Chapter A

Preparation of Chiral Anilino-isoquinolines by Diastereomeric Pairs Crystallization Technique

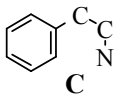
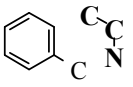
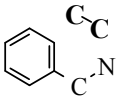
Racemates resolution *via* diastereomer pairs crystallization technique is the most straightforward route to optically active amines.[1] In this type of reaction, substrate (racemic amine) is treated with one enantiomer of a chiral substance (the resolving agent, chiral acid). Diastereomer pairs usually 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.

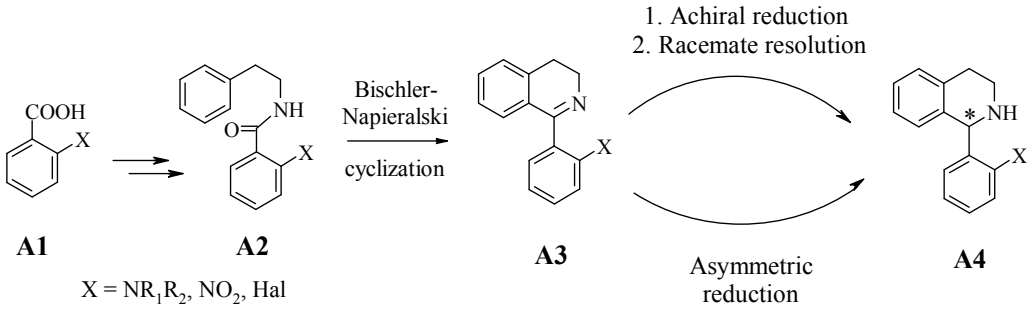
1. Synthesis of racemic 1-anilino-1,2,3,4-tetrahydroisoquinolines. Optimization of Bischler-Napieralski cyclization.

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**

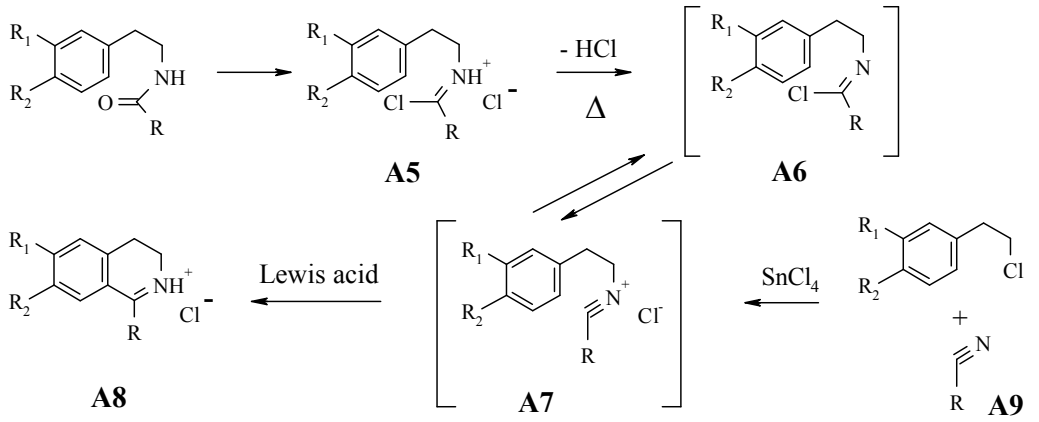
Bischler-Napieralski cyclization is somewhat more attractive compared to the alternatives because it employs relatively easily available substituted benzoic acids **A1** as the starting material. Moreover, the cyclization affords C=N double bond containing 3,4-dihydroisoquinolines **A3**, that potentially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



X = NR_1R_2, NO_2, Hal

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.**

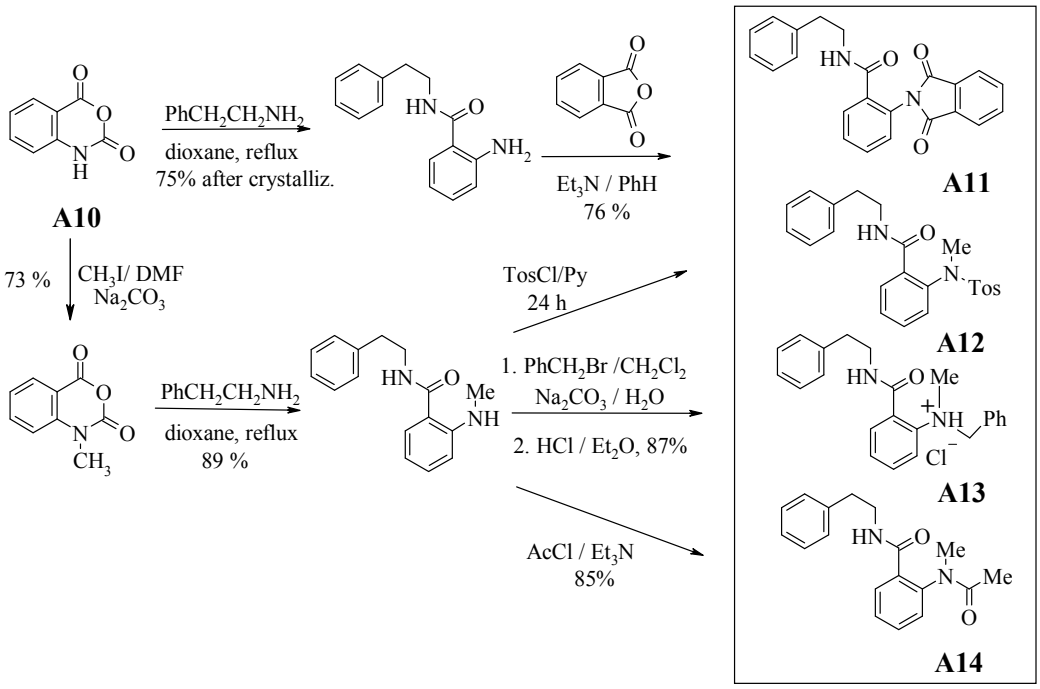
Scheme A1.



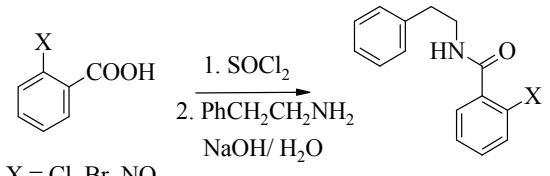
It was also shown that related nitrilium salts **A7** prepared by direct alkylation of the corresponding nitriles **A9** yield 3,4-dihydroisoquinolines **A8** in the presence of various Lewis acids ($SnCl_4$, $ZnCl_2$).[6] Employing P_2O_5 and polyphosphoric acid esters as dehydrating agents resulted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

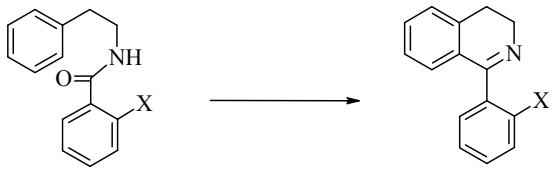


Electron-withdrawing N-protecting groups were chosen assuming that an electron-deficient 1-aryl substituent could polarize an amide carbonyl group, thus facilitating formation of the corresponding imidoyl chloride **A6** and, consequently, the nitrilium intermediate **A7** (Scheme A1). An alternative 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.



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**.



A11-A16 **A17-A21**

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.

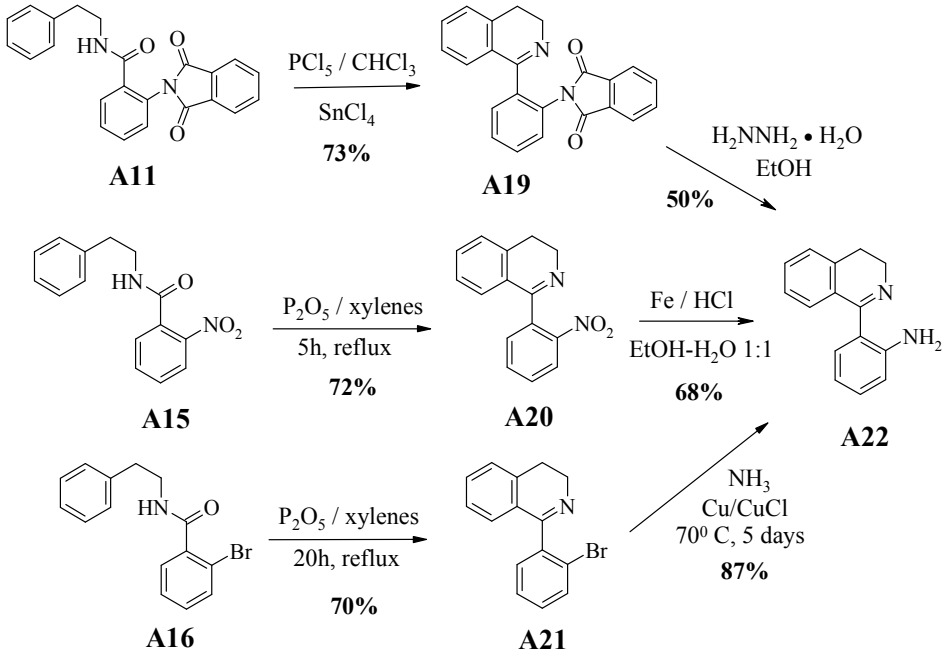
Initially, N-benzyl group was employed for N-methyl aniline protection (entry 1). The tertiary amine was converted to hydrochloric salt **A13** (See Scheme A2), making the aryl group electron-deficient and thus favoring imidoyl phosphate **A6** formation (see Scheme A1). Also, it was expected that ammonium 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]

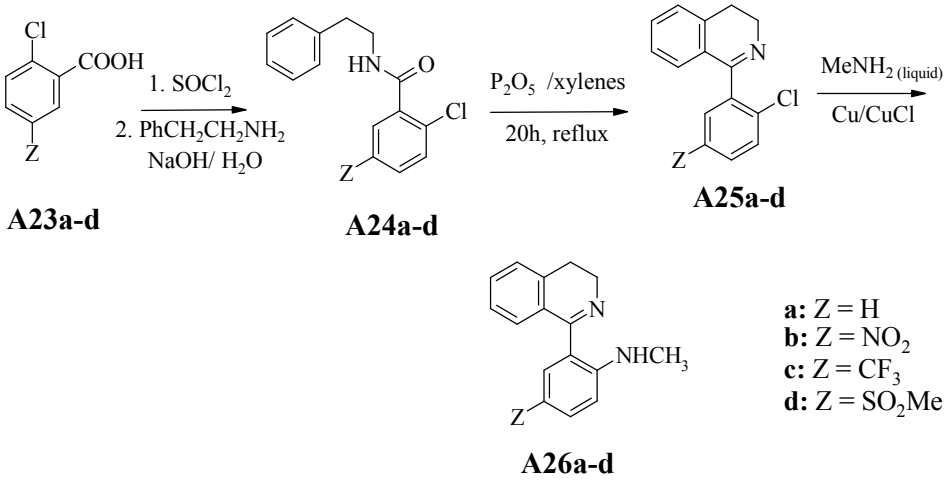
Since β-phenethylamides **A11**, **A15** and **A16** are almost equally good Bischler-Napieralski cyclization substrates, overall reaction sequence to 1-anilino-3,4-dihydroisoquinoline **A22** was examined for each amide **A11**, **A15** and **A16** in order to evaluate the most efficient route to the 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 37% overall yield. Higher overall yield (ca. 50%) 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 61% overall yield.

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).

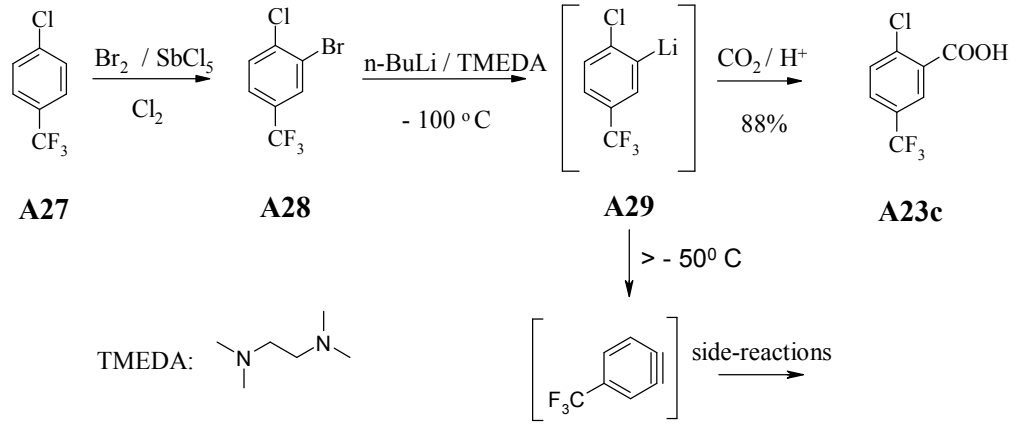
Scheme A4.



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

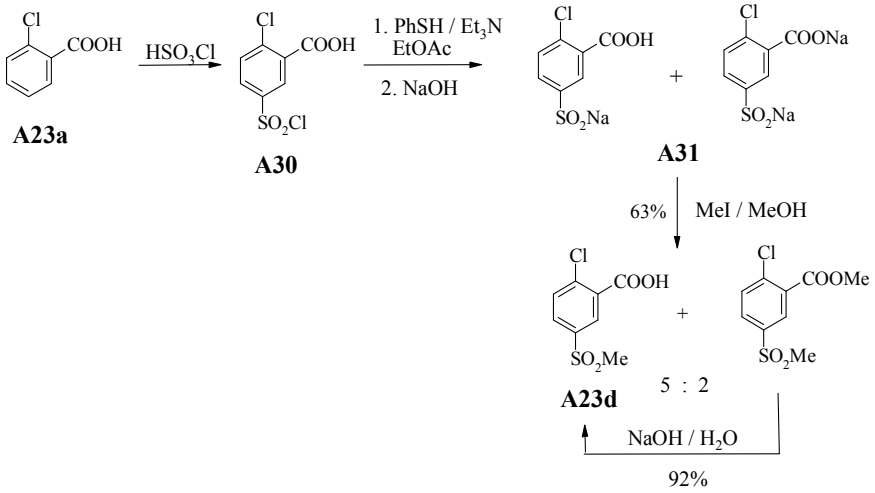
Scheme A5.



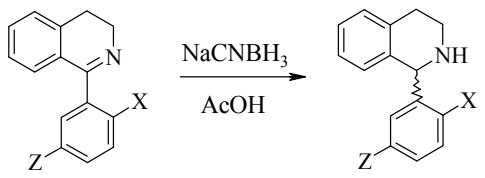
Bromination was performed according to the literature procedure[10] followed by selective lithium-bromine exchange in **A28**.[11] Low temperature (-100 ^{0}C) is crucial to achieve chemoselectivity in the metalation reaction as well as to avoid side-reactions *via* dehydrobenzene, which are dominant 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).



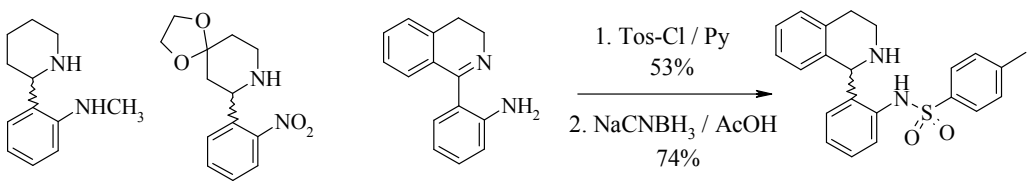
A20, A22, A26a-d

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-tetrahydroisoquinoline (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.

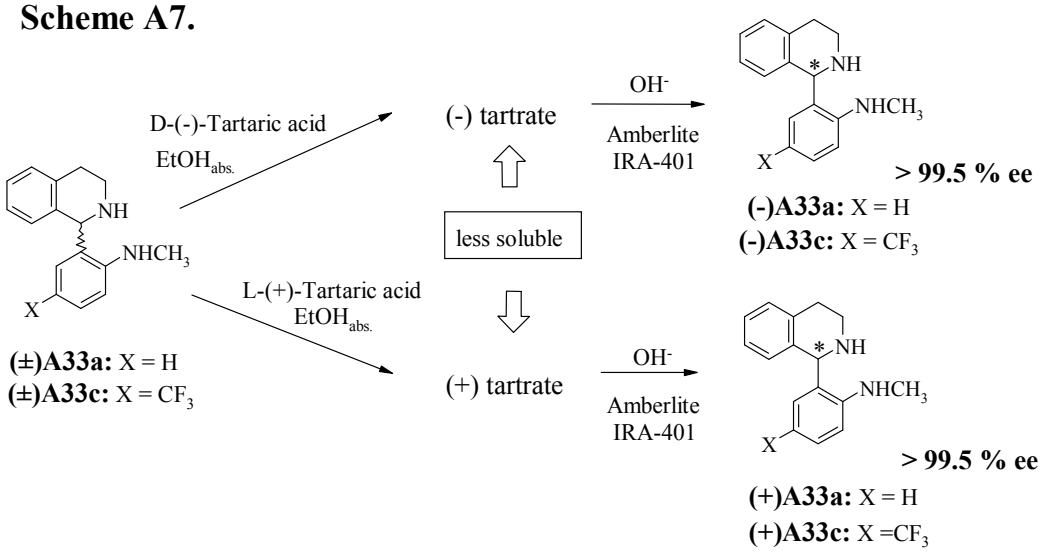


A34 **A35** **A22** **A36**

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**.

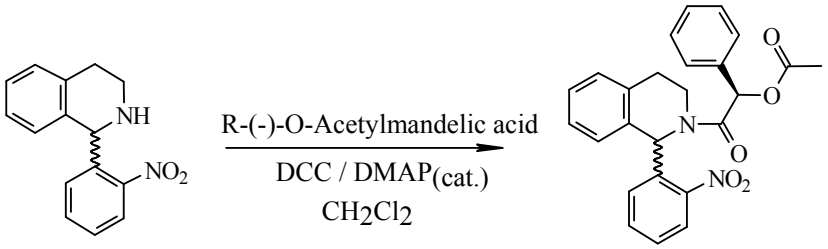
Thus, only moderate success has been achieved in the preparation of chiral diamines by diastereomeric salt crystallization. Moreover, it was clearly shown that the process is highly substrate-dependent and even small changes in substrate structure affect the efficiency of resolution. Consequently, racemates 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.

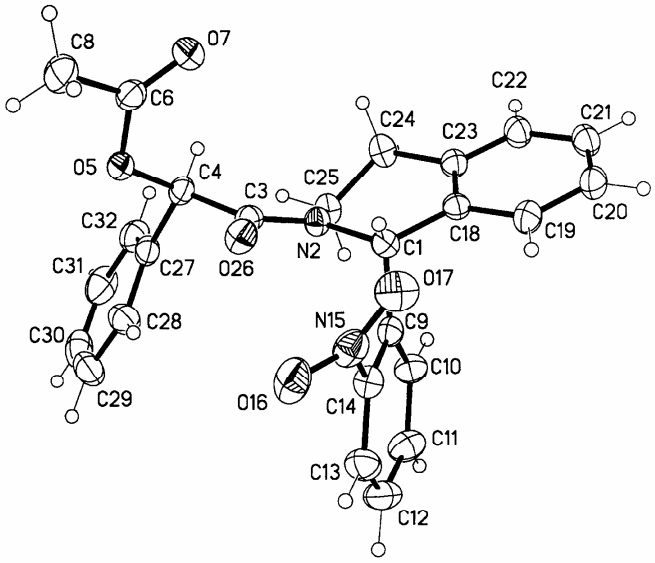
It has been recognized that multiple interactions between the resolution substrate and resolving agent are essential for successful resolution. Consequently, chiral acid should possess an aromatic ring and an additional functional group besides the acid functionality.[1c] A promising candidate is mandelic 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**.

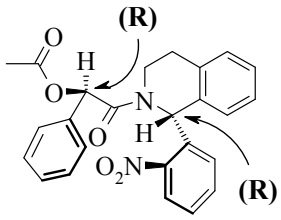
Treatment of nitro-isoquinoline **A31** with commercially available (*R*)-O-acetylmandelic acid in the presence of dicyclohexylcarbodiimide gave amide **A37** as a 1:1 mixture of diastereomers:



A31 **A37**

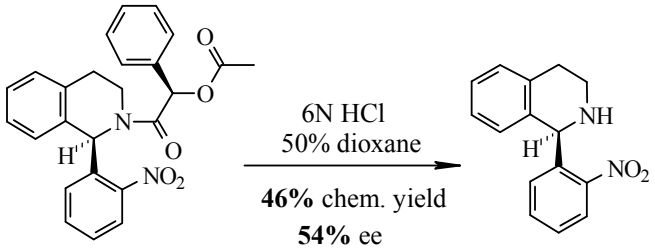
All attempts to separate **A37** diastereomers by flash chromatography on silica gel failed. As amide **A37** is solid, crystallization was applied in the hope that diastereomers have difference in solubility. Indeed, two crystallizations from ethyl acetate - hexanes gave a single amide **A37** diastereomer 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**

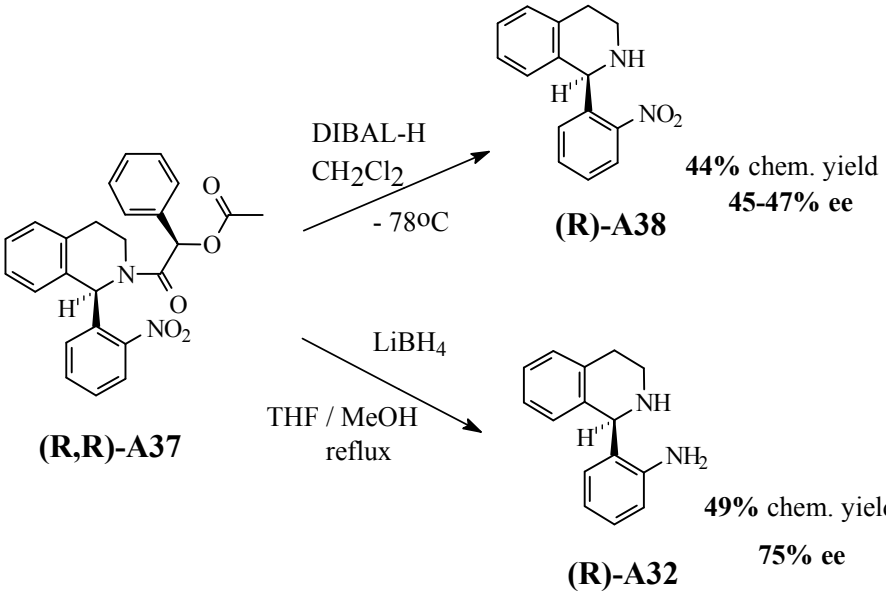
Although use of less concentrated hydrochloric acid (1N) resulted in a lower degree of racemization (67% ee), the chemical yield was too poor (10%) to utilize this method on a preparative scale.

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 substrate solubility in common solvents such as THF, ether and toluene. The

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

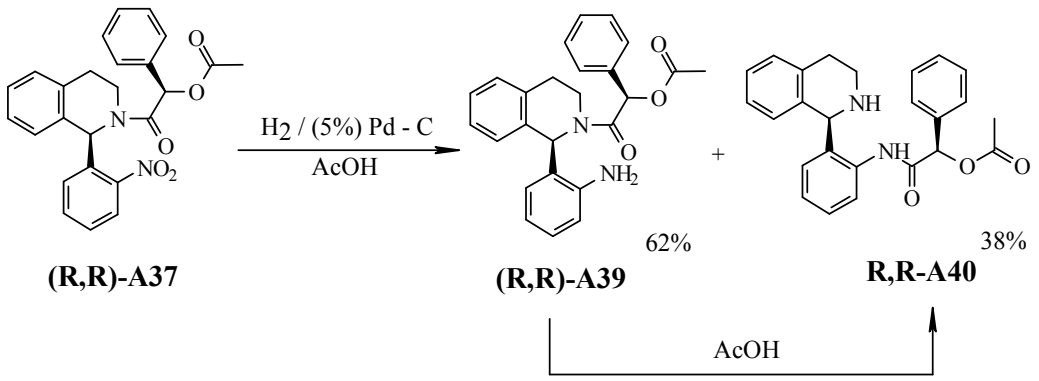
solubility of **(*R,R*)-A37** in CH_2Cl_2 allowed to perform the reduction with DIBAL-H (Scheme A8).[21]

Scheme A8.

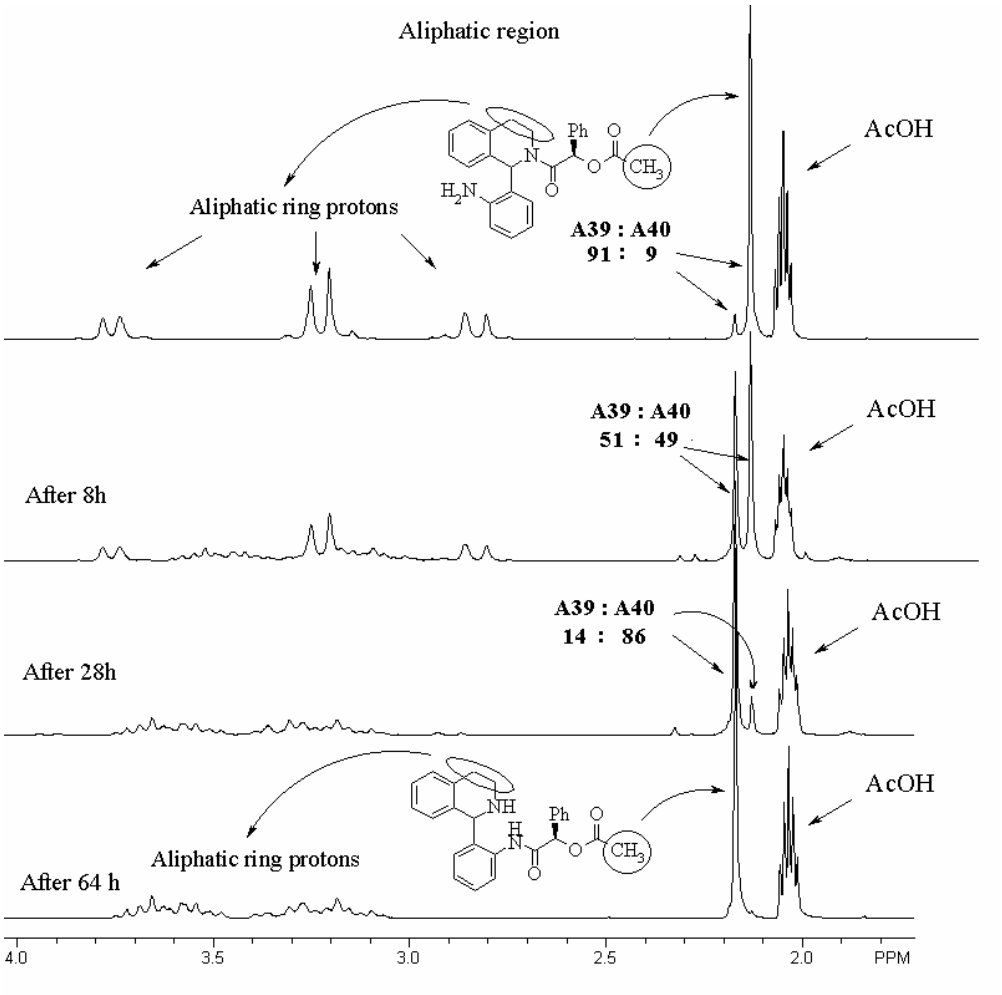


Surprisingly, product isoquinoline **A38** isolated in 44% yield, was again partially racemized. Optical yield did not improve even when the reaction was performed at –100 ^{0}C (by DIBAL-H addition to a melting surface of the reaction mixture). As expected, nitro group was left unaffected. Partial racemization (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 ($LiAlH_4$, $LiAlH(t\text{-}BuO)_3$, 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**.

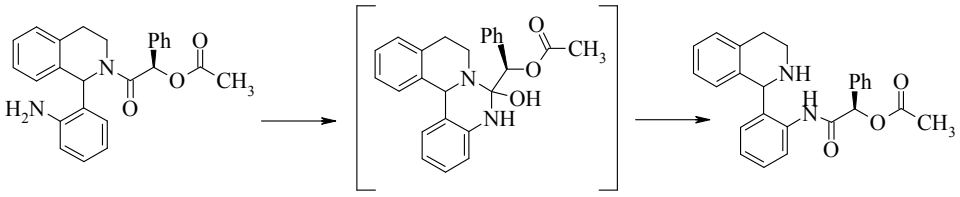


^{1}H-NMR experiments in acetic acid-d_4 showed that 50% of aniline **A39** has been already rearranged to isoquinoline **A40** after 8h at 20 ^{0}C, while complete acyl group migration was observed after 64 h at room temperature (ca. 4% of starting material **A39**).



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**:



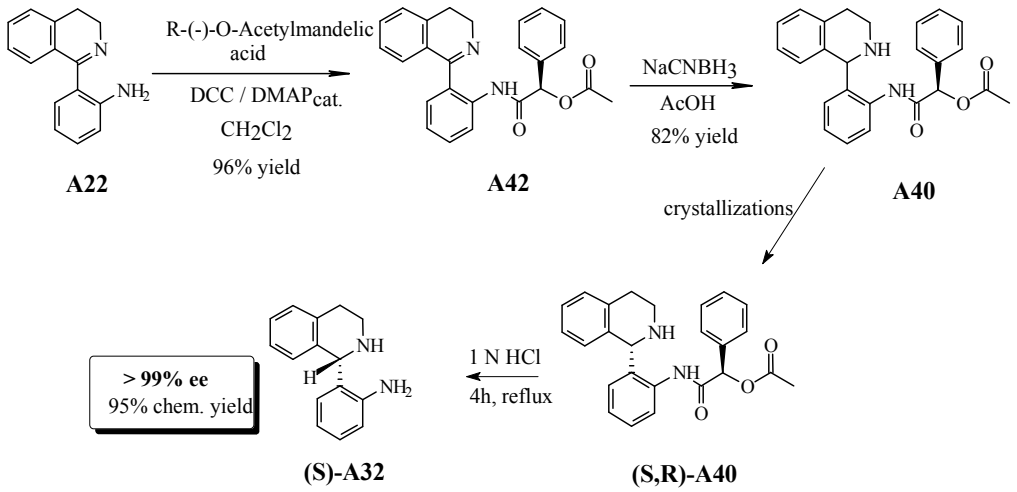
A39 **A41** **A40**

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.

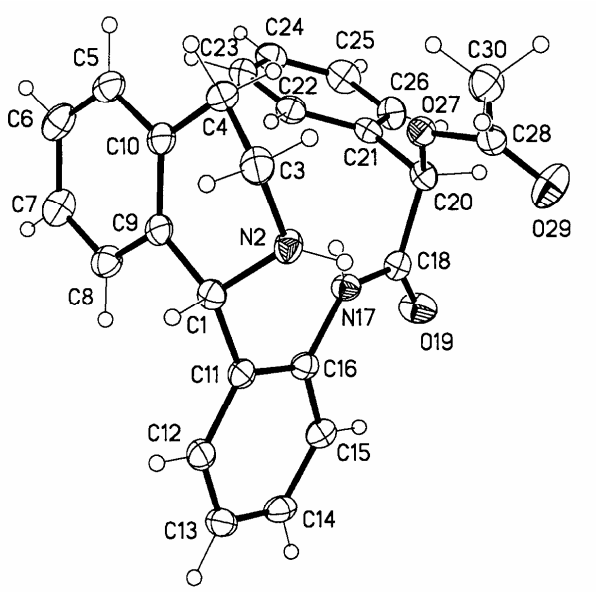
To verify the structure of the amide **A40**, it was decided to prepare it using an alternative pathway (Scheme A9). Besides, in the case of successful amide **A40** diastereomers separation, cleavage of the O-acetylmandelic auxiliary would cause fewer concerns because chiral N-unsubstituted isoquinolines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

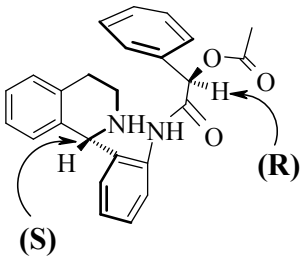
Scheme A9.



A22 **A42** **A40** **(S)-A32** **(S,R)-A40**

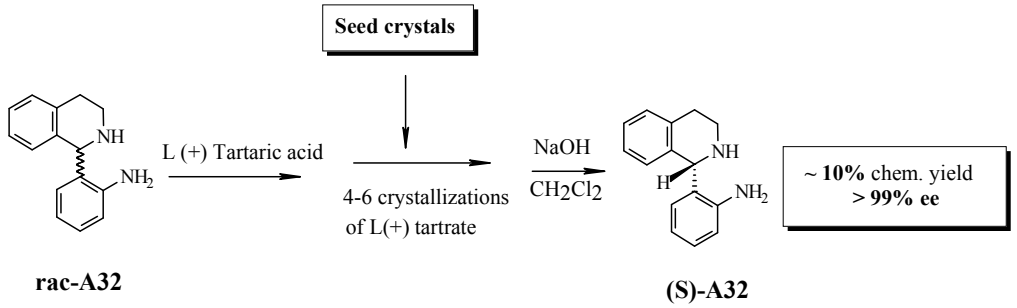
Since single diastereomer of nitro-amide **A37** could be obtained by crystallization technique, this approach was also applied to optical purification of **A40**. Two crystallizations afforded a single diastereomer with (*S,R*) absolute configuration according to X-rays analysis:





(S,R)-A40

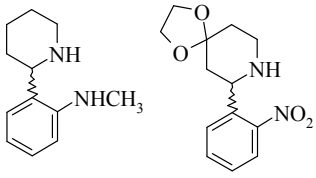
Hydrolytic cleavage of O-acetylmandelic auxiliary in refluxing 1N HCl for 4 hours proceeded without the complications encountered in the case of amide **(*R,R*)-A37**, and desired optically pure diamine **(*S*)-A32** was isolated in 95% yield (see Scheme A9). Thus, O-acetylmandelic acid turned out to 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**

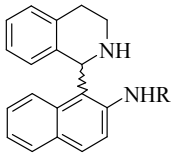
(C) Aldrich, 21.66 DM / g.

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



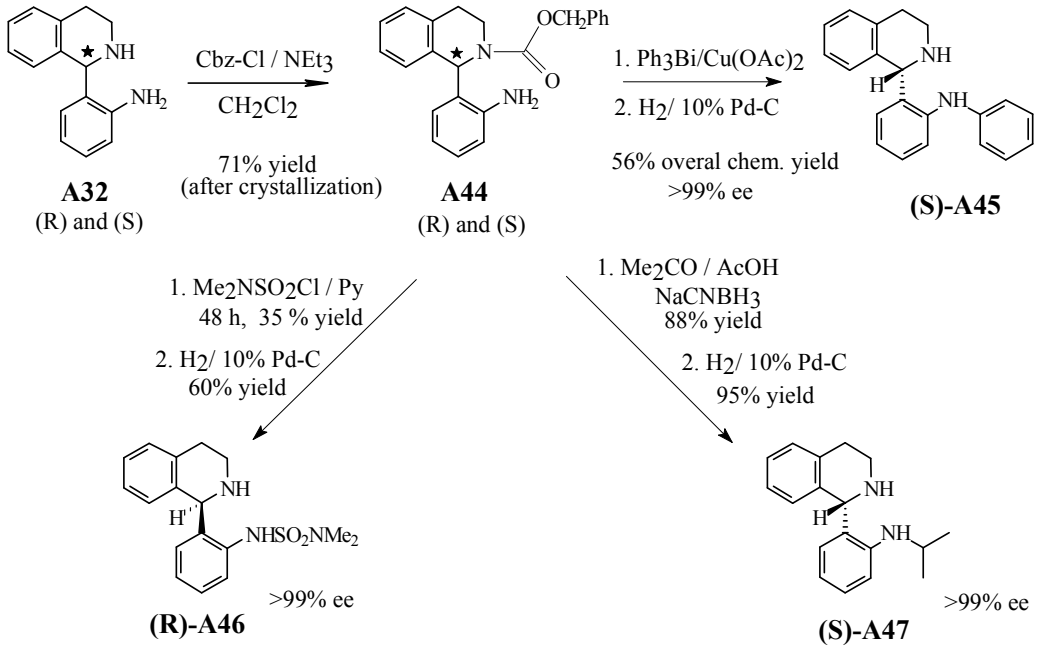
A43

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.

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