer.[12a] Since CAPTIQ shows unexpectedly high enantioselectivity (97%) in protonation reaction, it was proposed that either enolate isomer (*Z* or *E*) could afford the same dominant enantiomer. A speculative structure of lithium enolate-diamine complex shows that rotation around isoquinoline carbon-aryl bond may be able to compensate for enolate Z or E geometry *via* the initial formation of the two alternative complexes **A** and **B** which, after proton transfer, both produce the same enantiomer (Scheme C10).[G]

(F) Diamine should also compete with an excess of strong donor solvent THF for coordination site on lithium (see ref. 2).

(G) There is no information about the actual structure of enolate-diamine complex and simplified monomeric aggregates **A** and **B** are shown. Diamine in the proposed complex is assumed to have the same conformation as the starting aniline in the solid state (X-ray structure, ref. 17b).



Scheme C10.

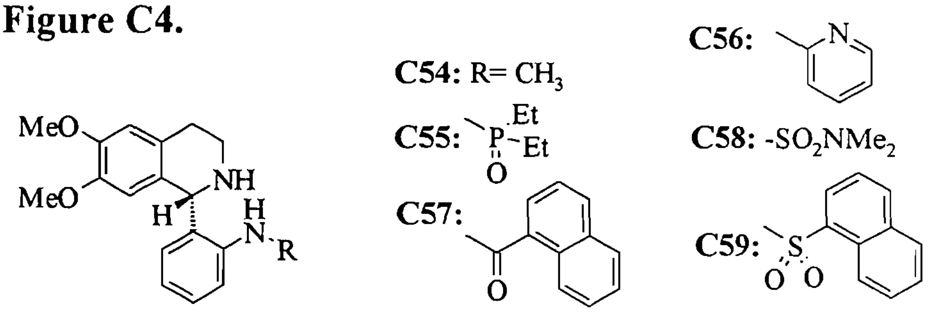


Presumably, rotational barrier around carbon - aryl bond would result in decrease of protonation enantioselectivity, however, no attempts have been made so far to prove this assumption.

2.3. Deracemization of esters and a lactone.

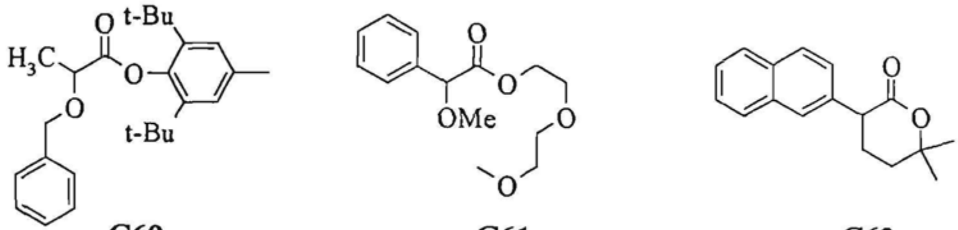
A number of a chiral isoquinoline CAPTIQ **35** analogs such as **C55-C59** were designed and prepared (see Chapter B) as potential proton donors for deracemization of various esters and amino acids (Figure C4).

Figure C4.



Equilibrium acidities for chiral acids **C55-C59** were estimated as described earlier for CAPTIQ analogs **C47-C52**, using available pKa values measured directly in DMSO for parent anilines. Similarly the equilibrium acidities of esters **C60-C61** and lactone **C62** were evaluated.

Isoquinolines **C55-C59** contain methoxy-substituents that were necessary to achieve higher enantiocontrol in asymmetric synthesis *via* Noyori transfer hydrogenation. To verify if remote alkoxy groups are tolerated in asymmetric protonation, diamine **C48** and its dimethoxy analog **C54** were compared in deracemization of naproxenamide **C46**. Surprisingly, the reaction proved somewhat more sensitive to temperature changes compared to the analogous process using **C48**. Thus, under standard conditions **C54** afforded enantioenriched naproxenamide with 82-84% ee, however, a procedure modified to control the exotherm resulting from addition of **C54** to the enolate gave **C46** with 88.8% ee. The corresponding experiment under standard conditions using **C48** resulted in 90% ee (entry 2, Table C3). Thus, methoxy substituents somehow diminish protonation enantioselectivity. On the other hand, the difference is relatively small and therefore methoxy-substituted chiral acids **C55-C59** were applied for the deracemization of esters **C60-C61** and lactone **C62** (Table C4).



C60 **C61** **C62**

Table C4. Protonation of esters **C60-C61** and lactone **C62** enolates.[a]

Entry	Substrate (pKa(DMSO))	Base	Chiral acid (pKa(DMSO))	ee (%)
1[b]	*C60 (~23)*	*sec-BuLi*	*C35 (27.7)*	**0**
2	**C60**	Mesityl-Li	**C55** (20-22)	**19**
3	**C60**	*sec*-BuLi	**C55**	**24**
4	**C60**	Mesityl-Li	**C56** (20.3)	**57**
5	**C60**	*sec*-BuLi	**C56**	**47**
6	**C60**	Mesityl-Li	**C57** (17.1-18.3)	**4**
7	**C60**	Mesityl-Li	**C58** (11.7)	**15**
8	**C60**	Mesityl-Li	**C59** (10.3)	**6**
9	**C61** (20-21)	Mesityl-Li	**C56** (20.3)	**17**
10	**C61**	Mesityl-Li	**C59** (10.3)	**23.5**
11[c]	*C62 (19.7-20.4)*	*Mesityl-Li* $BF_3 \cdot OEt_2$	*C35 (27.7)*	*72*
12	**C62**	Mesityl-Li	**C55** (20-22)	**17**
13	**C62**	Mesityl-Li	**C56** (20.3)	**0**
14	**C62**	Mesityl-Li	**C57** (17.1-18.3)	**2**
15	**C62**	*sec*-BuLi	**C52** (11.7)	**68**
16	**C62**	Mesityl-Li	**C58** (11.7)	**58**
17	**C62**	Mesityl-Li	**C59** (10.3)	**28**

(a) All reactions were performed in THF at –78 ^{0}C, using 1.75 eq of the corresponding base. (b) Entry from reference 17a, p. 32. (c) Entry from reference 17b, p. 136.

The enolates of esters **C60-C61** and lactone **C62** were generated by treatment with 1.75 equivalents of mesityl-Li at -78 ^{0}C, prepared *in situ* from bromomesitylene and *t*-BuLi. After 15 minutes 2 equivalents of a chiral proton source was added (within 5 minutes), the reaction mixture was kept at -78°C for 30 min and then slowly warmed up to 0°C. Quenching with saturated NH_4Cl solution afforded products, while acid/base extraction allowed to recover chiral acids **C55-C59**.

Mesityl-Li is usually used to minimize a risk of nucleophilic attack of alkyllithium (*sec*-BuLi) on ester carbonyl group. Entries 2-3 and 4-5 show that generally there is no difference between *sec*-BuLi and mesityl-Li. The best deracemization enantiocontrol in the case of BHT ester **C60** was achieved using N-pyridyl-aniline **C56** (entry 4). It should be noted that a chiral acid **C56** used in deracemization experiments could not be made crystalline and was used as an oil. It is known, however, that even minor impurities in chiral acid significantly decrease deracemization enantioselectivities.[G]

Deracemization of chelated ester **C61** enolate was less successful even employing the most acidic proton donors available (entries 9-10).

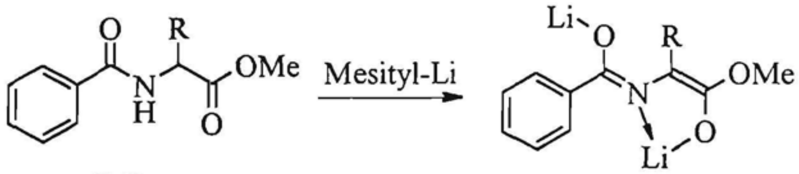
Somewhat more promising enantiocontrol was achieved in deracemization of 1-naphthylvalerolactone **C62** using chiral sulfonamides **C52** and **C58** (entries 15-16). Lower enantioselectivity was observed with methoxy substituted chiral acid **C58** (68% ee) compared to unsubstituted analog **C52** (58% ee).[H] Noteworthy, that 68% enantioselectivity (entry 15) so far is the best *direct protonation* example observed for valerolactone **C62**. CAPTIQ **C35** required BF_3•OEt_2 activation (*internal return protocol, 72% ee)*[12] because the substrate **C62** is more acidic than a chiral acid **C35** (entry 11). Use of Fehr catalyst **C8**[5] (see Schemes C2 and C3) affords product with low 10-12% enantioselecitivity[17a] and this is an additional evidence that all successful protonations are highly substrate sensitive and require laborious and careful optimization.

Thus, initial screening revealed two potentially effective chiral acids **C52** and **C56** for deracemization of various ester enolates. Further attempts will be directed toward optimizing both the chiral acid and deracemization conditions.

(G) Initially deracemization of naproxenamide **C46** by commercially available CAPTIQ **C35** (*Aldrich)* afforded 85% ee (refs. 17b), however, enantioselectivity was significantly improved to 97% ee simply by several crystallizations of the chiral acid (refs. 11).
(H) Similar effect of remote methoxy groups was observed for N-methyl anilines **C48** and **C54** (see above).

2.4. Protonation of amino acid enolates.

The acidic nitrogen in N-benzoyl-alanine methyl ester **C64** and the corresponding phenylglycine ester **C63** required two equivalents of base to form the anion enolates. Thus, treatment of the racemates **C63-C64** in THF with 2.5 eq mesityl-Li (prepared *in situ*) at –78 ^{0}C for 1 h was followed by quenching with chiral acid. After stirring for 30 min. the solution was allowed to warm to –20 ^{0}C and then NH_4Cl-H_2O was added.



C63: R = CH_3
C64: R = Ph

Table C5. Asymmetric protonation of amino acid esters **C63-64**.

Entry	Substrate (pKa(DMSO))	Temperature (^{0}C)	Chiral acid (pKa(DMSO))	ee (%)
1	**C63** (26-28)	-78	**C35** (27.7)	**73**
2	**C63**	-78	**C55** (20-22)	**0**
3	**C63**	-78	**C56** (20.3)	**5**
4	**C63**	-78	**C59** (10.3)	**0**
5	**C64** (19-21)	-78	**C55** (20-22)	**27**
6	**C64**	-100	**C55**	**28**
7	**C64**	-78	**C56** (20.3)	**15**
8	**C64**	-78	**C57** (17.1-18.3)	**2**
9	**C64**	-100	**C58** (11.7)	**12**
10	**C64**	-78	**C59** (10.3)	**36**

The most basic CAPTIQ **C35** showed the highest enantioselectivity for alanine ester (entry 1). All the more acidic analogs were either completely unselective (entries 2-4) or displayed a low enantiocontrol (entries 5-10). To avoid a risk of exceedingly rapid proton transfer from acidic sulfonamides **C58** and **C59** at –78 ^{0}C, the temperature was lowered to –100^{0}C. In contrast to promising enantiocontrol observed for lactone enolate **C62**, disappointing result was achieved with phenylglycine (entry 9). Furthermore, more acidic arylsulfonamide **C64** afforded enantioenriched **C64** with higher enantioselectivity (entry 10 vs. 9).

It is obvious that pKa values, enolate *E/Z* geometry and steric preferences of the proton donor-amino acid enolate aggregates are different from those of naproxenamide **C46**. Furthermore, evaluation of the pKa values of **C63** and **C64** is difficult, as the corresponding deprotonated form of these amino acids is dianion. On the other hand, relatively high enantiocontrol in deracemization of alanine ester **C63** with CAPTIQ **C35** (entry 1, Table C5) indicates that position of the transferable proton in a chiral pocket of CAPTIQ evidently is close to optimum also for alanine enolate.[I] Consequently, further efforts will be directed toward design of a chiral proton donor with enhanced acidity and the chiral environment at aniline nitrogen as close as possible to that in CAPTIQ.

(I) CAPTIQ **C35** was not tested in deracemization of phenylglycine **C64** because of insufficient acidity of the chiral proton source.

2.5. Summary.

1. Excellent enantioselectivities (90-93% ee) were achieved in asymmetric protonation of naproxen-*N,N*-diisopropylamide enolate **C46** using chiral N-methyl anilines **C48** and **C50**. Attempts to improve the best enantiocontrol obtained so far (97% ee) using commercially available chiral acid CAPTIQ **C35** have been unsuccessful.

2. Deracemization experiments suggested that for an essentially irreversible proton transfer, the chiral acid must have DMSO pKa > 3 units below that of protonated substrate ("*upper pKa level*"). On the other hand "*lower pKa level*", respectively, ultimate acidity of a chiral proton source below the crucial ΔpKa of 3 units is less important for high enantiocontrol if a chiral acid possesses functional groups with good lithium chelating ability.

3. CAPTIQ evidently has optimum positioning of the transferable proton within "chiral environment", what results in excellent enantiocontrol not only for naproxenamide **C46** but also for lactone **C62** and alanine Me-ester **C63**. Consequently, change of aniline nitrogen hybridization (bond angles) could eventually lead to the drop in deracemization enantioselectivity.

4. Promising enantioselectivities have been observed in deracemization of BHT ester **C60** (57% ee) using N-pyridyl aniline **C56** and in protonation of lactone enolate **C62** (68% ee) with *N,N*-dimethylsulfamoyl aniline **C52.** Deracemization of amino acids so far has afforded disappointing results. Further attempts will be directed toward optimization of deracemization conditions and the structure of a chiral acid using information obtained in preliminary experiments.

3. References.

1. Reviews: (a) "Enantioselective Protonation of Enolates and Enols" Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566. (b) "Asymmetric Protonations of Enol Derivatives" Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, 411. (c) "Enantioselective Protonation of Enolates in Natural Product Synthesis" Fehr, C. *Chimia* **1991**, *45*, 253. (d) "Asymmetric Protonations" Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1984**, II-421.

2. "Kinetics and Thermodynamics of Stereoselective Reactions" Nógrádi, M. in *Stereoselective Synthesis;* VCH, Weinheim, 1987, pp. 49-52.

3. (a) "Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective *C*-Alkylation of Peptides. Difficulties and Opportunities Afforded by Complex Structures" Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Collum, D.B. "Is N,N,N'N'-Tetramethylethylenediamine a Good Ligand for Lithium?" *Acc.Chem.Res.* **1992**, *25*, 448.

4. (a) "Deracemization by Enantioselective Protonation. A New Method for the Enantiomeric Enrichment of α-Amino Acids" Duhamel, L.; Plaquevent, J.-C. *J. Am. Chem. Soc.* **1978**, *100*, 7415. (b) "Déracémization par Protonation Énantiosélective. Application à un α-Aminoacide, la Phénylglycine" Duhamel, L.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1982**, II-75.

5. (a) see reference 1(a). (b) "Highly Enantioselective Protonation of Thiol Ester Enolates" Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1042.

6. (a) "Asymmetric Synthesis of Ketones by SmI_2-Mediated Allylation or Benzylation of Ketenes Followed by Enantioselective Protonation" Takeuchi S.; Miyoshi, N.; Ohgo, Y. *Chem. Lett.* **1992**, 551. (b) "SmI_2-Mediated Reductive Enolization of α-Hetero-Substituted Ketones and Enantioselective Protonation" Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron Lett.* **1997**, *38*, 2709.

7. "Stereoselektive Protonierung von Carbanionen. 5. Einfluß der reaktionsbedingungen auf die Enantioselektive Protonierung von Lacton-Enolaten" Gerlach, U.; Haubenreich, T.; Hünig, S. *Chem. Ber.* **1994**, *127*, 1981.

8. (a) "Enantioselective Protonation of Simple Enolates: Chiral Imide as a Chiral Proton Source" Yanagisawa, A.; Kuribayshi, T.; Kikuchi, T.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 107. (b) "Effects of Lithium Salts on the Enantioselectivity of Protonation of Enolates with a Chiral Imide" Yanagisawa, A.; Kikuchi, T.; Yamamoto, H. *Synlett.* **1998**, 174.

9. (a) "Remarkable Effect of Lithium Bromide in the Enantioselective Protonation with α-Sulfinylalcohols" Asensio, G.; Aleman, P.A.; Domingo, L.R.; Medio-Simón, M. *Tetrahedron Lett.* **1998**, *39*, 3277. (b) "Stereoselection Parameters and Theoretical Model in the Enantioselective Protonation of Enolates with α-Sulfinyl Alcohols"

Asensio, G.; Aleman, P.A.; Gil, J.; Domingo, L.R.; Medio-Simón, M. *J.Org.Chem.* **1998**, *63*, 9342.

10. (a) "Hydrochloride of Chiral Piperazine as a Chiral Proton Source" Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron Asymmetry* **1993**, *4*, 247. (b) "Preparation of Optically Active Ketones *via* Enantioface-Differentiating Protonation of Prochiral Ketones" Matsumoto, K.; Ohta, H. *Tetrahedron Lett.* **1991**, *32*, 4729. (c) "Highly Enantiofacial Protonation of Prochiral Lithium Enolates with Chiral β-Hydroxy Sulfoxides" Kosugi, H.; Hoshino, K.; Uda, H. *Tetrahedron Lett.* **1997**, *38*, 6861. (d) "Enantioface-differentiating Protonation with Chiral γ-Hydroxyselenoxides" Takahashi, T.; Nakao, N.; Koizumi, T. *Tetrahedron Asymmetry:* **1997**, *8*, 3293.

11. "Deracemization via Highly Enantioselective Enolate Protonation Using a Chiral Aniline as the "Acid"" Vedejs, E.; Lee, N.; Sakata, S. T. *J.Am.Chem.Soc.* **1994**, *116*, 2175.

12.(a) "Lewis Acid Induced Internal Proton Return: Enantiocontrolled Protonation of an Amide Enolate" Vedejs, E.; Lee N. *J. Am.Chem.Soc.* **1991**, *113*, 5483. (b) "Lewis-Acid-Induced Internal Proton Return in Enolate Complexes with Chiral Amines" Vedejs, E.; Lee, N. *J.Am.Chem.Soc.* **1995**, *117*, 891.

13. "Catalytic Asymmetric Protonation of Amide Enolates: Optimization of Kinetic Acidity in the Catalytic Cycle" Vedejs, E.; Kruger, A.W. *J. Org. Chem.* **1998**, *63*, 2792 and references cited therein.

14. (a) "Equilibrium Acidities in Dimethyl Sulfoxide Solution" Bordwell, F.G. *Acc.Chem.Res.* **1988**, *21*, 456. (b) "Acidities of the H-C Protons in Carboxylic Esters, Amides, and Nitriles" Bordwell, F.G.; Fried, H.E. *J.Org.Chem.* **1981**, *46*, 4327. (c) "Acidities of Anilines in Dimethyl Sulfoxide Solution" Bordwell, F.G.; Algrim, D.J. *J. Am. Chem. Soc.* **1988**, *110*, 2964. (d) "Effects of Sulfenyl, Sulfinyl and Sulfonyl Groups on Acidities and Homolytic Bond Dissociation Energies of Adjacent C-H and N-H Bonds" Bordwell, F.G.; Liu, W.-Z. *J.Phys.Org.Chem.* **1998**, *11*, 397.

15. (a) "Lithium and Cesium Ion-Pair Acidities of Diphenylamine in Tetrahydrofuran. The Aggregation of Lithium and Cesium Diphenylamide. A New Method for the Determination of Aggregation Constants in Dilute Solution" Krom, J.A.; Petty, J.T.; Streitwieser, A. *J.Am.Chem.Soc.* **1993**, *115*, 8024. (b) "Equilibrium Ion Pair Acidities in Tetrahydrofuran of Benzylic Carbon Acids Stabilized by an Adjacent Cyano, Carboalkoxy, and Sulfonyl Substituent. Delocalization and Aggregation of Ion Pairs" Kaufman, M.J.; Gronert, S.; Bors, D.A.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 602. (c) "Ion Pair Acidities and Aggregation of Some Amide and Oxazoline Enolates in THF" Facchetti, A.; Streitwieser, A. *J.Org.Chem.* **1999**, *64*, 2281.

16. March, J. in *Advanced Organic Chemistry*, 4th ed.; Wiley&Sons: New-York, 1992; pp 263-272.

17. (a) Kruger, A. Studies in the Stoichiometric and Catalytic Enantioselective Protonation of Enolates and The Allylic Directing Effect of Carboxamides in Osmylations and Hydroborations. Ph.D. Thesis, University of Wisconsin-Madison, 1998. (b) Lee, N. Enantioselective Protonations of Enolates Using Optically Pure Amines. Ph.D. Thesis, University of Wisconsin-Madison, 1992.

Conclusions.

1. N-phthalyl group was found to be the best protection for aniline in Bischler-Napieralski cyclization. Nitro-substituted β-phenethylamide is superior as cyclization substrate to the corresponding N-protected anilines. Cyclization of bromo(or chloro)phenyl-β-phenethylamides and halogen displacement by liquid ammonia or lower alkylamines is the method of choice for the synthesis of 1-anilino-3,4-dihydroisoquinolines.

2. Resolution of racemic tetrahydroisoquinolines *via* diastereomeric salts crystallization technique requires extensive trial-and-error procedure for every particular substrate. The method was effective (>99.5% ee) only for preparation of non-racemic 1-(5-trifluoromethyl-2-methylamino)phenyl-1,2,3,4-tetrahydroisoquinoline and its 5-unsubstituted analog by the crystallization of diastereomeric tartrates.

3. (*R*)-O-Acetylmandelic acid is an excellent chiral auxiliary for resolution of tetrahydroisoquinolines with aniline subunit. Chiral auxiliary cleavage afforded seed crystals of (*S*)-1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline **A32** with >99% ee. Crystallization of diastereomeric tartrates in the presence of seed crystals was successful for the preparative scale resolution of racemic **A32**.

4. Asymmetric transfer hydrogenation using Ru catalyst is effective for the enantioselective hydrogenation of N,N-disubstituted 1-anilino-3,4-dihydroisoquinolines. N-Unsubstituted analogues were hydrogenated with moderate enantioselectivity (71-85% ee), but required impractical purity levels for the substrate. Presence of nitrogen functionality in the substrate diminishes chemical yields and requires increased chiral Ru catalyst loading (up to 7.5 mol%).

5. The best hydrogenation results were achieved with bromophenyl imine **B85.** (*S*)-1-(2-bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was obtained with 98.7% ee using 0.67 mol% of a chiral Ru catalyst. Hydrogenation was readily scaled-up with a 10% loss in yield, but without encountering other complications.

6. Reaction of (S)-bromophenyl-isoquinoline with liquid NH_3 in the presence of Cu/CuCl gave (*S*)-1-(2-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline. Asymmetric hydrogenation of bromo-imine **B85** combined with the copper-catalyzed amination currently is the method of choice for the synthesis of CAPTIQ analogs.

7. High enantioselectivities (90-93% ee) were achieved in asymmetric protonation of naproxen-*N,N*-diisopropylamide using chiral 1-(5-trifluoromethyl-2-methylamino)phenyl-1,2,3,4-tetrahydroisoquinoline and its 5-unsubstituted analog. Promising enantioselectivities have been observed in deracemization of O-benzyl-lactic acid BHT ester (57% ee) using chiral N-pyridyl aniline and in protonation of 3-(2-naphthtyl)-6,6-dimethylvalerolactone enolate (68% ee) with *N,N*-dimethylsulfamoyl aniline.

8. Deracemization results affirmed that pKa relationship between a proton donor and an enolate is crucial for high enantiocontrol. For essentially irreversible proton transfer, the chiral acid must have DMSO pKa > 3 units below that of protonated substrate.

Appendix 1

Э. Суна, П.Трапенциерис

СИНТЕЗ РАЦЕМИЧЕСКИХ 1,2,3,4-ТЕТРАГИДРОИЗОХИНОЛИНОВ И ИХ РАЗДЕЛЕНИЕ

Различными путями в реакции Бишлера-Напиральского получены 1-анилинзамещенные 3,4-дигидроизохинолины IIIа-л. Изучено влияние защитных групп у анилинового азота на ход реакции и найдена N-фталильная защита, устойчивая в условиях циклизации. Полученные дигидроизохинолины восстановлены до рацемических 1,2,3,4-тетрагидроизохинолинов IVа-ж и проведено их разделение кристаллизацией диастереомерных тартратов. В двух примерах 1,2,3,4-тетрагидроизохинолины (IVб, IVд) получены в оптически чистом виде (>99,5% ee).

Повышенный интерес к 1,2,3,4-тетрагидроизохинолинам (ТГИХ) связян с нахождением его производных в составе природных алкалоидов. В течение последних двух десятилетий проведен успешный энантиоселективный синтез многих изохинолиновых алкалоидов (например, лауданозина, ретикулина, ксилопинина, и салсалодина). Успехи синтеза изохинолиновых алкалоидов наглядно отражены в обзорной статье Развадовской [1]. Некоторые производные этого класса соединений проявляют свойства депрессантов центральной нервной системы [2] и блокаторов рецепторов НМДА [3]. Но только в последние годы разработаны более интересные и оригинальные методы синтеза производных 1,2,3,4-тетрагидроизохинолинов [3-7].

Совсем недавно один из представителей хиральных ТГИХ - 1-(2'-метиламино-5'-хлор)фенил-1,2,3,4-тетрагидроизохинолин (*CAPTIQ*; реагент фирмы *Aldrich*) успешно применен в качестве эффективного донора протонов в стехиометрических [8-9], а также в каталитических количествах [10]. Хотя в последние годы разработаны некоторые интересные и оригинальные методы синтеза производных 1,2,3,4-тетрагидроизохинолинов [3-7], публикации не дают общие методики по синтезу хиральных замещенных 1-анилин-ТГИХ.

В настоящей работе разработаны удобные методы синтеза рацемических 1-анилин-ТГИХ, и их разделение кристаллизацией диастереомерных солей с хиральными органическими кислотами (например, тартратами). Метод удобен в пользовании и недорогой, так как хиральный реагент можно использовать повторно после несложной кислотно-щелочной обработки.

Изохинолиновый цикл получают различными способами, используя один из числа известных методов Бишлера-Напиральского, Пикте-Шпенглера, Померантса-Фритша или Шлитлера-Миллера [1]. Формирование хиральных тетрагидроизохинолинов путем циклизации Бишлера-Напиральского является наиболее привлекательной из числа выше названных методов, из-за возможности использования легко доступных бензойных кислот I в качестве исходного вещества для получения амидов II. Циклизация последних приводит к 3,4-дигидроизохинолинам III, которые далее могут быть превращены в хиральные 1,2,3,4-тетрагидроизохинолины IV двумя способами: прямым асимметрическим восстановлением двойной C=N связи, или восстановлением с последующим разделением рацемата кристаллизацией его диастереомерных солей. Асимметрическое восстановление является предметом отдельной публикации, а возможности кристаллизации диастереомерных солей изложены в настоящей работе.

Циклизация Бишлера-Напиральского хорошо изучена [6, 11, 12] и проходит через образование хлористоводородных солей имидоил хлоридов под действием хлорангидридов фосфора (PCl_5, $POCl_3$) или серы ($SOCl_2$). Отщепление HCl приводит к равновесной смеси имидоил хлоридов с соответствующими солями нитрилия. Последние под действием кислот Льюйса циклизуются до дигидроизохинолинов III. Поскольку нашей целью является синтез разных 1-анилин-ТГИХ IVа-ж, выбор подходяшей защитной группы для анилинового азота являлся ключевой проблемой. Известно, что циклизация моно-N-замещенных анилин-β-фенилэтиламидов [2] в условиях Бишлера-Напиральского была безуспешной в случаях N-ацетил и N-тозил замещенных субстратов. Наш выбор электронакцепторных заместителей в 1-арил-ТГИХ был основан на предположении, что повышенная поляризация амидной группы в β-фенэтиламидах II способствовало бы образованию имидоилхлорида и нитрилиевой соли. Сначала наш выбор защитных групп пал на N-бензильную защитную группу (соединение IIж, таблица 1). Мы предположили, что хлористоводородная соль IIж увеличит электрондефицитный характер анилинового заместителя, тем самим способствуя образованию дигидроизохинолинов. Однако, имеют место побочные реакции и с 16% выходом был выделен лишь дебензилированный продукт IIIд. Также безуспешной оказалась циклизация β-фенилэтиламида 2-(N-метил-N-ацетил)аминобензойной кислоты. Повышение выхода (30%) при использовании электронакцепторной тозильной группы у анилинового азота (амид IIе) направило нас на использование двух акцепторных групп у анилинового азота.

Закономерно, наиболее успешным оказался выбор фталильной группы. Первоначальный результат в классических условиях циклизации был неудачным (выход 20%). Основываясь на цикле работ [11-12] по механизму реакции Бишлера-Напиральского, была произведена замена дегидратирующего агента (P_2O_5 на PCl_5) и растворителя (ксилол на хлороформ), а также добавлена кислота Льюйса ($SnCl_4$), что дало 3,4-дигидроизохинолин IIIк с хорошим (73%) выходом. Это является первым примером сохранения фталильного фрагмента в условиях Бишлера-Напиральского. Так, кипячение в течении 30 минут в хлороформе привело к образованию желтого осадка, который после прибавления кислоты Льюйса ($SnCl_4$) изменил окраску до кирпично-красного. Изменение окраски указывает на формирование циклического продукта IIIк (3,4-дигидроизохинолины в кислой среде имеют интенсивно красную окраску). Увеличение загрузки (до 85 г) не влияло на выход реакции. Снятие защитных групп проводили как описано ранее [13] и в результате дигидроизохинолин IIIк превращен в незамещенный анилин IIIл с общим выходом 38% в двух стадиях.

Альтернативу прямой циклизации амидов IIд-и мы нашли в прямом аминировании 1-(2-хлорфенил)-3,4-дигидроизохинолинов IIIа-г (схема 1) в условиях обменной реакции Ульмана [2]. Таким образом получены дигидроизохинолины IIIд-з. Соединение IIIз ранее не описано, а IIIж не выделено в свободном виде, а охарактеризовано только после восстановления до конечного продукта IVб.

Исходные имины IIIа-д получены из моно- или ди-замещенных бензойных кислот I (схема 1) или изатоангидридов Vа и Vб (схемы 2 и 3). Бензойные кислоты Iа-в коммерчески доступны, но некоторые из них (например, трифторметил производное Iб) дорогие. Поэтому, мы разработали метод двухстадийного синтеза последнего из 4-хлортрифторметилбензола (VI) (схема 4), путем селективного, низкотемпературного (-100^{0}С) металлирования соответствующего *о*-бром-хлорбензола VII.

Монобромирование 4-хлортрифторметилбензола (VI) проводили как описано ранее [14]. Проведение металлирования бромида VII (схема 4) при низких температурах существенно по двум причинам: 1) проходит селективное замещение атома брома в присутствии хлора [15], 2) снижается количество побочных реакций, в том числе дегидробромирование. При температурах выше –50^{0}С доминируют побочные реакции и реализуется формирование нежелаемого дегидробензола. Дополнительное стабилизирование карбаниона VIII наблюдается при использовании бидентатного лиганда – тетраметилэтилендиамина, использование которого в литийорганической химии хорошо известно [16]. Обработка промежуточного карбаниона VIII сухим льдом приводит к карбоновой кислоте Iб с общим выходом 52% в трех стадиях. Метилсульфонилбензойная кислота Iг получена в трех стадиях по известной методике [17].

Альтернативный подход синтеза 1-анилин-ТГИХ связан с выбором защитной группы более устойчивой для тяжелых условий реакции Бишлера-Напиральского. Подходящим кандидатом является нитро группа, которую легко удается восстановить до аминной группы в присутствии C=N двойной связи 3,4-дигидроизохинолинов [18].

Все полученные 3,4-дигидроизохинолины восстановлены до ТГИХ IVа-ж цианоборгидридом натрия в уксусной кислоте [19]. Восстановление протекает в мягких условиях и дает более высокие выхода по сравнению с восстановлением $NaBH_4$ в этиловом спирте [2].

Для разделения рацемических ТГИХ [20] по литературной аналогии разделения 1-(2’-метиламино-2’-хлор)фенил-1,2,3,4-тетрагидроизохинолина (*CAPTIQ)* были выбраны оптически активные винные кислоты [2]. Также известно разделение диастереомерных тартратов N-незамещенного аналога [21].

Для двух рацемических тетрагидроизохинолинов IVб и IVд разделение диастереомерных тартратов после двухкратной кристаллизации из этилового спирта была весьма успешной (схема 5). Последующая обработка тартратов сильноосновным анионитом ИРА-401 (в OH^- форме) дала свободные основания IVб и IVд с >99.5% оптической чистотой.

Однако, нам до сих пор не удалось найти подходящий растворителяь для мало растворимых тартратов рацемического нитро соединения IVв. Неудачным оказалось также и разделение рацемического метилсулфонил-ТГИХ IVг путем кристаллизации его тартратов из различных растворителей, а также солей с (+)-яблочной кислотой. Очевидно, различия растворимости диастереомерных солей IVг не достаточны для селективной кристаллизации. Процесс кристаллизации диастереомерных солей таким образом является строго субстрат-специфичным, что существенно затрудняет разработку общей методики для решения вопроса.

ЭКСПЕРИМЕНТАЛЬНАЯ ЧАСТЬ

Температуры плавления определены на нагревательном приборе *Gallenkamp* и не корректированы. Спектры ^{1}H и ^{13}C ЯМР зарегистрированы на приборе *Varian Mercury 200*, внутренний стандарт ТМС. ИК спектры зарегистрированы на спектрометре *Perkin Elmer 580B* в нуйоле или в таблетках KBr. Анализы ВЭЖХ проведены на системе *Knauer* с интегратором *Hewlett-Packard HP 3396A*. Колоночная хроматография проведена на силикагеле фирмы *Acros* (0.06-0.2 мм). Контроль за ходом реакций осуществляли с помощью ТСХ на пластинках *Merck Kieselgel* 60_{F254}. Значения оптического вращения определены на поляриметре *Perkin Elmer 141* с использованием линий Na 589. Растворители – гексан, этилацетат, ацетонитрил, ДМФА, хлористый метилен и эфир перегнаны над $CaCl_2$ или CaH_2, метанол перегнан над Mg, ТГФ перегнан над $CaCl_2$ и Na-бензофеноном.

2-Хлор-5-трифторметилбензойная кислота (Iб). В 250 мл трехгорлой колбе, в атмосфере аргона помещают 120 мл сухого (перегнанного над Na-бензофеноном) эфира, 50 мл 1,6 М (80 ммоль) раствора n-BuLi в гексане и 7,0 мл (70,1 ммоль) свежеперегнанного (над натрием) тетраметилэтилендиамина. Полученную смесь охлаждают до $-100^{0}C$ (смесь метанола и жидкого азота) и в течении 5 минут прибавляют раствор 18,1 г (70 ммоль) 2-хлор-5-трифторметилбромбензола (VII) (полученного по методике [14]) в 50 мл сухого эфира. Перемешивание при той же температуре продолжают еще в течении 20 минут, затем пропускают ток сухого углекислого газа. Через 3 часа реакционную смесь нагревают до комнатной температуры, выливают в 250 мл воды, добавляют 1 н. соляную кислоту до pH 4 и отделяют органический слой. Водный слой экстрагируют 3x40 мл хлористого метилена. Обьединенных органических экстрактов упаривают при пониженном давлении. Остаток растворяют в 100 мл гексана и экстрагируют 4x20 мл 1 н. раствора NaOH. Водный слой подкисляют 1 н. соляной кислотой до pH 4, осадок фильтруют, промывают водой и сушат (Na_2SO_4). Выход 13,8 г (88%) 2-хлор-5-трифторметилбензойной кислоты (Iб) с Тпл 90...91^{0}C (в литературе [22] Тпл 90...91^{0}C). Спектр ПМР (хлороформ-D_3): 7,51-7,74 (2H, м, арил), 8,11 (1H, с, арил), 9,7-10,2 м.д. (1H, шс, COOH).

Общая методика получения N-β-фенилэтиламидов дизамещенных бензойных кислот (IIа-г). 90 ммоль дизамещенной бензойной кислоты (Iа-г) растворяют в 75 мл хлористого тионила, добавляют 1 мл ДМФА и нагревают при кипячении в течении 12 часов. Избыток хлористого тионила упаривают, хлорангидрид закристаллизовывают при помощи сухого гексана, фильтруют и промывают несколько раз гексаном (5-нитро и 5-метилсульфонил производные), или перегоняют в вакууме (5-незамещенный и 5-трифторметил производные). Полученные хлорангидриды растворяют в 100 мл сухого диоксана и при 0^{0}C медленно прибавляют по каплям к суспензии 10,9 г (90 ммоль) фенэтиламина в 100 мл 1 н. раствора NaOH. Полученный осадок фильтруют, промывают 2 н. соляной кислотой, водой и сушат на воздухе. Спектры ЯМР, ИК приведены в таблице 2, выхода, температуры плавления, данные элементного состава приведены в таблице 5.

N-β-фенилэтиламид 2-метиламинобензойной кислоты (IIд) с 79% выходом получен из 97,5 г (620 ммоль) N-метилизатоевого ангидрида (Vа) по методике [23]. Спектры ЯМР, ИК приведены в таблице 2, температура плавления и данные элементного состава приведены в таблице 5.

N-β-фенилэтиламид 2-[N-4-метилфенилсульфонил-N-метиламино]-бензойной кислоты (IIе) с 60% выходом получен из 48,8 г (192 ммоль) амида IIд по методике [2]. Спектры ЯМР, ИК приведены в таблице 2, температура плавления и данные элементного состава приведены в таблице 5.

N-β-фенилэтиламид 2-(N-бензил-N-метиламино)бензойной кислоты (IIж). К раствору 2,54 г (10 ммоль) амида IIд в 25 мл хлористого метилена добавляют раствор 2,12 г (20 ммоль) Na_2CO_3 в 10 мл воды и 1,71 г (10 ммоль) свежеперегнанного бензилбромида. Реакционную смесь кипятят в течении 2 дней, водный слой отделяют и экстрагируют 2x10 мл хлористого метилена. Обьединенныt органическиt экстрактs сушат (Na_2SO_4), растворитель отгоняют. Остаток растворяют в сухом эфире, и пропускают ток сухого хлористого водорода. Бесцветный осадок фильтруют, промывают эфиром и сушат. Получают 3,31 г (87%) амида IIж. Спектры ЯМР, ИК приведены в таблице 2, температура плавления и данные элементного состава приведены в таблице 5.

N-β-фенилэтиламид 2-аминобензойной кислоты (IIз) с 75% выходом получен из 163,0 г (1.0 моль) изатоевого ангидрида по методике [2]. Спектры ЯМР, ИК приведены в таблице 2, температура плавления и данные элементного состава приведены в таблице 5.

N-β-фенилэтиламид 2-(N-фталимидо)бензойной кислоты (IIи). 24,0 г (100 ммоль) амида IIз и 14,8 г (100 ммоль) фталевого ангидрида растворяют в 150 мл сухого бензола, добавляют 30,5 г (300 ммоль) триэтиламина и нагревают при кипячении с насадкой Дина-Старка в течении 48 часов. После добавления 3,0 г (20 ммоль) фталевого ангидрида кипячение продолжают еще

12 часов. После охлаждения выпадает осадок, который фильтруют, промывают бензолом, сушат (Na_2SO_4) и получают 20,1 г бесцветного амида IIи. Обьединенные фильтраты промывают 5x40 мл 4 н. HCl, потом 2x40 мл насыщенного раствора $NaHCO_3$ и сушат (Na_2SO_4). После упаривания растворителя, масло закристаллизовывают зародышами кристаллов. Фильтрация, промывка бензолом дает дополнительно 12,0 г продукта. Общий выход 32,1 г (87%) амида IIи. Спектры ЯМР, ИК приведены в таблице 2, температура плавления и данные элементного состава приведены в таблице 5.

Общая методика получения 3,4-дигидроизохинолинов (IIIа-г; IIIи-к). К горячему раствору 60 ммоль амида II в 300 мл ксилола, добавляют 300 ммоль P_2O_5 и нагревают при кипячении 6-48 часов. Затем реакционную смесь охлаждают, ксилол сливают и остаток переносят в ледяную воду. После образования прозрачной смеси остаток ксилола отделяют и водный слой подкисляют 4 н. HCl до pH 2. Полученное масло экстрагируют эфиром или хлористым метиленом, сушат (Na_2SO_4) и растворитель упаривают. Продукт растирают (иногда после колоночной хроматографии) и перекристаллизовывают. Спектры ЯМР, ИК приведены в таблице 3, температуры плавления и данные элементного состава приведены в таблице 5.

Общая методика получения 3,4-дигидроизохинолинов (IIIд-з). 15,0 ммоль 1-(2-хлорфенил)-3,4-дигидроизохинолинов IIIа-г помещают в 150 мл стеклянную ампулу, приливают 50 мл жидкого метиламина, 0,17 г медных опилков и 0,17 г CuCl. Ампулу запаивают и нагревают при 60^0C в течении 72 часов. После охлаждения ампулу осторожно открывают и оставляют в тяге до упаривания основного количества метиламина. К темно синему остатку приливают 100 мл хлористого метилена, медные соли фильтруют и остаток упаривают при пониженном давлении. После хроматографической очистки на силикагеле продукт перекристаллизовывают. Спектры ЯМР, ИК приведены в таблице 3, температура плавления и данные элементного состава приведены в таблице 5.

1-(2'-N-Фталимидо)фенил-3,4-дигидроизохинолин (IIIк). 88,7 г (240 ммоль) амида IIи растворяют в 1200 мл сухого хлороформа (свежеперегнанного над P_2O_5) и при интенсивном перемешивании добавляют 100,0 г (480 ммоль) PCl_5 в один прием. Реакционную смесь кипятят с обратным холодильником в течении 1 часа, при этом образуется ярко-желтый осадок. После охлаждения реакционной смеси до -30^0C, медленно прибавляют по каплям раствор 85,5 г (330 ммоль) $SnCl_4$ в 480 мл сухого хлороформа и температуру реакционной смеси поднимают до комнатной. Наблюдают кирпично-красную окраску смеси. В продолжении кипятят 8 часов, охлаждают и выливают в щелочную ледяную воду, органический слой отделяют, а водный слой экстрагируют 4x150 мл хлороформа. Хлороформные экстракты промывают 3x100 мл 2 н. KOH, 3x100 мл водой и сушат (Na_2SO_4). После упаривания растворителя, остаток кристаллизуют эфиром. После перекристаллизации из петролейного эфира- толуола получают 61,7 г (73%) 1-(2-N-фталимидо)фенил-3,4-дигидроизохинолина (IIIк). Спектры ЯМР, ИК приведены в таблице 3, температура плавления и данные элементного состава приведены в таблице 5.

1-(2'-аминофенил)-3,4-дигидроизохинолин (IIIл). К горячей суспензии 6,43 г (18.2 ммоль) фталимида IIIк в 60 мл этилового спирта в один прием приливают 4,44 г (88.6 ммоль) гидразингидрата. В прозрачном растворе через 5 минут наблюдается образование осадка. После кипячения реакционной смеси в течении 15 минут, осадок фильтруют, промывают этанолом, филтрат упаривают. Полученный остаток переводят в эфир, фильтруют осадок, эфирный слой экстрагируют 4x20 мл 1 н. HCl. Солянокислые экстракты подщелачивают 2 н. KOH до pH 10, экстрагируют 4x20 мл эфира, сушат (Na_2SO_4) и фильтруют через силикагель. После упаривания растворителя при пониженном давлении получают 2.0 г (50%) светло-желтых кристаллов. Спектры ЯМР, ИК приведены в таблице 3, температура плавления и данные элементного состава приведены в таблице 5.

Общая методика получения 1,2,3,4-тетрагидроизохинолинов (IVа-ж). Реакции проводят в атмосфере аргона. К раствору 3,5 ммоль 3,4-дигидро-изохинолина III в 15 мл ледяной уксусной кислоты при перемешивании по порциям прибавляют 7,0 ммоль $NaBH_3CN$. Реакцию выдерживают 3 часа при комнатной температуре, затем нагревают в течение 1 ч при 60^0C и оставляют перемешиваться при комнатной температуре на 10 часов. Окраска реакционной смеси меняется от красной до желто-зеленой, что является признаком окончания реакции. Содержимое колбы охлаждают до 0^0C, прибавляют 30 мл 50%-ного раствора NaOH, экстрагируют 4x20 мл хлористого метилена, промывают насыщенным раствором NaCl и растворитель упаривают. Остаток растворяют в хлористом метилене и фильтруют через силикагель. После упаривания растворителя все полученные твердые вещества перекристаллизовывают. Спектры ЯМР, ИК приведены в таблице 4, температура плавления и данные элементного состава приведены в таблице 5.

Разделение рацемического 1-(2-метиламино-5-трифторметил)-1,2,3,4-тетрагидроизохинолина (IVб). К горячему раствору 153,2 мг (0,5 ммоль) рацемата IVб в 1 мл этилового спирта добавляют горячий раствор 75,0 мг (0,5 ммоль) D-(-)-винной кислоты в 1 мл этилового спирта. Сразу после добавления начинается кристаллизация. Реакционную смесь охлаждают, осадок фильтруют, перекристаллизовывают из абс. этилового спирта, сушат и получают 76,8 мг (67%) тартрата- IVб с $[\alpha]_D^{20}$ -43.2^0 (c=1,01, ДМФА). Полученный (-)-тартрат растворяют в 0.5 мл воды и пропускают через колонну с анионитом Амберлит ИРА-401 (в хлоридной форме) и элуириуют этиловым спиртом. Выход свободного амина (-)-IVб из колонны контролируют УФ детектором при 254 нм. После упаривания элюента получают оптически чистый амин (-)-IVб с $[\alpha]_D$=-48,8^0 (c=0,67, $CHCl_3$), который соответствует >99,5% оптической чистоты (ВЭЖХ на хиральной колонке *Chiralcel OJ*, подвижная фаза - 1% этанол в гексане, поток – 1,0 мл/мин, детектор - UV_{254}, время задерживания - 11,4 мин).

Аналогично получают (+)-тартрат (+)-IVб с $[\alpha]_D$=+41,1^0 (c=1,05, ДМФА) и свободный оптически чистый амин (+)-IVб с $[\alpha]_D$=+48,7^0 (c=0,67, $CHCl_3$), который соответствует >99,5% оптической чистоты (ВЭЖХ на хиральной колонке *Chiralcel OJ*, подвижная фаза - 1% этанол в гексане, поток – 1,0 мл/мин, детектор - UV_{254}, время задерживания – 12,7 мин).

Разделение рацемического 1-(2-метиламино)-1,2,3,4-тетрагидро-изохинолина (IVд) проводили аналогично разделению IVб. В реакции 3,0 г (12,6 ммоль) рацемата IVд с (-)-винной кислотой получили 1,76 г (36%) (-)-тартрат-IVд (из метанола) с $[\alpha]_D^{20}$ –37,3^0 (c=1,04, ДМФА) и оптически чистый амин (-)-IVд с $[\alpha]_D$=-5.3^0 (c=0,67, $CHCl_3$), который соответствует >99,5% оптической чистоты (ВЭЖХ на хиральной колонке *Chiralcel OD*, подвижная фаза – 5% изо-пропиловый спирт в гексане, поток – 0,8 мл/мин, детектор - UV_{254}, время задерживания – 10,2 мин).

Аналогично получают (+)-тартрат-IVд (из метанола) с $[\alpha]_D^{20}$ +40,2^0 (c=1,06, ДМФА) и оптически чистый амин (+)-IVд с $[\alpha]_D$=+5,3^0 (c=0,67, $CHCl_3$), который соответствует >99,5% оптической чистоты (ВЭЖХ на хиральной колонке *Chiralcel OD*, подвижная фаза – 5% изо-пропиловый спирт в гексане, поток – 0,8 мл/мин, детектор - UV_{254}, время задерживания – 11,8 мин).

Авторы признательны Латвийскому совету по науке за финансирование настоящего исследования (грант 722), а также профессору Э. Ведейсу за плодотворные дискуссии во время работы.

СПИСОК ЛИТЕРАТУРЫ

1. Razwadowska M.D. // Heterocycles - 1994. - Vol.39. - P.903.
2. Ott H., Hardtmann G.E., Denzer M., Frey A.J., Gogerty J.H., Leslie G.H., Trapold J.H. // J. Med. Chem. - 1968. - Vol.11. - P.777.
3. Wanner K.T., Beer H., Höfner G., Ludwig M. // Eur. J. Org. Chem.- -1998. - P.2019.
4. Barbier D., Marazano C., Riche C., Das B.C., Potier P. // J. Org. Chem. – 1998. – Vol.63. – P.1767.
5. Wünsch B., Nerdinger S. // Eur. J. Org. Chem.- -1999. - P.513.
6. Doi S., Shirai N., Sato Y. // J. Chem. Soc. Perkin Trans. I. - 1997. - P.2217.
7. Carrillo L., Badia D., Dominguez E., Ortega F., Tellitu I. // Tetrahedron: Asymmetry. – 1998. – Vol.9. – P.151.
8. Vedejs E., Lee N., Sakata T. // J. Amer. Chem. Soc. - 1994. - Vol.116. - P.2175.

9. Vedejs E., Lee N. // J. Amer. Chem. Soc. - 1995. - Vol.117. - P.891.

10. Vedejs E., Kruger A.W. // J. Org. Chem. - 1998. - Vol.63. - P.2792.

11. Nagubandi S., Fodor G. // J. Heterocycl. Chem. – 1980. – Vol.17. – P.1457.

12. Fodor G., Nagubandi S. // Tetrahedron. – 1980. – Vol.36. – P.1279.

13. Sasaki T., Minamoto K., Itoh H. // J. Org. Chem. - 1978. - Vol.43. - P.2320.

14. McBee E.T., Sanford R.A. // J. Amer. Chem. Soc. - 1950. - Vol.72. - P.1651.

15. Al-Jabar N.A., Massey A.G. // J. Organomet. Chem. – 1985. – Vol.288.- P.145.

16. Collum D.B. // Acc. Chem. Res. – 1992. – Vol.25. – P.448.

17. Lee C., Field L. // Synthesis. – 1990. – P.391.

18. Vedejs E., Suna E., Trapencieris P. // J. Org. Chem. – 1999. - в печати.

19. Gribble G.W., Heald P.W. // Synthesis. – 1975. – P.650.

20. Newman P. // Optical resolution procedures for chemical compounds. Amines and related compounds. Riverdale, N.Y.: Optical resolution information center, 1984.

21. Pat. 3297696 USA /Ott H. // C.A. 1967. – Vol.66. – 65505.

22. Loev B. // Can. J. Chem. - 1964 – Vol.42.- P.1488.

23. Pat. 3409668 USA /Palazzo G., Silvestrini B. // C.A. 1969. – Vol.70. – 37496.

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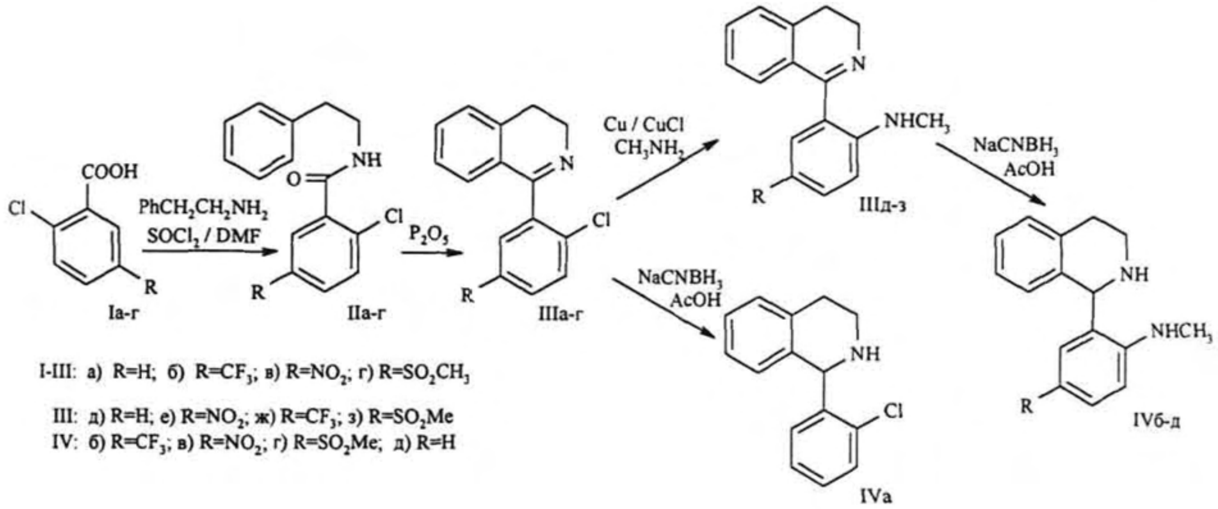
Схема 1



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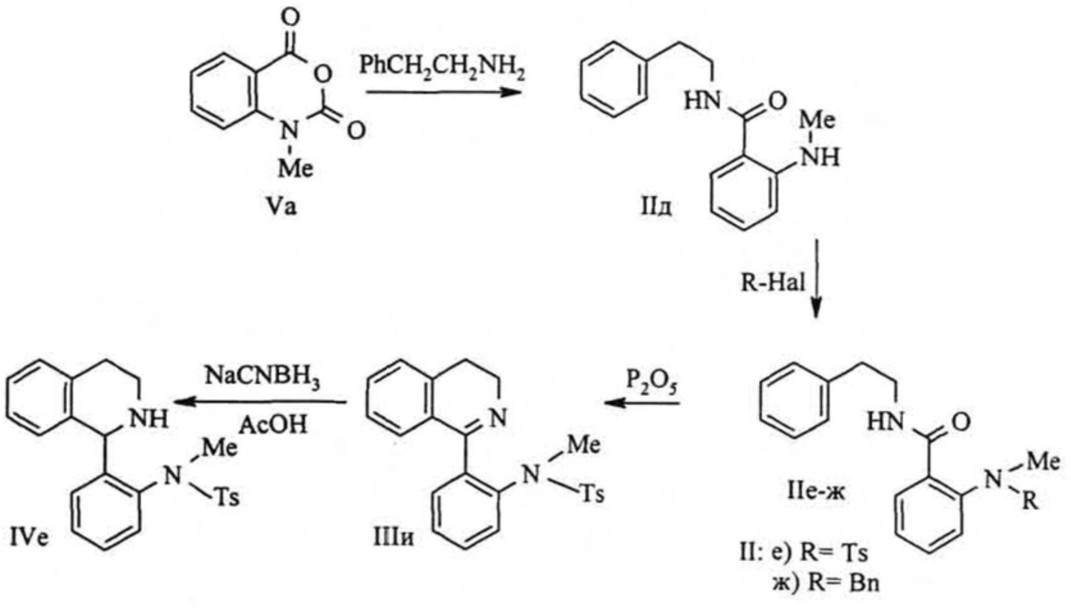

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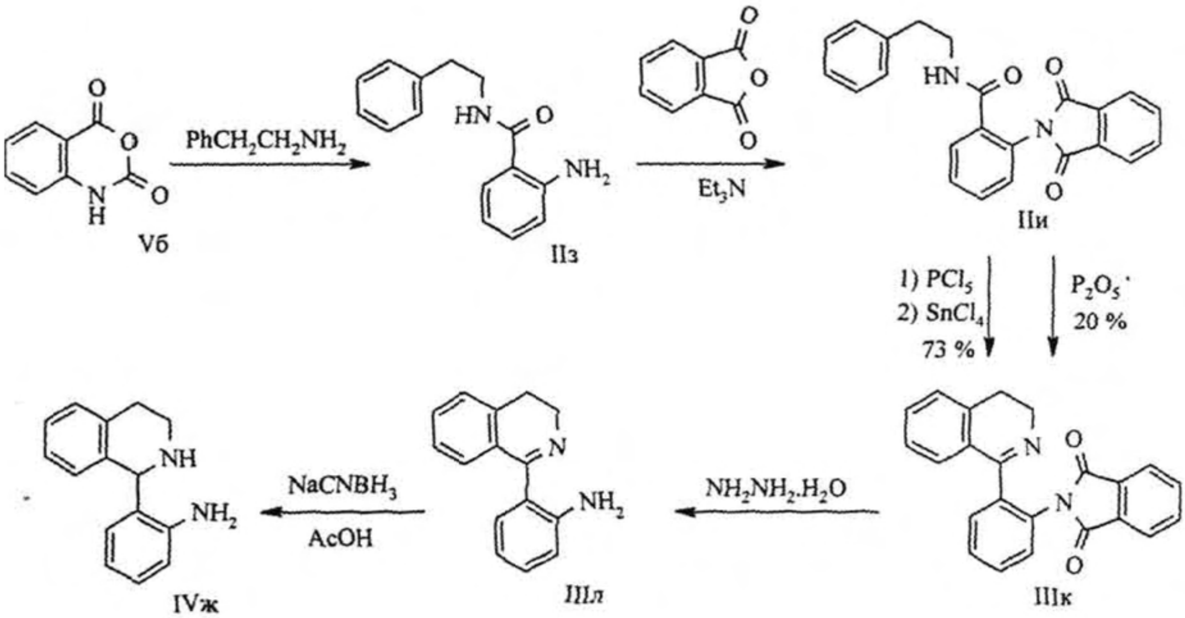

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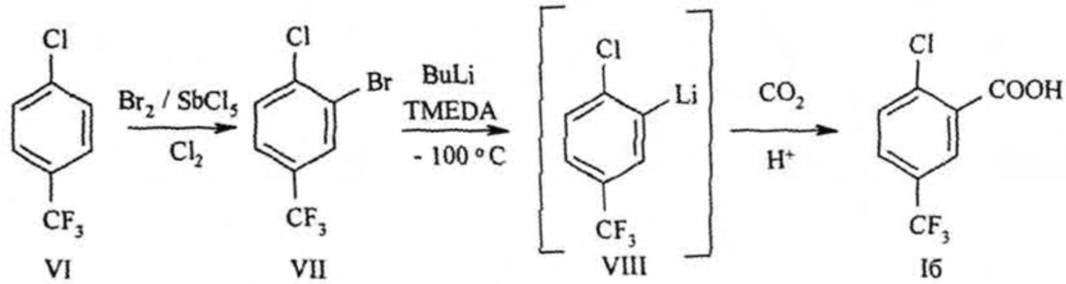

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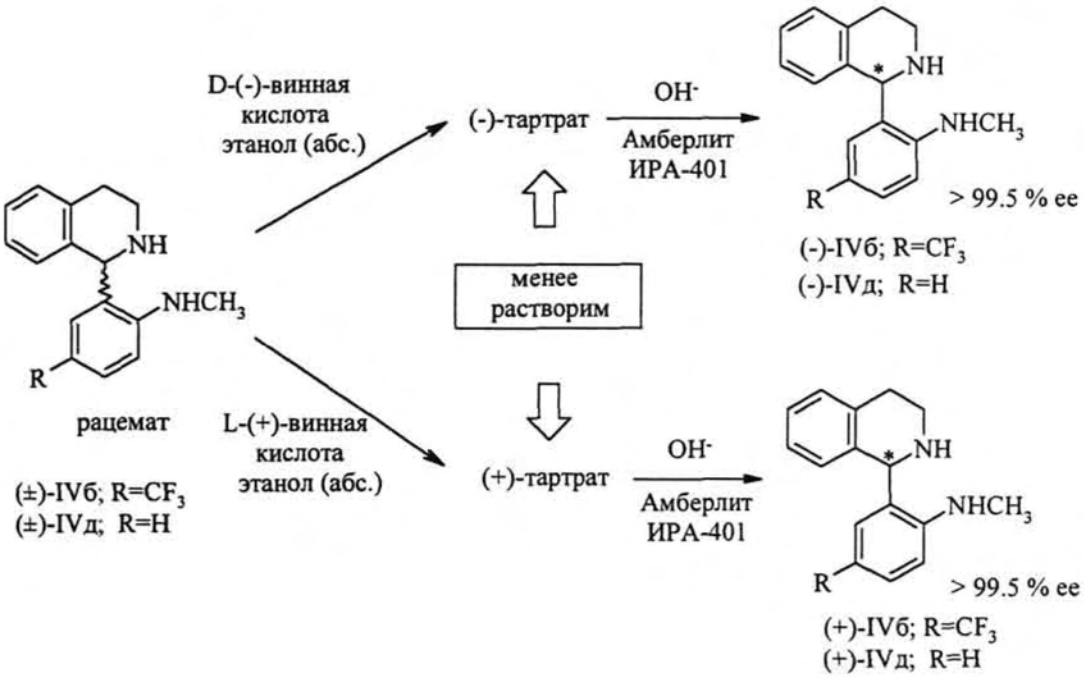
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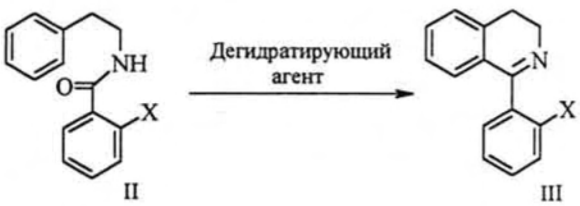
R
> 99.5 % ee
(-)-IVб; R=CF3
(-)-IVд; R=H
менее
растворим
NH
NHCH3
R
рацемат
(±)-IVб; R=CF3
(±)-IVд; R=H
L-(+)-винная
кислота
этанол (абс.)
(+)-тартрат
OH-
Амберлит
ИРА-401
NH
NHCH3
R
> 99.5 % ee
(+)-IVб; R=CF3
(+)-IVд; R=H

Таблица 1

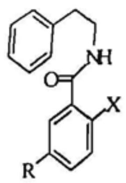
Циклизация β-фенилэтиламидов II



№	Субстрат	X	Дегидратирующий агент	Условия циклизации	Продукт	Выход (%)
1	IIз	$N(CH_3)CH_2Ph$ HCl соль	P_2O_5	6ч, ксилол, кипячение	IIIд	16
2	IIе	N(Me)Tos	P_2O_5	20ч, ксилол, кипячение	IIIи	30
3	IIи	N-фталильная	P_2O_5	24ч, ксилол, кипячение	IIIк	20
4	IIи	N-фталильная	PCl_5	30мин, $CHCl_3$, кипячение, потом $SnCl_4$, 8ч	IIIк	73
5	IIа	Cl	P_2O_5	20h	IIIа	70

~~Таблица 2~~

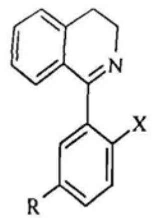
Спектры ИК, ПМР и ЯМР [13]C β-фенилэтиламидов II



Соедине ние	R	X	ИК спектры, ν, см$^{-1}$	Спектры ПМР, δ, м.д.	Спектры ЯМР ^{13}C, δ, м.д.
IIa	H	Cl	3275 (N-H) 1642 (C=O)	7,60 (1H, m); 7,40-7,18 (8H, m); 6,20 (1H, br s); 3,75 (2H, dt, J= 6,8; 6,0 Hz); 2,96 (2H, t, J= 6,8 Hz)	166,4; 138,6; 135,1; 131,1; 130,5; 130,1; 129,9; 128,7; 128,6; 128,4; 128,3; 126,9; 126,6; 41,2; 35,4
IIб	CF_3	Cl	3270 (N-H) 1650 (C=O)	7,85 (1H, d, J= 1,8 Hz); 7,58 (1H, dd, J= 8,4; 1,8 Hz); 7,49 (1H, d, J= 8,6 Hz); 7,38-7,20 (5H, m); 6,20 (1H, br s); 3,77 (2H, dt, J= 6,8; 6,0 Hz) 2,97 (2H, t, J= 6,8 Hz)	165,0; 138,6; 135,8; 134,4; 130,8; 129,3; 128,7; 128,5; 127,7; 127,2; 126,7; 126,4; 125,9; 120,5; 41,3; 35,3
IIв	NO_2	Cl	3260 (N-H) 1650 (C=O)	8,44 (1H, d, J= 2,8 Hz); 8,19 (1H, dd, J= 8,8; 2,8 Hz); 7,56 (1H, d, J= 8,8 Hz); 7,40-7,20 (5H, m); 6,14 (1H, br s); 3.79 (2H, dt, J= 6,8 Hz); 2,99 (2H, t, J= 6,8 Hz)	164,1; 146,4; 138,2; 137,5; 136,4; 131,3; 128,8; 128,75; 128,5; 127.6; 126,8; 125,5; 125,1; 41,4; 35.3
IIг	SO_2Me	Cl	3260 (N-H) 1645 (C=O)	8,10 (1H, d, J= 2,2 Hz); 7,89 (1H, dd, J= 8,4; 2,2 Hz); 7,58 (1H, d, J= 8,4 Hz); 7,39-7,21 (5H, m) 6,14 (1H, br s) 3,77 (2H, dt, J= 7,0; 6,0 Hz); 3,06 (3H, s); 2,97 (2H, t, J= 7,0 Hz)	164,7; 139,4; 138,2; 136,74; 136,66; 131,3; 129,5; 128,8; 128,75; 128,70; 126,7; 44,4; 41,3; 35,3
IIд	H	NHMe		7,42-7,15 (8H, m); 6,65 (1H, d, J= 8,2 Hz); 6,57-6,49 (1H, m); 6,05 (1H, br s); 3,65 (2H, dt, J= 7,1; 5,6 Hz); 2,91 (2H, t, J= 7,1 Hz); 2,85 (3H, d, J= 4,8 Hz)	
IIe	H	NMeTs	3380 (N-H) 1655 (C=O)	7,73 (1H, dd, J= 7,4; 1,5 Hz); 7,60 (2H, d, J= 8,0); 7,41-7,00 (10H, m); 6,51 (1H, d, J= 8,0 Hz); 3,78 (2H, dt, J= 7,0; 6,0 Hz); 3,10 (3H, s); 3,02 (2H, t, J= 7,0 Hz); 2,48 (3H, s)	166,8; 144,2; 138,9; 138,1; 137,2; 133,9; 130,4; 130,3; 129,6; 128,8; 128,7; 128,4; 128,3; 128,1; 126,6; 126,2; 41,2; 39,7; 35,4; 21,5
IIж	H	NMeBn		7,40-6,96 (15H, m); 3,91 (2H, s); 3,76 (2H, dt, J= 7,0; 6,0 Hz); 2,92 (2H, t, J= 7,0 Hz); 2,41 (3H, s)	
IIз	H	NH_2	3410 (N-H) 3290 (N-H) 1620 (C=O)	7,38-7,14 (7 H, m); 6,66 (1 H, d, J= 8,6 Hz); 6,60 (1 H, ddd, J= 8,0, 8,0, 0,8 Hz); 6,03 (1 H, br s); 5,49 (2 H, br s); 3,73-3,63 (2 H, m); 2,92 (2 H, t, J= 7,0 Hz)	169,2; 148,6; 138,9; 132,2; 128,8; 128,7; 126,9; 126,5; 117,2; 116,5; 116,1; 40,8; 35,7
IIи	H	NPhth	3255 (N-H) 1630 (C=O) 1720 (C=O)	7,93 (1H, dd, J= 5,6; 3,0 Hz); 7,89 (1H, d, J= 3,8 Hz); 7,80 (1H, d, J= 3,8 Hz); 7,77 (1H, dd, J= 5,6; 3,0 Hz); 7,62-7,16 (9H, m); 6,10 (1H, t, J= 5,8 Hz); 3,54 (2H, dt, J= 7,0; 6,2 Hz); 2,80 (2H, t, J= 7,0 Hz)	167,4; 166,8; 138,8; 134,2; 132,0; 131,2; 130,0; 129,9; 129,0; 128,7; 128,6; 128,3; 127,8; 126,5; 123,8; 41,0; 35,5

Таблица 3

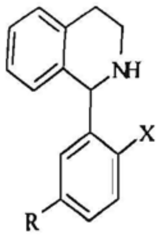
Спектры ИК, ПМР и ЯМР ^{13}C 3,4-дигидроизохинолинов III



Соединение	R	X	ИК спектры, ν, см$^{-1}$	Спектры ПМР, δ, м.д.	Спектры ЯМР ^{13}C, δ, м.д.
IIIа	H	Cl	1615 (C=N)	7,46-7,16 (7H, m); 6,91 (1H, d, J= 7,4 Hz); 4,14-3,64 (2H, br s); 2,88 (2H, t, J= 7,0 Hz)	166,0; 138,3; 137,1; 132,5; 130,8; 130,3; 129,7; 129,5; 128,8; 127,3; 126,80; 126,77; 126,71; 47,7; 25,8
IIIб	CF_3	Cl	1620 (C=N)	7,72 (1H, d, J= 2,0 Hz); 7,64 (1H, dd, J= 8,4 Hz, 2,0 Hz); 7,55(1H, d, J= 8,4 Hz); 7,40 (1H, dt, J= 7,4; 1,2 Hz); 7,27 (2H, m); 7,19 (1H, dd, J= 7,4; 1,2 Hz); 6,86 (1H, d, J= 7,6 Hz); 3,97 (2H, m); 2,89 (2H, t, J= 7,2 Hz)	165,1; 139,0; 137,1; 136,5; 131,3; 130,2; 128,3; 127,6; 127,5; 127,0; 126,6; 126,5; 97,2; 47,8; 25,7
IIIв	NO_2	Cl	1620 (C=N)	8,33 (1H, d, J=2,6 Hz); 8,24 (1H, dd, J= 8,6; 2,6 Hz); 7,61 (1H, d, J= 8,6 Hz); 7,41 (1H, dd, J= 7,6; 1,2 Hz); 7,32-7,16 (2H, m); 6,85 (1H, d, J= 7,6 Hz)	164,4; 146,6; 139,69; 139,65; 137,1; 131,4; 130,7; 129,5; 128,5; 128,0; 127,6; 127,0; 126,4; 47,9; 44,5; 25,6
IIIг	SO_2Me	Cl	1620 (C=N)	8,03 (1H, d, J= 2,4 Hz); 7,95 (1H, dd, J= 8,4; 2,4 Hz); 7,65 (1H, d, J= 8,4 Hz); 7,41 (1H, ddd, J= 7,6; 7,6; 1,2 Hz); 7,28 (1H, d, J= 7,6 Hz); 7,21 (1H, ddd, J= 7,6; 7,6; 1,2 Hz); 6,82 (1H, d, J= 7,6 Hz); 4,22-3,64 (2H, m); 3,10 (3H, s); 3,00-2,82 (2H, m)	164,8; 139,7; 139,4; 138,8; 137,0; 131,4; 130,7; 129,5; 128,5; 128,0; 127,6; 127,0; 126,4; 47,9; 44,5; 25,7
IIIд	H	NHMe	3315 (N-H) 1610 (C=N)	7,42-7,21 (6H, m); 7,09 (1H, br s); 6,75 (1H, d, J= 8,4 Hz); 6,64 (1H, ddd, J= 7,4; 7,4; 1,0 Hz); 3,87-3,80 (2H, m); 2,88 (3H, d, J= 2,6 Hz); 2,80-2,73 (2H, m)	167,8; 149,1; 139,0; 131,3; 130,3; 129,4; 128,4; 127,1; 126,3; 120,2; 114,4; 110,5; 94,2; 47,0; 30,0; 26,4
IIIе	NO_2	NHMe	3260 (N-H) 1610 (C=N)	8,82 (1H, br s); 8,27 (1H, d, J= 2,6 Hz); 8,18 (1H, dd, J= 9,2; 2,6 Hz); 7,47-7,25 (4H, m); 6,70 (1H, d, J= 9,2 Hz); 3,86-3,78 (2H, m); 3,00 (3H, d, J= 5,2 Hz); 2,79-2,72 (2H, m)	166,9; 154,3; 139,1; 135,5; 131,0; 128,6; 128,5; 127,8; 127,5; 126,9; 126,8; 117,4; 109,5; 47,0; 29,8; 26,3
IIIз	SO_2Me	NHMe	3320 (N-H) 1610 (C=N)	8,19 (1H, br s); 7,83-7,76 (2H, m); 7,45-7,21 (4H, m); 6,78 (1H, d, J= 8,6 Hz); 3,87-3,79 (2H, m); 2,98 (3H, s); 2,95 (3H, d, J= 5.0 Hz); 2,79-2,72 (2H, m)	167,0; 153,0; 139,0; 131,3; 130,9; 129,7; 128,6; 127,7; 127,5; 126,9; 124,4; 118,6; 110,1; 47,1; 45,0; 29,7; 26,2
IIIи	H	NMeTs	1611 (C=N) 1350 (SO_2N)	7,49-7,14 (10H, m); 7,04-6,99 (2H, m); 3,84 (2H, br s); 2,98 (3H, s); 2,82 (2H, t, J= 7,2 Hz); 2,39 (3H, s)	166,1; 143,2; 140,2; 140,0; 137,6; 130,6; 130,5; 129,7; 129,3; 129,2; 128,1; 127,96; 127,95; 127,8; 127,4; 127,1; 126,5; 47,6; 39,6; 25,9; 21,5
IIIк	H	NPhth	1780 (C=O) 1730 (C=O) 1715 (C=O) 1610 (C=N)	7,74 (2H, dd, J= 5,8; 2,9 Hz); 7,68-7,61 (4H, m); 7,58 (1H, dd, J= 7,4; Hz); 7,54 (1H, dd, J= 7,4; 1,6 Hz); 7,41 (1H, dd, J= 7,7; 1,3 Hz); 7,15-6,95 (3H, m); 3,61 (2H, t, J= 7,0 Hz); 2,64 (2H, t, J= 7,0 Hz)	166,88; 165,3; 138,1; 136,7; 133,86; 133,8; 131,61; 131,6; 130,4; 130,2; 129,6; 129,2; 128,7; 128,3; 126,81; 126,5; 123,13; 123,12; 47,5; 25,5
IIIл	H	NH_2	3419 (N-H); 3307 (N-H); 1610 (C=N)	7,39-7,12 (6H, m); 6,75 (1H, dd, J= 7,6; 1,3 Hz); 6,69 (1H, ddd, 7,6; 7,6; 1,2 Hz); 5,11 (2H, br s); 3,87-3,81 (2H, m); 2,79-2,73 (2H, m)	167,4; 146,9; 138,8; 131,1; 130,4; 129,8; 129,1; 128,1; 127,2; 126,4; 121,4; 116,6; 116,5; 47,1; 26,2

Таблица 4

Спектры ИК, ПМР и ЯМР ^{13}C 1,2,3,4-тетрагидроизохинолинов IV



Соеди-нение	R	X	ИК спектры, ν, см$^{-1}$	Спектры ПМР, δ, м.д.	Спектры ЯМР ^{13}C, δ, м.д.
IVa	H	Cl	3320 (N-H) 3260 (N-H)	7,41 (1H, dd, 7,2; 2,2 Hz); 7,26-7,12 (4H, m); 7,07 (1H, dd, J= 8,0; 4,6 Hz); 7,00 (1H, dd, J= 7,2; 2,2 Hz); 6,77 (1H, d, J= 7,6 Hz); 5,65 (1H, s); 3,20-2,80 (4H, m); 2,02 (1H, br s)	142,0; 136,9; 135,8; 134,0; 131,0; 129,5; 129,1; 128,4; 128,0; 126,6; 126,4; 125,7; 57,5; 41,2; 29,6
IVб	CF_3	NHMe	3330 (NH-)	7,45 (1H, dd, J= 8,8; 1,8 Hz); 7,21 (1H, d, J= 1,8 Hz); 7,17-7,00 (3H, m); 6,76 (1H, d, J= 7,8 Hz); 6,58 (1H, d, J= 8,8 Hz); 6,36 (1H, br s); 5,10 (1H, s); 3,33-3,25 (1H, m); 3,14-3,03 (2H, m); 2,88-2,60 (1H, m); 2,73 (3H, s); 1,95 (1H, br s)	151,1; 136,5; 134,9; 129,0; 127,6; 126,7; 126,5; 126,1; 126,0; 125,6; 117,0; 116,6; 109,4; 62,3; 43,0; 29,9; 29,6
IVв	NO_2	NHMe	3240 (N-H)	8,15 (1H, dd, J= 9,0; 2,6 Hz); 7,95 (1H, d, J= 2,6 Hz); 7,26-7,02 (4H, m); 6,78 (1H, d, J= 7,6 Hz); 6,51 (1H, d, J= 9,0 Hz); 5,14 (1H, s); 3,33-3,23 (1H, m); 3,13-3,02 (2H, m); 2,88-2,75 (1H, m); 2,79 (3H, d, J= 5,0 Hz); 2,07 (1H, br s)	153,9; 136,4; 135,7; 134,8; 129,2; 127,0; 126,9; 126,3; 126,1; 126,0; 124,8; 108,6; 62,1; 42,8; 29,8; 29,4
IVг	SO_2Me	NHMe	3320 (N-H)	7,75 (1H, dd, J= 8,4; 2,2 Hz); 7,55 (1H, d, J= 2,2 Hz); 7,18-7,00 (3H, m) 6,77 (1H, br s); 6,73 (1H, d, J= 7,8 Hz); 6,59 (1H, d, J= 8,8 Hz); 5,13 (1H, s); 3,32-3,18 (2H, m); 3,10-2,76 (2H, m); 3,03 (3H, s); 2,73 (3H, d, J= 5,0 Hz); 2,05 (1H, br s)	152,7; 135,9; 134,9; 129,7; 129,1; 129,0; 126,8; 126,2; 125,9; 125,5; 125,2; 109,4; 62,4; 45,1; 43,1; 29,7; 29,5
IVд	H	NHMe	3307 (N-H)	7,23-7,13 (4H, m); 6,93 (1H, dd, J= 7,8; 1,8 Hz); 6,82 (1H, d, J= 7,8 Hz); 6,68-6,61 (1H, m); 6,62 (1H, d, J= 7,8 Hz); 5,10 (1H, s); 3,31-2,96 (3H, m); 2,87-2,66 (1H, m); 2,71 (3H, s); 2,1-1,4 (1H, br s)	148,6; 137,5; 135,0; 130,7; 128,9; 128,6; 126,8; 126,5; 126,3; 125,7; 115,5; 110,5; 61,8; 42,7; 30,3; 29,6
IVe	H	NMeTs	3321 (N-H) 1342 (SO_2N)	7.68-7,56 (2H, m); 7,33 (2H, d, J= 8,0 Hz); 7,26-6,92 (6H, m); 6,61-6,42 (2H, m); 5,74 (1H, s); 3,37-2,74 (4H, m); 3,26 (3H, s); 2,47 (3H, s); 1,85-1,50 (1H, br s)	145,8; 143,7; 140,2; 139,3; 136,0; 134,1; 131,7; 129,48; 129,47; 128,9; 128,8; 128,21; 128,20; 127,8; 127,5; 125,8; 125,7; 125,4; 56,1; 43,4; 40,0; 29,9; 21,6
IVж	H	NH_2	3388 (N-H) 3323 (N-H) 3261 (N-H)	7,18-6,98 (5H, m); 6,81 (1H, d, J= 7,8 Hz); 6,69 (1H, ddd, J= 7,5; 7,5; 1,5 Hz); 6,62 (1H, dd, J= 8,1; 1,2 Hz); 5,09 (1H, s); 4,49 (2H, br s); 3,31-3,22 (1H, m); 3,13-3,00 (2H, m); 2,84-2,75 (1H, m); 2,00 (1H, br s)	146,2; 137,5; 135,2; 131,2; 129,1; 128,6; 127,3; 127,0; 126,6; 126,0; 117,5; 116,9; 62,0; 43,1; 29,8

Таблица 5

Данные элементного анализа и температуры плавления соединений II-IV

Соединение	Брутто-формула	*Найдено, %* Вычислено, %				$T_{пл}$, °C [а]	$T_{пл}$, °C [б]	Выход[в], %
		C	H	N	S			
IIа	$C_{15}H_{14}ClNO$	*69,26* 69,37	*5,43* 5,43	*5,41* 5,39	-	101…102 (А)		89
IIб	$C_{16}H_{13}ClF_3NO$	*58,67* 58,64	*3,99* 4,00	*4,27* 4,27	-	99…100 (А)		80
IIв	$C_{15}H_{13}ClN_2O_3$	*59,13* 59,12	*4,21* 4,30	*9,18* 9,19	-	159…160 (А)	155 (Б)	44 (90)
IIг	$C_{16}H_{16}ClNO_3S$	*56,81* 56,89	*4,93* 4,77	*4,13* 4,15	*9,41* 9,49	145…146 (А)		76
IIд	$C_{16}H_{18}N_2O$	*73,10* 72,98	*6,95* 6,89	*10,78* 10,64	-	105…106 (А)	106…107 (В)	79 (76)
IIе	$C_{23}H_{24}N_2O_3S$	*67,40* 67,62	*6,11* 5,92	*6,85* 6,86	*7,75* 7,85	89…90 (А)		62
IIж	$C_{23}H_{24}N_2O$	*80,05* 80,20	*6,88* 7,02	*7,93* 8,13	-	89…91 (А)		87
IIз	$C_{15}H_{16}N_2O$	*74,87* 74,97	*6,75* 6,71	*11,63* 11,66	-	89…90 (Г)	90…91 (Д)	75 (83)
IIи	$C_{23}H_{18}N_2O_3$	*74,05* 74,58	*4,62* 4,90	*7,12* 7,56	-	133…134 (Г)		87
IIIа	$C_{15}H_{12}ClN$	*74,31* 74,53	*4,92* 5,00	*5,78* 5,79	-	79…80 (Е)		72
IIIб	$C_{16}H_{11}ClF_3N$	*61,87* 62,05	*3,54* 3,58	*4,45* 4,52		213…214 (А)	212…214 (Ж)	86 (40)
IIIв	$C_{15}H_{11}ClN_2O_2$	*73,84* 74,53	*4,87* 5,00	*5,77* 5,79	-	151…153 (А)	150 (Б)	84 (73)
IIIг	$C_{16}H_{14}ClNO_2S$	*60,09* 60,09	*4,45* 4,41	*4,34* 4,38	-	161…162 (З)		76
IIIд	$C_{16}H_{16}N_2$	*81,33* 81,32	*6,84* 6,82	*11,81* 11,85	-	75…76 (А)	масло	87 (95)
IIIе	$C_{16}H_{15}N_3O_2$	*67,05* 68,31	*5,36* 5,37	*14,55* 14,94	-	149…150 (А)	148 (Б)	66 (92)
IIIз	$C_{17}H_{18}N_2O_2S$	*65,03* 64,94	*5,88* 5,77	*8,84* 8,91	-	165…166 (З)		53
IIIи	$C_{23}H_{22}N_2O_2S$	*70,65* 70,74	*5,59* 5,68	*7,16* 7,17	*8,23* 8,21	139…140 (А)	138…140 (Б)	30 (43)
IIIк	$C_{23}H_{16}N_2O_2$	*78,37* 78,39	*4,53* 4,58	*7,92* 7,95	-	189…190 (Г)		20
IIIл	$C_{15}H_{14}N_2$	*80,98* 81,05	*6,36* 6,35	*12,60* 12,56	-	96…97 (А)	95…96 (В)	85 (94)
IVа	$C_{15}H_{14}NCl$	*74,50* 73,92	*5,94* 5,79	*6,05* 5,75	-	масло		
IVб	$C_{17}H_{17}F_3N_2$	*66,20* 66,66	*5,44* 5,59	*8,94* 9,14	-	131…132 (Е)	131…133 (Д)	75 (40)
IVв	$C_{16}H_{17}N_3O_2$	*66,71* 67,83	*5,81* 6,05	*14,62* 14,83	-	185…186 (Г)	182 (Б)	69 (76)
IVг	$C_{17}H_{20}N_2O_2S$	*64,66* 64,53	*6,44* 6,37	*8,80* 8,85	*10,02* 10,13	163…164 (Г)		76
IVд	$C_{16}H_{18}N_2$	*79,63* 80,63	*7,69* 7,61	*11,64* 11,75	-	87…88 (И)	масло	84 (98)
IVе	$C_{23}H_{24}N_2O_2S$	*70,31* 70,38	*6,24* 6,16	*7,10* 7,14	*8,20* 8,17	154…156 (Г)	72	
IVж	$C_{15}H_{16}N_2$	*80,09* 80,32	*7,37* 7,19	*12,43* 12,49	-	109-110 (А)	108 (Б)	(83)

[а] системы растворителей для кристаллизации: (А) гексан-этилацетат, (Б) эфир, (В) этанол, (Г) толуол-петролейный эфир, (Д) эфир-петролейный эфир, (Е) гексан, (Ж) ацетон-эфир, (З) этилацетат, (И) этанол-вода,

[б] температуры плавления в литературе [2]

[в] в скобках даны выходы из литературы [2]

Appendix 2

Resolution of 1-Aryl-1,2,3,4-Tetrahydroisoquinolines *via* Crystallization of O-Acetylmandelic Amides

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Chiral 1-anilinotetrahydroisoquinolines are useful bidentate diamine ligands in asymmetric synthesis. Commercially available non-racemic diamine CAPTIQ **1** has already found application as "chiral acid" in asymmetric protonation of amide enolates.[1] As a part of our studies toward synthesis of various CAPTIQ analogs we tested the most convenient route to desired chiral isoquinolines. Diastereomeric salts crystallization[2] required extensive trial-and-error procedure to evaluate the most appropriate resolving agent for each particular substrate and was effective only for certain diamines.[3] An alternative approach to various CAPTIQ analogs is the preparation of a key intermediate by resolution technique and subsequent chemical transformations of optically pure material. The most suitable candidate for the key structure is 1-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline **2** that would give access both to aniline **3** and its analogs such as arylhydroxylamines. Unsuccessful racemic nitro-isoquinoline **2** resolution *via* diastereomeric salts urged us to examine covalently bonded chiral auxiliaries that would allow to separate the diastereomer pair by chromatography if crystallization technique would be ineffective. Successful reports on O-acetylmandelic acid **4** mediated racemic amine resolution by chromatography[4] and crystallization technique[5] stimulated us to apply this chiral reagent for the resolution of nitro-isoquinoline **2**.

Crude amide **5** as a 1:1 mixture of diastereomers was easily prepared in 95% yield by DMAP catalyzed racemic nitro-isoquinoline **2** condensation with (*R*)-O-acetylmandelic acid **4** in the presence of dicyclohexylacarbodiimide (DCC). As the product was contaminated with dicyclohexylurea, crystallization from EtOAc-hexanes was employed affording amide **5a** as colorless needles. The ratio of diastereomers was determined for crystals by ^{1}H-NMR[6] and was shown to be > 95:5 (>90% de). Repeated crystallization form EtOAc-hexanes increased purity to >99% de, affording a single diastereomer **5a** in 31% overall yield. The absolute configuration at isoquinoline carbon was confirmed to be (*R*) by X-ray crystallography.

With single diastereomer **5a** in hand the racemization-free chiral auxilliary removal became a crucial issue. Cleavage with aqueous HCl[4b] caused partial racemization (54% ee with 6N HCl and 67% ee with 1N HCl). Similarly, reductive methods (DIBAL,[7] CH_2Cl_2, -100^0 C and $LiBH_4$ in MeOH-THF,[8] reflux) afforded partially racemized product **3a** with 47% and 75% ee, respectively. Poor solubility of **5a** in common solvents (toluene, Et_2O, THF) precluded use of alternative methods ($LiAlH_4/Et_2O$).[9] Presumably, nitro group conversion to amine could solve solubility issue. Pd-catalyzed hydrogenation of nitrobenzene **5a** in glacial acetic acid yielded anilino-isoquinoline **6a** (62% yield) accompanied with unexpected O-acetylmandelyl anilide **7a** (39%). ^{1}H-NMR experiment in acetic acid-d_4 showed that 50% of aniline **6a** had rearranged to isoquinoline **7a** in 8h at 20 ^{0}C and after 64 h at room temperature only 4% of starting material could be observed. Lack of O-acetylmandelyl group migration product **7a** in acetonitrile-d_3 (polar aprotic solvent) and methanol-d_4 (polar protic solvent) after 18h at 70 ^{0}C followed by 72h at 20 ^{0}C suggests that acidic media is crucial for the rearrangement. To avoid complications with chiral auxiliary cleavage one desirable option is to attach O-acetylmandelyl group to aniline nitrogen, leaving secondary amine unsubstituted. Corresponding anilide **9** was prepared in 79% overall yield from anilino-isoquinoline **8** and chiral acid **4** under standard conditions (DCC/cat.DMAP), followed by imine reduction with $NaCNBH_3$. Two crystallizations afforded diastereomerically pure product **9b** (28%, >99% de) with (*S*) absolute configuration at isoquinoline according to X-ray crystallography. Chiral auxiliary was readily cleaved without complications encountered with nitro analogue. Thus, reflux in 1N HCl for 4 hours gave single diamine **3b** enantiomer in 95% yield and with > 99% ee.

With practical access to >99% enantiomerically pure **3b** established, the problem of inexpensive preparative scale diamine **3a-b** synthesis was investigated. This was achieved by combination of (*R*)-O-acetylmandelyl auxiliary mediated racemate resolution with diastereomeric tartrate crystallization technique. Thus, chiral diamine **3a** and **3b** salts with L(+) tartaric acid were used as a seed in crystallization of racemic diamine **3** L(+) tartrates. Generally 4 to 6 crystallizations at 10 g loading level were necessary to obtain desired diamines **3a** or **3b** after acid-base extractive workup in ca. 10% overall yield and > 99% ee.

Tartrates crystallization with seeding provided sufficient chiral material to synthesize a number of CAPTIQ analogs. After protecting isoquinoline **3b** nitrogen as Cbz derivative **9b**, N-phenylation according to the Barton procedure[10] followed by N-protecting group hydrogenolysis afforded chiral N-phenylaniline **10** in 56% overall yield and with > 99% ee. (*S*)-N-isopropyl-diamine **11** was readily obtained by reductive alkylation procedure (84% overall yield) and reaction of (*R*)-diamine **3a** with N,N-dimethylsulfamoyl chloride afforded amide **12** in 18% overall yield.

All prepared CAPTIQ analogs will be tested as “chiral acids” in asymmetric protonation of amide enolates.

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References.

1. (a) Vedejs, E.; Kruger, A.W. *J.Org.Chem.* **1998**, *63*, 2792. (b) Vedejs, E.; Lee, N.; Sakata, S.T. *J. Am. Chem. Soc.* **1994**, *116*, 2175.
2. (a) Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates and Resolutions*; Krieger Publishing Company: Florida, 1994. (b) Newmann, P. *Optical Resolution Procedures for Chemical Compounds; Amines and Related Compounds*; Riverdale, N.Y.: Optical Resolution Information Center, 1984. (b) Ott, H.; Hardtmann, G.; Denzer, M.; Frey, A.- J.; Gogerty, J. H.; Leslie, G. H.; Trapold, J. H. *J. Med. Chem.* **1968**, *11*, 777. (c) Ott, H. US, 3,297,696, 1967; *Chem.Abstr.* **1967**, *66:* 65505a.
3. Suna, E.; Trapencieris, P. *Chem.Heterocycl.Comp.*, submitted.
4. (a) Helmchen, G.; Nill, G.; Flockerzi, D.; Schühle, W.; Youssef, S.K.M. *Angew.Chem.Int.Ed.Engl.* **1979**, *18*, 62. (b) Weerawarna, S.A.; Davis, R.D.; Nelson, W.L. *J.Med.Chem.* **1994**, *37*, 2856.
5. Corey, E.J.; Bakshi, R.K.; Shibata, S.; Chen, C.-P., Singh, V.K. *J.Am.Chem.Soc.* **1987**, *107*, 7925.
6. Parker, D. *Chem.Rev.* **1991**, *91*, 1441.
7. Evans, D.A.; Miller, S.J.; Ennis, M.D. *J.Org.Chem.* **1993**, *58*, 471.
8. Soai, K.; Ookawa, A. *J.Org.Chem.* **1986**, *51*, 4000.
9. Wanner, K.T.; Beer, H.; Höfner, G.; Ludwig, M. *Eur.J.Org.Chem.* **1998**, 2019.
10. Barton, D.H.R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1987**, *28*, 887.
11. Stanforth, S.P. *J.Heterocycl.Chem.* **1987**, *24*, 531.

Experimental Section.

1-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (2).

To a solution of 1-(2-nitrophenyl)-3,4-dihydroisoquinoline[11] (2.00 g, 7.93 mmol) in 20 mL of glacial acetic acid was added $NaCNBH_3$ (Aldrich; 0.93 g, 14.8 mmol) portionwise within 20 min. The reaction mixture was stirred under N_2 at RT for 3 hours, poured on crashed ice and basified by careful addition of concentrated NaOH solution. The mixture was extracted with CH_2Cl_2 (4x30 mL), the organic layer was washed with brine (2x30 mL) and dried (Na_2SO_4). Filtration and solvent evaporation (aspirator) afforded yellow oil that was dissolved in CH_2Cl_2 (20 mL) and filtered through a silica gel pad with CH_2Cl_2 rinse. The filtrate was concentrated *in vacuo* and the resulting yellow solid was recrystallized from EtOAc - hexane to obtain yellow crystalline material (1.74 g, 86%); analytical TLC on silica gel, 1:2 EtOAc/hexane, Rf= 0.47. Pure material was obtained by crystallization from EtOAc/hexane, mp 89-90 ^{0}C. No parent ion for $C_{15}H_{14}N_2$; M-1, 221.1075, error = 2 ppm; IR (KBr, cm^{-1}) 3253, N-H; 1520, NO_2; 300 MHz NMR ($CDCl_3$, ppm) δ 7.81 (1 H, dd, J= 7.8, 1.5 Hz) 7.44 (1 H, ddd, J= 7.8, 7.8, 1.5 Hz) 7.38 (1 H, ddd, J= 7.8, 7.8, 1.5 Hz) 7.18-7.14 (3 H, m) 7.09-7.01 (1 H, m) 6.71 (1 H, d, J= 7.8 Hz) 5.60 (1 H, s) 3.21-2.96 (3 H, m) 2.90-2.80 (1 H, m) 2.40 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 150.3, 138.9, 136.4, 136.0, 132.3, 132.0, 129.2, 128.03, 127.97, 126.6, 125.8, 123.8, 56.0, 41.3, 29.5.

2-[(*R*)-O-Acetylmandelyl)]-1-(*R*)-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (5a)

1-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (2) (325 mg, 1.29 mmol), (R)-O-acetylmandelic acid (4) (Aldrich; 257 mg, 1.33 mmol) and N,N-dimethylaminopyridine (Aldrich; 19 mg, 0.16 mmol) were placed in 20 mL of dry CH_2Cl_2 under N_2 and cooled to 0°C in an ice bath. Dicyclohexylcarbodiimide (Aldrich; 309 mg, 1.50 mmol) was slowly added *via* syringe as a solution in 5 mL of dry CH_2Cl_2. The reaction mixture was gradually warmed to RT and stirred for 12 h. White precipitate was removed by filtration and solvent evaporation *in vacuo* (aspirator) afforded a white solid. Crystallization from 1:1 EtOAc/hexane gave colorless needles and additional recrystallization from 1:1 EtOAc/hexane yielded diastereomerically pure product 5a (170 mg, 31%), mp 213-214 ^{0}C. Analytical TLC on silica gel, 1:1 EtOAc/hexane, Rf= 0.44; analytical HPLC on CSP (Daicel CHIRACEL OD, 25 cm x 4.6 mm I.D.), mobile phase 15%i-PrOH:85%Hex, flow rate 1.0 mL/min, retention time 14.4 min. (R,R-isomer, major) and 21.2 min. (S,R-isomer, minor), ratio 99.5:0.5 (>99% de). Optical rotation: $[\alpha]_D$= -53 (c=0.77, $CHCl_3$). No parent ion for $C_{25}H_{22}N_2O_5$; M+1, 431.1606, error = 7 ppm; IR (KBr, cm^{-1}) 1738, C=O; 1655, C=O; 1531, NO_2; 300 MHz NMR ($CDCl_3$, ppm) δ 7.83 (1 H, dd, J= 7.8, 1.2 Hz) 7.39-7.05 (11 H, m) 6.87 (1 H, dd, J= 7.2, 1.5 Hz) 6.30 (1 H, s) 3.95-3.88 (1 H, m) 3.26-3.08 (2 H, m) 2.91-2.81 (1 H, m) 2.11 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.4, 166.8, 150.4, 136.8, 133.9, 133.6, 133.1, 131.9, 129.7, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 127.8, 127.0, 126.8, 123.6, 118.3, 73.2, 51.5, 40.7, 29.2, 20.7.

1-(2-Aminophenyl)-3, 4-dihydroisoquinoline (8)

To a solution of 1-(2-nitrophenyl)-3,4-dihydroisoquinoline[11] (1.26 g, 5.00 mmol) in 15 mL of EtOH-H_2O 1:1 was added iron powder (0.87 g, 15.6 mmol) and reaction mixture was brought to reflux. Concentrated hydrochloric acid (0.1 mL) was added in one portion to the refluxing mixture and boiling was continued for 3 hours. After cooling the dark brown solution was filtered through a celite pad with EtOH rinse. The filtrate was concentrated *in vacuo* (aspirator) to give orange-red oil, which was treated with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3x20 mL). Combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* (aspirator) to give yellowish oil. The crude oil was dissolved in CH_2Cl_2 (10 mL) and filtered through a silica pad with CH_2Cl_2 rinse. The filtrate was concentrated *in vacuo* (aspirator) affording yellow crystalline material (0.75 g, 68 %); analytical TLC on silica gel, 1:1 EtOAc/hexane, Rf= 0.35. Pure material was obtained by crystallization from ethyl acetate/hexane, mp 96-97 ^{0}C. No parent ion for $C_{15}H_{14}N_2O_2$; M-1, 253.0983, error = 2 ppm; IR (KBr, cm^{-1}) 3419, N-H; 3307, N-H; 1610, C=N; 300 MHz NMR ($CDCl_3$, ppm) δ 7.39-7.12 (6 H, m) 6.77-6.66 (2 H, m) 5.11 (2 H, br s) 3.87-3.81 (2 H, m) 2.79-2.73 (2 H, m).

(*S*)-1-(2-[(*R*)-O-Acetylmandelyl]aminophenyl)-1, 2, 3, 4-tetrahydroisoquinoline (7b).

1-(2-Aminophenyl)-3,4-dihydroisoquinoline (8) (1.88 g, 8.48 mmol), (*R*)-O-acetylmandelic acid (4) (Aldrich; 1.69 g, 8.73 mmol) and N,N-dimethylaminopyridine (Aldrich; 136 mg, 1.11 mmol) were placed in dry CH_2Cl_2 (100 mL) under N_2 and cooled to 0°C in an ice bath. Dicyclohexylcarbodiimide (Aldrich; 2.59 g, 12.5 mmol) was gradually added *via* syringe as a solution in dry CH_2Cl_2 (10 mL) and the reaction mixture was warmed to RT and stirred overnight. White precipitate was removed by filtration, solvent was evaporated *in vacuo* (aspirator) and the resulting yellowish oil was dissolved in CH_2Cl_2 (20 mL). Filtered through a silica pad with CH_2Cl_2 rinse and filtrate concentration *in vacuo* (aspirator) afforded 1-(2-[(*R*)-O-acetylmandelyl]aminophenyl)-3,4-dihydroisoquinoline as a colorless oil (3.23 g, 96% yield). The crude material was used for the next step without further purification (starting material R_f=0.31, product R_f=0.56, EtOAc:hexane=2:5).Thus, to a solution of the crude oil (3.23 g, 8.11 mmol) in 30 mL of glacial acetic acid was added $NaCNBH_3$ (Aldrich; 1.02 g, 16.2 mmol) portionwise within 25 min. The reaction mixture was stirred under N_2 at RT for 3 hours, poured on crashed ice and basified by careful addition of concentrated NaOH solution. The mixture was extracted with CH_2Cl_2 (4x20 mL), combined organic extracts were washed with brine (2x20 mL), dried (Na_2SO_4) and concentrated *in vacuo* (aspirator). The resulting yellowish oil was dissolved in CH_2Cl_2 (20 mL) and filtered through a silica pad with CH_2Cl_2 rinse. Concentration of the filtrate *in vacuo* (aspirator) afforded white solid, which was recrystallized twice from EtOAc-hexane to obtain diastereomerically pure (*S,R*)-acetylmandelyl-isoquinoline **7b** as a colorless prisms (0.90 g. 28%), mp 191-192 °C. Analytical TLC on silica gel, 1:1 EtOAc/hexane, Rf= 0.14. Optical rotation: $[\alpha]_D$= -220 (c=1.09, DMF). Molecular ion calcd for $C_{25}H_{24}N_2O_3$: 400.17871; found m/e= 400.1805, error = 4 ppm; IR (KBr, cm^{-1}) 3311, N-H; 1738, C=O; 1685, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 11.25 (1 H, s) 8.33 (1 H, dd, J= 8.1, 1.2Hz) 7.38-7.02 (9 H, m) 6.82-6.79 (2 H, m) 6.64 (1 H, d, J= 8.1 Hz) 6.10 (1 H, s) 5.11 (1 H, s) 3.43-3.17 (3 H, m) 2.91-2.83 (1 H, m) 2.21 (3 H, s) 1.66 (1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.8, 166.2, 136.9, 136.5, 135.3, 133.9, 130.8, 130.4, 128.9, 128.6, 128.5, 128.4, 127.8, 126.7, 126.5, 126.2, 123.5, 122.1, 75.9, 63.2, 43.9, 28.9, 20.7.

(S)-1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinoline (3b)

(S,R)-Acetylmandelyl-isoquinoline **7b** (200 mg, 0.5 mmol) as a solid material was added to 1N HCl (20 mL) and reaction mixture was refluxed for 4 hours. The clear solution was cooled to 0°C and basified by careful addition of concentrated NaOH solution. The mixture was extracted with CH_2Cl_2 (3x10 mL), organic layer was washed with brine (2x10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to obtain a white solid (106 mg, 95%), analytical TLC on silica gel, 1:1 EtOAc/hexane, Rf= 0.2; analytical HPLC on CSP (Daicel CHIRACEL OD, 25 cm x 4.6 mm I.D.), 20%i-PrOH:80%Hex:0.1%Et_2N, flow rate 0.9 mL/min, retention time 23.2 min (S-isomer, major) and 37.4 min (R-isomer, minor), ratio 99.5:0.5 (>99% ee). Pure material was obtained by crystallization from ethyl acetate/hexane, mp 113-114 °C, colorless needles. Optical rotation: $[\alpha]_D$= +5.2 (c=1.5, 95% EtOH). Molecular ion calcd for $C_{15}H_{16}N_2$: 224.13139; found m/e= 224.1312, error = 1 ppm; IR (KBr, cm^{-1}) 3388, N-H; 3323, N-H; 300 MHz NMR ($CDCl_3$, ppm) δ 7.18-6.98 (5 H, m) 6.81 (1 H, d, J= 7.8 Hz) 6.62 (1 H, dd, J= 8.1, 1.2 Hz) 6.69 (1 H, ddd, J= 7.5, 7.5, 1.5 Hz) 5.09 (1 H, s) 4.49 (2 H, br s) 3.31-3.22 (1 H, m) 3.13-3.00 (2 H, m) 2.84-2.75 (1 H, m) 2.00 (1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 146.2, 137.5, 135.2, 131.2, 129.1, 128.6, 127.0, 127.3, 126.0, 126.6, 117.5, 116.9, 62.0, 43.1, 29.8.

(S)-1-(2-Aminophenyl)-2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline (9b)

To a solution of (S)-diamine **3b** (1.0 g, 4.46 mmol) in dry CH_2Cl_2 (100 mL) at room temperature was added triethylamine (1.9 mL, 13.4 mmol) followed by neat benzyl chloroformate (Aldrich; 1.1 mL, 7.8 mmol) and the mixture was stirred for 12 h. The reaction was poured into water (100 mL) and extracted with CH_2Cl_2 (4x50 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* (aspirator) to give a yellowish oil, which was purified by flash column chromatography (150 mL of silica gel, column size 4x18 cm, eluent CH_2Cl_2). Collected fractions #6 - #31 (50 mL ea) afforded a colorless oil 1.13 g (71%), analytical TLC on silica gel, 2:5 EtOAc/hexane, Rf= 0.7. Optical rotation: $[\alpha]_D$= -191 (c=1.29, 95% EtOH). Molecular ion calcd for $C_{23}H_{22}N_2O_2$: 358.16815; found m/e= 358.1681, error = 0 ppm; IR (KBr, cm^{-1}) 3431, N-H; 1658, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 7.37-7.33 (5 H, m) 7.24-7.11 (3 H, m) 7.08-7.02 (1 H, m) 6.97 (1 H, d, J= 7.5 Hz) 6.68 (1 H, d, J= 8.1 Hz) 6.54-6.47 (3 H, m) 5.22 (1 H, d, J= 12.3 Hz) 5.14 (1 H, d, J= 12.3 Hz) 4.81 (1 H, br s) 4.10 (1 H, dd, J= 13.5, 5.5 Hz) 3.28-3.00 (2 H, m) 2.82 (1 H, dd, J= 16.5, 3.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 155.9, 145.9, 136.2, 135.3, 134.5, 130.7, 128.8, 128.6, 128.5, 128.4, 127.97, 127.95, 127.73, 127.70, 126.7, 126.0, 125.4, 116.6, 115.4, 67.4, 54.0, 37.1,

(S)-1-(2-Phenylaminophenyl)-1, 2, 3, 4-tetrahydroisoquinoline (10)

(S)-Cbz-diamine **9b** (1.13 g, 3.15 mmol), triphenylbismuth (Aldrich, 1.66 g, 3.78 mmol) and copper (II) acetate (dried overnight at 105 °C *in vacuo* over P_2O_5) (572 mg, 3.15 mmol) were placed in dry CH_2Cl_2 (50 mL) and stirred at RT under N_2 for 90 hours. The mixture was filtered through a celite pad with CH_2Cl_2 rinsing, the filtrate was evaporated (aspirator) and the residue was purified by flash column chromatography (200 mL of silica gel, column size 4x17 cm, gradient elution from CH_2Cl_2:hexane=1:4 to CH_2Cl_2:hexane=1:1) and collected fractions (R_f=0.48, CH_2Cl_2:hexane=1:1) gave a colorless oil (840 mg, 61%). The crude oil (840 mg, 1.93 mmol) was dissolved in 2:1 mixture of methanol (20 mL) and EtOAc (10 mL) and 10% Pd/C (215 mg) was added. The reaction mixture was stirred under H_2 atmosphere at RT and it was monitored by TLC analysis. The reaction was completed within 1 hour and Pd/C was filtered through a celite pad with MeOH rinsing. The filtrate was concentrated *in vacuo* (aspirator) to give a yellow oil, which was purified by preparative TLC (silica gel, plate size 20x20 cm, elution: EtOAc:Hex=1:5) and yellowish oil (640 mg, 95%) was obtained: analytical TLC on silica gel, 2:5 EtOAc/hexane, Rf= 0.4; analytical HPLC on CSP (Daicel CHIRACEL OD, 25 cm x 4.6 mm I.D.), mobile phase 5%i-PrOH:95%Hex :0.1%Et_2NH, flow rate 0.9 mL/min, retention time 16.6 min. (S-isomer, major) and 21.2 min. (R-isomer, minor), ratio >99:1 (99% ee). Optical rotation: $[\alpha]_D$= +3.5 (c=1.58, $CHCl_3$). Molecular ion calcd for $C_{21}H_{20}N_2$: 300.16269; found m/e= 300.1628, error = 0 ppm; IR (neat, cm^{-1}) 3290, N-H; 1591, C-(Ar); 300 MHz NMR ($CDCl_3$, ppm) δ 8.31 (1 H, br s) 7.36 (1 H, dd, J= 4.0, 1.2 Hz) 7.21-6.75 (12 H, m) 5.15 (1 H, s) 3.27-3.20 (1 H, m) 3.12-2.94 (2 H, m) 2.83-2.75 (1 H, m) 2.12 (1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 143.3, 142.9, 137.3, 134.8, 131.2, 131.0, 128.95, 128.91, 128.1, 126.9, 126.3, 125.7, 119.8, 119.5, 117.4, 117.3, 61.1, 42.2, 29.5.

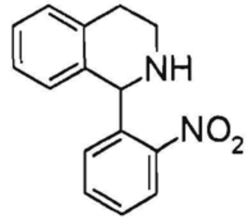
(S)-1-(2-Isopropylaminophenyl)-1, 2, 3, 4-tetrahydroisoquinoline (11)

To a solution of (S)-Cbz-diamine **9b** (1.01 g, 2.82 mmol) in 4:1 mixture of reagent grade acetone (20 mL) and glacial acetic acid (5 mL) was added $NaCNBH_3$ (Aldrich; 350 mg, 5.63 mmol) portionwise within 15 min. The reaction mixture was stirred under N_2 at RT and it was monitored by TLC analysis. The reaction was completed in less than 2 hours (starting material R_f=0.12, product Rf=0.41, 10% EtOAc in hexane). The reaction mixture was concentrated *in vacuo* (aspirator) and to the residue 2 N NaOH (60 mL) was added. NaOH layer was washed with CH_2Cl_2 (4x20 mL). Organic extracts were combined, washed with 2 N NaOH (20 mL), water (2x20 mL), brine (20 mL) and dried (Na_2SO_4). Solvent removal (aspirator) afforded a yellowish oil that was dissolved in 5 mL CH_2Cl_2. After filtration through a silica pad with CH_2Cl_2 rinsing and solvent evaporation (aspirator) (S)-Cbz-N-isopropylisoquinoline was obtained as a colorless oil (1.01 g, 89% yield). The crude oil (1.01 g, 2.52 mmol) was dissolved in 2:1 mixture of methanol (20 mL) and EtOAc (10 mL) and 10% Pd/C (400 mg) was added. The reaction mixture was stirred under H_2 atmosphere using H_2 balloon at RT and it was monitored by TLC analysis. The reaction was completed within 1.5 hour and Pd/C was filtered through a celite pad with MeOH rinsing. The filtrate was concentrated *in vacuo* to give a yellow oil, which was purified by flash column chromatography (150 mL of silica gel, column size 4x18 cm, eluent 20% EtOAc in hexane) and collected fractions #5 - #10 (50 mL each) gave a colorless oil (640 mg, 95%): analytical TLC on silica gel, 2:5 EtOAc/hexane, Rf= 0.5; analytical HPLC on CSP (Daicel CHIRACEL OD, 25 cm x 4.6 mm I.D.), mobile phase 0.5%EtOH:95.5%Hex:0.1%Et_2NH, flow rate 1.0 mL/min, retention time 6.3 min. (S-isomer, major) and 8.6 min. (R-isomer, minor), ratio > 99:1 (99% ee). Optical rotation: $[\alpha]_D$= -22.4 (c=0.78, $CHCl_3$); IR (neat, cm^{-1}) 3329, N-H; 1603, C-H(Ar); 300 MHz NMR ($CDCl_3$, ppm) δ 7.18-7.07 (3 H, m) 7.01-6.94 (2 H, m) 6.76 (1 H, d, J= 7.7 Hz) 6.63-6.56 (2 H, m) 5.03 (1 H, s) 3.44 (1 H, sept, J= 6.3 Hz) 3.27-3.18 (1 H, m) 3.08-2.97 (2 H, m) 2.82-2.70 (1 H, m) 1.09 (3 H, d, J= 6.3 Hz) 0.73 (3 H, d, J= 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 146.8, 137.9, 135.1, 131.1, 128.6, 128.5, 126.8, 126.7, 126.1, 125.7, 115.1, 112.1, 62.4, 43.7, 43.1, 29.8, 23.0, 22.4.

(R)-1-(2-Dimethylsulfamoylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (12).

To a solution of (R)-Cbz-diamine **9a** (1.11 g, 3.10 mmol) in dry pyridine (20 mL) was added N,N-dimethylsulfamoyl chloride (Aldrich, 1.7 mL, 15.8 mmol) as a neat solution via syringe and stirred under N_2 at 90°C for 6 hours. The reaction mixture was poured into 2N HCl (250 mL) and extracted with $CHCl_3$ (5x20 mL). Organic extracts were combined, washed with water (2x20 mL).

brine (20 mL) and dried (Na_2SO_4). After filtration and solvent removal (aspirator) the residue was purified by flash column chromatography (200 mL of silica gel, column size 4x19 cm, eluent CH_2Cl_2) and collected fractions #8 - #14 (50 mL each, R_f=0.32, 40% EtOAc in Hex) gave a colorless oil (510 mg, 35%). The crude oil (510 mg, 1.18 mmol) was dissolved in EtOAc (10 mL) and 10% Pd/C (250 mg) was added. The mixture was stirred under H_2 atmosphere at RT and it was monitored by TLC analysis. The reaction was completed within 3 hour and filtration through a celite pad with EtOAc rinsing, followed with solvent removal (aspirator) afforded a white solid (234 mg, 60%); analytical TLC on silica gel, 1:1 EtOAc/hexane, Rf= 0.45; analytical HPLC on CSP (Daicel CHIRACEL OD, 25 cm x 4.6 mm I.D.), mobile phase 5%EtOH:95%Hex:0.1%Et_2NH, flow rate 1.0 mL/min, retention time 21.7 min. (S-isomer, minor) and 29.4 min. (R-isomer, major), ratio > 99:1 (99% ee). Pure material was obtained by crystallization from ethyl acetate/hexane, mp 123-124 ^{0}C, colorless needles. Optical rotation: $[\alpha]_D$= +60.2 (c=0.67, $CHCl_3$). No parent ion for $C_{17}H_{21}N_3O_2S_1$; M-45, 286.0786, error = 3 ppm; base peak = 221 amu; IR (KBr, cm^{-1}) 3314, N-H; 1139, SO_2; 300 MHz NMR ($CDCl_3$, ppm) δ 11.5-9.5 (1 H, br s) 7.54 (1 H, dd, J= 8.1, 1.2 Hz) 7.29-7.20 (2 H, m) 7.14-7.08 (2 H, m) 7.04-6.97 (2 H, m) 6.71 (1 H, d, J= 8.1 Hz) 5.13 (1 H, s) 3.38 (1 H, ddd, J= 10.8, 5.1, 2.3 Hz) 3.28-3.17 (1 H, m) 3.08 (1 H, td, J= 10.8, 3.5 Hz) 2.82 (1 H, br d, J= 15.9 Hz) 2.27 (6 H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 138.1, 136.5, 135.2, 131.1, 129.2, 129.3, 129.0, 127.1, 126.2, 126.9, 122.0, 118.3, 62.7, 43.2, 37.4, 29.6.



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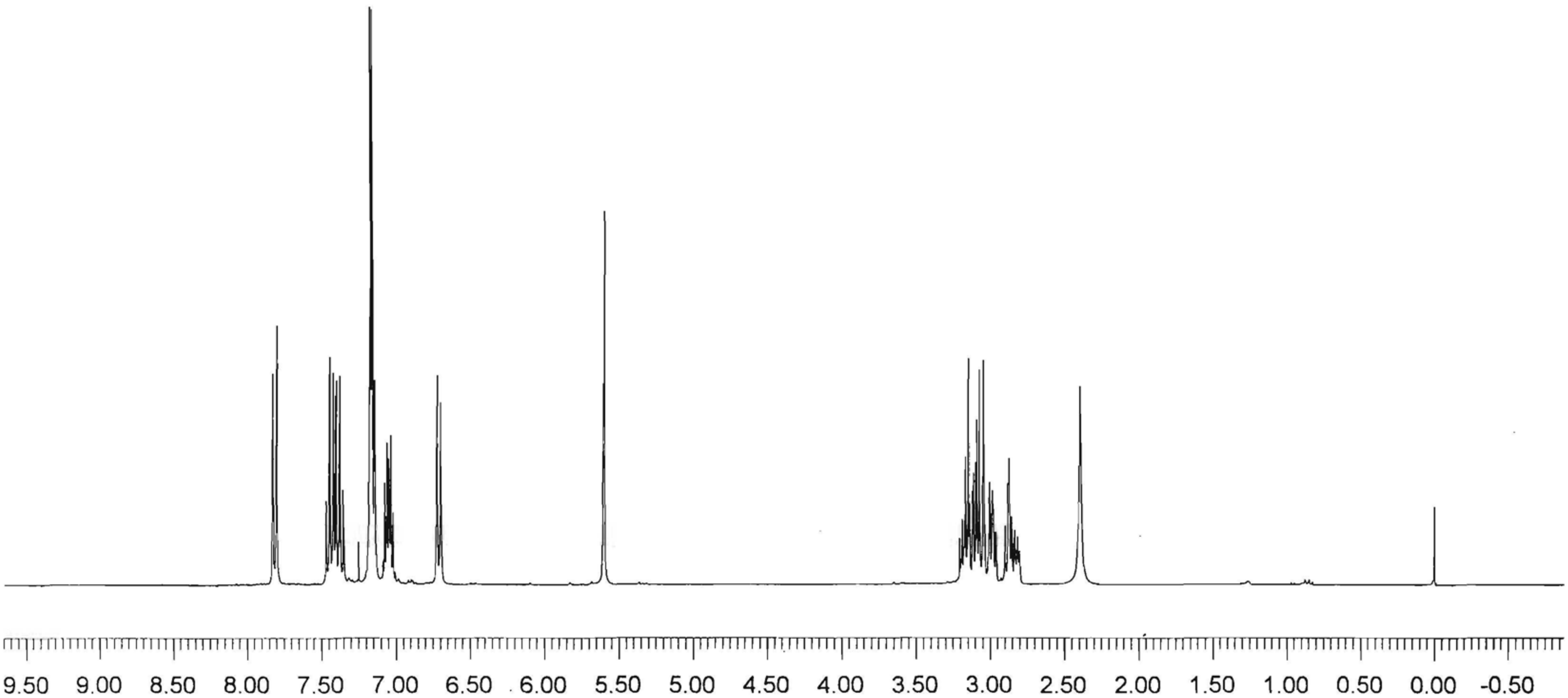

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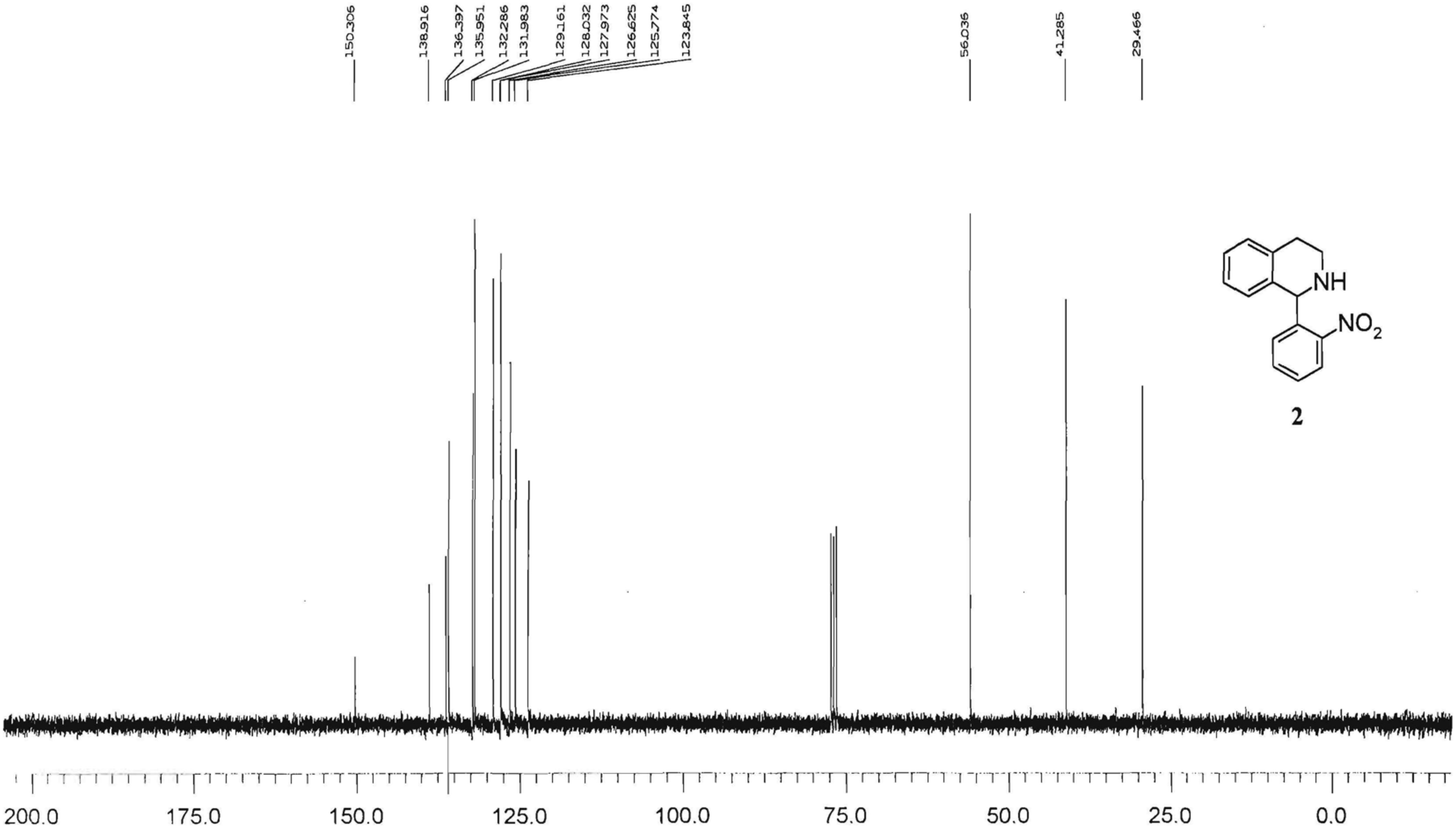

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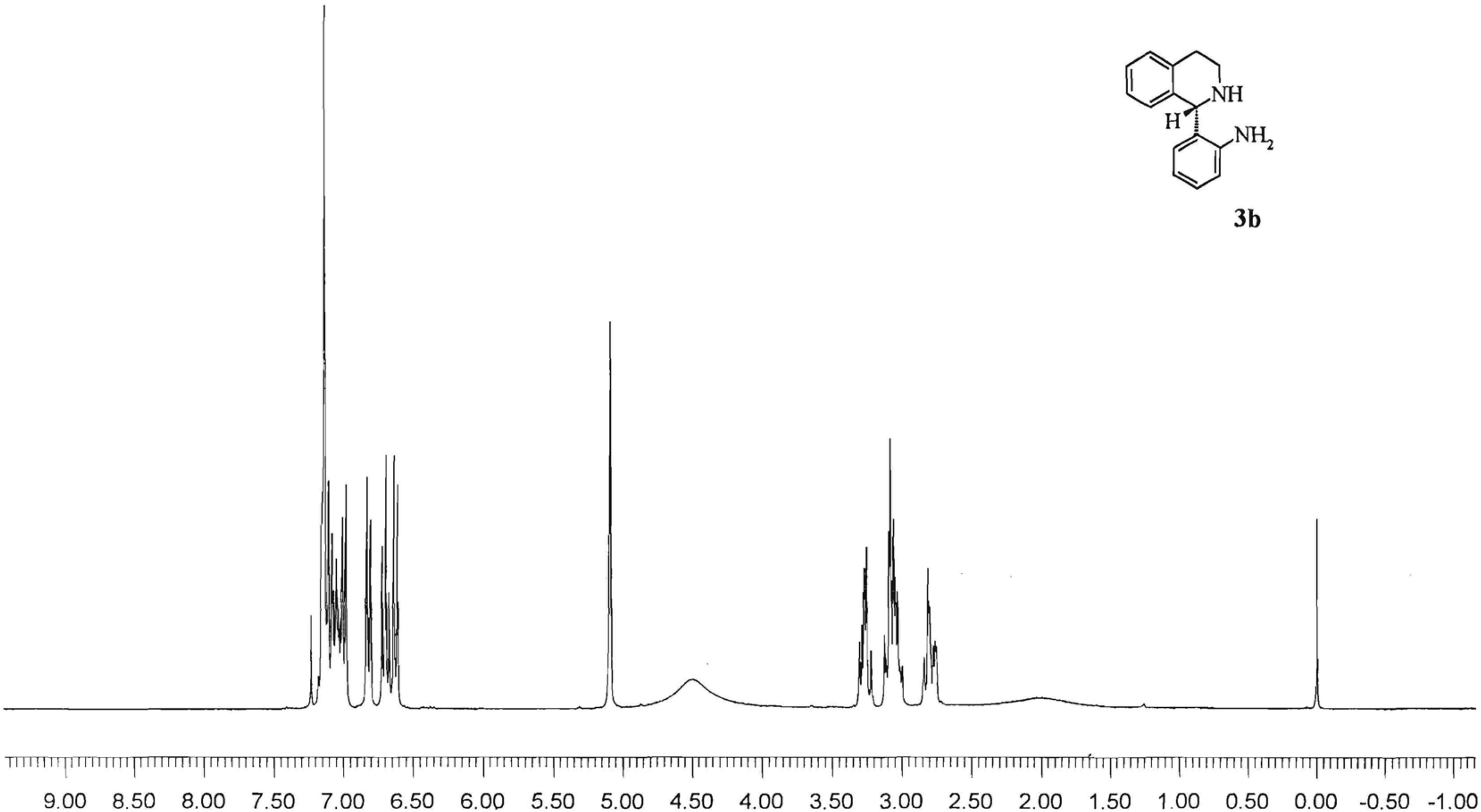

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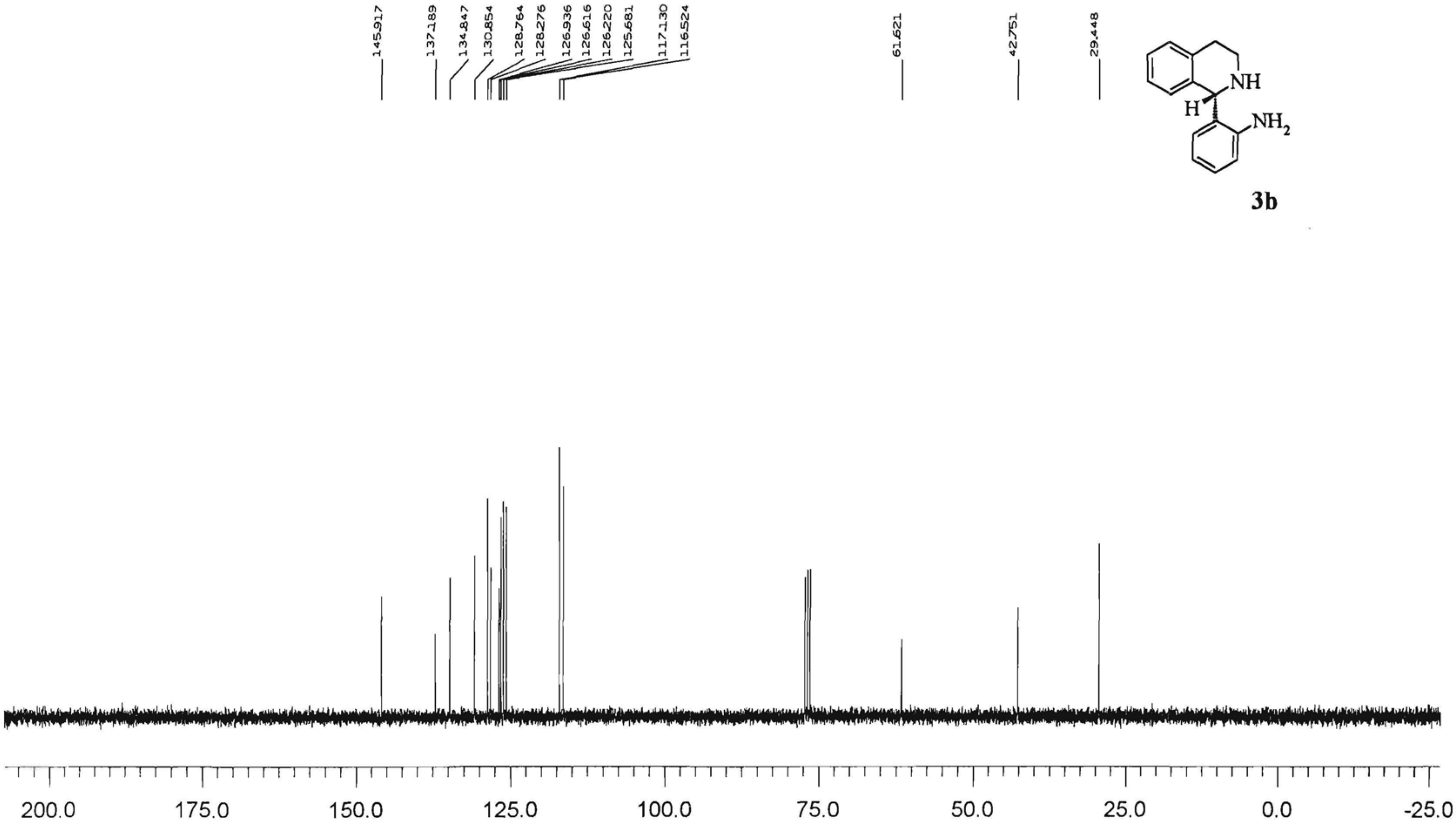

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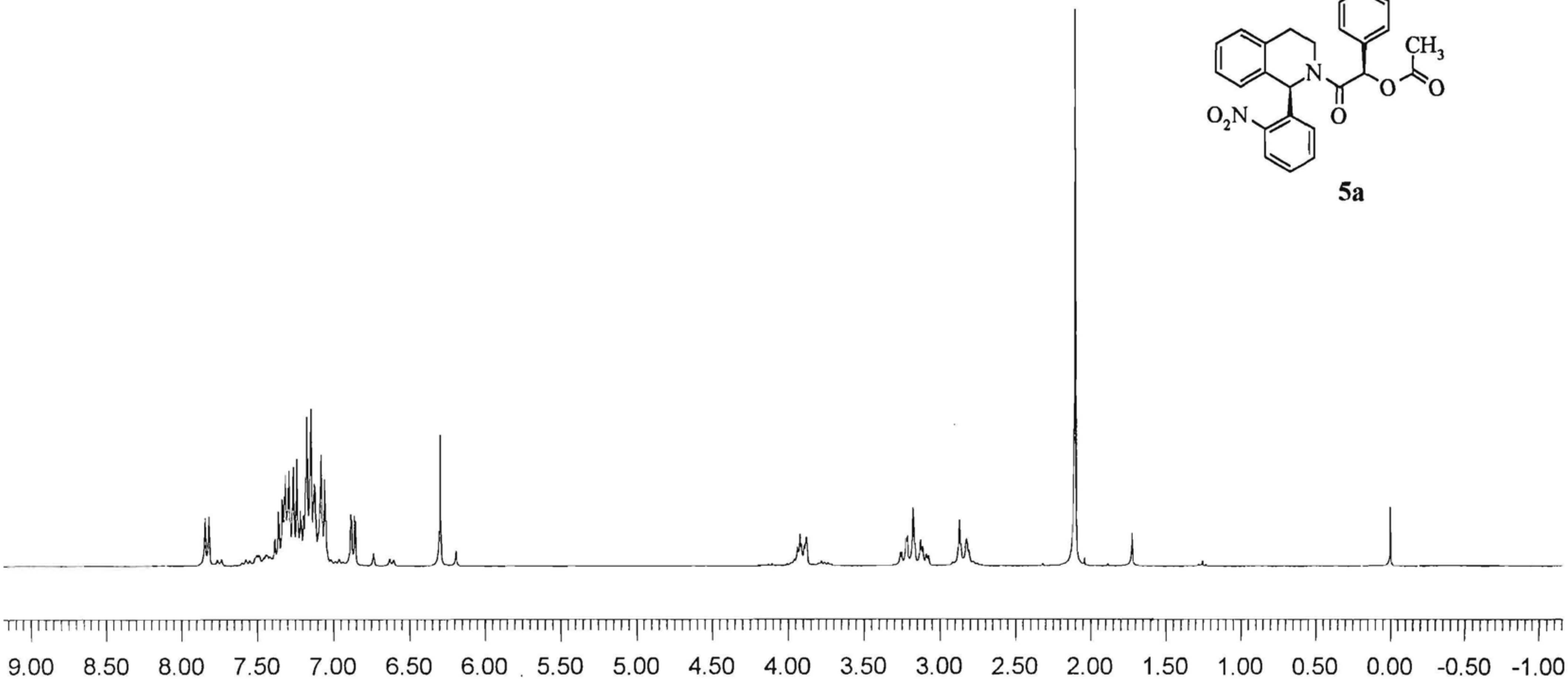

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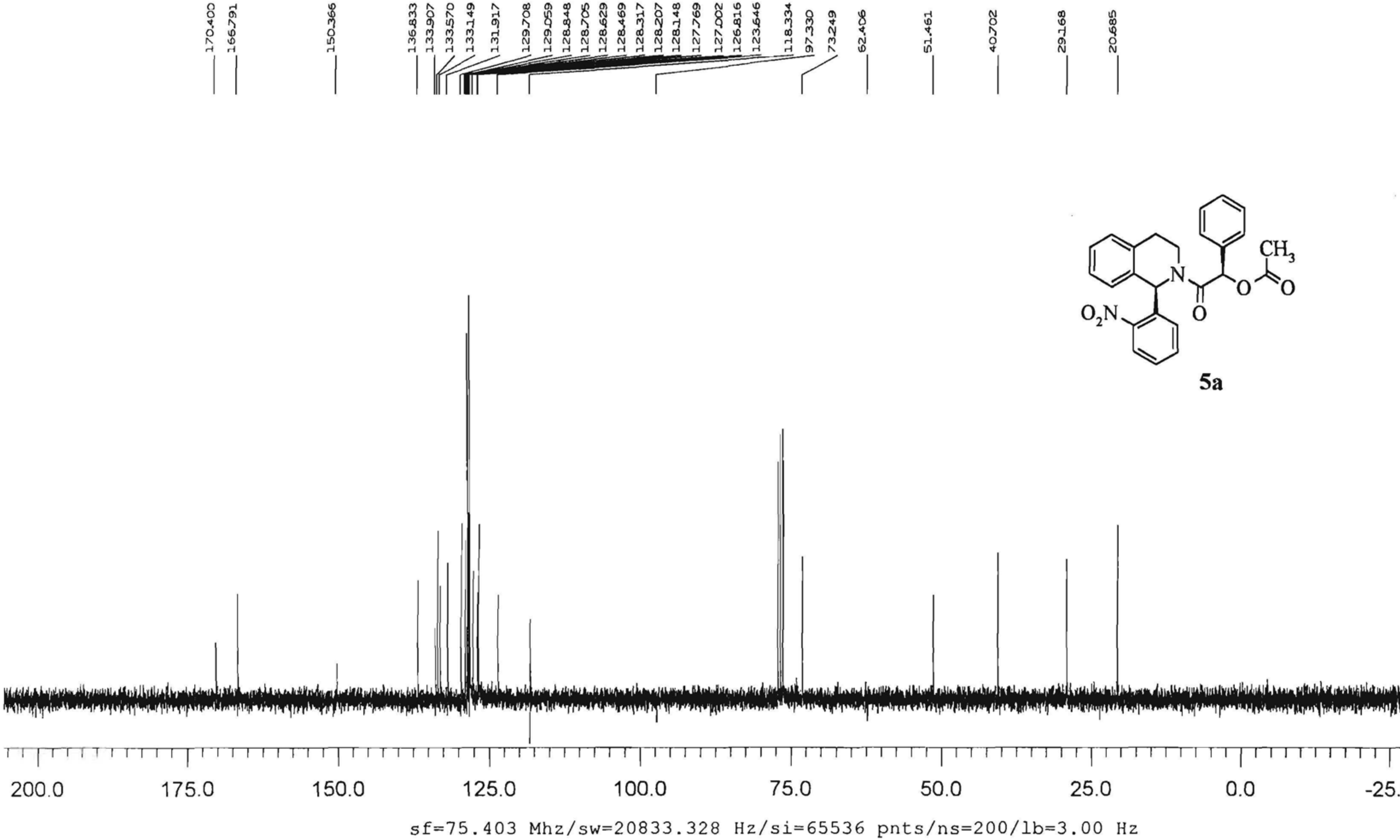

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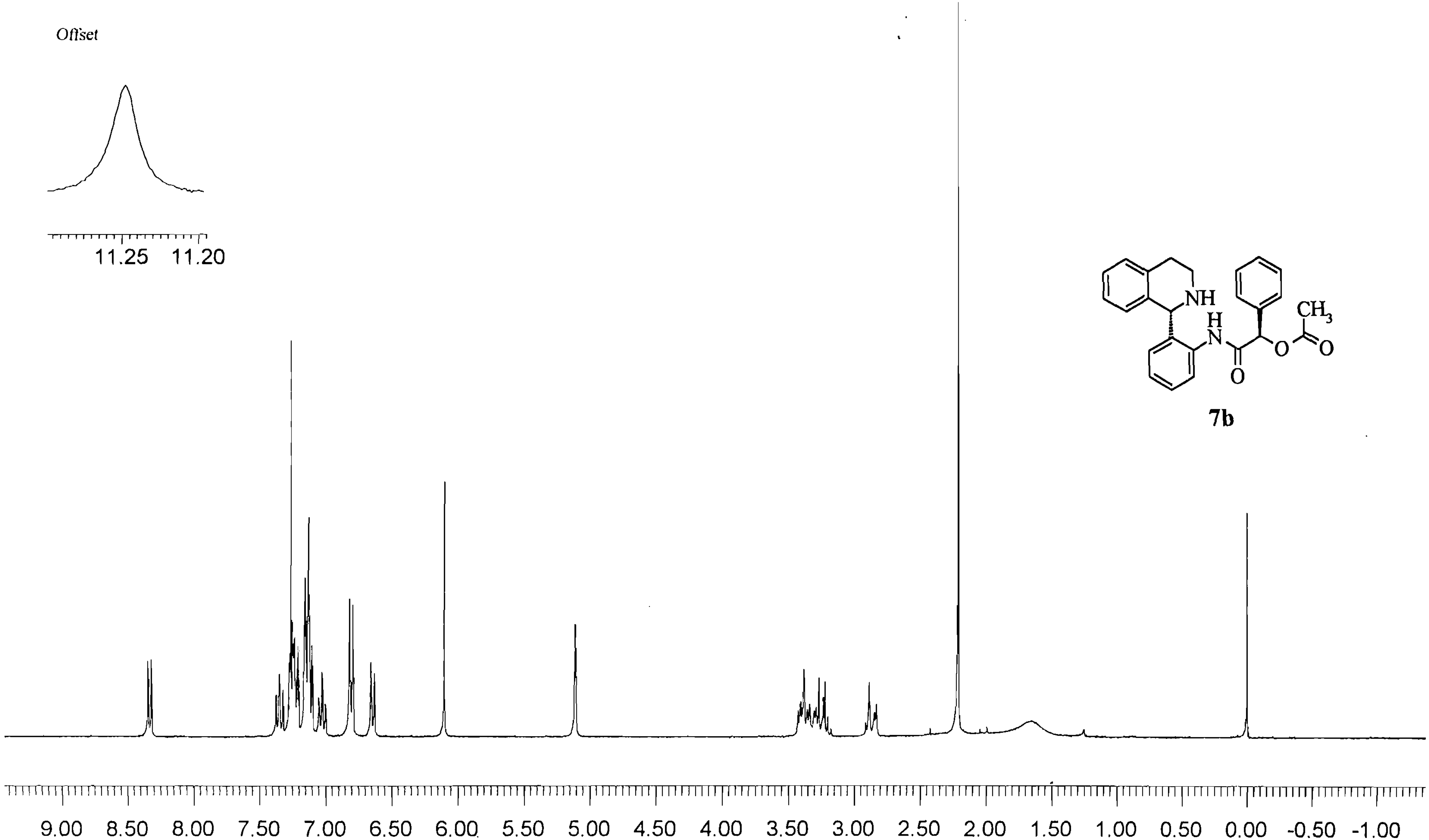

7b

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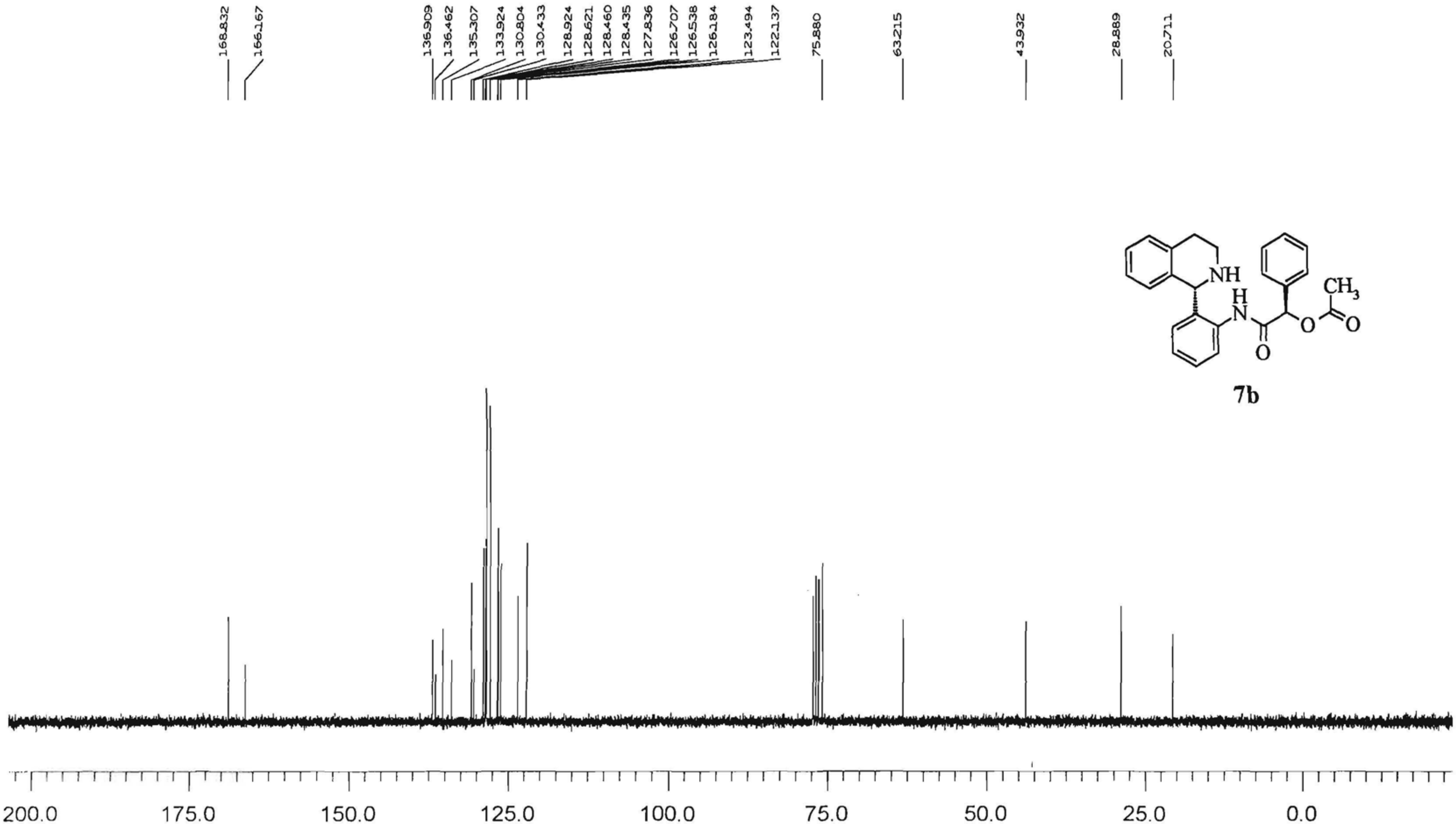

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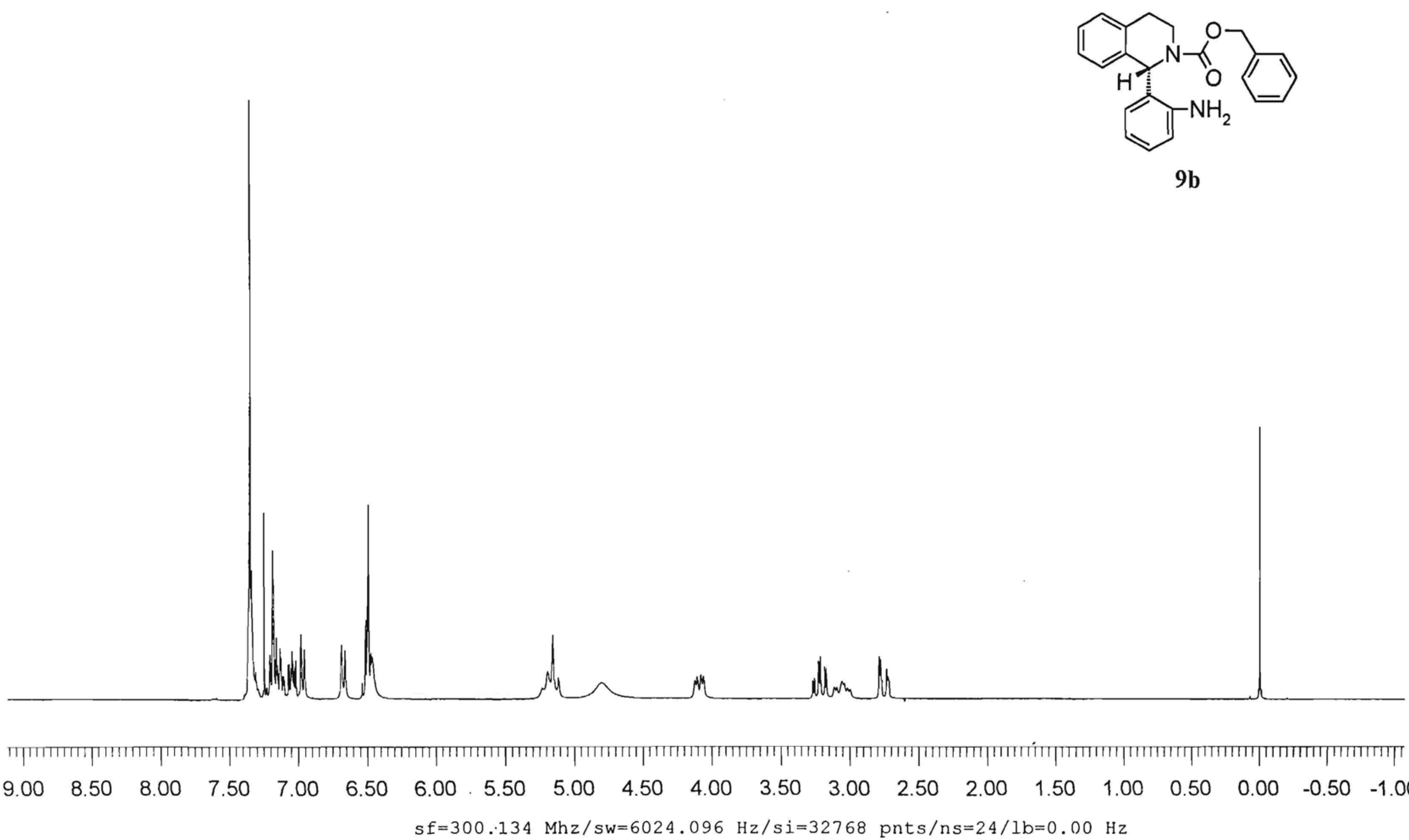
9b
9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00 -0.50 -1.00
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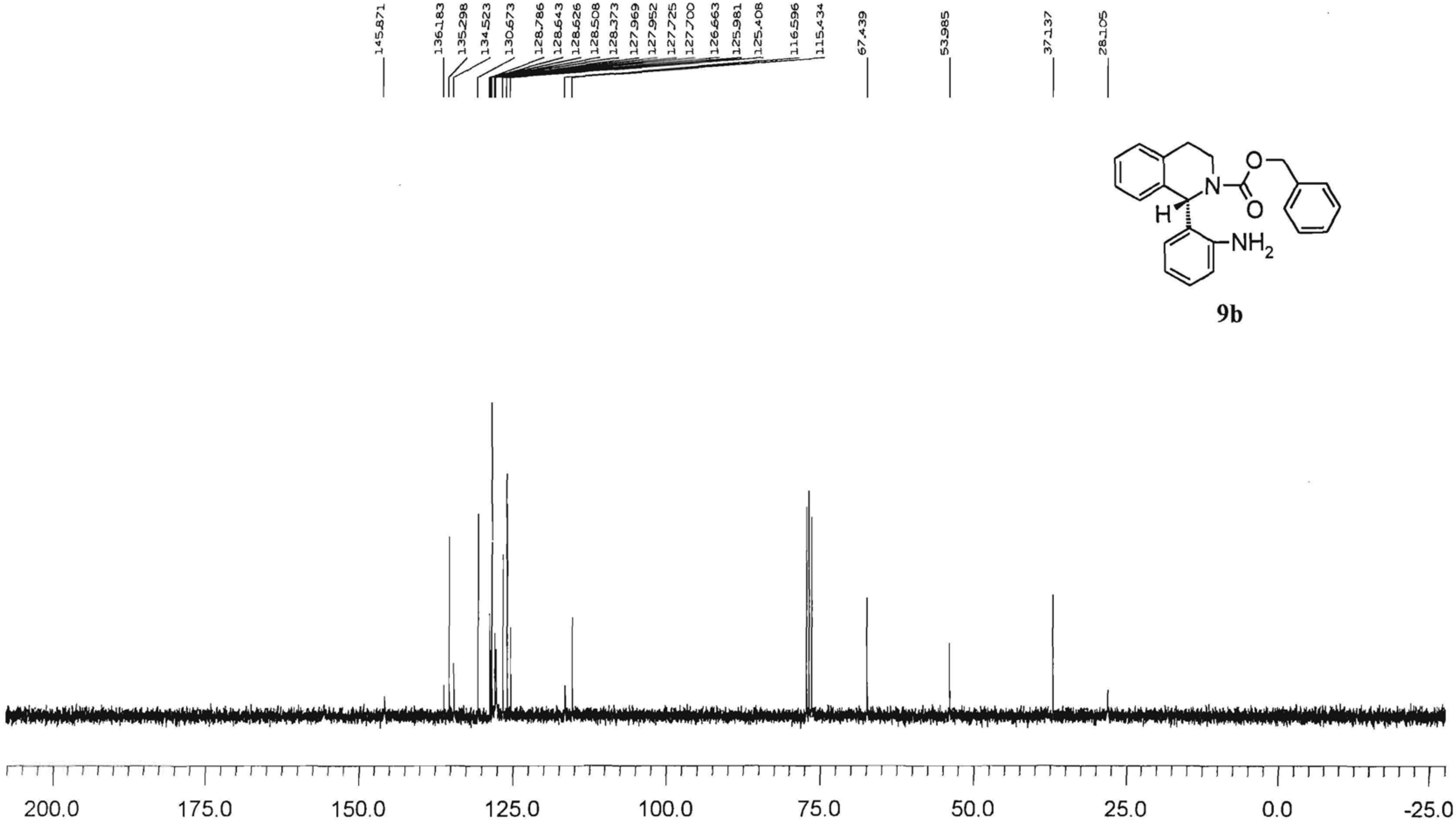

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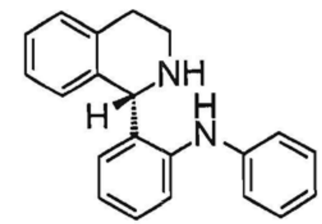
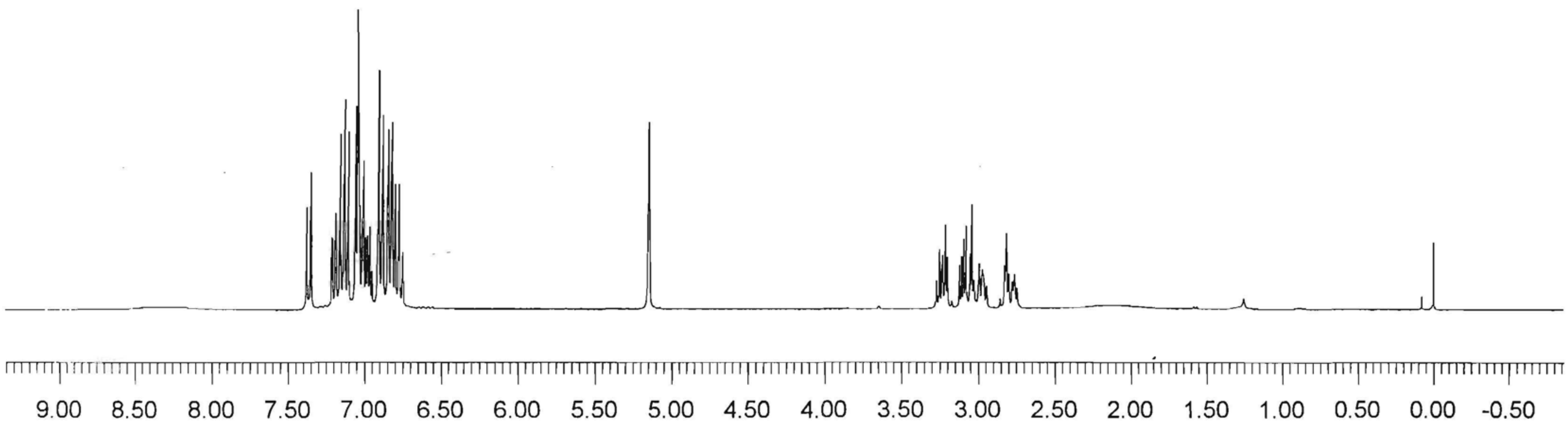


10



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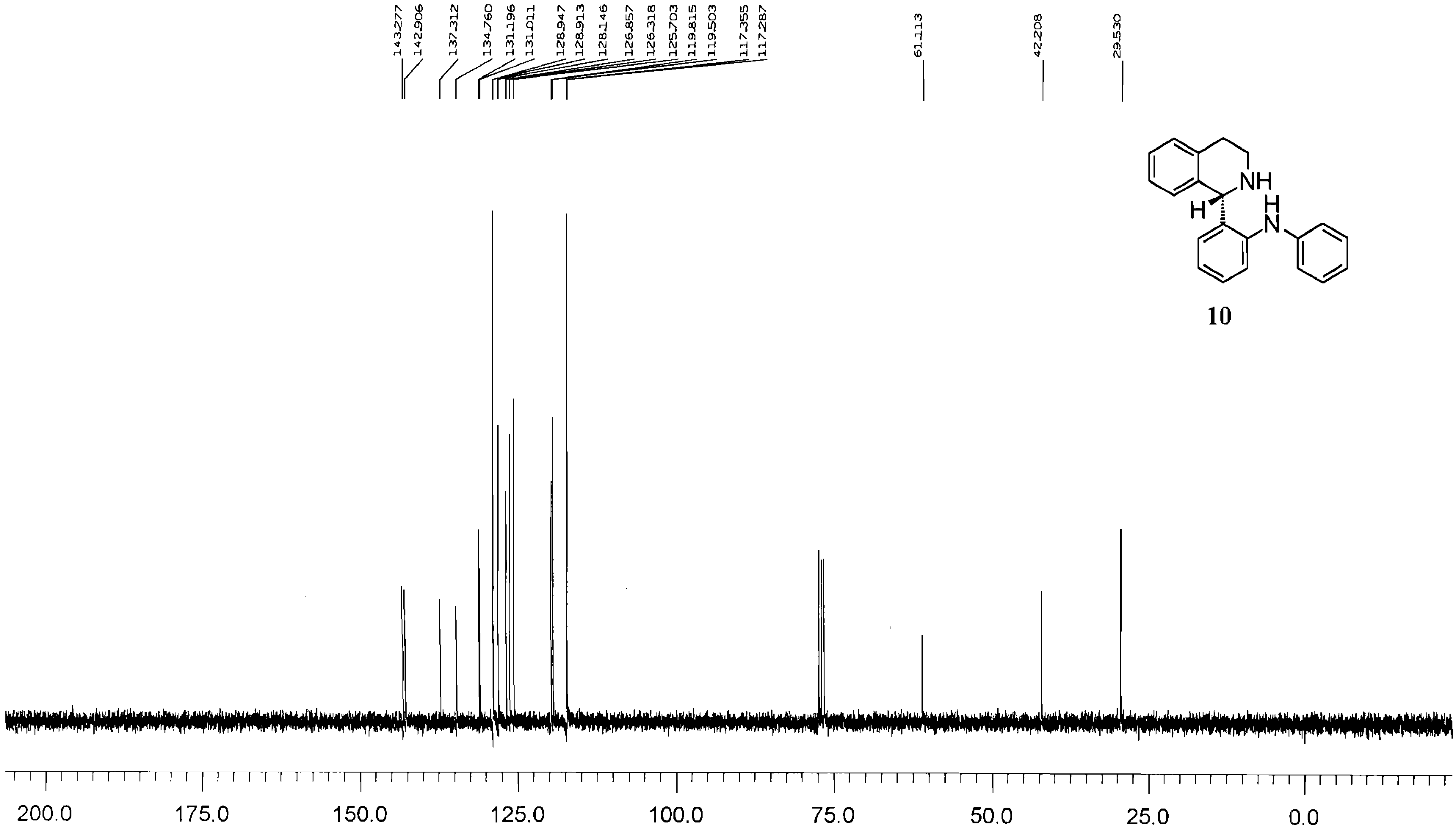

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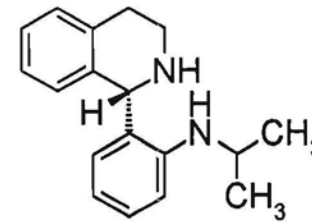

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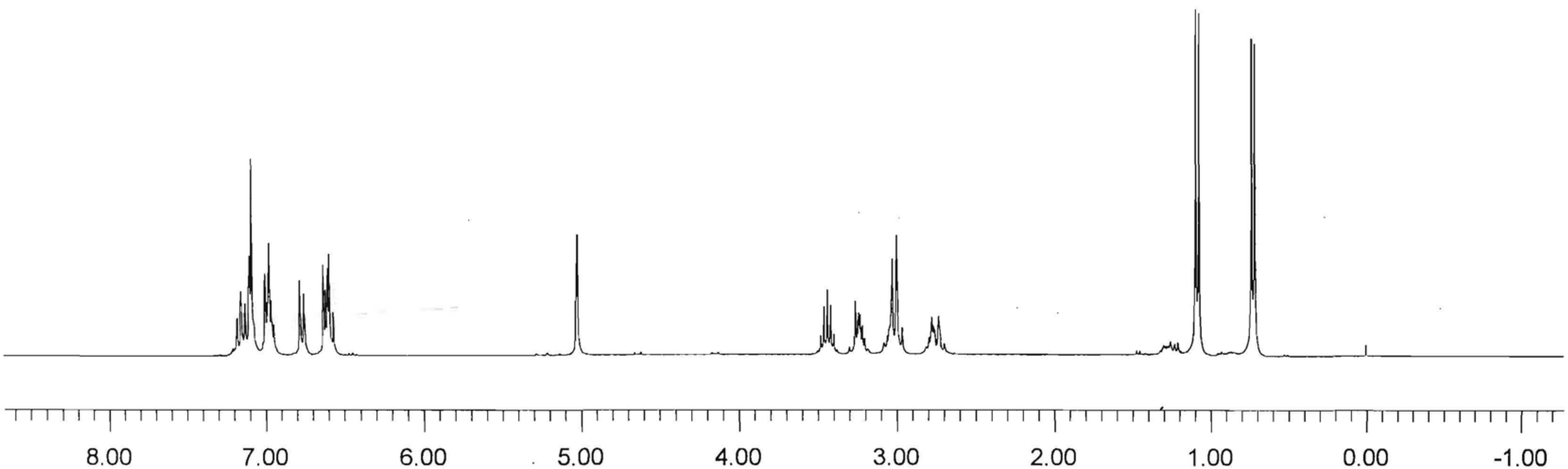

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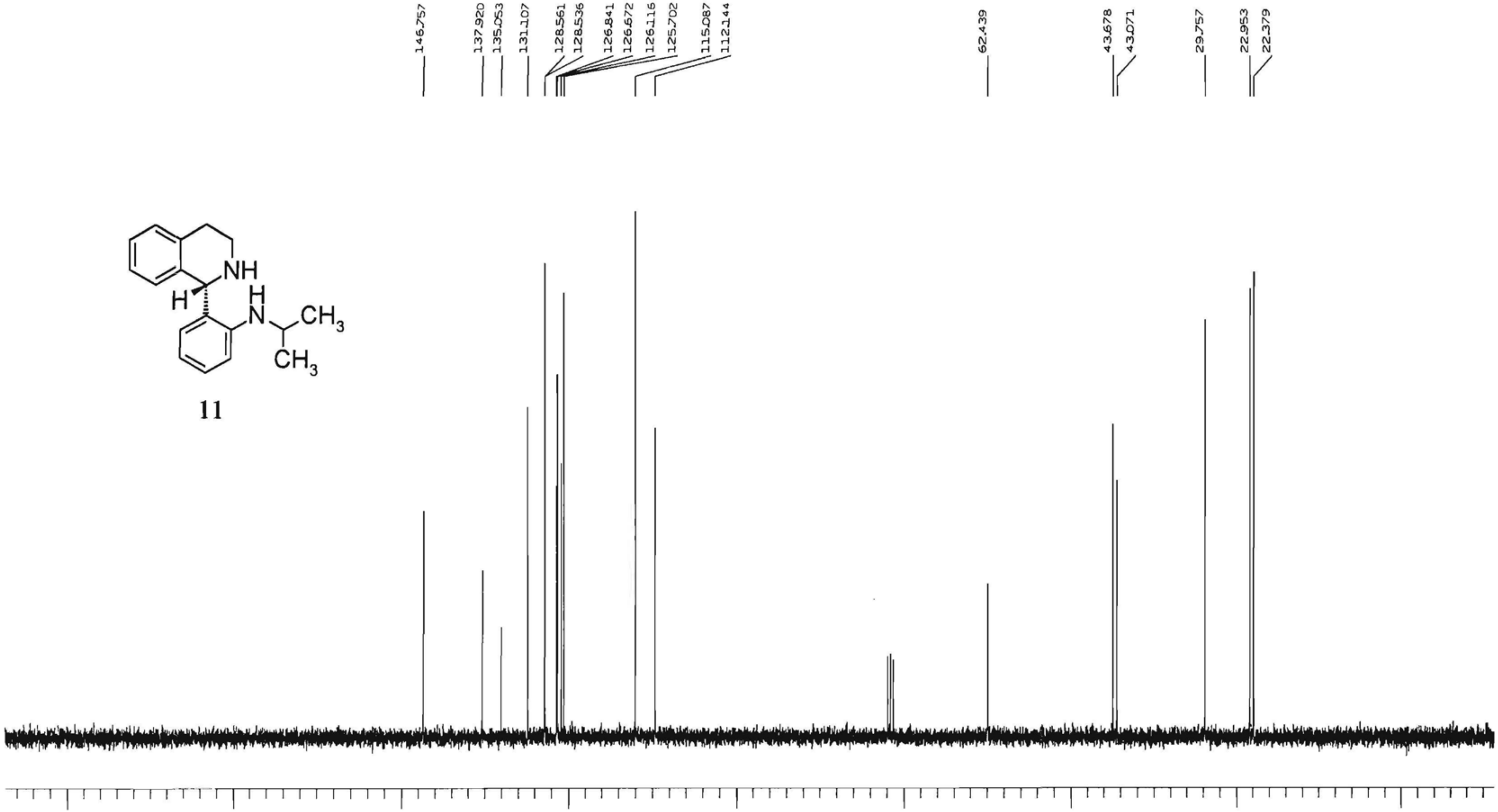

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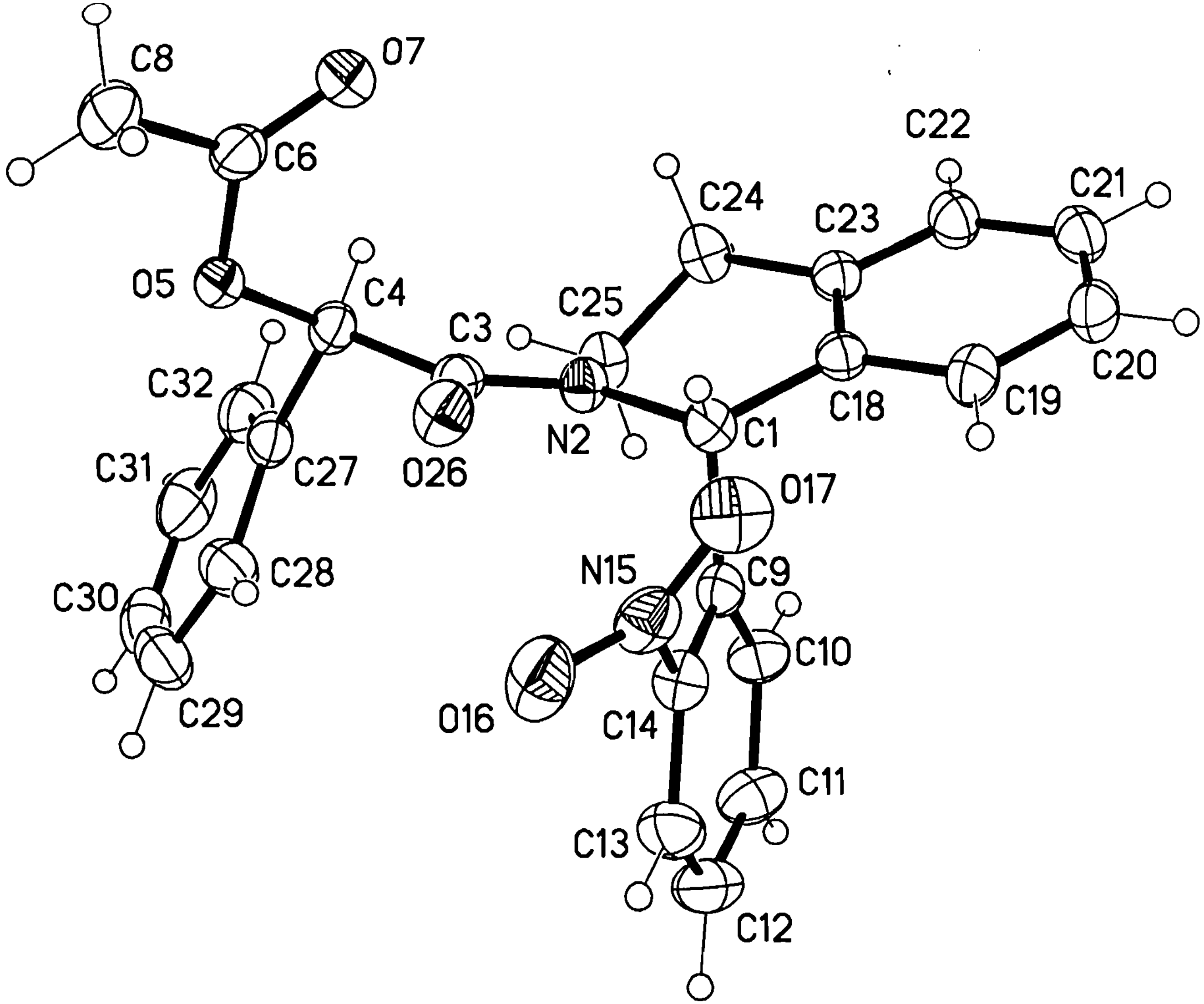

C8
O7
C6
O5
C4
C3
C25
C24
C23
C22
C21
C20
C19
C18
C1
N2
O26
C32
C31
C27
C28
C30
C29
O17
N15
C9
C10
O16
C14
C11
C13
C12

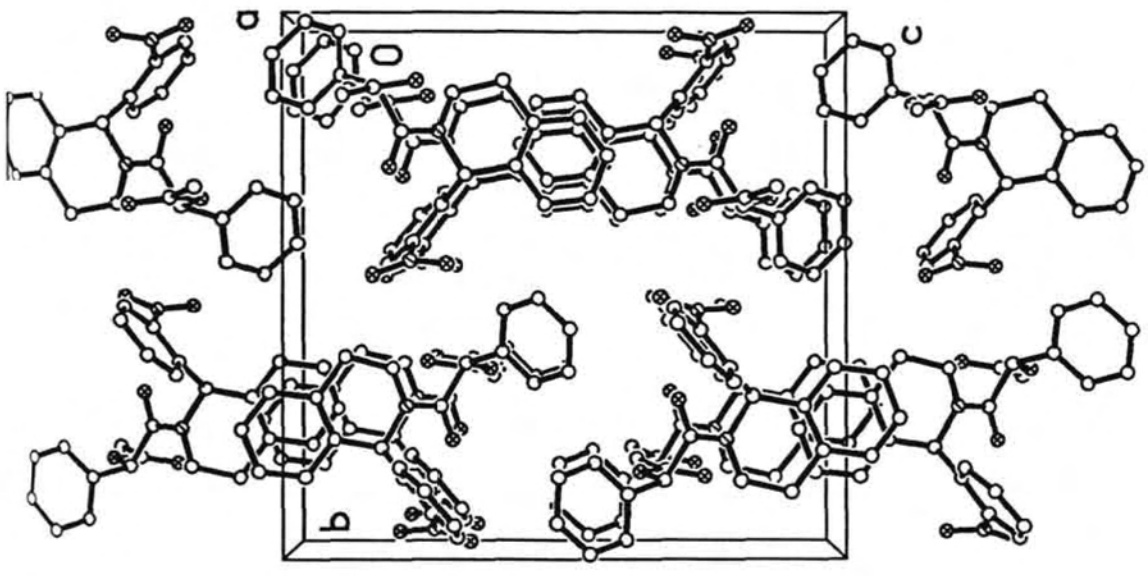

a
0
b
c

Table 1. Crystal data and structure refinement for 1.

Identification code	es01
Empirical formula	$C_{25}H_{22}N_2O_5$
Crystal color, habit	colorless transparent prism
Crystal size	0.45 x 0.45 x 0.35 mm
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.1269(2) Å α = 90°
	b = 16.2685(2) Å β = 90°
	c = 16.7232(3) Å γ = 90°
Volume	2211.02(7) $Å^3$
Peaks to determine cell	7345
θ range of cell peaks	3.0 to 25.5°
Temperature	133(2) K
Wavelength	0.71073 Å
Z	4
Formula weight	430.45
Density (calculated)	1.293 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	904

Data Collection

Diffractometer	Siemens P4/CCD
θ range for data collection	1.75 to 25.96°
Index ranges	$-9 \leq h \leq 5$, $-19 \leq k \leq 14$, $-20 \leq \ell \leq 20$
Scan Type	phi scan frames
Scan Time	30 sec / frame
Scan Range	0.3 ° in phi
Detector-to-sample distance	5.700 cm
Standard peaks	250 peaks remeasured at end showed a maximum variation of 0.52 %.
Reflections collected	8107
Independent reflections	3810 (R_{int} = 0.0231)

Solution and Refinement

Solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Hydrogen atoms	riding
Weighting scheme	

$$w = 1/[\sigma^2(F_o^2) + (0.0278P)^2 + 1.0223P]$$

$$\text{where } P = [F_o^2 + 2F_c^2]/3$$

Data / restraints / parameters	3808 / 0 / 290
Goodness-of-fit on F^2	1.193
Final R indices [$I>2\sigma(I)$]	R1 = 0.0357, wR2 = 0.0819
R indices (all data)	R1 = 0.0422, wR2 = 0.0932
Observed data [$I>2\sigma(I)$]	3543
Absolute structure parameter	-0.9(11) (not reliable)
Extinction coefficient	0.0133(9)
Largest diff. peak and hole	0.166 and -0.186 eÅ^{-3}
Largest and mean Δ / esd	-0.001 and 0.000

References

Data Collection:

SMART Software Reference Manual (1994). Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

Data Reduction:

SAINT Version 4 Software Reference Manual (1995). Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

Structure Solution, Refinement and Graphics:

G. M. Sheldrick (1994). SHELXTL Version 5 Reference Manual. Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

Neutral atom scattering factors were taken from:

International Tables for Crystallography, Vol C, Tables 6.1.1.4, 4.2.6.8, and 4.2.4.2, Kluwer: Boston.

Method of Absolute Structure Determination:

H. D. Flack (1983). Acta Cryst. A39, 876-881.

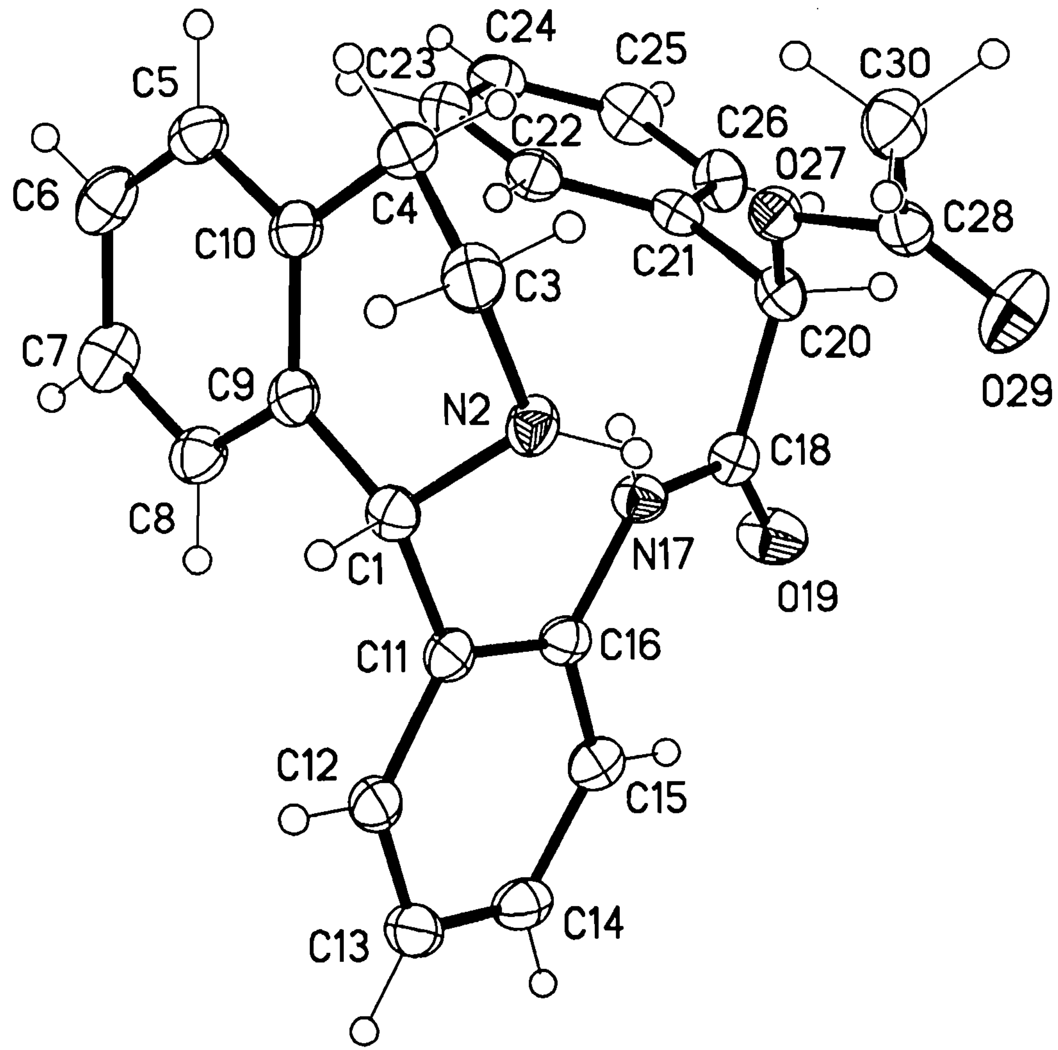
Acknowledgement

Please acknowledge funds from NSF(grant CHE-9310428) and from the the University of Wisconsin for the purchase of the x-ray instrument and computers.

This structure was determined by Timothy K. Firman.

Miscellaneous

The displacement ellipsoids were drawn at the 50% probability level.



C24
C23
C25
C30
C5
C22
C26
C6
O27
C4
C28
C10
C21
C3
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C12
C15
C14
C13

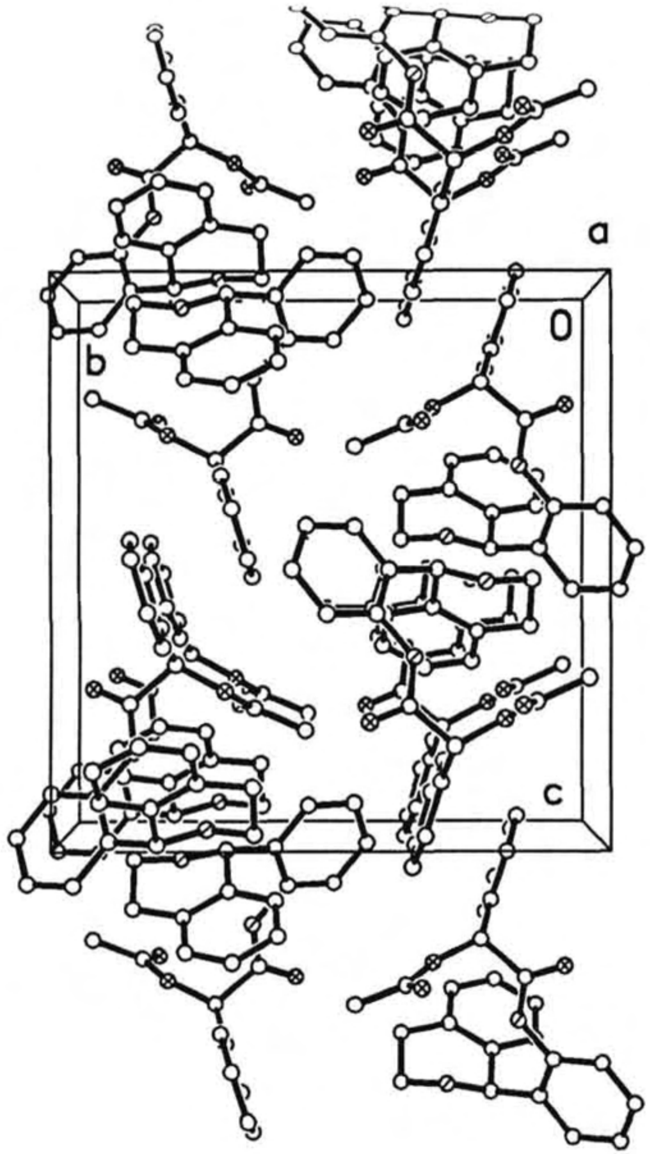

a
0
b
c

Table 1. Crystal data and structure refinement for 1.

Identification code	es02
Empirical formula	$C_{25}H_{24}N_2O_3$
Crystal color, habit	colorless transparent
Crystal size	0.54 x 0.54 x 0.50 mm
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 10.1689(2) Å α = 90°
	b = 14.0652(4) Å β = 90°
	c = 14.4694(4) Å γ = 90°
Volume	2069.52(9) $Å^3$
Peaks to determine cell	741
θ range of cell peaks	3.0 to 25.0°
Temperature	133(2) K
Wavelength	0.71073 Å
Z	4
Formula weight	400.46
Density (calculated)	1.285 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	848

Data Collection

Diffractometer	Siemens P4/CCD
θ range for data collection	2.02 to 25.84°
Index ranges	$-12 \leq h \leq 6$, $-17 \leq k \leq 15$, $-16 \leq \ell \leq 12$
Scan Type	phi scan frames
Scan Time	10 sec / frame
Scan Range	0.3 $^{\circ}$ in phi
Detector-to-sample distance	5.700 cm
Standard peaks	138 peaks remeasured at end showed a maximum variation of -0.52 %.
Reflections collected	7442
Independent reflections	3422 (R_{int} = 0.0172)

Solution and Refinement

Solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Hydrogen atoms	riding
Weighting scheme	

$$w = 1/[\sigma^2(F_o^2) + (0.0372P)^2 + 0.5777P]$$

$$\text{where } P = [F_o^2 + 2F_c^2]/3$$

Data / restraints / parameters	3422 / 0 / 272
Goodness-of-fit on F^2	1.081
Final R indices [$I>2\sigma(I)$]	R1 = 0.0296, wR2 = 0.0772
R indices (all data)	R1 = 0.0300, wR2 = 0.0776
Observed data [$I>2\sigma(I)$]	3385
Absolute structure parameter	0.1(10)
Extinction coefficient	0.0066(10)
Largest diff. peak and hole	0.378 and -0.384 eÅ^{-3}
Largest and mean Δ / esd	0.000 and 0.000

References

Data Collection:

SMART Software Reference Manual (1994). Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

Data Reduction:

SAINT Version 4 Software Reference Manual (1995). Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

Structure Solution, Refinement and Graphics:

G. M. Sheldrick (1994). SHELXTL Version 5 Reference Manual. Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

Neutral atom scattering factors were taken from:

International Tables for Crystallography, Vol C, Tables 6.1.1.4, 4.2.6.8, and 4.2.4.2, Kluwer: Boston.

Method of Absolute Structure Determination:

H. D. Flack (1983). Acta Cryst. A39, 876-881.

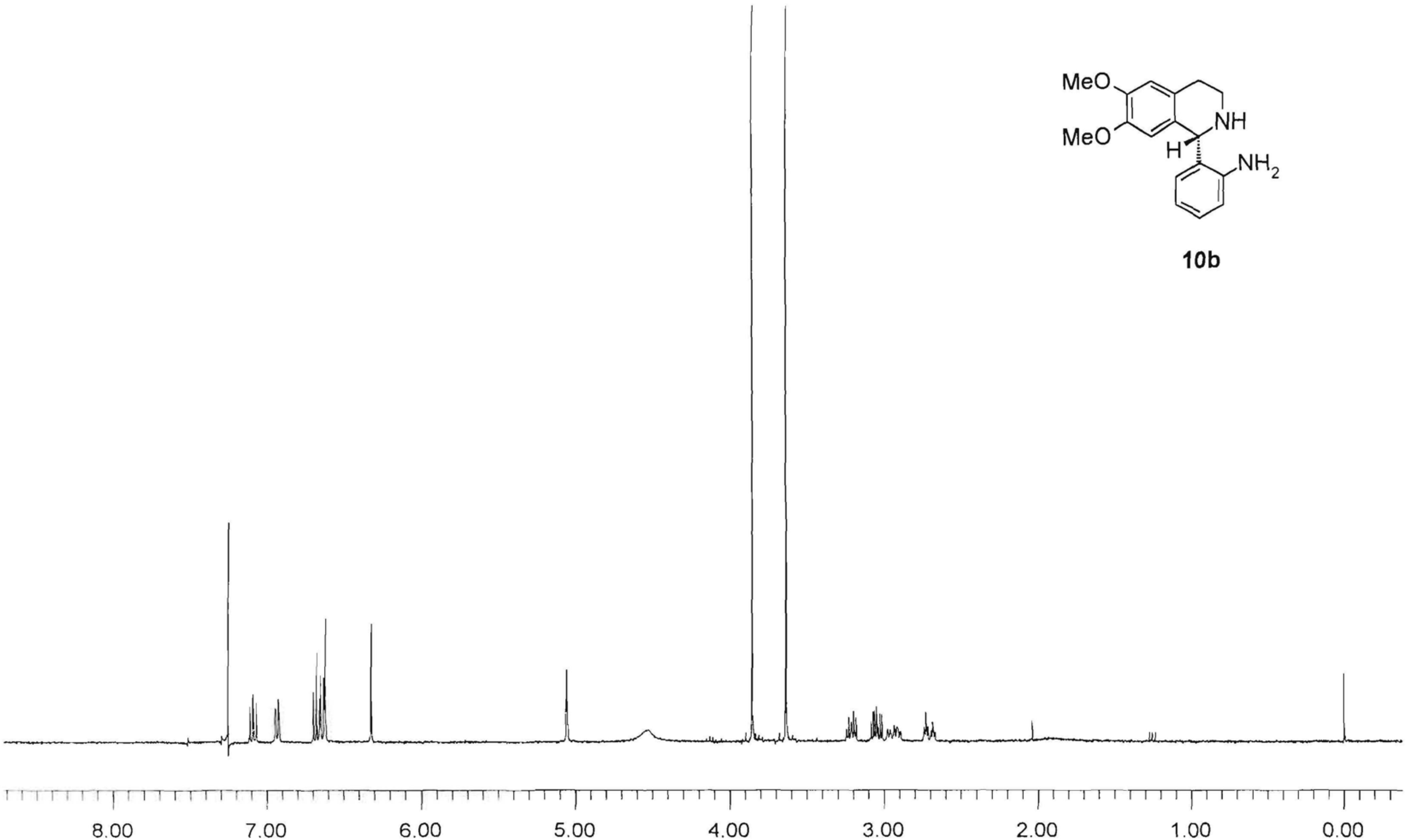
Acknowledgement

Please acknowledge funds from NSF(grant CHE-9310428) and from the the University of Wisconsin for the purchase of the x-ray instrument and computers.

Miscellaneous

The displacement ellipsoids were drawn at the 50% probability level.

Appendix 3



10b

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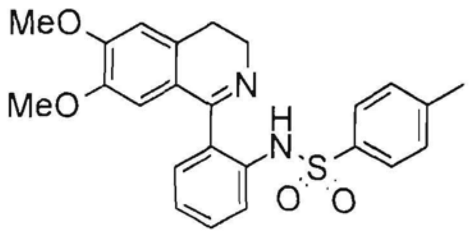

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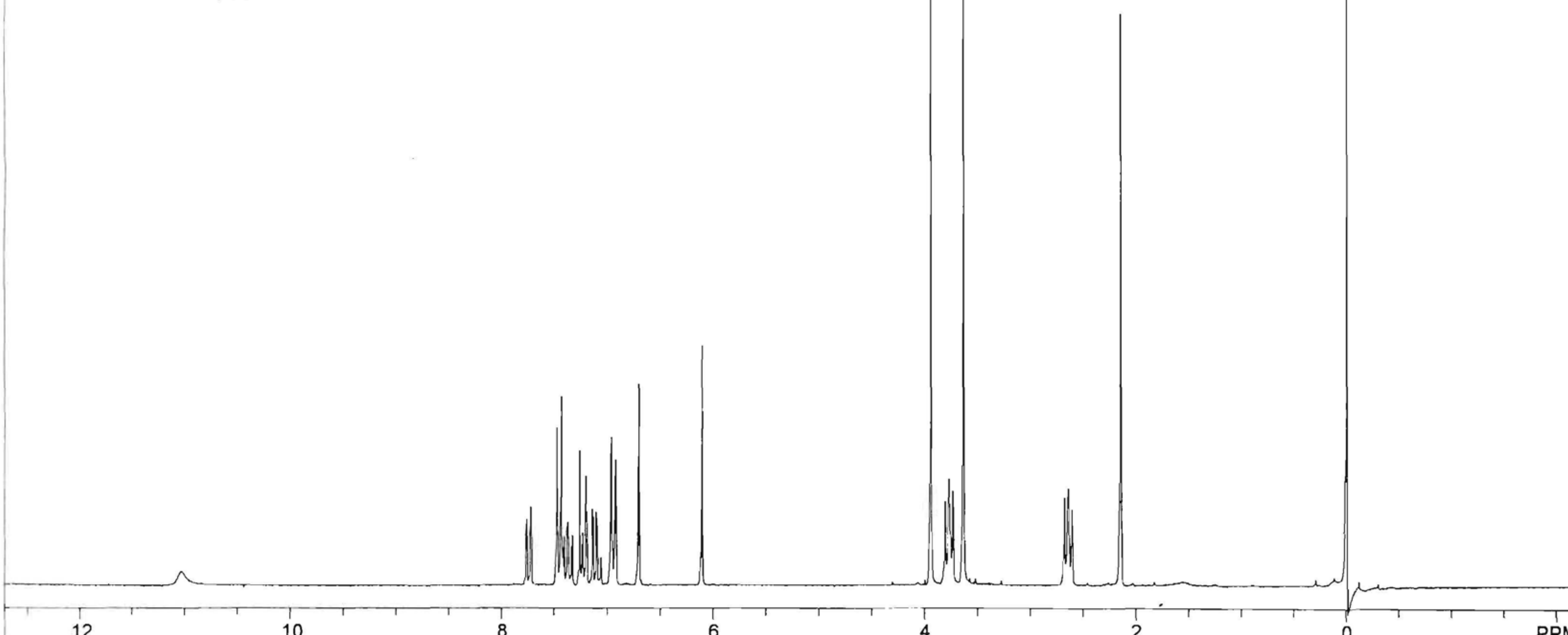

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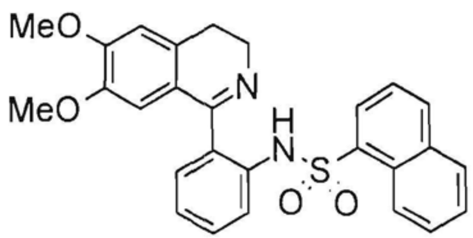
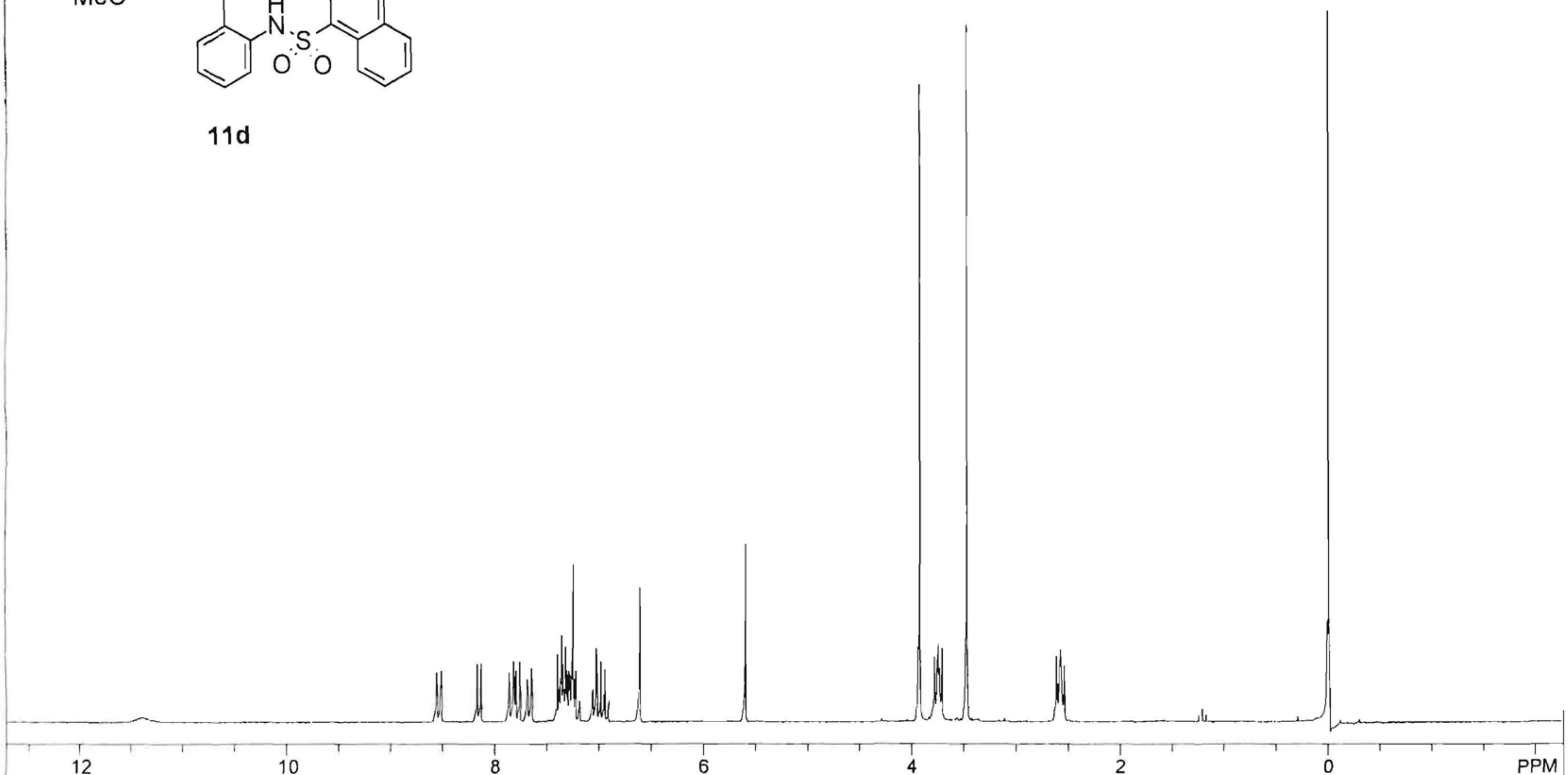


11d



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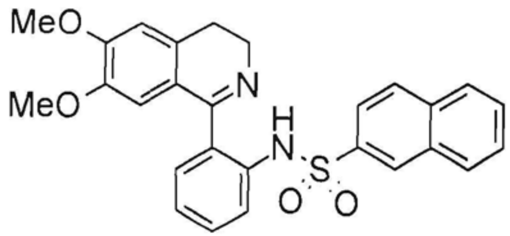
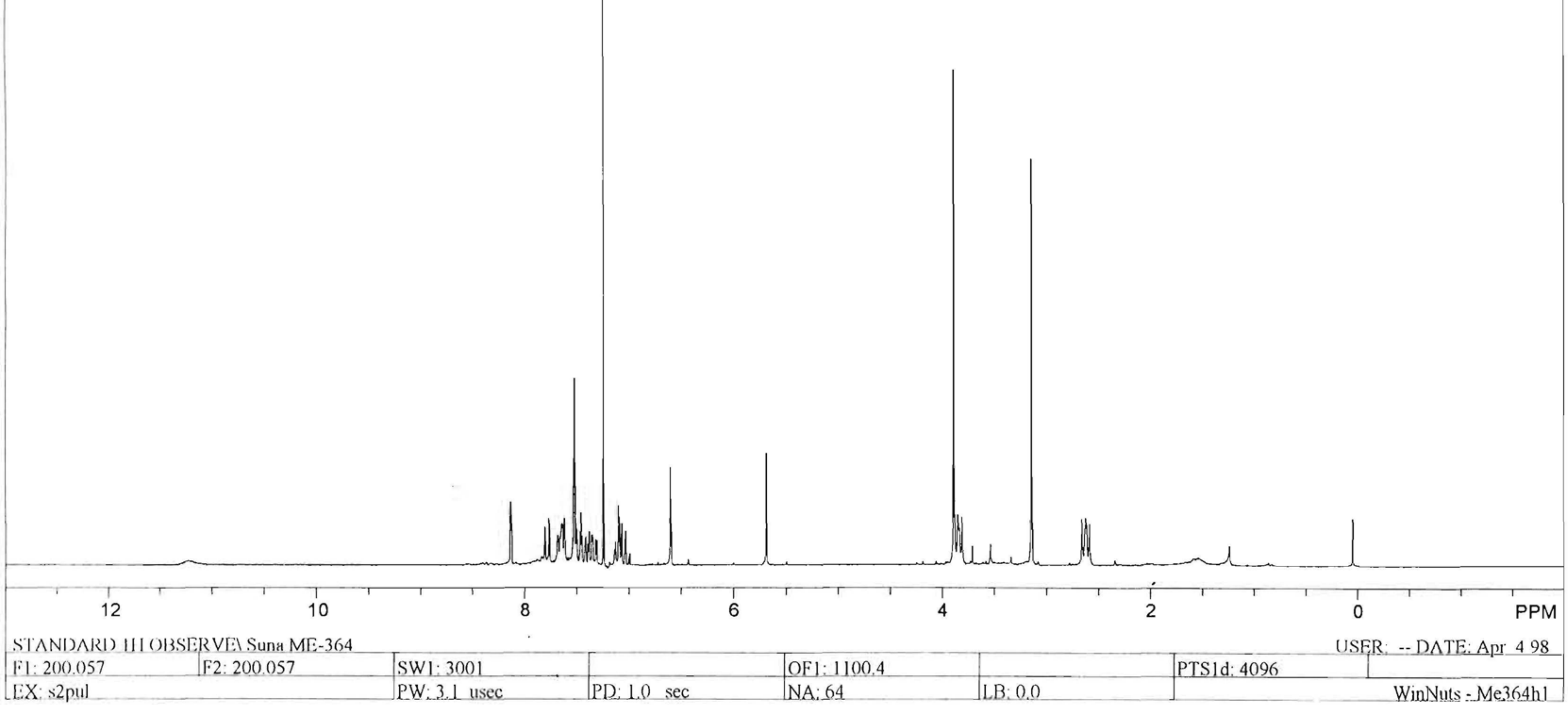


11e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4
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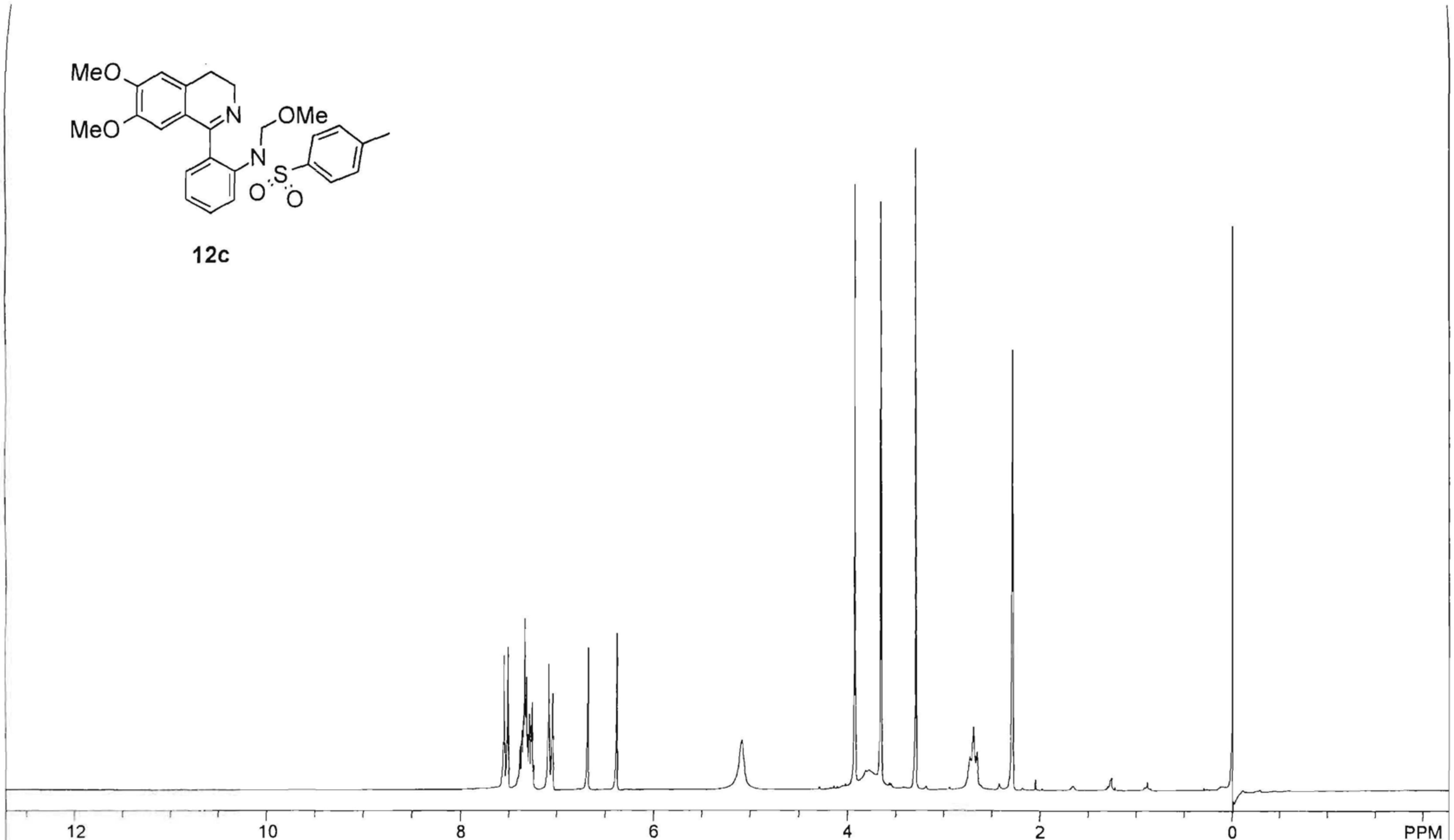

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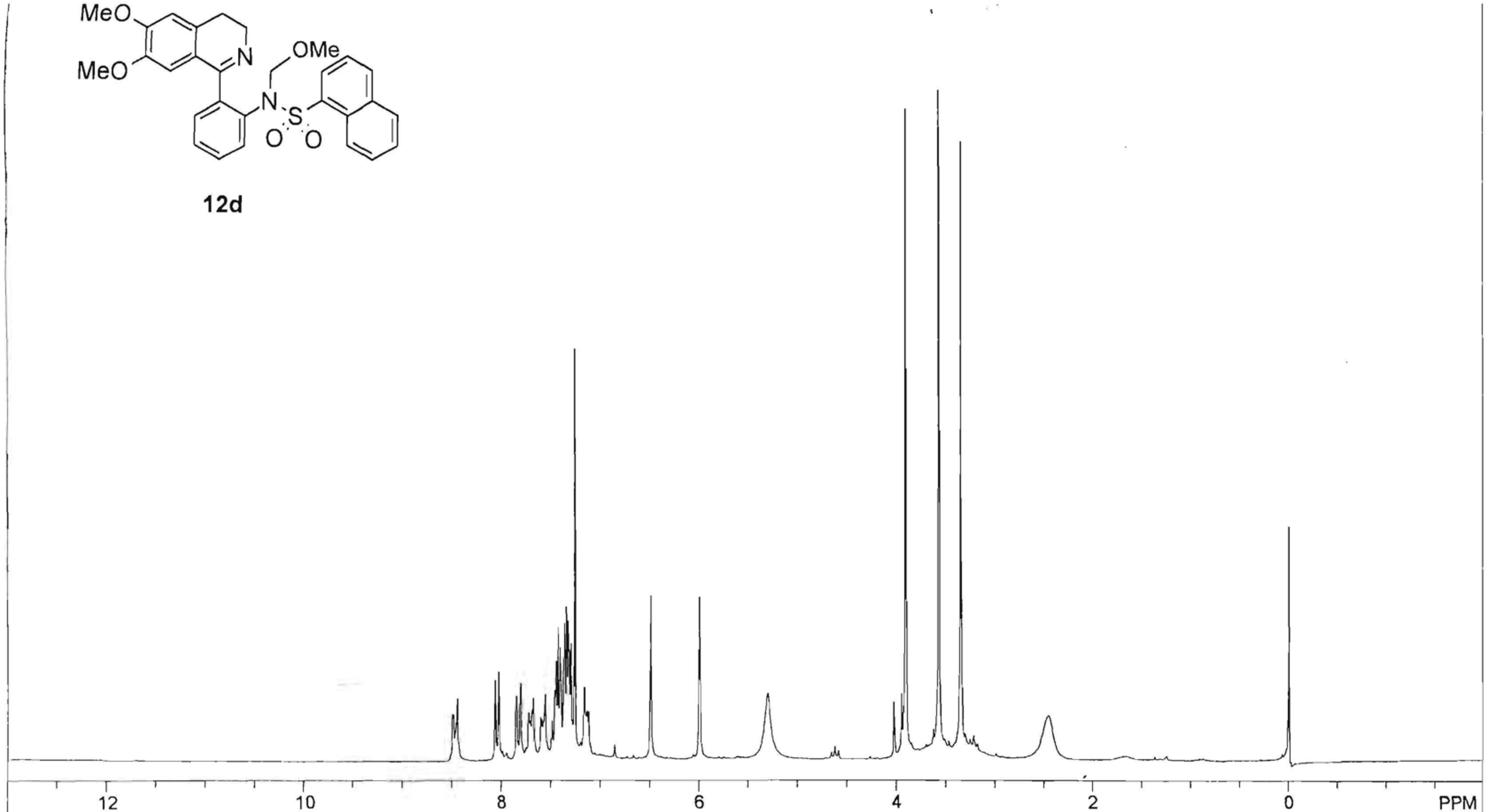

12d

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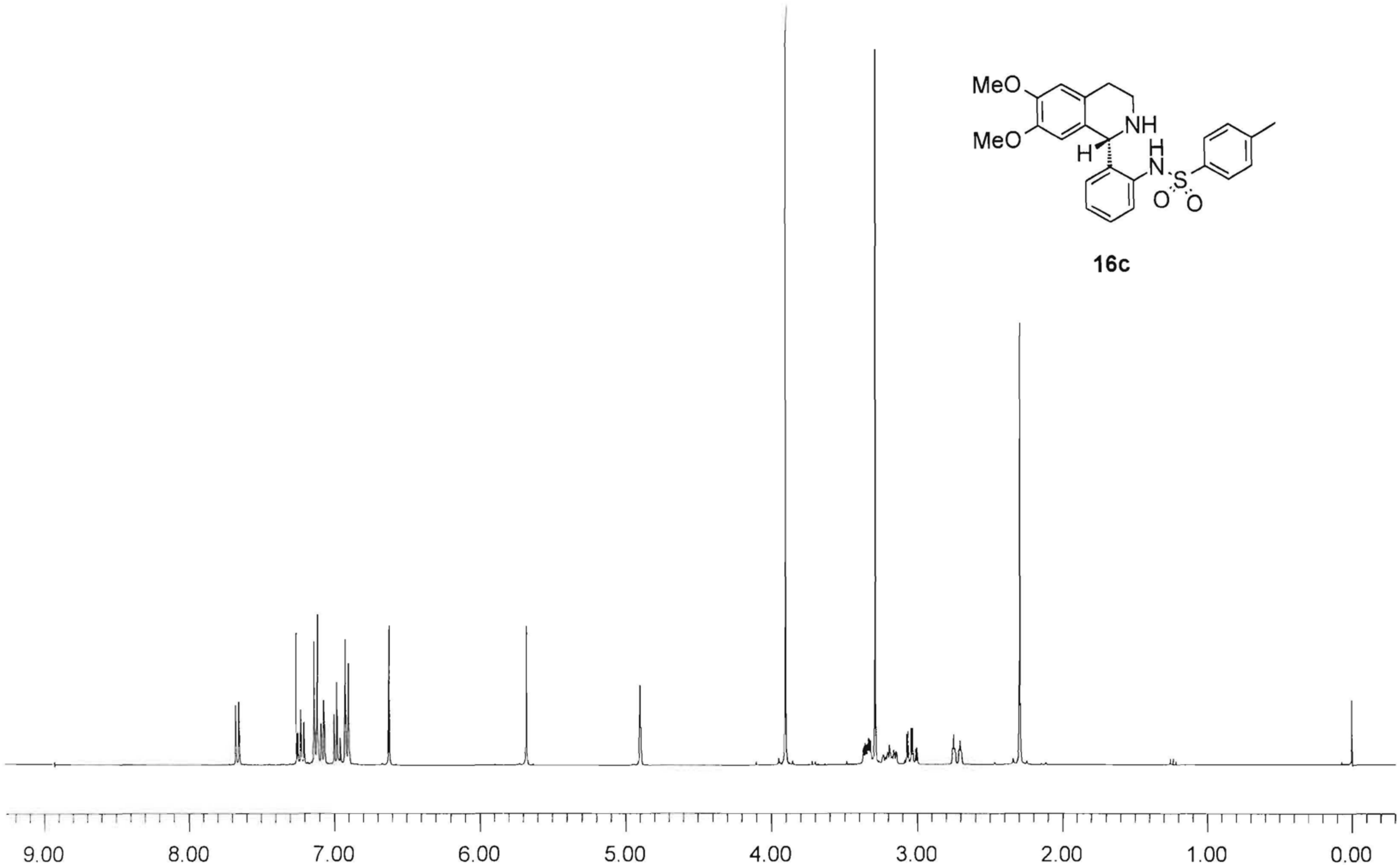

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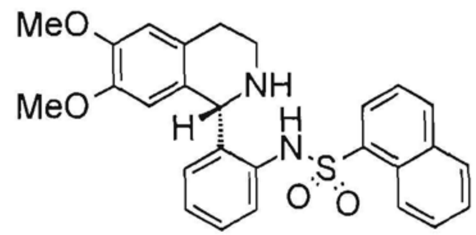
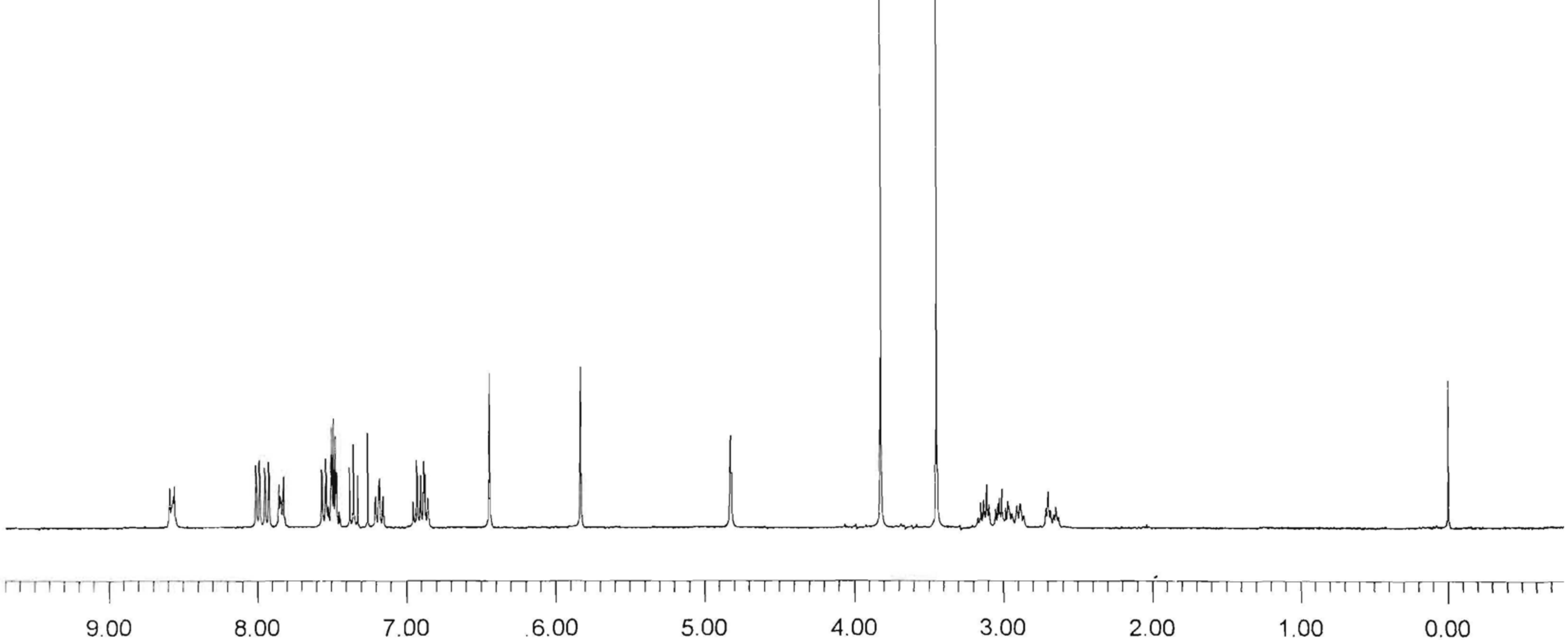


16d



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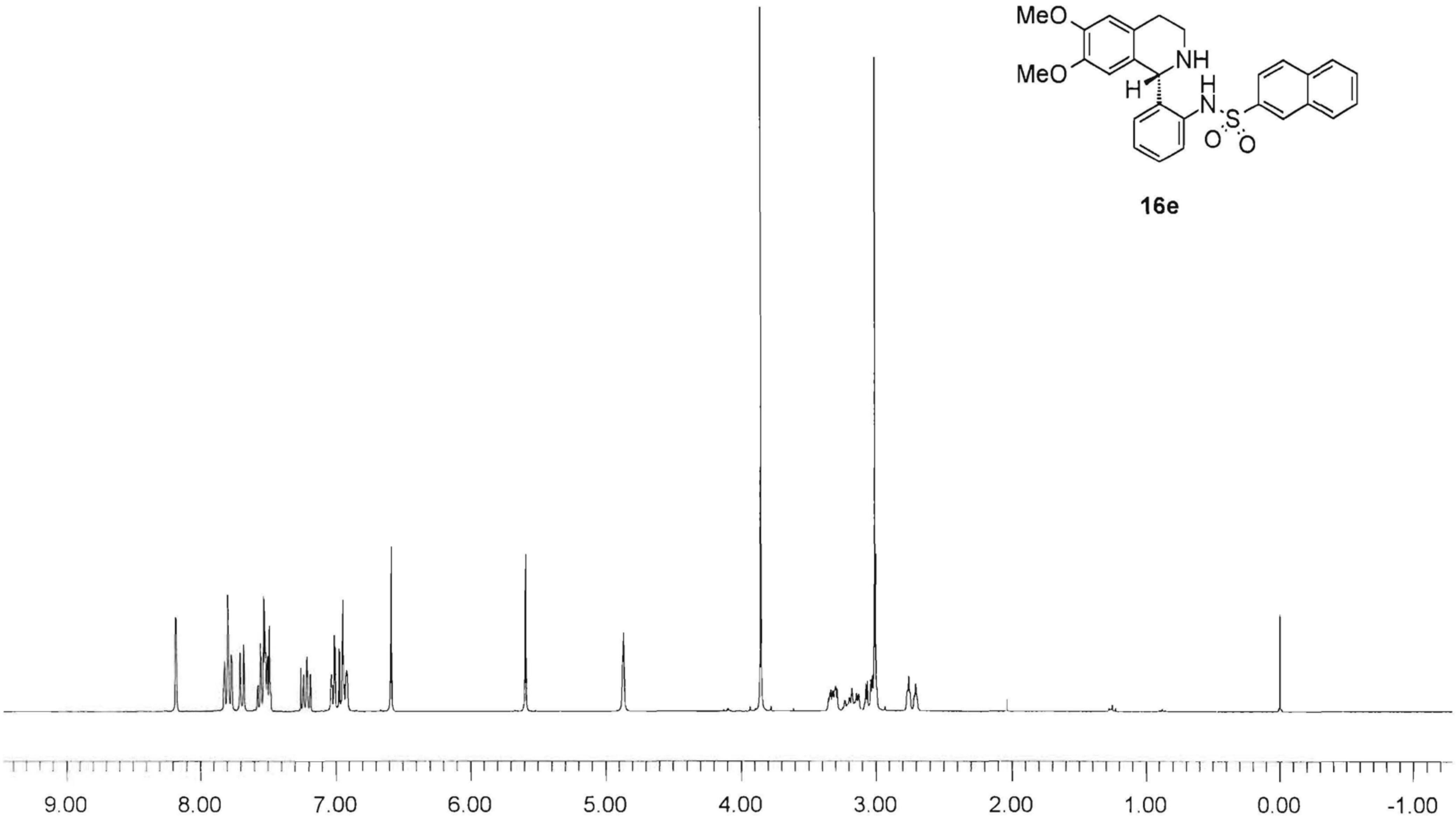

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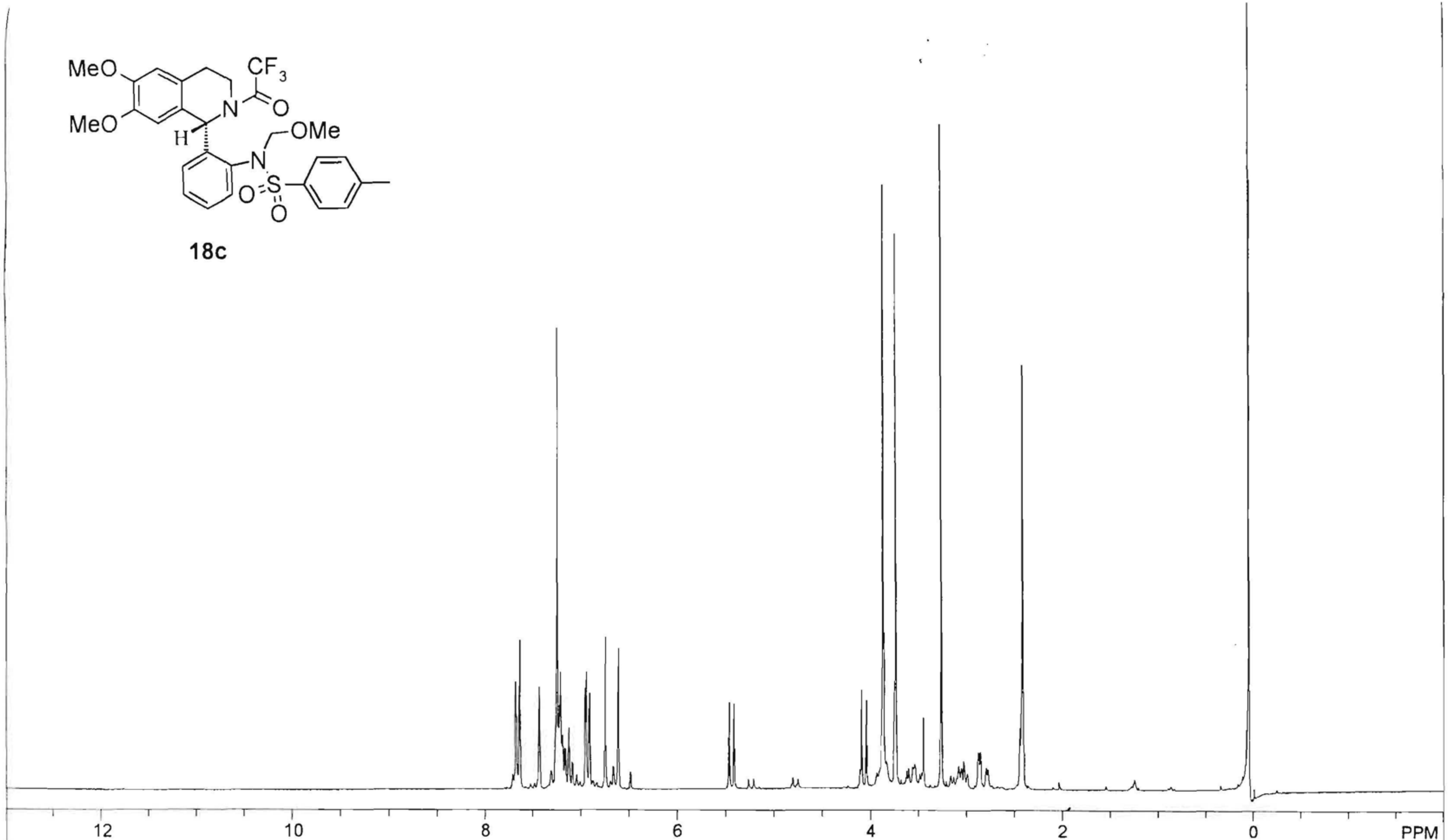

18c

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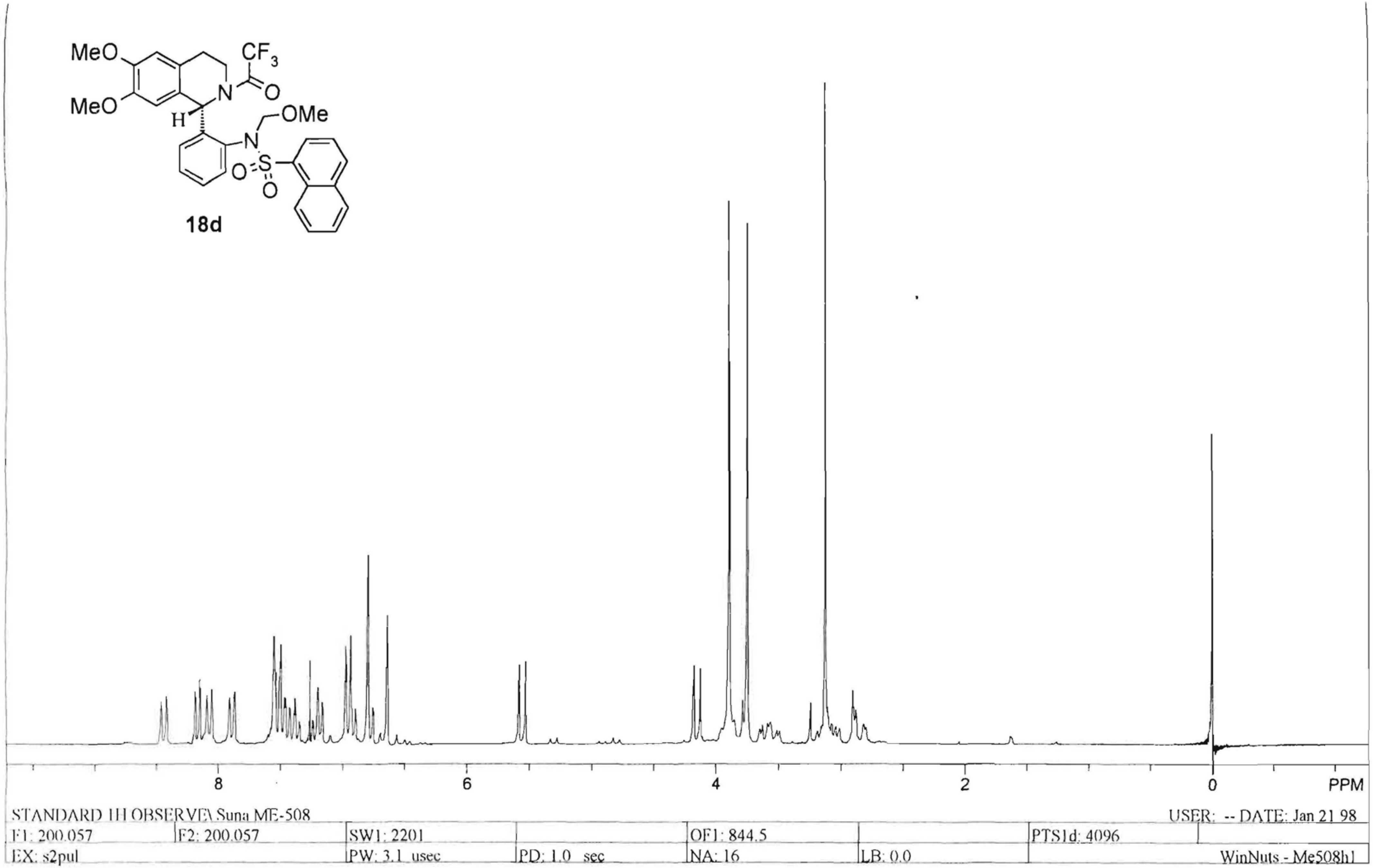

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F2: 200.057
SW1: 2201
OF1: 844.5
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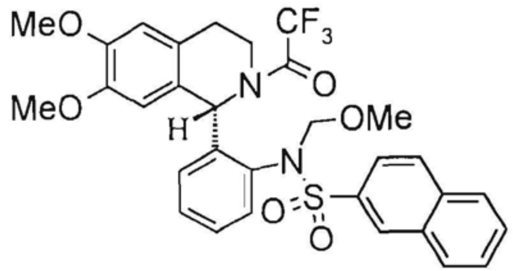

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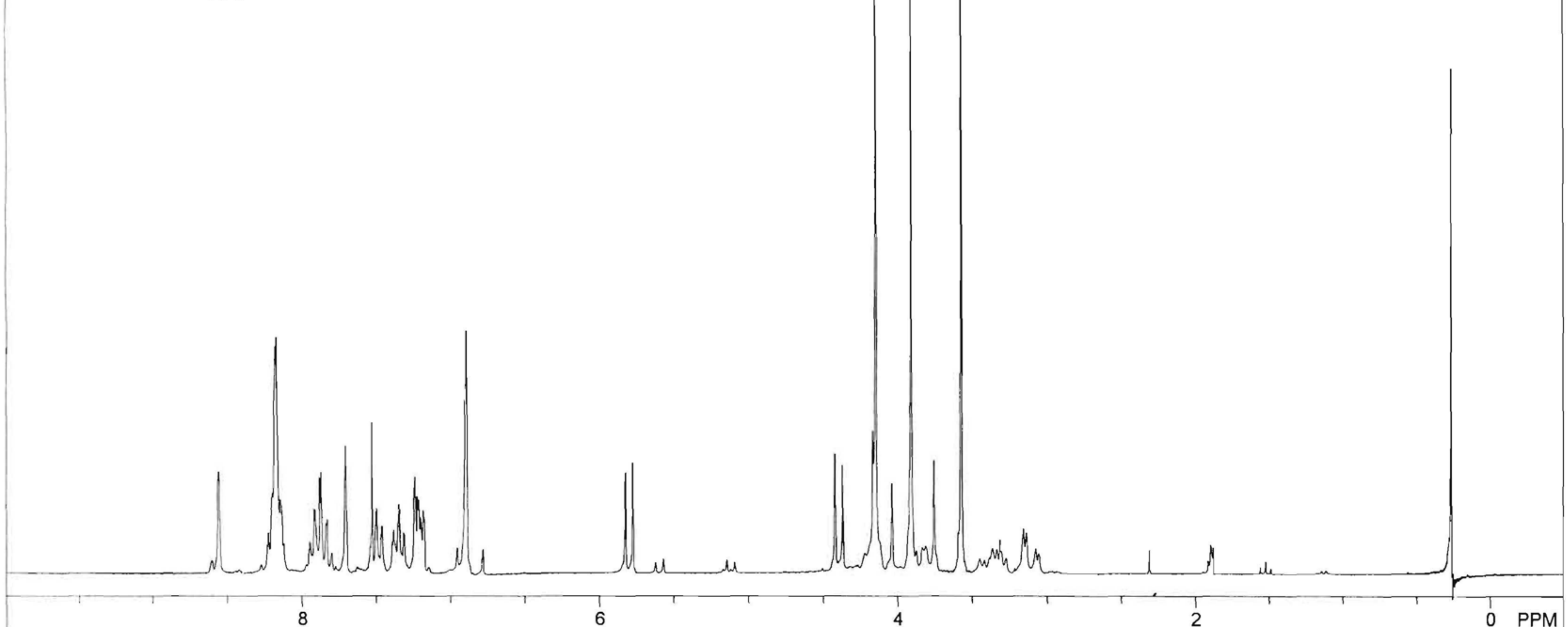

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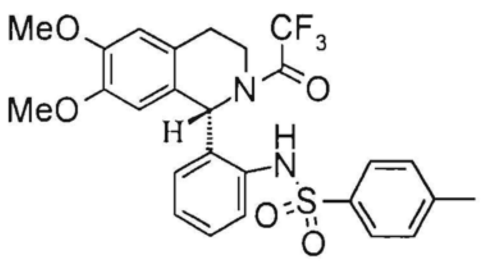
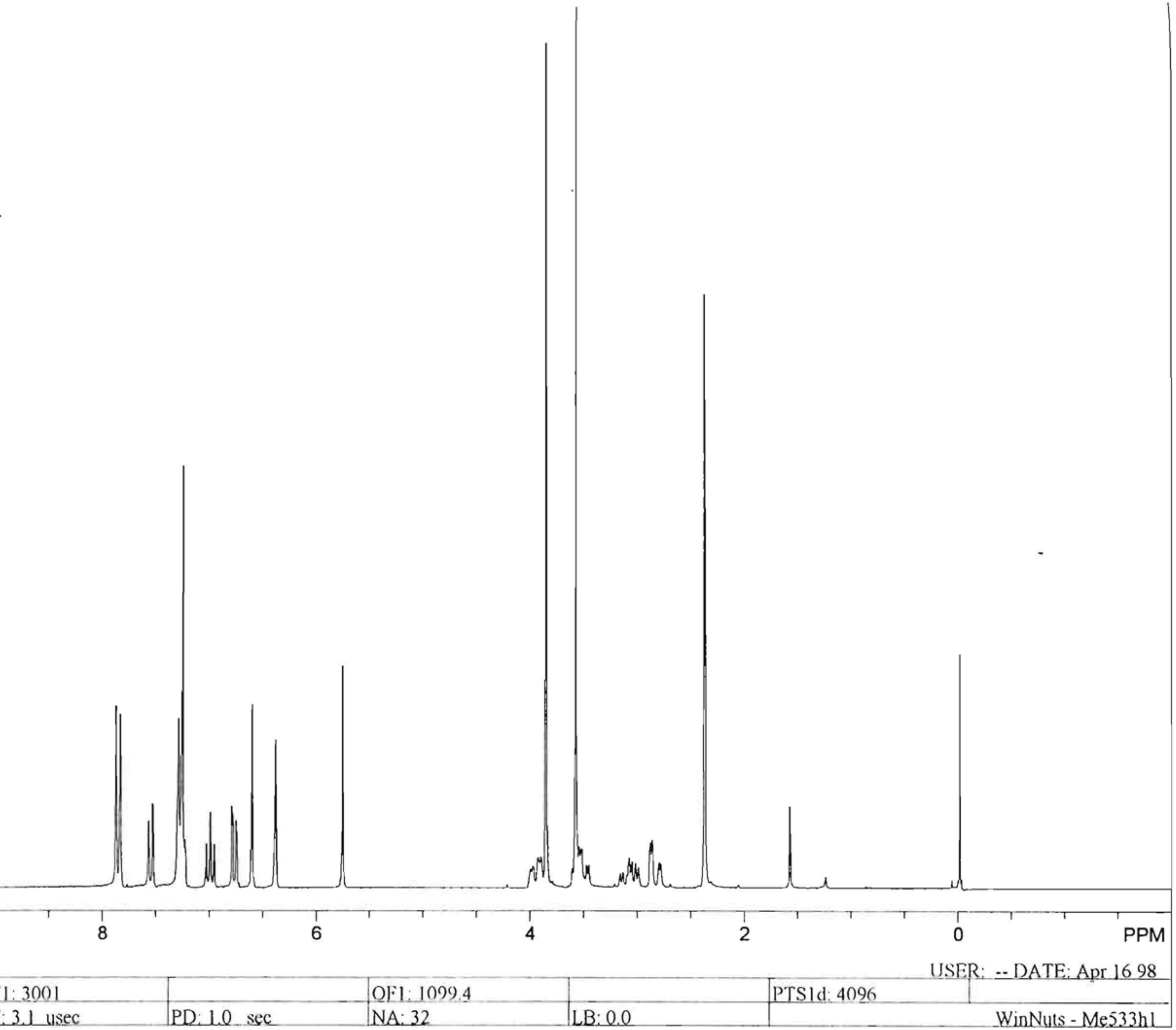


19c



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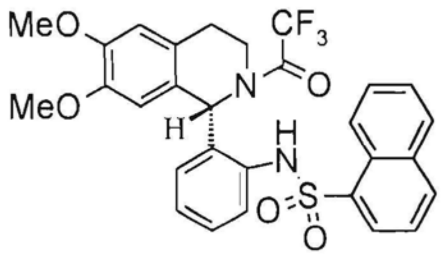
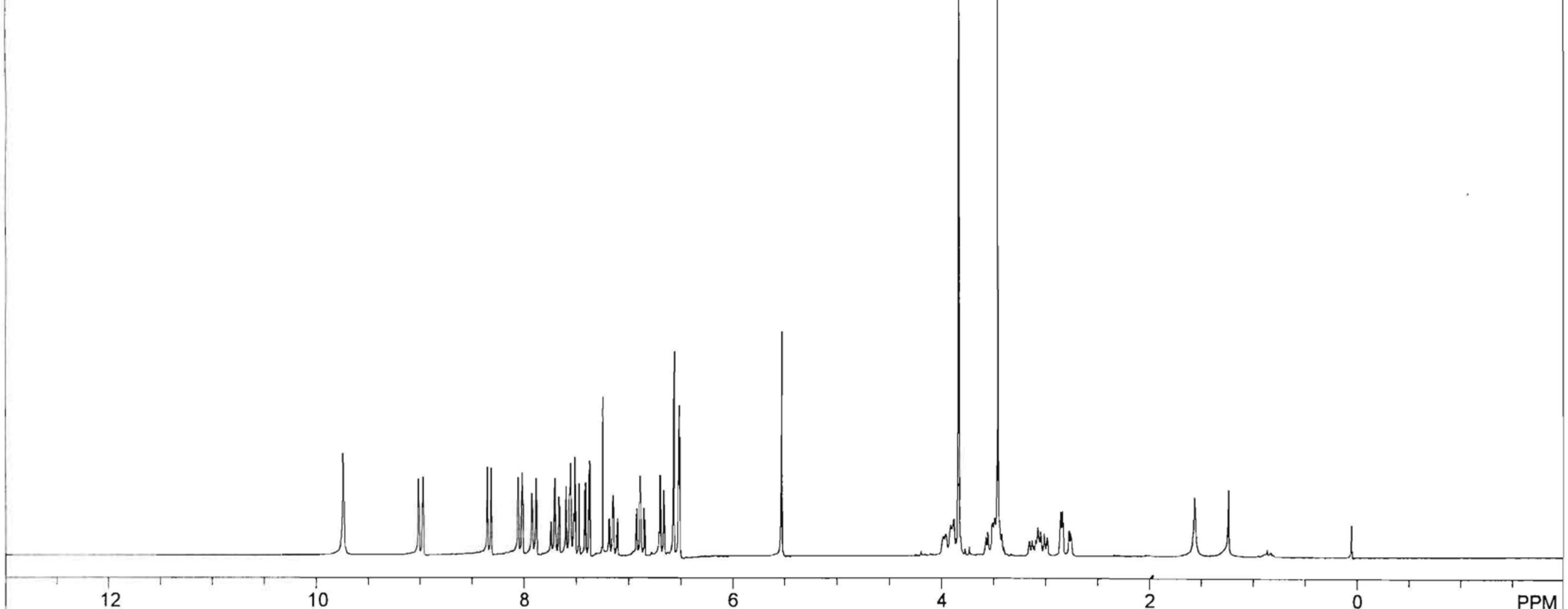


19d



STANDARD 1H OBSERVE\ Suna ME-545 USER: -- DATE: Apr 1 98

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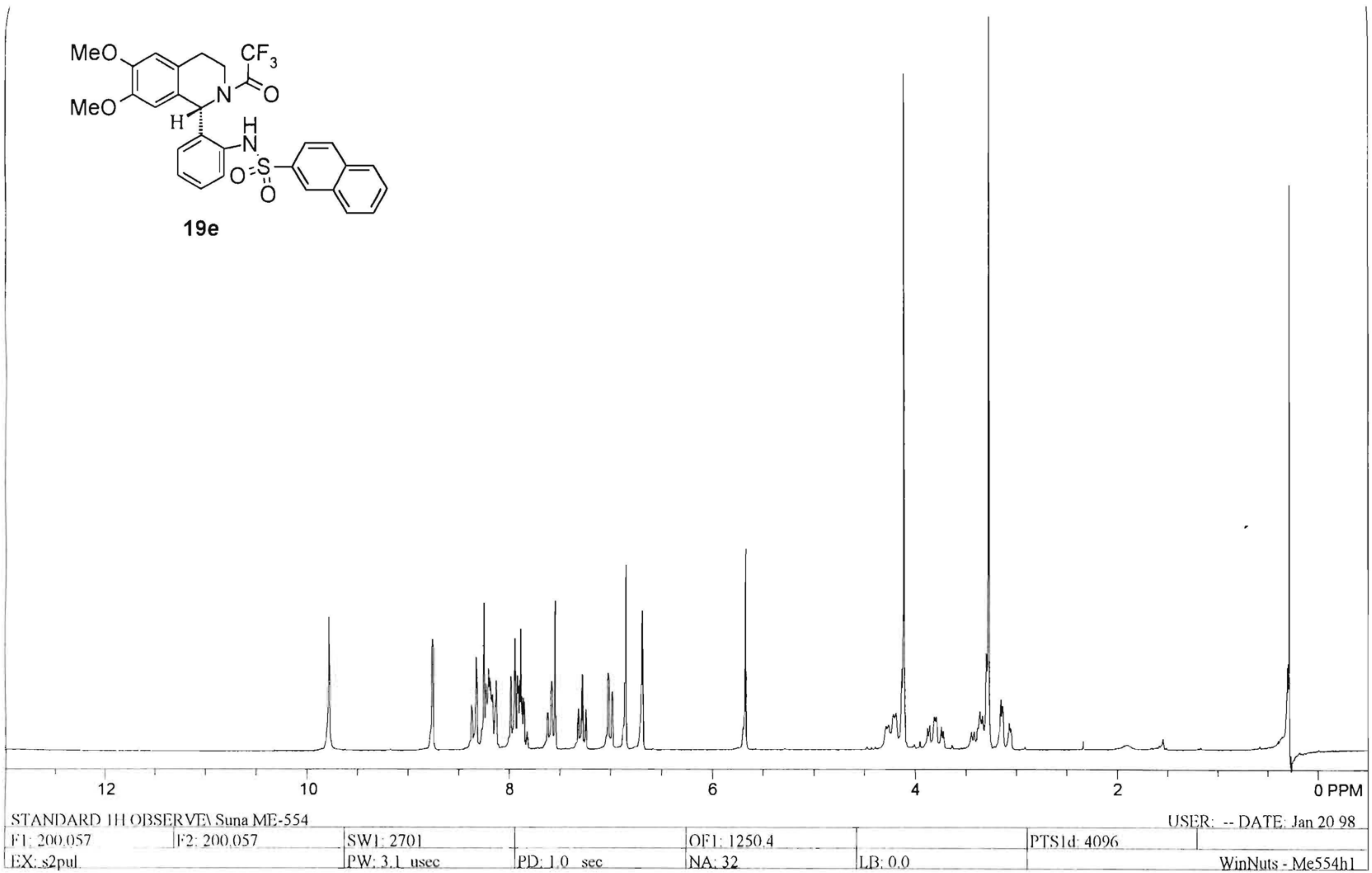
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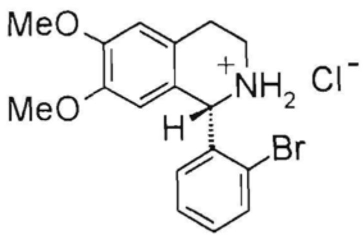
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Cl-
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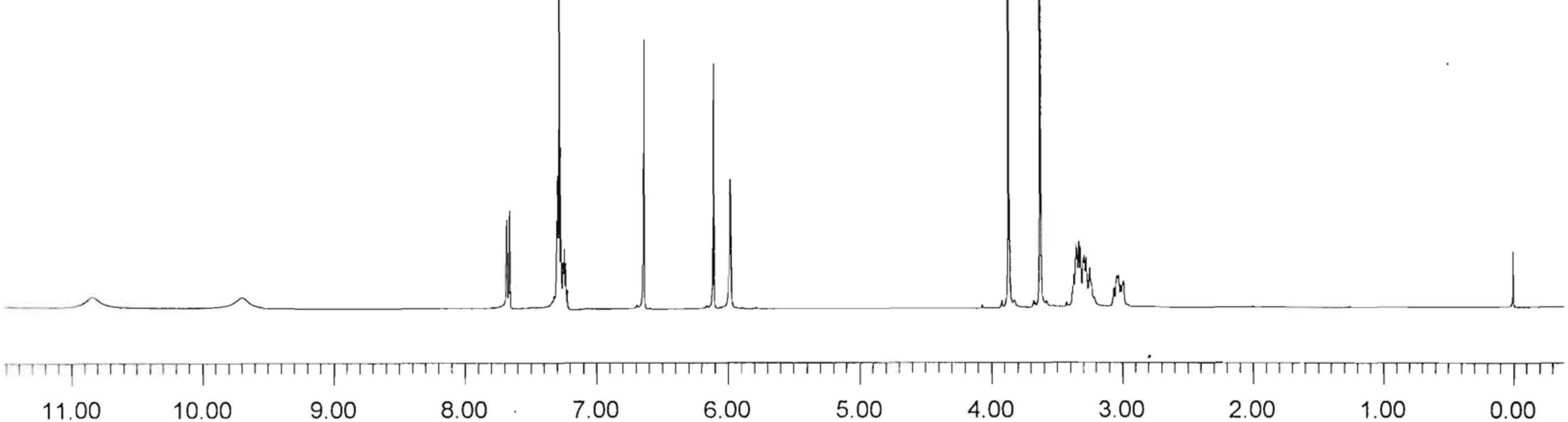
Br

21b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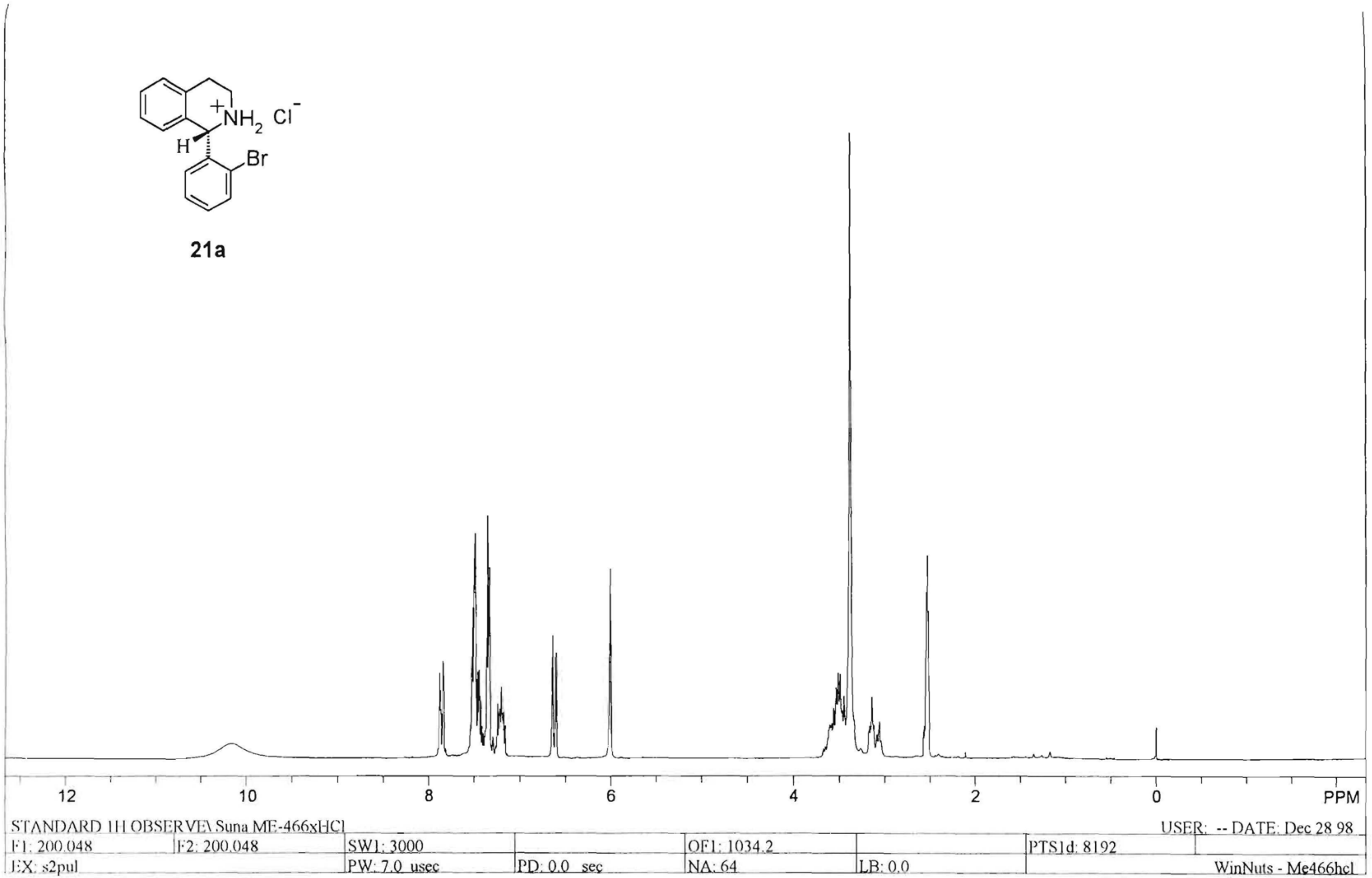
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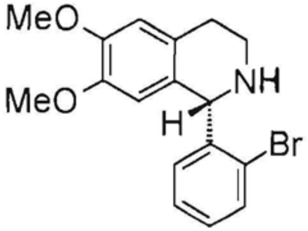

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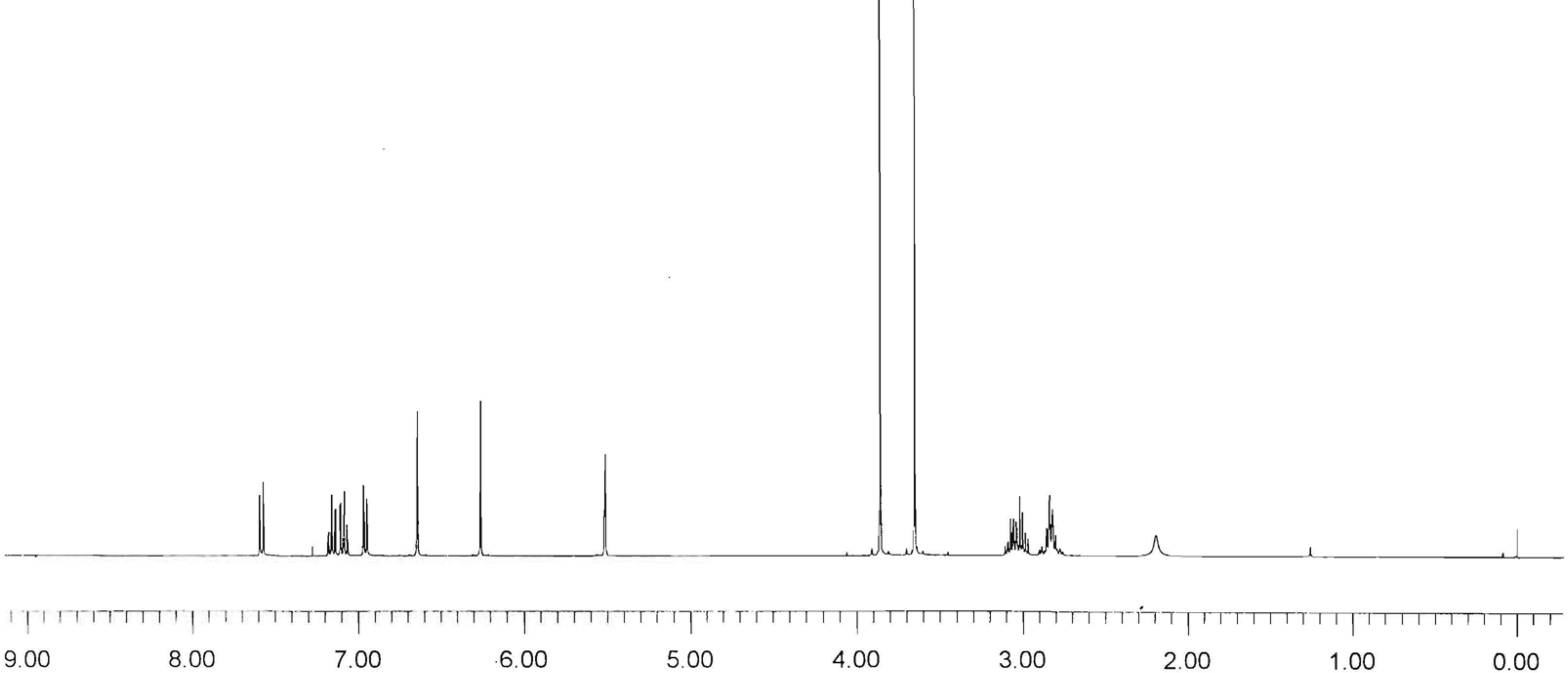

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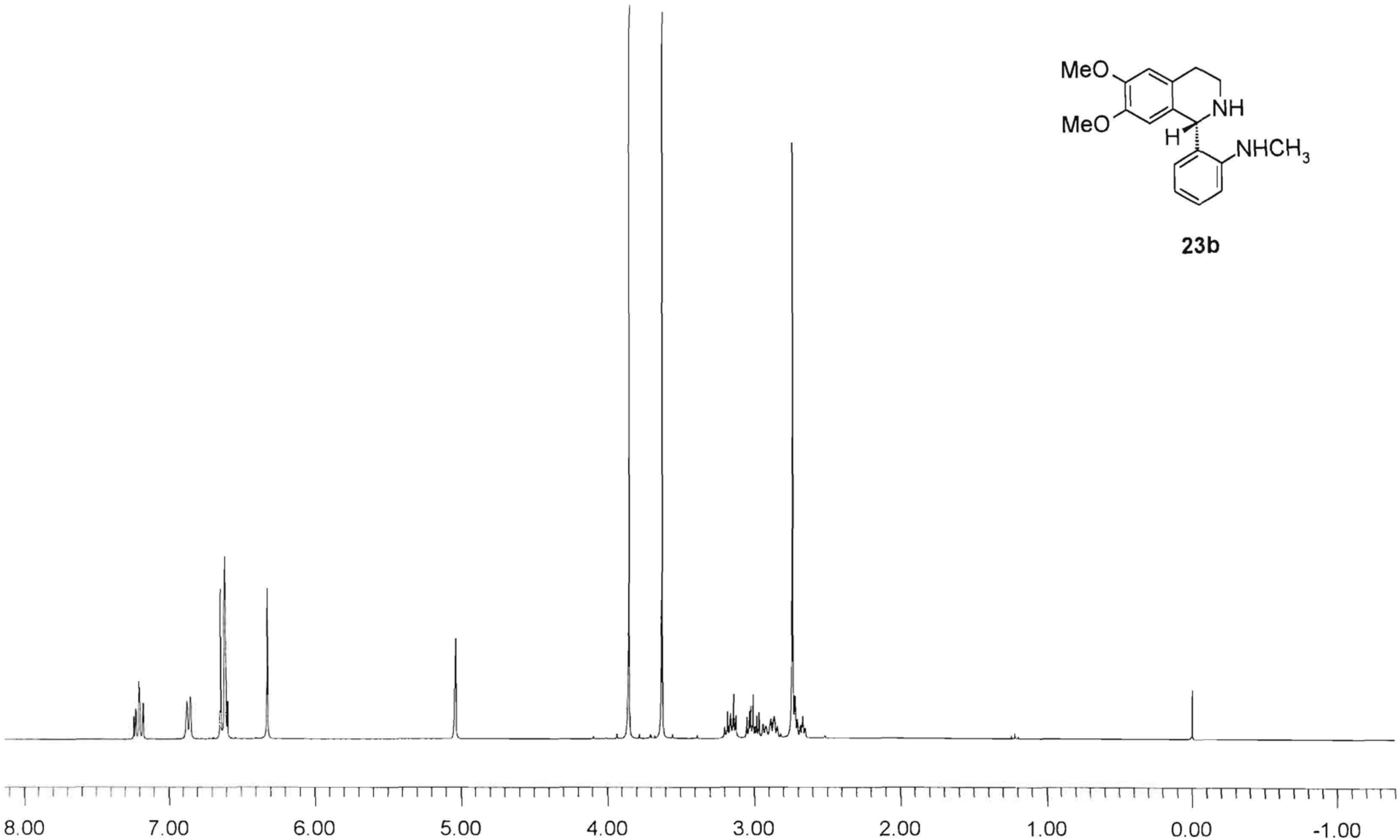

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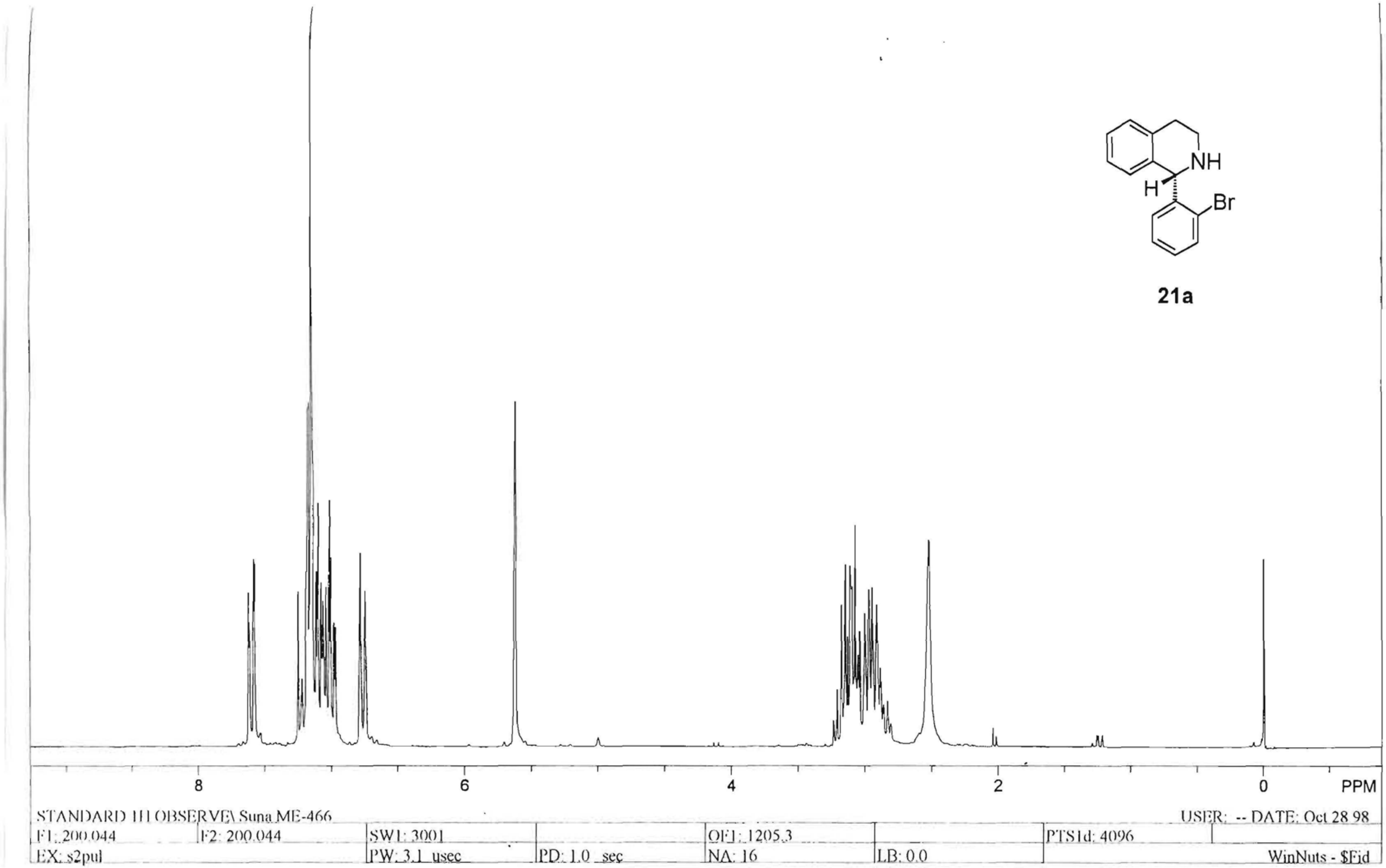
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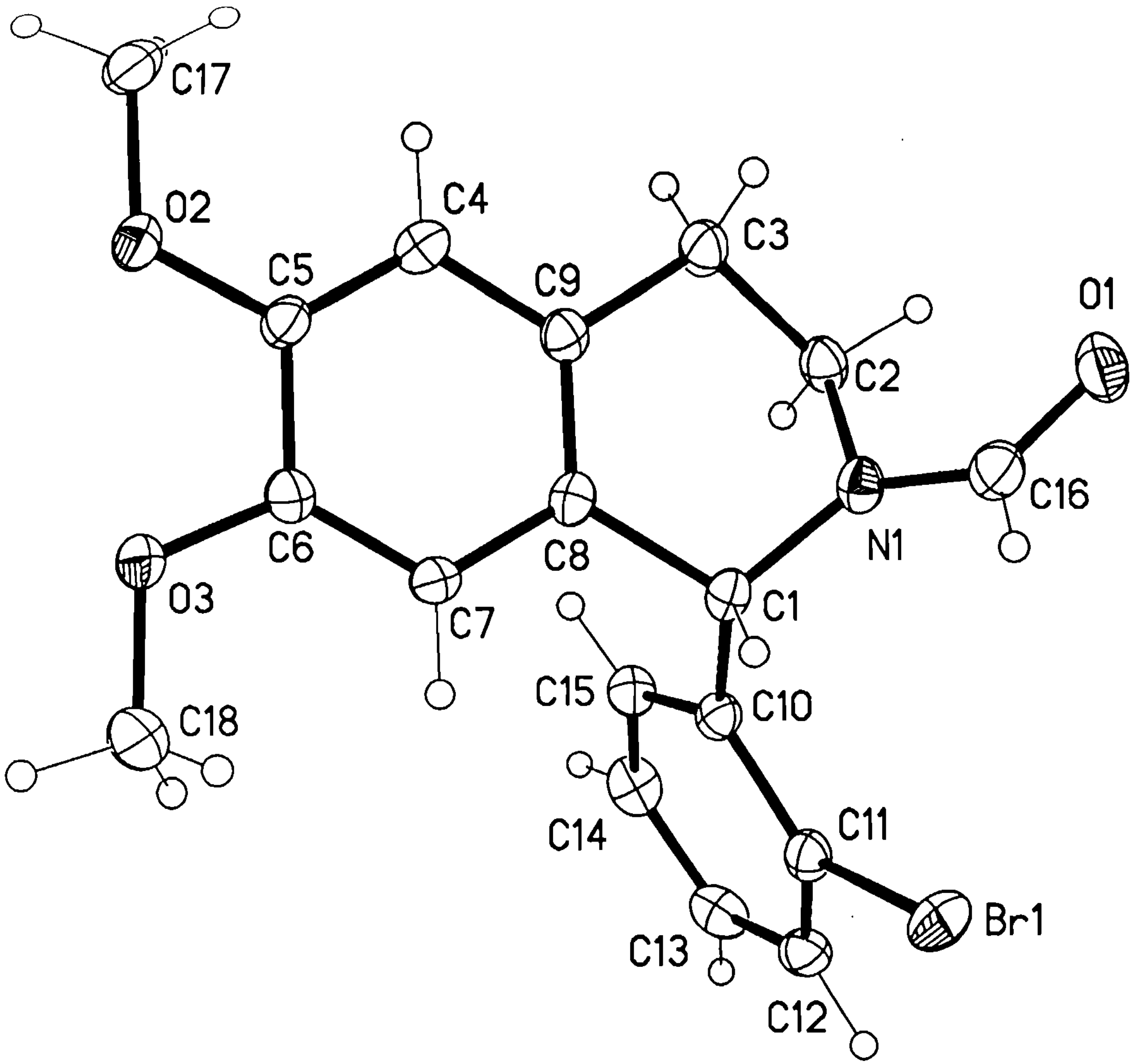
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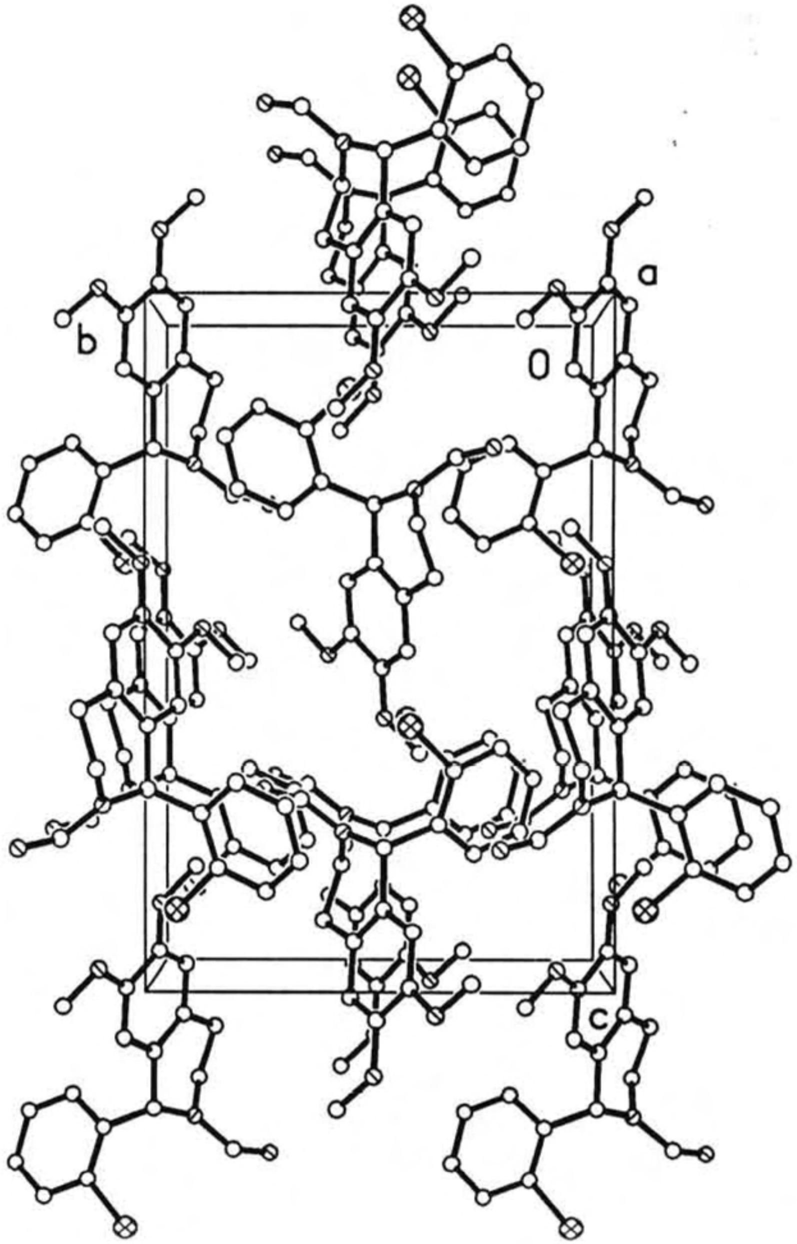
b
0
a
c

Experimental

A colorless prism-shaped crystal of dimensions 0.48 x 0.42 x 0.36 mm was selected for structural analysis. Intensity data for this compound were collected using a Siemens SMART ccd area detector(1) mounted on a Siemens P4 diffractometer equipped with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The sample was cooled to 133(2) K. The intensity data, which nominally covered one and a half hemispheres of reciprocal space, were measured as a series of ϕ oscillation frames each of 0.4 ° for 15 sec / frame. The detector was operated in 512 x 512 mode and was positioned 5.26 cm from the sample. Coverage of unique data was 99.9 % complete to 25.00 degrees in θ. Cell parameters were determined from a non-linear least squares fit of 5423 peaks in the range $3.0 < \theta < 25.0°$. The first 50 frames were repeated at the end of data collection and yielded a total of 253 peaks showing a variation of -0.32 % during the data collection. A total of 8282 data were measured in the range $2.38 < \theta < 29.19°$. The data were corrected for absorption by the empirical method (2) giving minimum and maximum transmission factors of 0.671 and 0.928. The data were merged to form a set of 4139 independent data with R(int) = 0.0271.

The orthorhombic space group P212121 was determined by systematic absences and statistical tests and verified by subsequent refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 (3). Hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. A total of 209 parameters were refined against 4139 data to give $wR(F^2) = 0.0526$ and S = 0.918 for weights of $w = 1/[\sigma^2(F^2) + (0.0218\ P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. The final $R(F)$ was 0.0274 for the 3609 observed, $[F > 4\sigma(F)]$, data. The largest shift/s.u. was 0.005 in the final refinement cycle. The final difference map had maxima and minima of 0.422 and -0.305 e/Å^3, respectively. The absolute structure was determined by refinement of the Flack parameter(4).

Comment

The displacement ellipsoids were drawn at the 50% probability level.

Acknowledgment

The authors thank the National Science Foundation (grant CHE-9310428) and the University of Wisconsin for funds to purchase of the X-ray instrument and computers.

This structure was determined by Douglas R. Powell.

References

(1) (a) Data Collection: SMART Software Reference Manual (1994). Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA. (b) Data Reduction: SAINT Software Reference Manual (1995). Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

(2) G. M. Sheldrick (1996). SADABS. Program for Empirical Absorption Correction of Area Detector Data. University of Göttingen, Germany.

(3) (a) G. M. Sheldrick (1994). SHELXTL Version 5 Reference Manual. Siemens Analytical X-ray Instruments, 6300 Enterprise Dr., Madison, WI 53719-1173, USA. (b) *International Tables for Crystallography, Vol C,* Tables 6.1.1.4, 4.2.6.8, and 4.2.4.2, Kluwer: Boston (1995).

(4) H. D. Flack, *Acta Cryst. A39*, 876-881 (1983).

Table 1. Crystal data and structure refinement for 98130.

Identification code	98130
Empirical formula	C18 H18 Br N O3
Formula weight	376.24
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 8.6374(7) Å α= 90°
	b = 11.5364(10) Å β= 90°
	c = 17.0869(14) Å γ= 90°
Volume	1702.6(2) Å^3
Z	4
Density (calculated)	1.468 Mg/m^3
Wavelength	0.71073 Å
Temperature	133(2) K
F(000)	768
Absorption coefficient	2.428 mm^{-1}
Absorption correction	Empirical
Max. and min. transmission	0.928 and 0.671
Theta range for data collection	2.38 to 29.19°.
Reflections collected	8282
Independent reflections	4139 [R(int) = 0.0271]
Data / restraints / parameters	4139 / 0 / 209
wR(F^2all data)	wR2 = 0.0526
R(F obsd data)	R1 = 0.0274
Goodness-of-fit on F^2	0.918
Observed data [I > 2σ(I)]	3609
Absolute structure parameter	-0.005(6)
Extinction coefficient	0.0060(4)
Largest and mean shift / s.u.	0.005and 0.001
Largest diff. peak and hole	0.422 and -0.305 e/Å^3

Appendix 4

"Enantioselective Enolate Protonation: Matching Chiral Aniline and Substrate Acidity"

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Chemistry Department, University of Wisconsin, Madison WI 53706

Abstract. A comparison of chiral anilines **1a-f** in the asymmetric protonation of enolate **15** shows that the optimum Δ pKa value (chiral acid vs. protonated enolate) for the highest enantioselectivity is *ca.* 3 (Table 2). An extension of this concept to amino acid enolates was possible, and **1e** was found to give the best enantioselectivity (85% ee) with the alanine-derived N-lithioenolate **5a** (Table 3). Changes in aniline pKa due to variation of substituents at the aniline nitrogen were evaluated briefly, but these changes did not show consistent trends in the enantioselectivity vs. pKa.

Enolate desymmetrization by protonation with chiral acids has reached practical levels of enantioselectivity in a number of studies.[1] In the best examples, ee values in the range of 95-99% have been demonstrated, and catalytic as well as stoichiometric procedures are known at this level of enantioselectivity. Progress with the mechanistic aspects of the proton transfer step has been slower. Enolates have several structural options in solutions that contain other species such as lithium amides, lithium halides, enolate dimers, mixed aggregates, and so on.[2] Experimental variables are also potentially complex. In our own work, the optimized procedures have typically been developed by empirical means.[1b,3] The effort required to isolate and to understand individual variables has inevitably taken much more time than the empirical optimization. On the other hand, the need to improve our understanding of the key variables is clear. Despite extraordinary levels of enantioselectivity for the best applications, the available chiral acids tend to be effective only for a narrow range of enolate substrates.

As discussed in a recent review by Fehr,[1a] highly enantioselective proton transfer between a chiral acid and a prochiral enolate is likely only if the rate of proton transfer is slow. A strongly exothermic protonation event would probably be unselective, especially if the chiral acid is so potent that proton transfer approaches diffusion control. On the other hand, the ideal chiral acid A*-H for a given enolate substrate E(-) must be strong enough to completely protonate the enolate and to resist the reverse reaction where the chiral carbonyl product E-H is deprotonated reversibly by the anion A*(-). This is essential if formation of racemic E-H is to be avoided.

Complete protonation of the enolate requires proton transfer on a convenient laboratory time scale, and therefore involves both the kinetic and the thermodynamic acidity of the chiral acid. The latter term can be evaluated by comparing the pKa's of the chiral acid and the protonated enolate, while the former (kinetic acidity) can be approximated by assuming that the rate of proton transfer will increase as the Δ pKa (the value of [$pKa_{E\text{-}H}$]-[$pKa_{A^{\bullet}\text{-}H}$]) increases.[4] However, there has been limited information regarding the acceptable range of Δ pKa values (chiral acid vs. protonated enolate) that allow enantioselective proton transfer. In a prior investigation from this laboratory, evidence was presented that Δ pKa should be *ca.* 3, based on the behavior of two enolates that differ in the degree of anion stabilization. However, some of the earliest promising examples of enolate desymmetrization (Duhamel *et al.*) used chiral carboxylic acids as the proton donors, and the Δ pKa relevant to these experiments appears to be considerably larger.[5]

We have considered the possibility that an optimum Δ pKa range might be identified for different classes of enolate substrates in asymmetric protonation using structurally similar chiral acids based on the chiral diamine skeleton **1**. Previous studies have established that the commercially available *p*-chloro derivative **1b** functions as an excellent chiral "acid" in the enantioselective protonation of strongly basic β,γ-unsaturated amide enolates.[1b] If Δ pKa is an important variable, then the issue can be probed by studying derivatives of **1** where the substituent X is varied systematically to change acidity. Alternatively, chiral acid pKa can be adjusted by varying the aniline nitrogen substituent. In principle, this could be an easier approach starting from the aniline **2**, but enantiomerically pure **2** is not easy to prepare.[6] On the other hand, a dimethoxy analog **3a** is readily available via an asymmetric hydrogention approach, and the N-methyl derivative **3b** is comparable to**1b** as a chiral acid in the protonation of amide enolates. Conversion of **3a** to **3c** has already been reported, and **3d** can be made in a similar way (Cbz protection of the secondary amine followed by N-benzoylation and deprotection).[6] The DMSO pKa values for **3c** and **3d** can be estimated as *ca.* 12 and 19, respectively, by comparison with the parent aniline derivatives (N-phenylsulfonylaniline, pKa

11.95; N-benzoylaniline, pKa= 18.77) studied by Bordwell *et al.*[7] However, preliminary attempts to find possible applications with carboxylic acid-derived enolates were not promising. Thus, the sulfonamide **3c** gave <10% ee in test reactions with ester enolates **4** or **5**, and only marginally improved results were obtained with enolates **6** or 7 (36%ee and 28% ee, respectively). The analogous amide **3d** was ineffective in all cases (<5% ee with **5-7**). Only the N-sulfamoyl derivative **3e** gave a promising result among the anilines containing an electron-withdrawing substituent (58% ee with lactone enolate 7), but similar experiments with **5** (15% ee) and **6**(12% ee) were not encouraging. Furthermore, **3e** was difficult to make and to purify (N-Cbz protection of **3a** followed by treatment with Me_2NSO_2Cl/pyridine resulted in a mixture of disproportionation products; see experimental).

The asymmetric protonations with **3c** suggest a modest trend for improved enantioselectivity with the less basic enolates, as might be expected if the optimum Δ pKa value should be relatively small. However, no trend is evident with **3e** and the lack of any significant enantioselectivity with **3d** is problematic for an investigation of related chiral acids having varied pKa. Other electron-withdrawing nitrogen substituents can be considered, but the preliminary results indicate that comparisons will be difficult because steric and electronic changes near aniline nitrogen may be large enough to obscure the possible role Δ pKa.

An alternative approach to matching the pKa values of chiral acid and enolate substrate was pursued, based on variations in the aniline ring substituent in **1**. The pKa values of the series of chiral diamines **1** can be estimated from the known pKa's of the parent anilines (Table 1) by comparison with the value determined by Bordwell and Satish for the commercially available **1b**.[8a] The measured pKa for **1b** is 27.7 (DMSO conditions), while the parent *p*-chloroaniline **8b** has a DMSO pKa of

29.4.[8b] The difference of 1.7 pKa units reflects the net contribution by the N-methyl group and the tetrahydroisoquinoline subunit. We will assume that the same correction of 1.7 pKa units can be applied to the other anilines **8** as an approximate way to estimate the pKa values of the structurally related diamines **1**. Thus, anilines having a range of DMSO pKa values from ca. 19-29 would be available for study as the aromatic substituent in **1** is modified from strong acceptors such as X=NO_2 (**1f**) to the unsubstituted aniline **1a** (X=H). Because the variable substituent X is relatively far from the aniline nitrogen, the asymmetric protonation of enolates would encounter little if any change in steric effects as the pKa is changed. Electronic factors would also be less than in the examples **3c** or **3d** (where the nitrogen substituents were altered), although a trend toward sp^2 hybridized nitrogen might be expected in **1f** and perhaps also in **1d** due to delocalization involving the nitrogen electron pair and the *para* acceptor group.

Table 1. pKa(DMSO) of *p*-Substituted Anilines 8 and Chiral Acids 1.

p-Substituent X	aniline **8** pKa(DMSO)[a]	chiral acid **1** pKa(DMSO)	chiral acid **1**
H	30.7	29.0 [b]	**1a**
Cl	29.4	27.7 [c]	**1b**
CF_3	27.0	25.3 [b]	**1c**
CO_2Et	26.5[d]	24.8 [b]	**1d**
Ts	24.9[e]	23.3 [b]	**1e**
NO_2	20.9	19.3 [b]	**1f**

(a) pKa(DMSO) from ref. 8b unless noted otherwise. (b) Estimated as described in text. (c) Ref. 1b (d) Calculated from σ^-_p = 0.74 and ρ= 5.67 using the Hammett equation, $pKa_{p\text{-}CO2R} - pKa_{p\text{-}H} = \Delta pKa = \rho\sigma^-_p$ according to ref. 9. (e) The pKa value for phenylsulfonyl is listed as an estimate for toluenesulfonyl.

The synthesis of the chiral diamines began with the commercially available **1b**. Conversion to the aminal **9** was easily carried out using isobutyraldehyde in the presence of acetic acid. With the N-H bonds temporarily blocked, **9** could be transformed into the Grignard reagent **10**. Forcing conditions were necessary, but mechanically activated magnesium in refluxing THF proved sufficient for essentially complete chlorine-magnesium exchange.[10] Upon quenching the Grignard solution with aqueous ammonium chloride, **11** was recovered in high yield. Alternatively, electrophilic trapping with diethyl carbonate[11a] or *p*-toluenesulfonyl fluoride[11b] gave the ester **12** or the sulfone **13** in 71% and 85% yield, respectively. Hydrolytic cleavage of the aminals **9**, **11**, or **12** with dilute HCl gave the desired diamines **1a**, **1d**, and **1e**. The unsubstituted diamine **1a** was also prepared by a nickel-catalyzed dechlorination with $LiAlH_4$.

For access to the more acidic *p*-nitro analog **1f**, the direct nitration of **1a** was briefly explored. However, this reaction proved difficult to control for the desired regioisomer. Better results were obtained by nitrating the aminal **11** with nitronium tetrafluoroborate at -40□C. This gave the mono-nitro derivative **14**, and hydrolysis to **1f** proceeded without complications (55% overall yield). The site of nitration was confirmed by X-ray crystallography.

A modified approach was needed to prepare the trifluormethyl diamine **1c**. The racemic parent compound is known and can be made by a standard Bischler-Napieralski cyclization sequence, followed by reduction.[12] We therefore opted to resolve the racemate, following the precedent reported for the resolution of **1b** with tartaric acid. The resolution required multiple crystallizations of the salt, but sufficient **1c** was obtained with >99% enantiomeric purity for several test experiments involving enolate protonation.

Because the estimated pKa values for several of the chiral anilines **1** should be relatively high (pKa= *ca.* 25 or above for **1a** - **1d**), the asymmetric protonation studies began with the strongly basic naproxen enolate **15**. Conversion to the amide **16** was carried out by treatment with **1** at -78 °C, followed by warming to 0 °C and quenching with dilute aqueous NH_4Cl. The protonated amide was recovered, and the enantioselectivity was established by hplc assay using a chiral stationary phase (hplc/csp). As summarized in Table 2, the original lead compound **1b** was the most highly enantioselective proton donor. Lower enantioselectivity resulted for diamines **1c-f**, and the most acidic *p*-nitro derivative **1f** gave racemic product. This was also the fastest reaction in terms of discharge of the orange-red enolate color (seconds at - 78 °C). A smaller decrease in enantioselectivity was observed when the pKa value of the chiral acid was increased (**1a**), and complete fading of the enolate color was slower in this experiment compared to the others.

Table 2. Asymmetric Protonation of Amide Enolate 15 with 1.

chiral acid	X	pKa (DMSO)	ee (%)
1a	H	29.0 [a]	90
1b	Cl	27.7 [b]	97 [b]
1c	CF_3	25.3 [a]	93
1d	CO_2Et	24.8 [a]	40
1e	Ts	23.3 [a]	37
1f	NO_2	19.3 [a]	0

(a) Estimated; see Table 1 discussion. (b) reference 1b

The DMSO pKa of the amide **16** is too high for accurate measurement, but a value of *ca.* 31 has been estimated.[13] Thus, the optimum chiral acid **1b** among the available *p*-substituted anilines **1** has a Δ pKa value= ca. 3 compared to the protonated carbonyl product **16**. Reasonably high enantioselectivities are also obtained with **1a** and with **1c**, suggesting that Δ pKa can be in the range of 2-5. Of course, the measured pKa values are strictly relevant only to DMSO conditions, while the protonation experiments were conducted in THF (ion pair conditions). The ion pair pKa's would probably be several units lower in THF for all of the chiral acids and for the carbonyl product,[14] but it is likely that the Δ pKa would vary less than the individual values, assuming similar solvent effects on both the enolate and the lithiated aniline. If this is correct, then it may be possible to anticipate the best chiral acid among the derivatives of **1** for a given enolate by evaluating estimated DMSO pKa values.

Among the enolates considered earlier, the lactone-derived **7** should have the lowest pKa value, previously estimated as pKa= *ca.* 20 in DMSO.[3] According to the pKa's in Table 2, only the most acidic *p*-nitro aniline **1f** would have any chance for effecting the direct proton transfer to **7**. However, treatment of **7** with **1f** gave racemic lactone product. Since the estimated Δ pKa = *ca.* 1, this is not a surprising result. Proton transfer should be reversible, and racemization could occur if the initial protonation event is enantioselective. More strongly basic enolates are needed to match the chiral aniline series **1** with Δ pKa in the range of 3-5 where optimum enantioselectivity is expected.

We could find no pKa values reported for enolates such as **4**, **5** or **6**, but it is possible that **5** would be the most strongly basic among these substrates due to electron repulsion in the dianion. This enolate was therefore studied in asymmetric protonation experiments using several of the more readily available anilines **1**. As shown in Table 3 (entries 1-4), the optimum chiral acid proved to be the *p*-phenylsulfonyl derivative **1e** (85% ee). The less acidic analogs **1d** and **1b** gave lower enantioselectivities, while the most acidic **1f** afforded racemic methyl N-benzoylalaninate. Structural modifications in the nitrogen substituent or the ester O-alkyl group in alanine-derived enolates resulted in lower enantioselectivity (entries 5-9). Other amino acid environments were not explored in detail, but promising enantioselectivity was observed in two cases using the optimum proton donor **1e** (entries 10,11).

Table 3. Asymmetric Protonation of Dilithiated Amino Acid Esters 5.

Entry	R_1	R_2	R_3	Chiral Acid	ee (%) (*S*)
1 (**5a**)	C_6H_5	CH_3	CH_3	**1b**	58
2 (**5a**)	C_6H_5	CH_3	CH_3	**1d**	71
3 (**5a**)	C_6H_5	CH_3	CH_3	**1e**	85
4 (**5a**)	C_6H_5	CH_3	CH_3	**1f**	0
5 (**5b**)	OBn	CH_3	CH_3	**1e**	50
6 (**5c**)	mesityl	CH_3	CH_3	**1e**	78
7 (**5d**)	α-naphthyl	CH_3	CH_3	**1e**	83
8 (**5e**)	C_6H_5	CH_3	Et	**1e**	81
9 (**5f**)	C_6H_5	CH_3	*t*-Bu	**1e**	47
10 (**5g**)	C_6H_5	Et	CH_3	**1e**	80
11 (**5h**)	C_6H_5	Bn	CH_3	**1e**	65

Based on the DMSO pKa estimate for **1e** (23.3) and an optimum Δ pKa= *ca.* 2-4, the pKa for singly protonated 5 could be in the range of 25-27. If the lithiated amido subunit C(OLi)=N in 5 is treated as an unsaturated substituent, then the closest literature analogy having a known pKa value could be ethyl phenylacetate ($PhCH_2CO_2Et$; DMSO pKa ≈22.6), with phenyl as the unsaturated group.[7b] Evidently, C(OLi)=N is not as effective as phenyl in stabilizing the enolate, but there is some stabilization, given that ethyl acetate has a pKa of *ca.* 30.[15]

One final series of experiments was performed using enolate **4a** as the substrate and the most important chiral acids **1b** and **1e**. Racemic products resulted in each case. Modest enantioselectivities in the range of 37-50% ee were obtained with the analogous enolate **4b** as the substrate and with **1e** as the chiral proton source, but **1b** gave 16% ee under similar conditions. These results were not deemed sufficiently promising to warrant a more detailed investigation.

Summary.

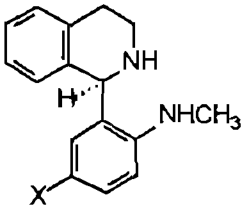
The data summarized in Table 2 provide some support for the notion that asymmetric protonation of the amide enolate **15** is optimal when Δ pKa (chiral acid vs. **16**) is *ca.* 3. The proton transfer process is essentially complete and irreversible under the optimum conditions, as required to minimize the formation of racemic product. The knowledge of chiral acid pKa's is helpful in the selection of chiral acids for other purposes, as in the amino acid enolate protonations summarized in Table 3. Of course, pKa alone does not control enantioselectivity and other factors remain to be optimized. Furthermore, the enantioselectivities in Table 2 do not reflect the relative pKa values in detail. Thus, the behavior of **1d** (*p*-ethoxycarbonyl) and **1c** (*p*-trifluoromethyl) is rather different even though the difference in effective pKa's is probably small compared to the error inherent in extending the numbers from DMSO to THF solution. Furthermore, the absence of any enantioselectivity in the case of **1f** in Table 2 (as well as with the other enolates that were treated with **1f**) suggests that pKa is not the only reason why **1f** is ineffective. A hybridization change at aniline nitrogen due to delocalization with the *p*-nitro group is one possible explanation for the large difference between **1f** and the other chiral diamines.[16] A similar effect may be the reason why the p-ethoxycarbonyl example **1d** differs so much from **1c**. The hybridization argument could also explain why **3d** is an ineffective chiral acid, but there are other variables to consider in this case. In any event, the pKa trends in Table 2 show that there is an optimum pKa match in terms of enantioselectivity with a given enolate, and the trend is clear.

Extension of the optimum pKa concept to other systems is possible, as shown by the amino acid examples. The results of Table 3 describe the best asymmetric protonations for an alanine-derived substrate reported to date, but further effort will be needed to obtain high enantioselectivity and broader substrate tolerance.[5] The latter problem remains a difficult challenge for the asymmetric protonation of enolates.

Acknowledgement. This work was supported by NIH (GM 44724).

Supporting Information Available: NMR spectra of new compounds and X-ray data tables for **1f**.

Scheme 1



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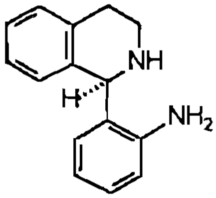
c. X= CF_3 d. X= CO_2Et
e. X= SO_2*Tol* f. X= NO_2



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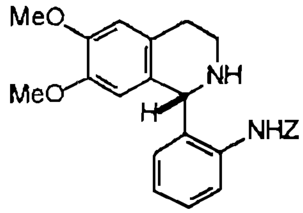

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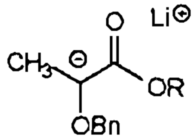
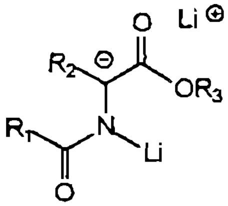
c. Z= SO_2-2-Napthyl
d. Z= Bz e. Z= SO_2NMe_2

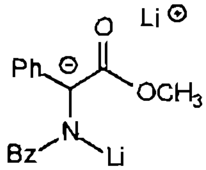


4a R= BHT
4b R= Me

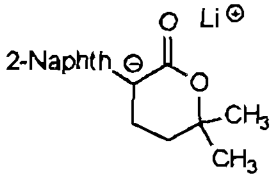


5

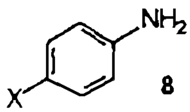
a. R_1= Ph; R_2= R_3= Me
b. R_1= BnO; R_2= R_3= Me
c. R_1= mesityl; R_2= R_3= Me
d. R_1= α-Naphthyl; R_2= R_3= Me
e. R_1= Ph; R_2= Me, R_3= Et
f. R_1= Ph; R_2= Me, R_3= *tert*-Bu
g. R_1= Ph; R_2= R_3= Me
h. R_1= Ph; R_2= Bn, R_3= Me



6



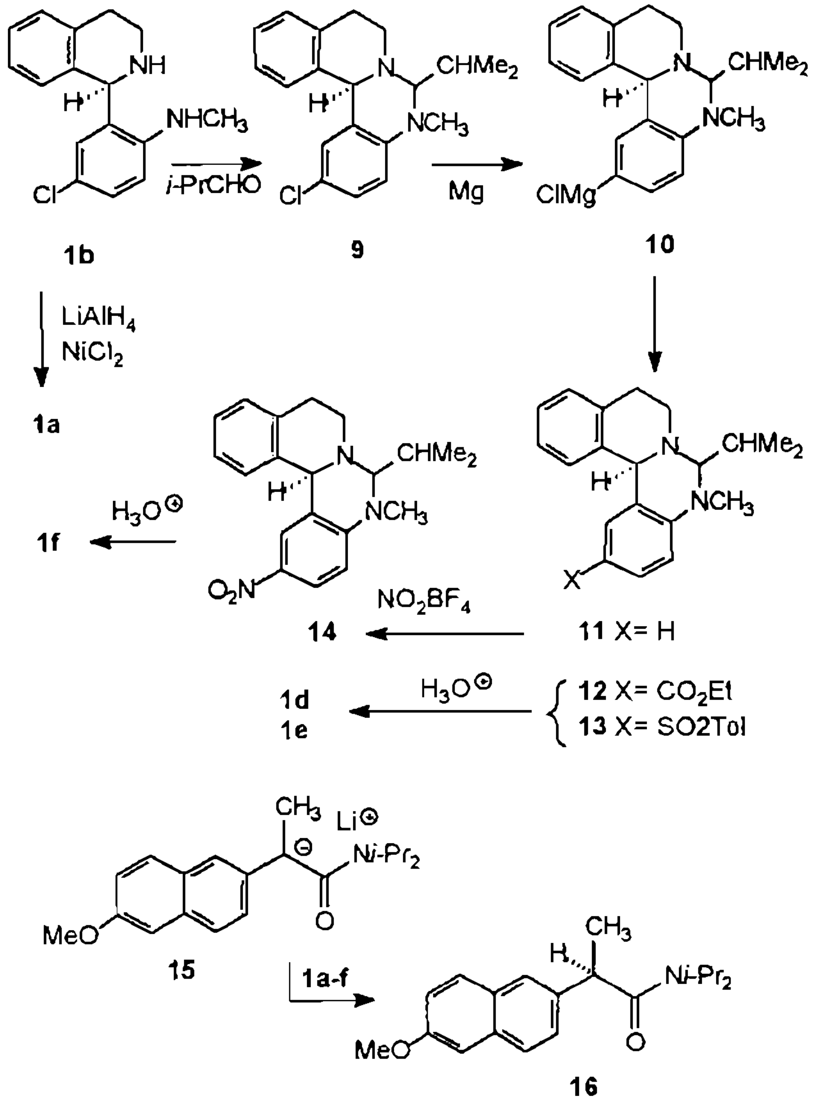
7



8

a. X= H b. X= Cl
c. X= CF_3 d. X= CO_2Et
e. X= SO_2Tol f. X= NO_2

Scheme 2



NH
NHCH3
H
Cl
i-PrCHO
N
CHMe2
NCH3
Mg
ClMg
1b
9
10
LiAlH4
NiCl2
1a
H3O⊕
1f
O2N
X
NO2BF4
14
11 X= H
H3O⊕
1d
1e
12 X= CO2Et
13 X= SO2Tol
CH3
Li⊕
Ni-Pr2
O
MeO
15
1a-f
16

Experimental:

General: HPLC analysis was performed on a Gilson system using chiral stationary phases with detection by UV. All air and/or moisture sensitive reactions were run under an atmosphere of nitrogen in oven or flame dried glassware. Materials were purified as follows: tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl under N_2. Organolithium reagents were titrated using the menthol/phenanthroline procedure.

Chiral Acids:

Diamine derivatives **3a-3d** are available in >99% ee as previously described. Diamine **1b** has also been described,[12] but the following procedure was used to ensure high enantiomer purity. The commercially available (-)-1-[5'-chloro-2'-(methylamino)-phenyl]-1,2,3,4-tetrahydroisoquinoline (-) tartrate (5.0 g, 14.4 mmol, Aldrich) was refluxed in 800 mL methanol for 1 h. After filtration of the hot solution, the filtrate was allowed to cool to room temperature followed by cooling to -20 °C overnight. Filtration yielded a cake of white solid. The free diamine was isolated by partitioning the tartrate salt between 40 mL ether and a solution of potassium hydroxide (2.4 g, 43.0 mmol) in 40 mL water with vigorous stirring. After dissolution was complete (2-3 h) the aqueous layer was washed with ether (40 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated to a solid 2.7 g (70%). Pure **1b** was obtained by recrystallization from ether (mp 99-99.5 °C; lit.[12] mp 98-99 °C).

(S)-1-(2-N,N-Dimethylsulfamoylamino)phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3e).

Conversion of **3a** to the N-benzyloxycarbonyl derivative at the secondary nitrogen has been reported.[6] To a solution of the N-Cbz protected diamine (2.5 g) in pyridine (100 mL, distilled from CaH_2) was added N,N-dimethylsulfamoyl chloride (Acros, 6.4 mL, 59.7) and the mixture was stirred at rt for 48 h. Pyridine was evaporated (aspirator, below 40 °C), and the oily residue was dissolved in $CHCl_3$ (150 mL) and washed with 1N HCl (3x30 mL), water, brine and dried (Na_2SO_4). After filtration and solvent removal (aspirator) the resulting oil was purified by flash column chromatography (column size: 150X50 mm) with petroleum ether-EtOAc 5:2 (fractions #1-45, 50 mL ea), and then petroleum ether-EtOAc 1:1 (fractions #46-68, 50 mL ea). Fractions #9-16 contained solid $Me_2NSO_2NMe_2$ (^{1}H-NMR: single peak at 2.82 ppm in $CDCl_3$), 1.03 g. Fractions #19-

36 gave a mixture of starting material and product in a ratio 3:7 as a colorless oil that was used in the deprotection step, below. Fractions #41-59 contained 1.11 g of material having no N-methyl signals in the ^{1}H-NMR spectrum, consistent with replacement of a NMe_2 fragment by a second diamine molecule. The crude oil from fractions 19-36 (1.03 g) was dissolved in 30 mL of glacial acetic acid and 10% Pd-C (400 mg) was added. The reaction was stirred under H_2 at rt. After 8 h, additional 10% Pd-C was added (200 mg) and hydrogenolysis was continued for 6 h. The reaction mixture was filtered through Celite with methanol rinsing and solvent was removed (aspirator, < 30 □C). The residue was dissolved in water (10 mL) and the solution was basified by slow addition of NH_4OH. The white crystalline precipitate formed was filtered, dried *in vacuo* (ca. 1 mm Hg) over P_2O_5 and twice recrystallized from EtOAc-Hex to give 660 mg of crystalline sulfonamide **3e** containing ca. 10% of diamine **3a** (^{1}H-NMR assay). Two recrystallizations yielded pure sulfonamide **3e** (560 mg, 24% overall); analytical tlc on silica gel, 1:1 hexane/EtOAc, Rf= 0.17; analytical hplc, CHIRALCEL OD (60:40 hex/isopropanol, 0.6 mL/min) T_R=14.5 min (*S*)-isomer); by comparison with a racemic sample, the (*R*)-isomer elutes at 18.8 min. **3e**: mp 156 °C, dec., colorless needles. $[\alpha]_D$= +8.1 (c=1, $CHCl_3$). Anal. calcd: C, 58.28; H, 6.45; N, 10.73, S, 8.19, found: C, 58.23; H, 6.40; N, 10.62; S, 8.11; IR ($CDCl_3$ film, cm^{-1}) 3325, N-H; 1330, SO_2N; NMR ($CDCl_3$, ppm) δ 7.6-6.95 (4H, m) 6.62 (1H, s) 6.22 (1H, s) 5.11 (1H, s) 3.84 (3H, s) 3.60 (1H, s) 3.39-3.28 (1H, m) 3.19-3.10 (2H, m) 2.80-2.68 (1H, m) 2.39 (6H, s).

(-)-1-[2'-(Methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1a).

To a suspension of anhydrous $NiCl_2$ (1.59 g, 12.3 mmol) and **1b** (1.16 g, 4.10 mmol) in 50 mL dry THF at -40□C under N_2 was slowly added $LiAlH_4$ in THF (Aldrich, 1.0M; 12.3 mL, 12.3 mmol) and the mixture was stirred for 10 min at -40°C. The reaction mixture was warmed to RT gradually and stirred for 48 h at RT The resulting black mixture was quenched with saturated Na_2SO_4 (50 mL), the inorganic salts were removed by filtration through a celite pad, the filter was washed well with THF, and the THF was evaporated (aspirator) to give a yellow oil. The oil was redissolved in ether, dried (Na_2SO_4) and concentrated, and the crude yellow oil was purified by flash column chromatography (silica gel, 2x15 cm) (gradient elution; 30% EtOAc in hexane with 1% NEt_3 to 50% EtOAc in hexane with 1% NEt_3) to give a yellow oil containing some solid (0.70 g, 71%).

The yellow oil was crystallized from hexane to give a pale yellow powder, analytical tlc on silica gel, 30% EtOAc in hexane with 1% NEt_3, Rf= 0.21. Pure material was obtained by recrystallization from hexane, mp 77-79 □C. Molecular ion calcd for $C_{16}H_{18}N_2$: 238.14705; found m/e= 238.1470, error= 0 ppm; base peak= 132 amu; IR (neat, cm^{-1}) 3310, N-H; 1586, C=C; 200 MHz NMR (acetone-d_6, ppm) δ 7.25-6.80 (5 H, m) 6.71 (1 H, d, J= 7.7 Hz) 6.58 (1 H, dd, J= 8.0, 1.2 Hz) 6.54 (1 H, d, J= 7.7 Hz) 6.25 (1 H, br s) 5.03 (1 H, s) 3.3-3.13 (1 H, m) 3.06-2.82 (2 H, M) 2.8-2.6 (1 H, m) 2.63 (3 H, s). ^{13}C NMR (68MHz, {H}, $CDCl_3$, ppm) δ 148.5, 137.4, 134.8, 130.6, 128.7, 128.5, 126.7, 126.3, 126.1, 125.6, 115.4, 110.3, 61.64, 42.5, 30.1, 29.4.

(-)-1-[5'-Trifluoromethyl-2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1c)

The racemic compound was prepared as previously described and was resolved by repeated crystallization of the tartrate salt from ethanol following the procedure reported for the resolution of **1b**. This gave ca. 10% of the crystalline tartrate salt. Base treatment as described for **1b**, above, afforded **1c**, mp 52-3 °C (hexane); Anal. calcd: C, 66.65; H, 5.59; N, 9.14; found: C, 66.71; H, 5.63; N, 9.17; analytical hplc ([S.S]-β-Gem 1, Pirkle covalent, 25 cm x 4.6 mm I.D., Regis), 1.0 mL/min, hexane; $[\alpha]_D$= -48.8 (c=0.67, $CHCl_3$); IR (KBr, cm^{-1}) 3339, N-H; 3292, N-H; 1320, C-F; 300 MHz NMR ($CDCl_3$, ppm) δ 7.44 (1 H, dd, J= 8.78.7, 2.1 Hz) 7.22-7.12 (3 H, m) 7.06-7.00 (1 H, m) 6.75 (1 H, d, J= 7.8 Hz) 6.57 (1 H, d, J= 8.7 Hz) 6.35 (1 H, br s) 5.09 (1 H, s) 3.32-3.21 (1 H, m) 3.11-3.00 (2 H, m) 2.84-2.70 (1 H, m) 2.70 (3 H, s) 1.96 (1 H, br s). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) δ 151.1, 136.5, 134.9, 129.0, 127.6 q, 126.1 q, 126.4, 126.7, 126.0, 125.6, 123.5, 116.7 q, 109.5, 62.3, 43.0, 30.0, 29.5.

1-[5'-chloro-2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline isobutylidene aminal, 9.

To a solution of **1b** (2.86 g, 10.50 mmol) in 180 mL of MeOH was added isobutyraldehyde (1.9 mL, 21 mmol, 2 equiv) and catalytic acetic acid (0.1 mL) and the mixture was stirred at rt for 2 h. After removal of solvent (aspirator), the residue was purified by plug filtration chromatography on EM silica gel 60, 1:4 EtOAc/hexane 1% triethylamine eluent to yield 3.6 g of crude solid. Pure material was obtained by crystallization from ether/hexane (crop 1, 1.98 g; crop 2, 0.94 g, 85%), mp 114.5-115.5 C. Analytical tlc on EM silica gel 60, 1:9 EtOAc/hexane 1% triethylamine, Rf= 0.60.

Molecular ion calcd for $C_{20}H_{23}ClN_2$: 326.15506; found m/e= 326.1541, error= 3 ppm; base peak= 283 amu; IR (KBr, cm^{-1}) 3058, =C-H; 2840-2975, C-H; 270 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.30-7.13 (4 H, m) 7.04 (1 H, dd, J= 8.8, 2.5 Hz) 6.86 (1 H, dd, J= 2.5, 1.2 Hz) 6.44 (1 H, d, J= 8.6 Hz) 5.11 (1 H, s) 3.37 (1 H, d, J= 9.6 Hz) 3.20-3.06 (1 H, m) 3.06 (3 H, s) 2.80-2.60 (3 H, m) 2.15-1.96 (1 H, m) 1.02 (3 H, d, J= 6.9 Hz) 0.97 (3 H, d, J= 6.6 Hz). ^{13}C NMR (68 MHz, {H}, DEPT135, $CDCl_3$, ppm) δ 141.3 s, 134.8 s, 134.6 s, 129.9 d, 129.5 d, 127.8 d, 127.4 d, 127.0 d, 125.0 d, 121.9 s, 120.0 s, 110.9 d, 87.8 d, 53.9 d, 46.1 t, 40.9 d, 33.6 q, 28.9 t, 19.9 q, 18.8 q.

1-[2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline isobutylidene aminal (11).

A dry 50-mL flask with condenser, containing a 1" stir bar and magnesium turnings (600 mg, 25 mmol, Baker and Adamson) was flame dried under nitrogen flush. Mechanical activation (dry stirring) of the magnesium turnings was done for at least 5 h following the literature precedent.[10]

To another flask was added the aminal **9** (201 mg, 0.62 mmol). The solid was dissolved in 2 mL THF and transferred via cannula into the activated magnesium, followed by rinsing with THF (2 x 1 mL). Then 1,2 dibromoethane (0.1 mL, 1.1 mmol) was added, and after bubble evolution was evident, the solution was heated to reflux. After 15 h, the Grignard solution containing **10** was cooled to room temperature, and 10 mL sat'd NH_4Cl was added. After filtration through Celite, the layers were separated and the aqueous phase was extracted with ether (2 x 30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated (aspirator) to afford **11,** 190 mg (100%) as an oil. Analytical tlc on EM silica gel 60, 7:3 hexane/EtOAc, Rf= 0.64. Molecular ion calcd for $C_{20}H_{24}N_2$: 292.1940; found m/e= 292.1932, error= 3 ppm; base peak= 249 amu; IR (neat, cm^{-1}) 2908, =C-H; 300 MHz NMR ($CDCl_3$, ppm) δ 7.32-7.08 (5H, m) 6.92 (1H, dt, J= 7.4, 1.2 Hz) 6.55-6.49 (2H, m) 5.16 (1H, s) 3.39 (1H, d, J= 9.2 Hz) 3.18-3.06 (1H, m) 3.09 (3H, s) 2.86-2.72 (1H, m) 2.68-2.62 (2H, m) 2.10 (1H, d sept, J= 9.2, 6.6 Hz) 1.03 (3H, d, J= 6.6 Hz) 0.98 (3H, d, J= 6.6 Hz).

1-[5'-Carboethoxy-2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline isobutylidene aminal (12).

The Grignard reagent **10** was prepared as described above from magnesium turnings (600 mg, 25 mmol) and aminal **9** (255 mg, 0.78 mmol). After 15 h, the stark black Grignard solution was transferred via cannula into diethylcarbonate[11a] (0.280 mL, 2.4 mmol), stirred for 15 h, and then quenched with saturated NH_4Cl. The organic layer was separated and washed with brine. The combined aqueous extracts were basified to pH 9 with 1M NaOH, and extracted with ether. All organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated (aspirator). The residue was purified by flash chromatography on EM silica gel 60 (14 x 1 cm), 3:17 EtOAc/hexane 1% triethylamine eluent, 5 mL fractions; fractions 6-12, 251 mg of **12** (88%); analytical tlc on EM silica gel 60, 1:9 EtOAc/hexane 1% triethylamine, Rf= 0.28. Pure material was obtained by crystallization from ethanol, mp 134.8-135.0 C. Molecular ion calcd for $C_{23}H_{28}N_2O_2$: 364.21509; found m/e= 364.2165, error= 4 ppm; base peak= 321 amu; IR (KBr, cm^{-1}) 1697, C=O; 300 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.80 (1 H, dd, J= 8.4, 2.1 Hz) 7.66 (1 H, br s) 7.37 (1 H, br d, J= 7.4 Hz) 7.33-7.19 (2 H, m) 7.13 (1 H, br d, J= 7.4 Hz) 6.51 (1 H, d, J= 8.6 Hz) 5.17 (1 H, s) 4.27-4.16 (2 H, m) 3.46 (1 H, d, J= 9.7 Hz) 3.20-3.05 (1 H, m) 3.12 (3 H, s) 2.79-2.61 (3 H, m) 2.17-2.04 (1 H, m) 1.28 (3 H, t, J= 7.2 Hz) 1.04 (3 H, d, J= 6.6 Hz) 1.00 (3 H, d, J= 6.6 Hz).

1-[5'-Toluenesulfonyl-2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline isobutylidene aminal (13).

The Grignard solution containing **10** was prepared as described above from magnesium turnings (715 mg, 30 mmol) and aminal **9** (1.24 g, 3.8 mmol). After 9 h, the mixture was cooled to 0 °C, and *p*-toluenesulfonyl fluoride[11b] (741 mg, 4.2 mmol, 1.1 equiv, Aldrich, purity 98%) was added as a solution in 10 mL THF. The reaction was allowed to warm to rt and was stirred for 13 h. After the addition of 10 mL water, the biphasic solution was extracted with ether (4 x 40 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to a foam (1.73 g). The residue was purified by flash chromatography on EM silica gel 60 (7 x 4 cm) 7:3 (100 mL) to 1:1 hexane/EtOAc eluent (10 mL fractions; fractions 2-3, 107 mg **11**, 10%; fractions 9-17, 1.43 g **13**, 85%); analytical tlc on EM silica gel 60, 7:3 hexane/EtOAc, Rf= 0.27. Molecular ion calcd for $C_{27}H_{30}N_2O_2S$: 446.20285; found m/e= 446.2005, error= 5 ppm; base peak= 405 amu; IR ($CHCl_3$, cm^{-1}) 1592, C=C; 300 MHz NMR ($CDCl_3$, ppm) δ 7.66 (2 H, d, J= 8.4 Hz) 7.62 (1 H, dd, J= 9.1, 2.3 Hz) 7.44 (1 H, dd, J= 2.3, 1.2 Hz) 7.34-7.16 (5 H, m,) 7.12 (1 H, br d, J= 7.4 Hz) 6.51 (1 H, d, J= 8.8 Hz) 5.10 (1 H, s) 3.45 (1 H, d, J= 9.3 Hz) 3.15-3.05 (1 H, m) 3.08 (3 H, s) 2.68-2.58 (3 H, m) 2.34 (3 H, s) 2.14-1.95 (1 H, m) 1.01 (3 H, d, J= 6.8 Hz) 0.97 (3 H, d, J= 6.6 Hz).

1-[5'-Carboethoxy-2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1d).

A 250-mL flask was charged with **12** (1.563 g, 4.29 mmol) and 150 mL of 10% HCl and the solution was heated to 60 °C under a nitrogen stream. After 3 h the mixture was cooled to rt, diluted with 60 mL of ether, neutralized with saturated sodium bicarbonate, and basified to pH 9 with 1M NaOH. The layers were separated and the aqueous layer extracted (3 x 60 mL) with ether. The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated (aspirator) to give **1d** (1.46 g) as a yellow oil. The residue was purified by flash chromatography on EM silica gel 60 (15 x 4 cm), 1:4 acetone/hexane 5% triethylamine eluent (15 mL fractions); fractions 10-26, 1.09 g **1d**, 82%; analytical tlc on EM silica gel 60, 1:4 EtOAc/hexane 5% triethylamine, Rf= 0.12. Molecular ion calcd for $C_{19}H_{22}N_2O_2$: 310.16815; found m/e= 310.1683, error= 0 ppm; IR ($CHCl_3$, cm^{-1}) 1692, C=O; 3325, N-H; 300 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.91 (1 H, dd, J= 8.6, 1.9 Hz) 7.75 (1 H, d, J= 1.9 Hz) 7.20-7.05 (2 H, m) 7.05-6.92 (1 H, m) 6.76 (1 H, br d, J= 8.0 Hz) 6.55 (1 H, br s) 6.52 (1 H, d, J= 8.7 Hz) 5.10 (1 H, s) 4.37-4.25 (2 H, m) 3.35-3.20 (1 H, m) 3.15-3.00 (2 H, m) 2.85-2.60 (1 H, m) 2.69 (3 H, br d, J= 3.1 Hz) 2.02 (1 H, br s) 1.36 (3 H, t, J= 7.1 Hz).

1-[5'-Toluenesulfonyl-2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (1e).

To **13** (437 mg, 0.98 mmol) was added 50 mL of 10% HCl and the mixture was heated to 60 °C under a nitrogen stream for 3 h. After cooling to rt, the solution was neutralized with sat'd Na_2CO_3 and taken to pH 10 with 1M NaOH. After extraction with CH_2Cl_2 (3 x 15 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated (aspirator) to give a yellow oil. The residue was purified by flash chromatography on EM silica gel 60 (12 x 1.5 cm) 1:1 hexane/EtOAc eluent (10 mL fractions); fractions 8-13, 345 mg **1e**, 90%; analytical tlc on EM silica gel 60, 1:1 hexane/EtOAc, Rf= 0.32. Molecular ion calcd for $C_{23}H_{24}N_2O_2S$: 392.1559; found m/e= 392.1542, error= 4 ppm; IR (neat, cm^{-1}) 3323, N-H; 1146, SO_2; 300 MHz NMR ($CDCl_3$, ppm) δ 7.78-7.70 (3H, m) 7.54 (1H, d, J= 2.2 Hz) 7.25 (2H, d, J= 8.1 Hz) 7.20-7.10 (2H, m) 6.98 (1H, td, J= 7.0, 2.6 Hz)

6.72 (1H, br s) 6.64 (1H, d, J= 7.7 Hz) 6.53 (1H, d, J= 8.8 Hz) 5.07 (1H, s) 3.28-3.18 (1H, m) 3.12-2.96 (2H, m) 2.85-2.71 (1H, m) 2.68 (3H, s) 2.38 (3H, s) 2.04 (1H, br s).

1-[5'-Nitro-2'-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline, (1f).

To **1a** (987 mg, 3.38 mmol) in 30 mL of acetonitrile at -40 °C was added a solution of nitronium tetrafluoroborate (497 mg, 3.21 mmol, 0.95 equiv, Aldrich) in 35 mL of acetonitrile over 1.5 h and the mixture was stirred at this temperature for an additional 30 min. The solution was warmed to 0 °C and quenched with sat'd $NaHCO_3$ solution (50 mL). The reaction was extracted with ether (3 x 50 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to give an orange/black solid. To this crude residue was added 50 mL 1.5N HCl and 50 mL THF and the mixture was stirred for 10 h, and then was heated to 55 °C under a constant nitrogen stream for 2 h. After cooling to rt, the reaction was neutralized with sat'd Na_2CO_3 solution and extracted with ether (4 x 50 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to give an orange oil. ^1H NMR analysis of this material indicated a small amount of dinitration product was present, so the crude residue was purified by flash chromatography on EM silica gel 60 (5 x 3 cm, fraction 8-22) CH_2Cl_2 eluent to give 526 mg (55%) of **1f**. Analytical tlc on EM silica gel 60, CH_2Cl_2, Rf= 0.30. Pure material was obtained by crystallization from benzene/pentane (mp 172-173.5 °C, orange cubes, 454 mg). Molecular ion calcd for $C_{16}H_{17}N_3O_2$: 283.13210; found m/e= 283.1315, error= 2 ppm; IR (neat, cm^{-1}) 3226, N-H; 1296, NO_2; 300 MHz NMR ($CDCl_3$, ppm) δ 8.14 (1H, dd, J= 9.2, 2.6 Hz) 7.95 (1H, d, J= 2.6 Hz) 7.29-7.10 (3H, m) 7.05 (1H, td, J= 7.1, 2.4 Hz) 6.77 (1H, d, J= 7.7 Hz) 6.50 (1H, d, J= 9.2 Hz) 5.14 (1H, s) 3.33-3.24 (1H, m) 3.15-3.05 (2H, m) 2.85-2.78 (1H, m) 2.79 (3H, d, J= 5.1 Hz) 2.06 (1H, br s).

***N*-2, 4, 6-trimethylbenzoylalanine methyl ester (5c).**

To 2,4,6-trimethylbenzoic acid (733 mg, 4.46 mmol) in 10 mL CH_2Cl_2 was added oxalyl chloride (0.40 mL, 4.46 mmol) and 1 drop DMF. After 3 h, the solvents were evaporated, and 15 mL CH_2Cl_2 and racemic alanine methyl ester hydrochloride (625 mg, 4.46 mmol) were added. With a room temperature bath for cooling, triethylamine (1.55 mL, 11.2 mmol) was added dropwise over 5 min and the solution was stirred at room temperature for 1 h. After the addition of 15 mL of 1.5

N HCl, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water:sat'd Na_2CO_3 (1:1, 10 mL), dried ($MgSO_4$), and evaporated (aspirator) to a golden oil. The residue was purified by flash chromatography on EM silica gel 60 (14 x 1.7 cm, 10 mL, fraction 4-8, 1.06 g, 71%), 7:3 hexane/EtOAc eluent; analytical tlc on EM silica gel 60, 7:3 hexane/EtOAc, Rf= 0.26. Pure **5c** was obtained by crystallization from ethyl acetate, mp 88.5-89.5 C. Molecular ion calcd for $C_{14}H_{19}NO_3$: 249.13650; found m/e= 249.1370, error= 2 ppm; base peak= 147 amu; IR (neat, cm^{-1}) 3263, N-H; 1751, C=O; 1639, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 6.84 (2H, s) 6.18 (1H, d, J= 7.0 Hz) 4.83 (1H, dq, J= 7.4, 7.4 Hz) 3.78 (3H, s) 2.29 (6H, s) 2.27 (3H, s) 1.51 (3H, d, J= 7.4 Hz). ^{13}C NMR ($CDCl_3$, ppm) δ 173.3 s, 169.9 s, 138.6 s, 134.3 d, 128.2 s, 128.2 s, 52.5 d, 47.9 q, 21.1 q, 19.0 q, 18.5 q.

_N_-1-Naphthoyl alanine methyl ester (5d).

To 1-naphthoic acid (735 mg, 4.27 mmol) in 10 mL CH_2Cl_2 and 1 drop DMF was added oxalyl chloride (0.417 mL, 4.70 mmol). After 6 h the solvent was evaporated and the residue was dissolved in 15 mL CH_2Cl_2. After the addition of racemic alanine methyl ester hydrochloride (596 mg, 4.27 mmol, Aldrich), triethyl amine (0.892 mL, 6.4 mmol) was added dropwise while cooling with a water bath. After 1 h, 15 mL 1.5 N HCl was added and extracted with CH_2Cl_2 (2x30mL). The CH_2Cl_2 layers were combined and extracted with 1:1 sat'd Na_2CO_3/water (10 mL) and the aqueous layer was back extracted with 10 mL CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated to a white solid (904 mg, 82%). ^1H NMR analysis showed the presence of 8% of an isomeric product, probably derived from 2-naphthoic acid. The residue was purified by flash chromatography on EM silica gel 60 (20 x 3 cm, 15 mL, fractions 11-15, 545 mg, 49%), 7:3 (100 mL) to 1:1 hexane/EtOAc eluent; analytical tlc on EM silica gel 60, 7:3 hexane/EtOAc, Rf= 0.21. Pure material was obtained by crystallization from ethyl acetate/hexane, mp 130.5-131.5 C. Molecular ion calcd for $C_{15}H_{15}NO_3$: 257.10520; found m/e= 257.1055, error= 1 ppm; base peak= 155 amu; IR (neat, cm^{-1}) 3280, N-H; 1743, C=O; 1643, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 8.36 (1H, d, J= 8.6 Hz) 7.95-7.86 (2H, m) 7.67 (1H, dd, J= 7.0, 1.1 Hz) 7.60-7.44 (3H, m) 6.56 (1H, d, J= 6.3 Hz) 4.93 (1H, dq, J= 7.4, 7.4 Hz) 3.82 (3H, s) 1.59 (3H, d, J= 7.4 Hz).

Deracemization of Naproxen Diisopropyl Amide (16); Representative procedure for Table 2.

To racemic **16**[3] (50.0 mg, 0.16 mmol) in 2 mL of THF was added *sec*-BuLi (202 μL, 0.28 mmol, 1.38 M in cyclohexane, 1.75 equiv) and the solution was stirred at -78 °C for 1 h. After dropwise addition of a solution of **1d** (99 mg, 0.32 mmol, 2 equiv) in 1.0 mL THF, the solution was stirred for 30 min at -78 °C, followed by warming to 0 °C over 1 h and quenching with 1 mL sat'd NH_4Cl. The reaction was partitioned between 10 mL ether and 10 mL 1.5N HCl and the aqueous layer was washed with 10 mL ether. The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to afford **16** (50 mg, 100%) in >95% purity by ^{1}H NMR assay. After silica plug filtration (EtOAc eluent), HPLC analysis as described in Table 4 indicated 40 % ee favoring the second eluting enantiomer (*R*)-**16**. In a similar experiment, the reaction mixture was quenched with a THF/sat'd NH_4Cl solution at -78 °C, but the same result was obtained. To recover the **1d**, the aqueous layer above was basified to pH 10 using a 1M NaOH solution and extracted with ether (3 x 15 mL). The combined ether layers were dried ($MgSO_4$) and evaporated to afford 75 mg (76%) **1d**.

Asymmetric protonation of 7.

The yellow lactone enolate 7 was generated as previously described[3] from 1.75 equiv. of mesityllithium. Sulfonamide **3e** (2.0 equiv) was added at -78 °C as described for **16**. A deepening of the yellow color was observed. After 30 min at -78 °C, the solution was allowed to warm to -23 °C and aqueous NH_4Cl was added. The enantiomer excess (58% ee) was determined as described previously.[3]

Deracemization of Amino Acid Derivatives; Representative procedure for Table 3.

The procedure for the deracemization of **5a**[17a] is shown as an example. The other amino acid substrates for Table 3 including entry 5 (**5b**; N-Cbz methyl alaninate),[17b] entry 6 (**5c**; methyl N-mesitoylalaninate)[17c], entry 7 (**5d**; methyl N-α-naphthoylalaninate), entry 8 (**5e**; ethyl N-benzoylalaninate),[17d] entry 9 (**5f**; *tert*-butyl N-benzoylalaninate),[17e] entry 10 (**5g**; methyl α-benzamidobutyrate),[17f] and entry 11 (**5g**; methyl N-benzoylphenylalaninate)[17g] were deracemized by the same method.

To bromomesitylene (55 µL, 0.359 mmol, 2.5 equiv, Aldrich) in 0.5 mL THF at -78 °C was added *t*-BuLi (391 µL, 0.704 mmol, 4.9 mmol, 1.80M in pentane, Aldrich) and the solution was stirred for 30 min with comcomitant formation of a white precipitate. In a separate flask, **5a** (29 mg, 0.14 mmol) was dissolved in 0.5 mL THF and added *via* cannula to the mesityl-Li. The flask was rinsed with an additional 0.5 mL THF (added by syringe and then added *via* cannula to the mesityl-Li solution . After stirring 1 h, **1e** (1.25 mL of a 0.35M solution in THF, 0.44 mmol, 173 mg) was added and the solution was stirred for 30 min at -78 °C, followed by warming to -20 °C over 20 min. The reaction was quenched with 1 mL sat'd NH_4Cl and partitioned between 10 mL 1.5N HCl and 10 mL ether, which produced an insoluble orange oil that crystallized on standing. After separation of the ether layer, the orange crystals (or oil) and aqueous layer were washed with 10 mL ether. The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to afford 29 mg of material that was greater than 90% **5a** by ^1H NMR assay and contained less than 10 % residual mesitylene. HPLC analysis was conducted as in Table 2 to afford a 7.5:92.5 ratio of peaks for the (*R*) and (*S*) enantiomers (85% ee). To recover **1e**, the aqueous layer and the orange crystals (or oil) (dissolved in THF) were basified to pH 10 with NaOH solution and extracted with ether (2 x 20 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated (aspirator) to give 176 mg of a golden foam (**1e**, >95%).

Deracemization of lactates; representative procedure.

The procedure for the deracemization of ethyl *O*-benzyl lactate **4b**[18] is given as a representative example. The BHT lactate ester **4a**[19] was deracemized by a similar method, but with *sec*-butyllithium as the base. To hexamethyldisilazane (63.2 µL, 0.30 mmol, 2.0 equiv, Aldrich) in 0.5 mL THF at -20 °C was added dropwise *n*-BuLi (187 µL, 0.30 mmol, 2.0 equiv, Aldrich) and the solution was stirred for 20 min. After cooling this solution to -78 °C, **4b** was added (0.81 mL of a 0.19 M solution in THF, 35 mg, 0.15 mmol) and the resulting solution was warmed to -40 □C for 2 h. After cooling to -78 °C, **1e** (0.85 mL of a 0.48M solution in THF, 161 mg, 0.41 mmol) was added and the solution was stirred for 30 min at this temperature. After warming to -20 °C over 30 min, 1 mL sat'd NH_4Cl was added. The resulting biphasic solution was partitioned between 10 mL ether and 10 mL 1.5N HCl and the aqueous layer was washed with 10 mL ether. The combined ether layers were dried ($MgSO_4$), and evaporated to give 30 mg (85%) ethyl *O*-benzyl lactate. HPLC analysis was conducted as in Table 4 to afford 45% ee favoring the second eluting enantiomer (*R*).

HPLC Methods.

General: Standard procedure for the HPLC analyses included equilibrating column to constant baseline. The enantiomer separation was validated by testing the racemic mixture at the beginning of each session. Detection was by UV at 240/254 nm or 220/240 nm depending on analyte and enantiomer ratios were obtained using both wavelengths. All flow rates are 1.0 mL/min unless otherwise stated.

Table 4. HPLC Assay Methods.

Material	Chiral Stationary Phase	Conditions, retention time (flow rate= 1 mL/min)
Naproxen *N,N*-diisiopropyl amide**16**	Pirkle type (*S, S*) Beta gem 1 (Regis)	9/1 hexane/IPA, RT 6.4 min (*S*), 9.5 min (*R*)[3]
BnOCH(CH_3)CO_2Et (**4b**)	Chiralcel OJ	93/7 hexane/IPA, RT 9.3 min (*S*), 10.6 min (*R*)
BnOCH(CH_3)CO_2BHT (**4a**)	(*R,R*)-Whelk-O 1 (Regis)	199/1 hexane/IPA, RT 5.0 min, 5.7 min

Table 5. HPLC Methods for the α-Amino Acid Derivatives.

Table 3 entry/substrate	Chiral Stationary Phase	Conditions, retention time (flow rate= 1 mL/min)
1-4 (**5a**)	(*R*,*R*)-Whelk-O 1 (Regis)	17/3 hexane/IPA, RT 20.9 min (*R*), 25.7 min (*S*)[a]
5 (**5b**)	α-Burke	19/1 hexane/IPA, RT 14.0 min (*R*), 14.7 min (*S*)[b]
6 (**5c**)	(*R*,*R*)-Whelk-O 1	17/3 hexane/IPA, RT 27.6 min (*R*), 34.2 min (*S*)[c]
7 (**5d**)	(*R*,*R*)-Whelk-O 1	7/3 hexane/IPA, RT 28.3 min (*R*), 35.6 min (*S*)[c]
8 (**5e**)	α-Burke	9/1 hexane/IPA, RT 11.5 min (*R*), 13.0 min (*S*)[c]
9 (**5f**)	α-Burke	11.5/1 hexane/IPA, RT 7.9 min (*R*), 8.6 min (*S*)[c]
10 (**5g**)	α-Burke	9/1 hexane/IPA, RT 11.6 min (*R*), 12.7 min (*S*)[d]
11 (**5h**)	α-Burke	39/1 hexane/IPA, RT 31.9 min (*R*), 34.4 min (*S*)[e]

Stereochemical assignments: (a) comparison with authentic methyl N-benzoyl-(*R*)-alaninate. (b) comparison with authentic methyl N-Cbz-(*S*)-alaninate. (c) by analogy to entries 1-4 based on similar structure and chromatographic behavior. (d) by analogy to entries 1-4 and entry 12 based on similar structure and chromatographic behavior. (e) from authentic methyl N-benzoyl-(*S*)-phenylalaninate.

11. (a) Frye, L. L.; Sullivan, E. L.; Cusack, K. P.; Funaro, J. M. *J. Org. Chem.* **1992**, *57*, 697. (b) Whitmore, F. C.; Loder, D. J. in *Organic Syntheses*, Wiley & Sons: New York, 1943; Collect. Vol. II, pp 282.

12. Ott, H.; Hardtmann, G.; Denzer, M., Frey, A.J.; Gogerty, J.H.; Leslie, G.H.; Trapold, J.H. *J. Med. Chem.* **1968**, 777.

13. The pKa= *ca.* 31 for **16** is reported in ref. 3 based on measurements by F. G. Bordwell and A. V. Satish.

14. Buncel, E.; Menon, B. *J. Org. Chem.* **1979**, *44*, 317. Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299. Streitwieser, A., Jr. *Acc. Chem. Res.* **1984**, *17*, 353. Kaufman, M. J.; Gronert, S.; Bors, D. A.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 602. Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6092. Krom, J. A.; Petty, J. T.; Streitwieser, A. *J. Am. Chem. Soc.* **1993**, *115*, 8024.

15. There is disagreement on the pKa(DMSO) of ethyl acetate (a) pKa (DMSO)= ca. 30, Bordwell, F. G.; Branca, J. C.; Bares, J. E.; Filler, R. *J. Org. Chem.* **1988**, *53*, 780. (b) pKa (DMSO)= 27.45, Arnett, E.M.; Harrelson, J.A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809.

16. Delocalization in the *p*-nitroaniline **1f** is consistent with planarization of the N-methyl bond and the adjacent aromatic carbons (1.3□ dihedral angle; see Supporting Information).

17. (a) Berkowitz, D. B. *Synth. Commun.* **1990**, *20*, 1819. (b) Kolar, A. J.; Olsen, R. K. *Synthesis* **1977**, 457. (c) Fuji, T.; Itaya, T.; Yoshida, S.; Matsubara, S. *Chem. Pharm. Bull.* **1989**, *37*, 3119. (d) Elliot, I. W. *J. Org. Chem.* **1962**, *27*, 3302. (e). Vollmar, A.; Dunn, M. S. *J. Org. Chem.* **1960**, *25*, 387. (f) Brunner, H.; Knott, A.; Kunz, M.; Thalhammer, E. *J. Organomet. Chem.* **1986**, *308*, 55. (g) Wightman, R. H.; Staunton, J.; Battersby, A. R.; Hanson, K. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2355.

18. Mislow, K.; O'Brien R. E.; Schaefer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1940.

19. Heathcock, C. H.; Pirrung, M. C.; Young S. D; Hagen, J. P.; Jarvi, E. T.; Badertscher U.; Märki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161.

11. (a) Frye, L. L.; Sullivan, E. L.; Cusack, K. P.; Funaro, J. M. *J. Org. Chem.* **1992**, *57*, 697. (b) Whitmore, F. C.; Loder, D. J. in *Organic Syntheses*, Wiley & Sons: New York, 1943; Collect. Vol. II, pp 282.

12. Ott, H.; Hardtmann, G.; Denzer, M., Frey, A.J.; Gogerty, J.H.; Leslie, G.H.; Trapold, J.H. *J. Med. Chem.* **1968**, 777.

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14. Buncel, E.; Menon, B. *J. Org. Chem.* **1979**, *44*, 317. Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299. Streitwieser, A., Jr. *Acc. Chem. Res.* **1984**, *17*, 353. Kaufman, M. J.; Gronert, S.; Bors, D. A.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 602. Kaufman, M. J.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6092. Krom, J. A.; Petty, J. T.; Streitwieser, A. *J. Am. Chem. Soc.* **1993**, *115*, 8024.

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18. Mislow, K.; O'Brien R. E.; Schaefer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1940.

19. Heathcock, C. H.; Pirrung, M. C.; Young S. D; Hagen, J. P.; Jarvi, E. T.; Badertscher U.; Märki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161.