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Stereoselective synthesis of optically active 1-substituted-1-pyridyl-methylamines

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Abstract—The stereoselective syntheses of chiral 1-substituted-1-(pyridyl)methylamines, bearing a stereogenic carbon bonded to the amino group and 2-, 3- or 4-position of the pyridine ring, are reviewed.

Contents

1. Introduction

Optically active 1-substituted-1-(pyridyl)methylamines (py-amines) have attracted much academic and commercial interest, primarily due to their existence in naturally occurring compounds such as tobacco alkaloids (nicotine, nornicotine, anabatine, etc.)[1] or as key fragments within potential drug candidates.[2] Moreover, they have proven utility as ligands in metal complexes for asymmetric catalysis.[3]

In general, the simplest entry to non-racemic samples of these chiral organic compounds is the separation of a racemate into its two enantiomer constituents. This approach has been performed by the classical resolution using inexpensive resolving agents or kinetic resolution catalyzed by enzymes.

Enantiomerically enriched py-amines, such as 1-(pyridin-2-yl)ethylamine,[4,5] 1-(pyridin-3-yl)ethylamine,[5] 1-(pyridin-4-yl)ethylamine,[5] 2-phenyl-1-(pyridin-2-yl)ethylamine[6] and the alkaloids, nicotine,[7] nornicotine,[8] anabatine[9] and some of their analogues, namely 3-bromo-5-pyrrolidin-2-yl-pyridine[10] and 3-bromo-5-(1-methylpyrrolidin-2-yl)-pyridine,[11] have been obtained by the resolution of the racemate.

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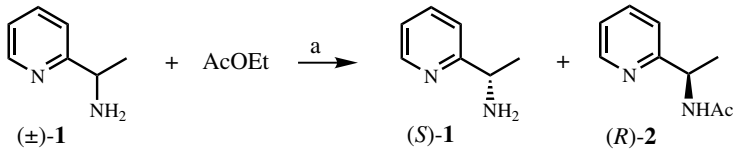


Scheme 1. Reagents and conditions: (a) *Candida antarctica* B lipase, 30 °C, solvent (AcOEt or 1,4-dioxane), 14–40 h.

An example of enzymatic resolution is the enantioselective acetylation of (±)-1-(pyridin-2-yl)ethylamine (±)-**1** carried out by using *Candida antarctica* B lipase (CAL-B) as the biocatalyst [AcOEt, solvent (AcOEt or 1,4-dioxane), 30 °C, 14–40 h, 47–50% conversion] (Scheme 1).[12] When the acetylation was performed in ethyl acetate, amine (*S*)-**1** and the related amide (*R*)-**2** were obtained in 90% and 66% enantiomeric excess (ee), respectively; while using 1,4-dioxane as the solvent the ee was 84% and 72%, respectively.

Although the preparation of this type of optically active amines by resolution has been successful in several cases, its use has been limited to only simple examples as it does not appear to be generally applicable. For example, the resolution of 1-phenyl-1-(pyridin-2-yl)methylamine failed.[13]

Asymmetric synthesis allowing the de novo synthesis of non-racemic chiral products provides a powerful tool to obtain enantiomerically enriched products.[14] This review considers the stereoselective syntheses of a range of optically active 1-substituted-1-(pyridyl)methylamines, bearing a stereogenic carbon bonded to the amino group and 2-, 3- or 4-position of the pyridine ring.

2. Synthesis

2.1. Cyclotrimerization of chiral 2-aminonitriles with acetylene

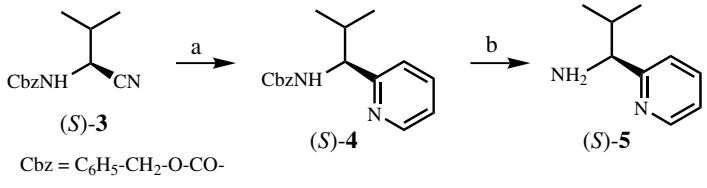
The cobalt-catalyzed cocyclotrimerization reaction of alkynes with nitriles represents a straightforward method for the construction of the pyridine ring.[15] When acetylene is used as the alkyne component in combination with chiral nitriles, the cocyclotrimerization reaction affords chiral 2-substituted pyridines.[16]

Chelucci et al. applied this methodology to prepare optically active 1-substituted-1-(pyridin-2-yl)methylamines, containing a stereogenic centre bonded to the heterocycle and adjacent to the heteroatom, by reaction of acetylene with *N*-protected α-aminonitriles. Naturally occurring amino acids were used as suitable starting materials. Initially, the synthesis of (*S*)-2-methyl-1-(pyridin-2-yl)propylamine **5** was undertaken (Scheme 2).[17] Thus, cocyclotrimerization of (*S*)-2-(benzyloxycarbonyl)amino-3-methylbutanenitrile **3** prepared from L-valine (99% ee)[18] with acetylene (14 atm) in the presence of (π-cyclopentadienyl)cobalt-1,5-cyclooctadiene [CpCo(COD)] (3.2 mol %) at 110 °C for 22 h gave pyridine **4** in moderate yield (40%). Deprotection of this derivative, conducted under reflux in a 6 M hydrochloric acid solution, gave **5** (44% yield) in only 15% ee. The stereochemical outcome of the reaction was tentatively ascribed to the presence of a hydrogen atom still bound to the amide nitrogen atom, which should have permitted racemization under severe conditions (110 °C, 72 h) of azaannulation. This was partially confirmed when the temperature was decreased by about 30 °C. A slight increase in the stereoselectivity of the process (20% ee) was achieved, but in a contemporaneous strong decrease in the conversion (12% after 110 h at 78 °C).

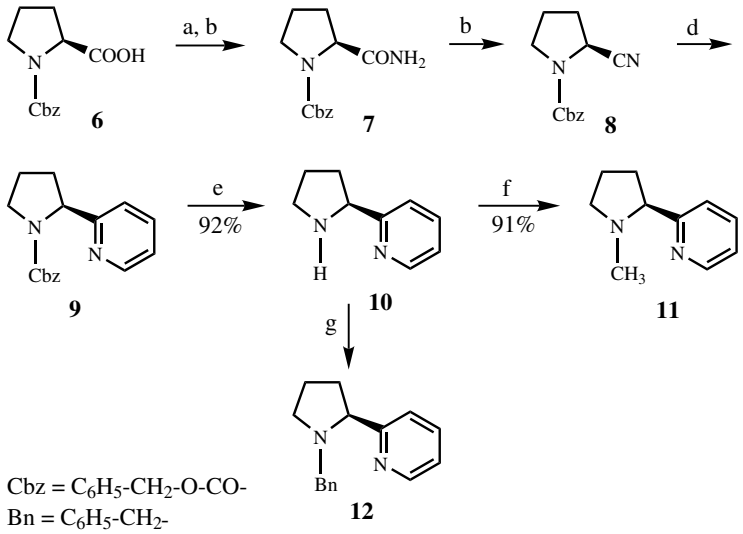
The cause of the racemization was unambiguously determined when the synthesis of 2-[(2*S*)-pyrrolidin-2-yl]pyridine from L-proline **10** was undertaken (Scheme 3).[19] Cocyclotrimerization of nitrile **8**, bearing a tertiary amide nitrogen, with acetylene in the presence of CpCo(COD) (3.2 mol %) at 110 °C for 22 h gave pyridine **9** in good yield (82%). Deprotection of **9** afforded in 92% yield pyridyl-pyrrolidine **10**, the enantiomeric excess (96%) of which was very close to that of L-proline (98% ee) used as starting material. From **10**, its derivatives **11** and **12** were also prepared.

This successful procedure was then extended to obtain the *N*-methyl-1-(pyridin-2-yl)alkylamines **17a–f** from which the *N*,*N*-dimethyl derivatives **18a–f** were prepared (Scheme 4).[17] In this instance, the reaction of cyclotrimerization occurred in only 4% of racemization.

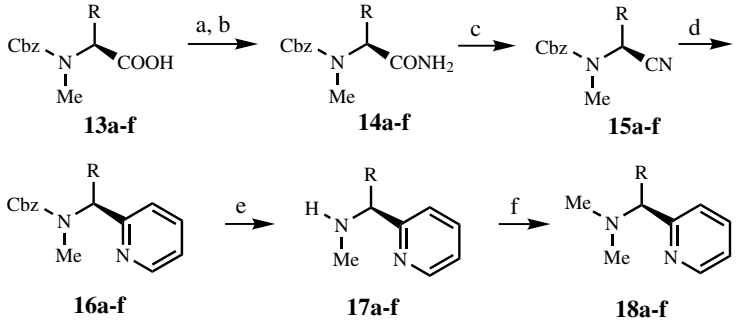
An example of non-*N*-alkylated 1-(pyridin-2-yl)alkylamines has already been reported (Scheme 5).[17] In this case, the nitrogen atom of the L-leucine (98% ee) was protected by the phthaloyl group to give an amino acid derivative without hydrogen atoms on the nitrogen atom. Cocyclotrimerization of nitrile **21**, carried out at



Scheme 2. Reagents and conditions: (a) CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm, 110 °C, 22 h, 40%; (b) HCl (6 N), reflux, 1 h, 44%.

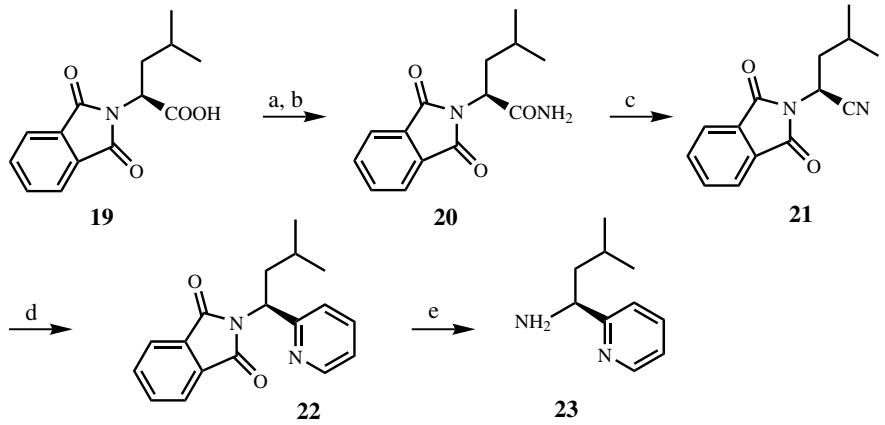


Scheme 3. Reagents and conditions: (a) $ClCO_2Et$, 4-methylmorpholine, THF, −12 °C, 10 min; (b) 25% NH_3, rt, 12 h; (c) *p*-TsCl/Py, 100 °C, 3–16 h; (d) CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm, 110 °C, 22 h, 80%; (e) 6 N HCl, reflux, 1 h, 92%; (f) $HCHO/HCO_2H$, reflux, 12 h, 91%; (g) BnCl, DMF, Na_2CO_3, NaI, reflux, 2 h, 93%.



a: R= *i*-Pr, **b**: R=Me, **c**: R=*i*-Pr, **d**: R=*i*-Bu, **e**: R=*s*-Bu, **f**: R=Bu
Cbz = C_6H_5-CH_2-O-CO-

Scheme 4. Reagents and conditions: (a) $ClCO_2Et$, 4-methylmorpholine, THF, −12 °C, 10 min; (b) 25% NH_3, rt, 12 h, 60–92%; (c) *p*-TsCl/Py, 100 °C, 3–16 h, 66–84%; (d) CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm, 80%; (d) HCl (6 N), reflux, 1 h, 65–66%; (f) $HCHO/HCO_2H$, reflux, 79–99%.



Scheme 5. Reagents and conditions: (a) $ClCO_2Et$, 4-methylmorpholine, THF, −12 °C, 10 min; (b) 25% NH_3, rt, 12 h, 85%; (c) *p*-TsCl/Py, 100 °C, 16 h, 70%; (d) CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm, 54%; (e) NH_2NH_2, H_2O, MeOH, rt, 12 h, 66%.

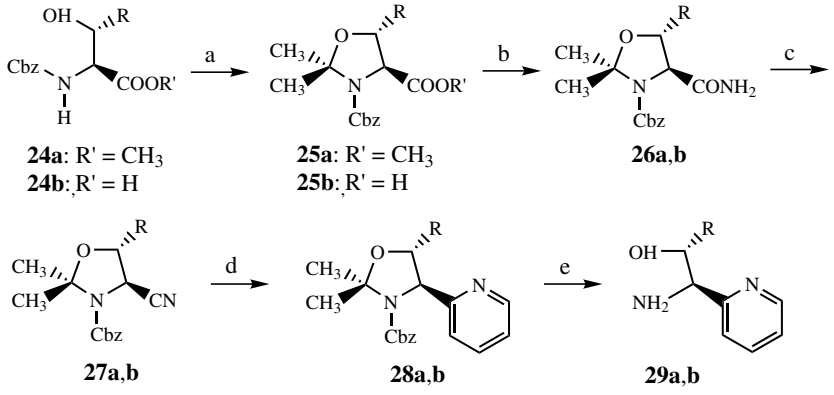
110 °C for 72 h, gave pyridine **22** (54% yield) which, by removal of the phthaloyl group, afforded aminopyridine **23** in 90% ee. An 8% of racemization was observed in the overall process.

Two new β-amino alcohols, namely (*R*)-1-hydroxy-1-(pyridin-2-yl)ethylamine **29a** and (1*R*,2*R*)-1-hydroxy-1-(pyridin-2-yl)propylamine **29b**, were prepared starting from L-serine and L-threonine, respectively (Scheme 6).[20] The synthesis involved the simultaneous protection of the hydroxy and amino groups of **24a** and **24b** by the formation of the 2,2-dimethyl-1,3-oxazolidine ring, followed by conversion to the nitriles **27a** and **27b**. Cocyclotrimerization of **27a** and **27b** was performed at 160 °C for 3–6 days. It is noteworthy that temperature plays a crucial role in this process. Up to 150 °C, no appreciable reaction was observed, while at 160 °C the reaction took place, although with moderate conversion owing to the degradation of the catalyst. By increasing the amount of catalyst, no improvement both in conversion and yield was obtained. No loss of enantiomeric purity in the overall process was observed.

2.2. Addition of organometallic reagents to chiral pyridyl imines

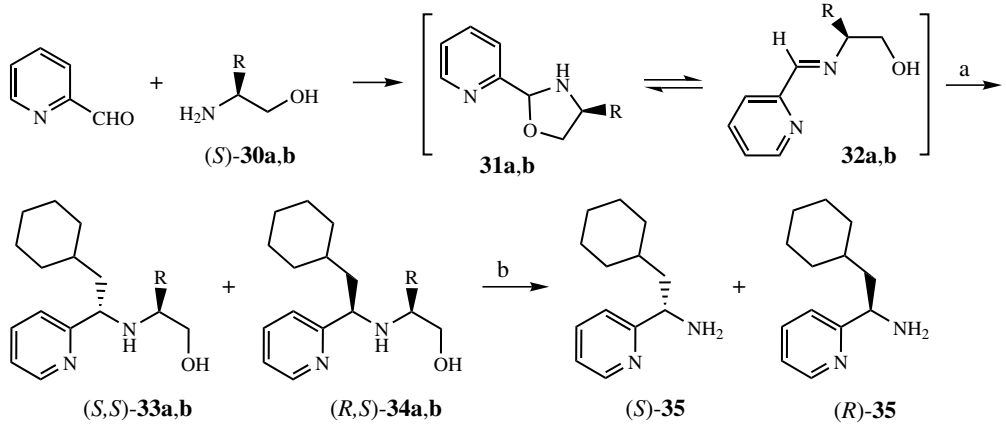
Amines carrying an α-stereocentre can be easily prepared by adding organometallic reagents to imines. Chiralty information can be incorporated in the nitrogen substituent, the proper choice of which allows a different range of organometallic reagents to be applied and variable levels of stereocontrol to be obtained.[21]

Miao et al. explored the use of an equilibrium mixture of 4-substituted 2-(pyridin-2-yl)-1,3-oxazolines **31a** and **31b** and corresponding imines **32a** and **32b** obtained by reaction of pyridine-2-carboxaldehyde with (*S*)-phenylglycinol or (*S*)-valinol (Scheme 7).[22] The ratio of **31** and **32** was found to be solvent dependent. Compound **32** is the predominant form in THF (R = Ph, **31a**:**32a** = 5:95; R = *i*-Pr, **31b**:**32b** = 1:3), while **31** predominates (R = Ph, **31a**:**32a** = 54:46; R = *i*-Pr, **31b**:**32b** = 80:20) in $CHCl_3$. Grignard addition to the **31** and **32** mixture gave diastereomers **33** and **34**. When R = *i*-Pr, a diastereomeric ratio of (*S*,*S*)-**33b**:(*R*,*S*)-**34b** was found to be



a: R = H, **b**: R = CH_3 Cbz= C_6H_5-CH_2-O-CO-

Scheme 6. Reagents and conditions: (a) $Me_2C(OMe)_2$, BF_3Et_2O, 24 h, 85%; (b) for **a** NH_3/MeOH, 3 d, rt; for **b** $ClCO_2Et$, THF, NEt_3, −20 °C, 30 min, then NH_3, −20 °C to rt, 20 h, 70%; (c) *p*-TsCl/pyridine, 80 °C, 1 h, 70–88%; (d) CpCo(COD) (3 mol %), toluene, acetylene, 12–14 atm, 160 °C, 3–6 d, 40–45%; (e) HCl (4 N), 24 h, 100 °C, 75–80%.



a: R = Ph; **b**: *i*-Pr

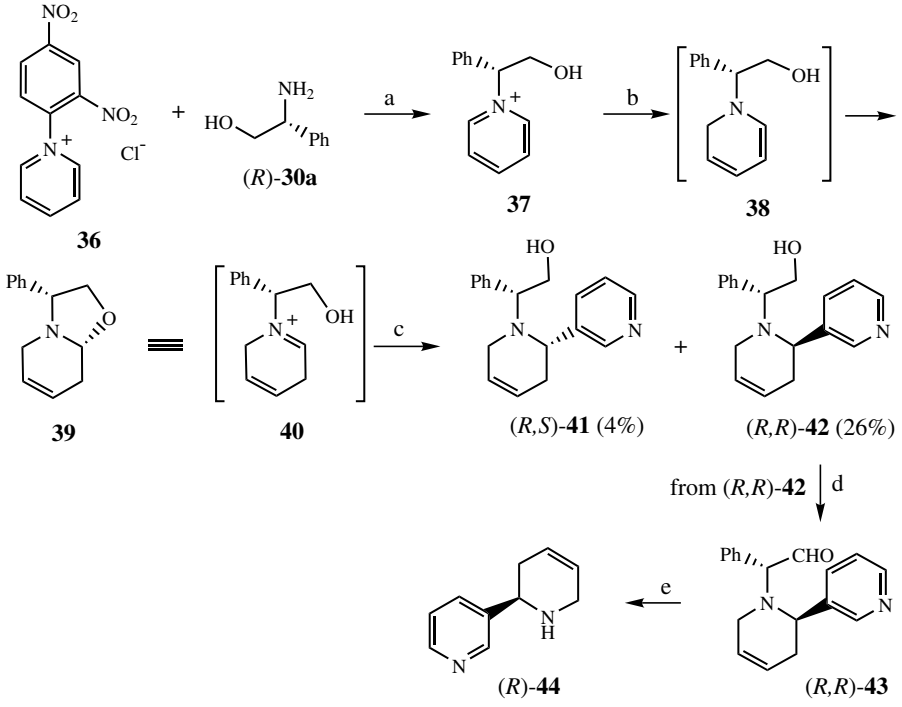
Scheme 7. Reagents and conditions: (a) C_6H_{11}-CH_2-MgBr, THF; (b) $NaIO_4$.

87:13. This mixture was oxidatively cleaved with $NaIO_4$ to give (*S*)-**35** in 35–40% yield and 75% ee.

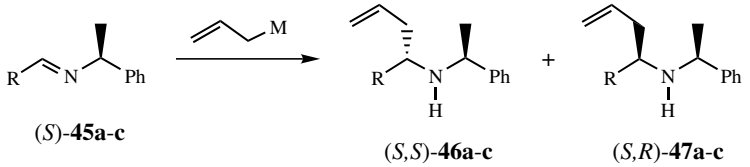
The nucleophilic addition of the Grignard reagent derived from 3-bromopyridine to a chiral oxazolidine was exploited for the first enantioselective synthesis of the alkaloid (*R*)-anatabine (Scheme 8).[23] Accordingly, the treatment of Zincke's salt **36** with 1 equiv of (*R*)-phenylglycinol **30a** (propan-1-ol, reflux, overnight, 70%) led to the pyridinium salt **37**. Reduction with $NaBH_4$ (5 M NaOH in Et_2O, 0 °C, 30 min, 70%) afforded oxazolidine **39**, presumably via the 1,2-dihydropyridine intermediate **40**. Addition of 3-pyridylMgBr (Et_2O, 30%) to **39** afforded a 1:6.5 mixture of diastereomers (*R*,*S*)-**41** and (*R*,*R*)-**42**, respectively. From the most abundant isomer (*R*,*R*)-**42**, purified by chromatography, the chiral auxiliary was removed by oxidation of the alcohol to the corresponding aldehyde group (Swern oxidation), followed by treatment with 2,4-dinitrophenylhydrazine (propan-1-ol/acetic acid, reflux, 24 h) to give (*R*)-anatabine **44** in 50% overall yield in the last two steps. The ee of (*R*)-**44** was determined to be 90%, meaning that the racemization during the removal of the chiral auxiliary did not exceed 10%.

The addition of allyl metal compounds to imines derived from pyridine-2-, 3- and 4-carboxaldehyde and (*S*)-1-phenylethylmine has been examined (Scheme 9 and Table 1).[24] The reactions were carried out at −78 °C using diethyl ether as the solvent in the case of *B*-allyl-9-borabicyclononane (allyl-BBN) and tetrahydrofuran for all the other allyl metal reagents.

The sense of the asymmetric induction as well as the degree of diastereoselectivity was dependent on the nature of both the metal and imine. Allyl-BBN was the most selective reagent (apart from the bidentate pyridine 2-imine **45c**), while dialkylcuprate was generally preferable to allyl copper. Low diastereoselectivity and the addition to both the azomethine group and pyridine ring were observed in the reaction of allylmagnesium chloride to **45a** and **b**; whilst the sense of asymmetric induction was inverted in the corresponding addition to **45c**. The diastereoselectivity was very low in the reaction of



Scheme 8. Reagents and conditions: (a) propan-1-ol, reflux, overnight, 70%; (b) $NaBH_4$, 5 M NaOH in Et_2O, 0 °C, 30 min, 70%; (c) 3-pyridylMgBr, Et_2O, rt, overnight, 30%, then chromatographic separation; (d) Swern oxidation; (e) 2,4-dinitrophenylhydrazine, propan-1-ol/acetic acid, reflux, 24 h, 50%.



a: 4-pyridyl, **b**: 3-pyridyl, **c**: 2-pyridyl

Scheme 9.

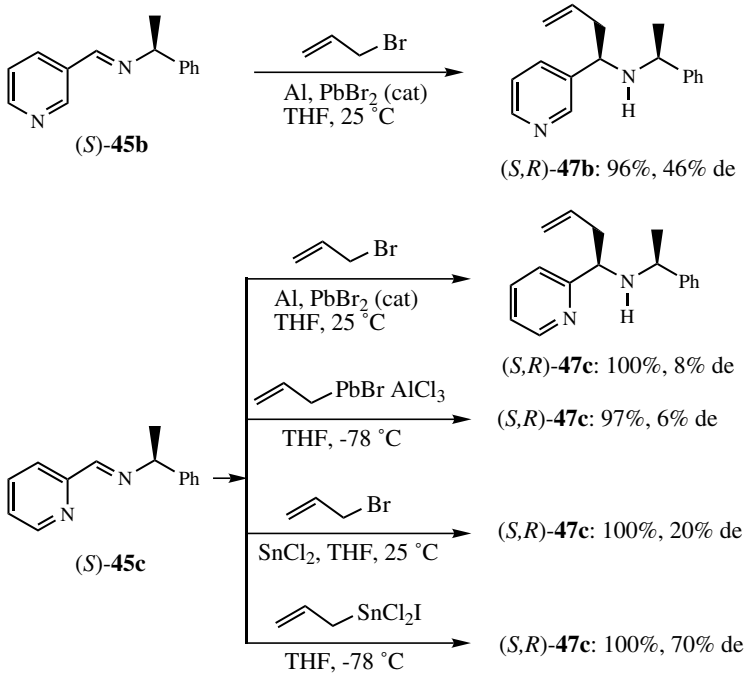
Table 1. Addition of allyl metal compounds to imines (*S*)-**45a–c** (Scheme 9)

Allylmetal (equiv)	Solvent	Ratio (*S*,*S*)-**46a**:(*S*,*R*)-**47a**	Ratio (*S*,*S*)-**46b**:(*S*,*R*)-**47b**	Ratio (*S*,*S*)-**46c**:(*S*,*R*)-**47c**
AllylBBN (2)	Et_2O	3:93	7:93	25:75
AllylMgCl (1.5)	THF	42:58	45:55	56:44
AllylZnBr (3)	THF	40:60	30:70	13:87
AllylCu·MgICl (3)	THF	20:80	22:78	48:52
$(Allyl)_2CuMgCl·MgICl$ (3)	THF	15:85	14:86	33:67

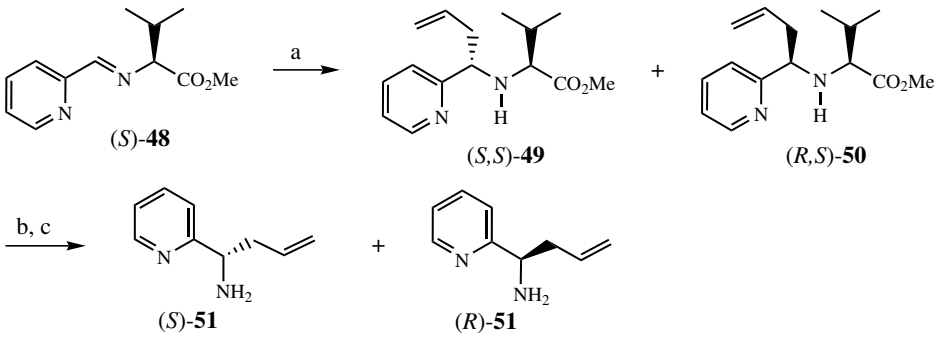
allylcopper with **45c**. However, with this imine allylzinc bromide it worked satisfactorily, even better than allyl-BBN, although the diastereoselectivity was far from good.

Savoia et al. also applied several different Barbier (allyl bromide, Zn) procedures to the imines **45b** and **45c** (Scheme 10).[24] The best results were achieved by generating the allyl metal species in situ from allyl bromide and the bimetal redox system Al/$PbBr_2$ (catalytic) from allyl iodide and tin dichloride.

Savoia performed the addition of several allyl metal reagents to imine (*S*)-**48**, derived from pyridine-2-carboxaldehyde and methyl (*S*)-valinate and its metal salt complexes (*S*)-**48**-M′X_n (Scheme 11).[25] Selected results obtained by following Grignard (THF, −78 °C) and Barbier (THF, 25 °C) procedures for the allylation are reported in Table 2. The prevailing formation of diastereomer (*S*,*S*)-**49** (up to 92% de) was observed except with allyltin trihalides, which gave the opposite sense of asymmetric induction (up to 92% de). The authors proposed mechanisms of the additions to explain the



Scheme 10.



Scheme 11. Reagents and conditions: (a) allylmetal reagents; (b) $LiAlH_4$, THF, −5 °C, 30 min; (c) H_5IO_6, $MeNH_2$, H_2O, 1 h.

Table 2. Preparation of secondary homoallylic amines from (*S*)-**48** (Scheme 11)

Allylmetal (equiv)	*T* (°C)	Time (h)	Yield (%)	(*S*,*S*)-**49**:(*R*,*S*)-**50**
AllylCu–MgICl (1.5)	−78	1.5	92	90:10
$(Allyl)_2CuMgCl$–MgICl (1.5)	−78	0.5	98	93:7
AllylZnBr (2)	−78	0.16	90	86:14
AllylBr (1.1), Zn (1.5)	25	0.5	75	80:20
AllylZnBr (1.1), $CeCl_3$ (1)	−78	0.08	99	78:22
AllylZnBr (1.1), $SnCl_2$ (1)	−78	0.08	98	80:20
AllylPbBr–MgBrCl (1.1)	−78	0.16	98	96:4
AllylBr (1.1), Al (1.5), $PbBr_2$ (1.1)	25	2.5	98	95:5
$AllylSnCl_3$ (1)	−78	0.16	100	13:87
$AllylSnICl_2$ (1.5)	−78	0.08	90	3:97
AllylI (1.5), $SnCl_2$ (1.1)	25	0.16	100	4:96
$AllylSnICl_2$ (1.1), $SnICl_2$ (1.1)	−78	0.08	98	7:93
AllylMgCl (1.1)	−78	0.5	70	83:17
AllylMgCl (1), $SnCl_4$ (1)	−78	0.08	80	65:35

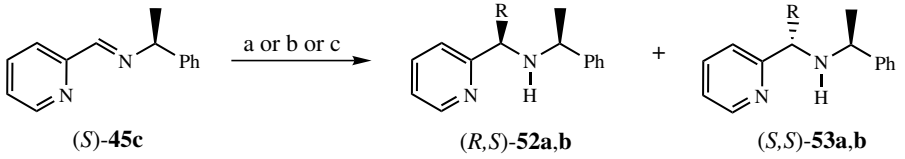
stereochemical results. After reduction of the ester with lithium aluminium hydride, followed by oxidative cleavage of the intermediate β-amino alcohol with H_5IO_6/$MeNH_2$, both the (*S*)- and (*R*)-1-(pyridin-2-yl)-3-butenamine were obtained in good yield (>90%) and enantiomeric excess (>86%).

Savoia tested the reactivity and diastereoselectivity of triorganozincates towards pyridyl-imines (*S*)-**45c** and (*S*)-**54** [from (*S*)-valinate] (Schemes 12 and 13).[26] The addition of triorganozincates to imine **45c** gave very good yields (92–100%) of the amines **52** and **53**, although only a moderate excess of the (*R*,*S*)-diastereomers was obtained. The diastereoselectivity was only slightly affected by the steric properties of the non-transferred alkyl group (Me, *t*-Bu) (Scheme 12).

On the other hand, mixed triorganozincate reagents, in which the methyl group was used as a non-transferable ligand, selectively transferred the alkyl and vinyl groups to imine **54** (Scheme 13 and Table 3).[26] The stereocontrol was high (84 to >99% de) apart from allyl, benzyl and *tert*-butyl groups. The diastereoselectivity was moderately dependent on the nature of the R group and decreased in the order vinyl >Et, *i*-Pr, *n*-Bu > Bn > *t*-Bu, allyl.

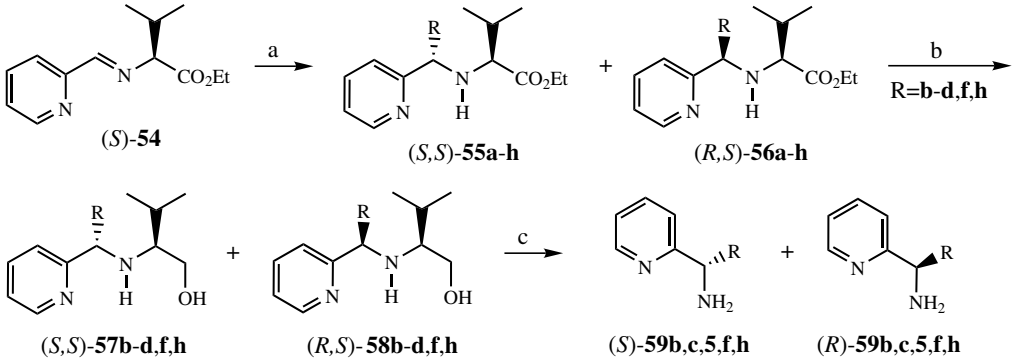
The removal of the auxiliary group of **55/56b–d,f,h** was carried out by reduction with $LiAlH_4$ to give the β-amino alcohols **57/58b–d,f,h** (69–80% yield), followed by oxidative cleavage with H_5IO_6/$MeNH_2$ to give **59b,c,5,f,h** in over 95% yield. No attempt was made to prepare the compounds **1**,**59e**,**51** because of the low yield and/or diastereomeric purity of their precursors **55/56a,e,g**.

Although, the use of imines (*S*)-**48** and (*S*)-**54** generally allows the synthesis of a variety of secondary amines in



(*S*)-**45c** (*R*,*S*)-**52a,b** (*S*,*S*)-**53a,b**

Scheme 12. Reagents and conditions: (a) Me_3ZnLi, THF, −40 to −20 °C, 2 h → **52a** and **53a** (R = Me): 100% (GC), (*R*,*S*)-**52a**/(*S*,*S*)-**53a** = 64:36; (b) $MeEt_2ZnLi$, THF, −78 °C, 10 min → **52b** and **53b** (R = Et): 92% (GC), (*R*,*S*)-**52b**/(*S*,*S*)-**53b** = 73:27; (c) *t*-$BuEt_2ZnLi$, THF, −78 °C, 10 min → **52b** and **53b** (R = Et): 98% (GC), (*R*,*S*)-**52b**/(*S*,*S*)-**53b** = 62:38.



(*S*)-**54** (*S*,*S*)-**55a-h** (*R*,*S*)-**56a-h**

(*S*,*S*)-**57b-d,f,h** (*R*,*S*)-**58b-d,f,h** (*S*)-**59b,c,5,f,h** (*R*)-**59b,c,5,f,h**

a: R = Me, **b**: R = Et, **c**: R = *n*-Bu, **d**: R = *i*-Pr, **e**: R = *t*-Bu, **f**: R = Bn, **g**: R = allyl, **h**: R = vinyl

Scheme 13. Reagents and conditions: (a) R-[zincate], THF; (b) $LiAlH_4$, THF, −5 °C, 30 min; (c) H_5IO_6, $MeNH_2$, H_2O, 1 h.

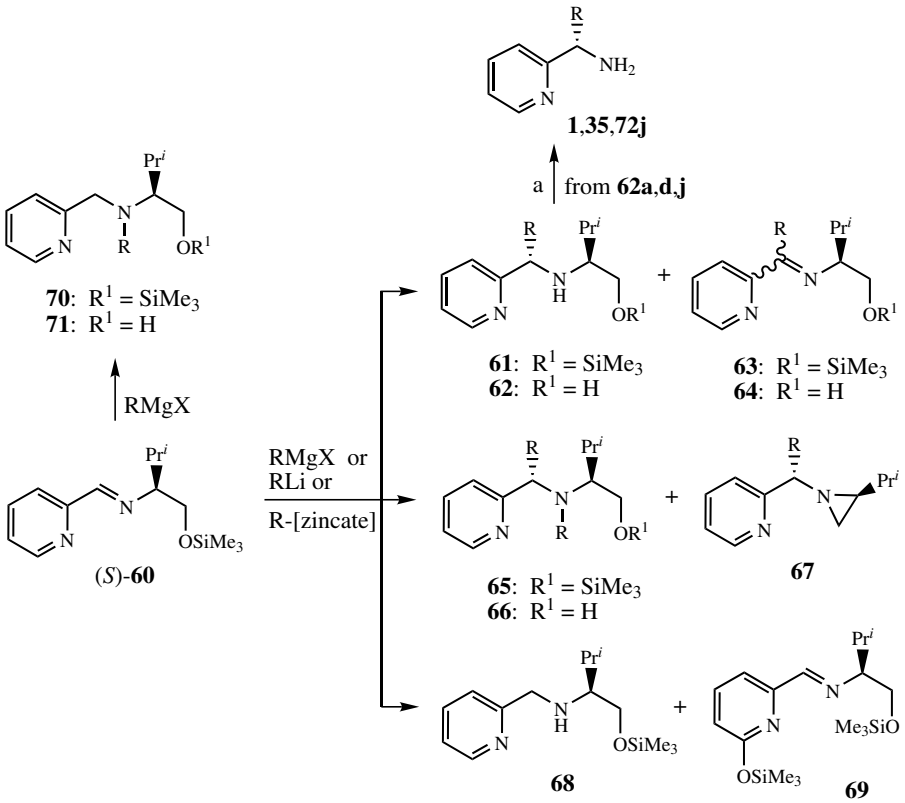
Table 3. Addition of triorganozincate reagents to imine (*S*)-**54** (Scheme 13)

R-Zincate (equiv)	*T* (°C)	Amines	Yield (%)	(*S*,*S*)-**55**:(*R*,*S*)-**56**
$Me_2ZnMgCl$ (2)	−78	**55a**,**56a**	50	92:8
Me_3ZnLi (2)	−78 to 20	**55a**,**56a**	50	77:23
$Et_2MeZnMgCl$ (1.1)	−78	**55b**,**56b**	90	96:4
t-$BuEt_2ZnMgCl$ (1.1)	−78	**55b**,**56b**	73	82:18
n-$BuMe_2ZnMgCl$ (1.1)	−78	**55c**,**56c**	86	94:6
n-$BuMe_2ZnLi$ (1.5)	−78	**55c**,**56c**	10	95:5
i-$PrMe_2ZnMgCl$ (1.1)	−78	**55d**,**56d**	90	95:5
t-$BuMe_2ZnMgCl$ (1.1)	−78	**55e**,**56e**	80	57:43
t-$BuMe_2ZnLi$ (1.5)	−78	**55e**,**56e**	45	74:26
t-$BuMe_2ZnLi$ (1.5)	0	**55e**,**56e**	75	75:25
$BnMe_2ZnMgCl$ (1.1)	−78	**55f**,**56f**	88	88:12
$AllylMe_2ZnMgBr$ (1.1)	−78	**55g**,**56g**	91	73:27
$VinylMe_2ZnMgBr$ (1.1)	−78	**55h**,**56h**	95	>99:1

good yield and enantiomeric purity (Tables 2 and 3), in some cases the results were unsatisfactory. Thus, the methyl group could not be efficiently transferred from trimethylzincates (Table 3), while mixed zincates prepared by addition of phenylmagnesium bromide, hept-1-yl-1-ynyllithium and 2-furyllithium to dimethylzinc proved unreactive.[26] On the other hand, the addition of cyclohexylmethylmagnesium bromide to the imine derived from (*S*)-valinol as a chiral auxiliary (Scheme 7) afforded only moderate diastereoselectivity (75% de).[22]

Savoia envisaged that the use of (*S*)-*O*-(trimethylsilyl)valinol as a chiral auxiliary could improve the diastereoselectivity of the organometallic addition of the corresponding pyridyl-imine.[27] It was considered that the protected hydroxy group should even allow the use of basic organometallic reagents (Li, Mg) in only small excess. Moreover, the trimethylsilyl group could easily be introduced and removed by simple work-up, thus shortening the procedure for removal of the auxiliary, which in the case of (*S*)-**48** and (*S*)-**54** requires the reduction step necessary to convert the ester group to the imino alcohol.

Accordingly, imine (*S*)-**60** (Scheme 14) was prepared by the condensation of pyridine-2-carboxaldehyde with (*S*)-



a: R = Me, **b**: R = Et, **c**: R = Bu, **d**: R = *c*-$HexCH_2$, **e**: R = *i*-Pr, **f**: R = *t*-Bu, **g**: R = Bn
h: R = allyl, **i**: R= vinyl, **j**: R = Ph

Scheme 14. Reagents and conditions: (a) MeOH–THF, $MeNH_2$ H_5IO_6, rt, 83–94%.

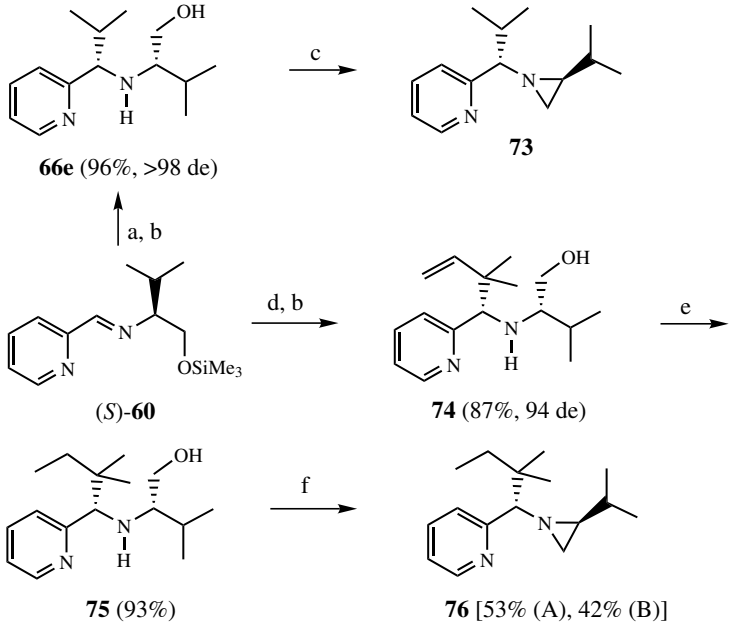
valinol (CH_2Cl_2, $MgSO_4$, 0 °C, 2 h, 100%), followed by protection of the hydroxy group as its trimethylsilyl ether ($ClSiMe_3$, CH_2Cl_2, NEt_3, 3 h, 95%).[27]

The organometallic reactions were performed (Scheme 14) by adding 2 mol equiv of Grignard and triorganozincate reagents or 1.2 equiv of organolithium reagents to siloxane **60** in THF, generally at −78 °C. Less reactive methyl-, vinyl- and phenylmagnesium halides required higher temperatures to go to completion. The composition of the mixture was dependent on the nature of the organometallic reagent (Table 5). In fact, the addition of the organometallic reagent occurs at either the carbon and/or nitrogen atom of the C=N double bond. Primary alkyl magnesium halides (R = Et, Bu, cyclohexylmethyl) added preferentially at the nitrogen to give tertiary amines. By using hex-5-enylmagnesium bromide as a probe for the single-electron-transfer mechanism, only the *N*-(hex-5-enyl) adduct was obtained. Other Grignard reagent RMgX (R = Me, *i*-Pr, Bn, allyl, vinyl, Ph) and organolithium and zincate reagents added at the carbon atom to give secondary amines as the main or exclusive regioisomers. Ketimines were the main by-products in the reactions of methyl-, isopropyl- and vinyl-magnesium halides, (isopropyl)-dimethylzincate and *tert*-butylmetal reagents. With the latter reagents, other by-products were also observed, presumably from C,N-dialkylation of the C=N double bond and attack on the pyridine ring. The C-alkylation products were formed with excellent or perfect diastereoselectivity (*si*-face attack), apart from the *tert*-butyl and benzyl reagents. After work-up, the (*S*,*S*)-amino alcohols were converted in good yields (83–94%) to (*S*)-1-(2-pyridyl)alkylamines by oxidative cleavage of the auxiliary (MeOH–THF, $MeNH_2$, H_5IO_6, room temperature). No attempt was made to prepare the primary amine **72f** because of the low diastereomeric purity of its precursor **62f** (dr = 70:30). It should be noted that compounds **1** and **72j** could not be prepared by the route starting from the imine (*S*)-**54**. Moreover, the route to amines **51**(**72h**) and **35**(**72d**) is preferable in terms of diastereoselectivity and/or overall yield to the previously reported syntheses from (*S*)-**45c**, (*S*)-**54** and **33a**, respectively.

The superior asymmetric induction provided by *O*-(trimethylsilyl)valinol as auxiliary, with respect to valine esters, was rationalized on the basis of the lower basicity of the oxygen atom. Polar and radical mechanisms, which explained the formation of regioisomeric products and by-products, were also discussed.

Savoia et al. planned a two step synthesis of enantiopure 1-(pyridin-2yl)allyl aziridines **73** and **76** (Scheme 15), which were designed as bidentate ligands for asymmetric catalysis.[28] Their synthesis involved the addition of organometallic reagents to imine (*S*)-**60** followed by cyclization of the β-amino alcohol moiety to the aziridine ring. Accordingly, aziridine **73** was quickly and quantitatively formed from β-amino alcohol **66e** (Scheme 15) by treatment with 1,1′-carbonyldiimidazole (CDI) in CH_2Cl_2.

In order to introduce a more bulky substituent at the C-stereocentre and considering that the addition of *tert*-butyl organometallic reagents to imine (*S*)-**60** (Table 5) was unsatisfactory,[25] the addition of 3-methyl-2-butenylzinc bromide to (*S*)-**60** at −78 °C in THF was carried out. After desilylation with NH_4F in MeOH, the branched alkylation product **74** was obtained in high yield and stereocontrol (96% de). This reaction was also carried in situ by treatment of the imine (*S*)-**60** with

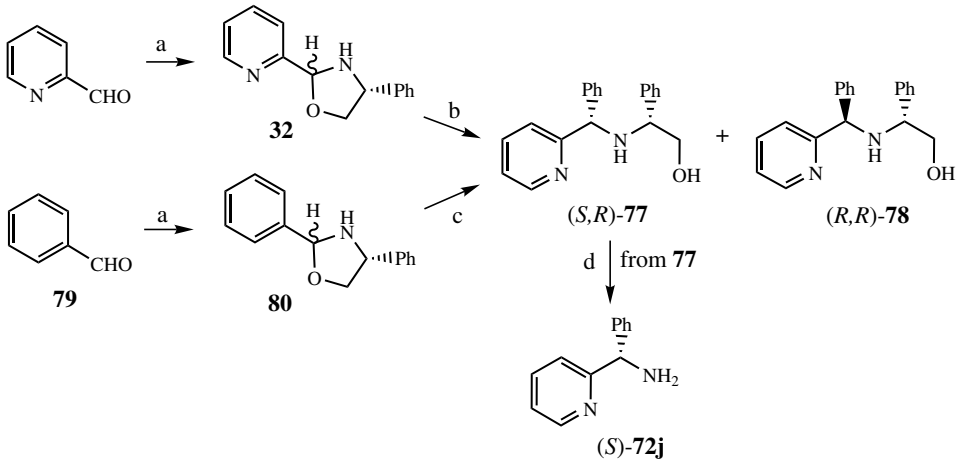


Scheme 15. Reagents and conditions: (a) *i*-PrMgCl, THF, −78 °C; (b) NH_4F, MeOH; (c) 1,1′-carbonyldiimidazole, CH_2Cl_2 20 °C; (d) $Me_2C{=}CHCH_2Br$, Zn, $CeCl_3$, $7H_2O$ (cat), THF, 20 °C; (e) H_2, Pd/C, MeOH; (f) (A) MsCl (3 equiv), Et_3N, THF, −78 to 20 °C or (B) PPh_3, DEAD, benzene, 81 °C.

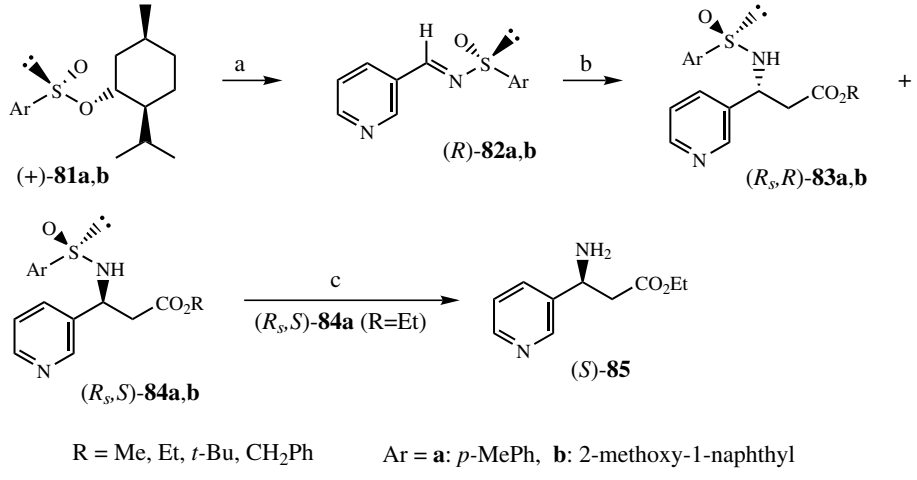
1-bromo-3-methyl-2-butene and cerium trichloride heptahydrate in THF at 0–20 °C. Following double bond hydrogenation, the saturated compound **74** was finally obtained. The desired aziridine **76** was achieved by reaction of **75** with 3 equiv of mesyl chloride in the presence of triethylamine at −78 to 20 °C (53% yield). Attempts to obtain **76** from **75** by reaction with CDI failed and the classical Mitsunobu reaction afforded a moderate yield (42%).

As intermediates for the synthesis of substituted tripodal ligands, Canary et al. required a number of optically active 1-substituted-1-(pyridin-2-yl)methylamines (substituents: Et, *i*-Pr, Bn, Ph).[12] Whereas the first three examples of the series were prepared as previously reported[29] (see Scheme 45), the phenyl derivative was obtained as described in Scheme 16. The addition of the Grignard reagent of the chlorobenzene to the (*R*)-phenyl glycinol oxazolidine **31a** gave a 1:1 mixture of diastereomers (*S*,*R*)-**77** and (*R*,*R*)-**78**. On the other hand, the addition of the Grignard reagent of 2-iodopyridine to oxazolidine **80** derived benzaldehyde afforded (*S*,*R*)-**77** and (*R*,*R*)-**78** in 44% yield. Amine (*S*)-**72j** was obtained in moderate yield (38%) with 81% ee by removal of the chiral auxiliary with $Pb(OAc)_4$ from (*S*,*R*)-**77**.

Davis et al., in order to obtain the ethyl 3-amino-3-(pyridin-3-yl)propanoate (*S*)-**85**, examined the sequence involving the diastereoselective addition of the enolate of several acetates to sulfinimines (*R*)-**82a** and **82b** (−78 °C in THF) (Scheme 17).[30] These sulfinimines were prepared by the reaction of the *p*-toluenesulfinate (+)-**81a** and naphthalenesulfinate (+)-**81b** with 1.5 equiv of lithium bis(trimethylsilyl)amide at −78 °C, followed by reaction with 2 equiv of pyridine-3-carboxaldehyde in the presence of caesium fluoride (70% and 71% yield, respectively). The diastereoselectivity of the addition was examined by the variation of the counterion (Na or Li) and the R group (Me, Et, *t*-Bu, CH_2Ph) in the



Scheme 16. Reagents and conditions: (a) (*R*)-phenylglycinol; (b) PhMgCl, THF, reflux; (c) 2-pyridylMgI, THF, reflux, 5 h, 44%; (d) $Pb(OAc)_4$, CH_2Cl_2/MeOH, 0 °C, 40 min, 38%.



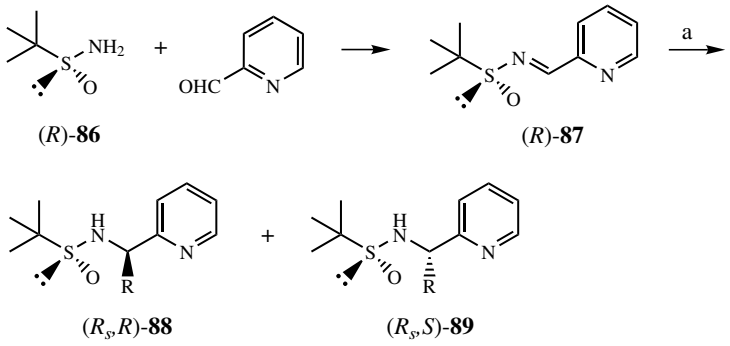
Scheme 17. Reagents and conditions: (a) LiHMDS, −78 °C, then pyridine-3-carboxaldehyde, CsF, 0 °C to rt, 70%; (b) CH_3CO_2R, base (NaHMDS or LiHMDS or LDA), THF; (c) CF_3CO_2H, EtOH, 0 °C to rt, 90%.

enolate. The best results were obtained with (*R*)-**81a** and (*R*)-**81b** using methyl acetate/NaHMDS (74% de, 80% yield) and ethyl acetate/LiHMDS (78% de, 85% yield), respectively.

In all cases, the prevailing diastereoisomer was that with an (*S*)-configuration at the amino carbon generated in **84**. This result was correctly predicted by the chair-like transition state model that was proposed for enolate additions to sulfinimines.[31] The major isomer (R_s,*S*)-**84a** (R = Et) was isolated by chromatography and hydrolyzed by treatment with 4 equiv of trifluoroacetic acid in EtOH (0 °C to room temperature) to give (*S*)-**85** in 90% yield and >97% de.

The addition of Grignard reagents to chiral *tert*-butyl sulfinyl imine (*R*)-**87** derived from pyridine 2-carboxaldehyde and (*R*)-*tert*-butyl sulfinamide **86** to obtain 2-pyridylamines has been recently considered (Scheme 18).[32] The results reported in Table 4 show that good yields and diastereoselectivities have been obtained. However, the observed sense of chiral induction was opposite to that predicted by coordination of an organometallic moiety with the sulfoxide oxygen to form a chelation-controlled, chair-like transition state (model **A**, Scheme 19). The result can be explained by considering that the coordination of the metal is favoured between the imine and the pyridine nitrogens to afford organo-magnesium complex **B** (Scheme 19). Subsequent addition of the nucleophile then occurs via an open transition state. The reaction conditions were also systematically modified in order to gain insight into the factor that governs the addition. The results obtained under the best reaction conditions are reported in Table 5.

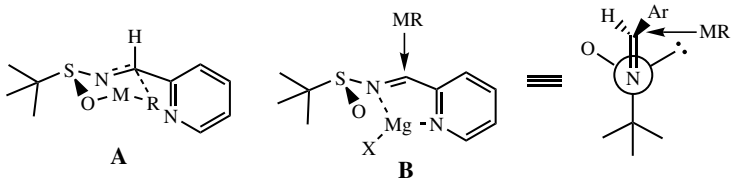
The stereoselective addition of organometallic reagents to pyridyl sulfinimines has been exploited in a four step synthesis of enantiomerically enriched (*S*)-anatabine (Scheme 20).[33] When the dianion of 4-phenylsulfonyl *cis*-but-2-en-1-ol **90** (2.4 equiv, LiHMDS, −78 to −70 °C, 0.5 h) was treated with the enantiopure pyridyl sulfinimine **82** [prepared from pyridine-3-carboxaldehyde and (*R*)-*tert*-butyl sulfinamide **86**][34] at −100 °C and then allowed to warm to −60 °C (1.5 h), compound **91** was obtained in 57% yield as a 82:18 inseparable mixture of diastereomers. Hence, the *N*-sulfoxide group was



Scheme 18. Reagents and conditions: (a) R–MgCl, THF; R = Me, *i*-Pr, vinyl, propynyl, Ph.

Table 4. Addition of organometallic reagents to the imine (*S*)-**60** (Scheme 14)

RM	Temp (°C)	Time (h)	Intermediate products (%)	dr of **61**	Isolated products (%)
MeLi	−78	0.5	**61a**(97)	>97:3	**62a**(93)
MeMgCl	−20	4	**61a**(81),**63a**(9)	>97:3	**62a**(90)
EtMgBr	−78	0.5	**61b**(28),**70b**(67)	>99:1	
(i) MeMgCl; (ii) Et_2Zn	−78	0.5	**61a**(<2),**61b**(94)	>99:1	**62b**(95)
BuLi	−78	0.5	**61c**(92),**70c**(2),**63c**(<1)	>99:1	**62c**(90)
BuMgCl	−78	0.5	**61c**(5),**70c**(90)	>99:1	**71c**(85)
c-HexCH_2MgBr	−78	0.5	**61d**(2),**71d**(91)		**71d**(84)
(i) Me_2Zn; (ii) *c*-HexCH_2MgBr	−78 to −50	1	**61a**(7),**71d**(88)	99:1	**62d**(83)
Pr^iMgCl	−78	0.5	**61e**(86),**70e**(<4),**63e**(6),**68e**(1)	>99:1	**62e**(76)
(i) Me_2Zn; (ii) Pr^iMgCl	−78	1	**61e**(86),**71e**(1),**63e**(<8)	>99:1	**62e**(74)
$Me_2Pr^iZnMgCl$	−78	1	**61e**(92),**63e**(6)	>99:1	**62e**(91)
Bu^tLi	−78	0.5	**61f**(73),**63f**(8),**68f**(5)	70:30	**62f**(51)
Bu^tMgCl	−78	0.5	**61f**(71),**63f**(17),**68f**(3)	63:37	
BnMgCl	−78	1	**61g**(92)	81:19	**62g**(91)
(i) Me_2Zn; (ii) BnMgCl	−78	1	**61g**(90)	87:13	**62g**(90)
AllylMgCl	−78	0.5	**61h**(96)	>99:1	**62h**(87)
VinylMgBr	−78	1	**61i**(53),**63b**(3),**68**(2)	>99:1	
(i) Me_2Zn; (ii) vinylMgBr	−78	1	**61i**(92),**63b**(3)	>99:1	**62i**(93)
PhLi	−78	1	**61j**(96)	>98:2	**62j**(95)
PhMgBr	−78 to 20	12	**61j**(87),**69**(4)	>99:1	**62j**(80)



Scheme 19.

Table 5. Addition of Grignard reagents to the chiral *tert*-butyl sulfinamine (*R*)-**87** (Scheme 18)[a]

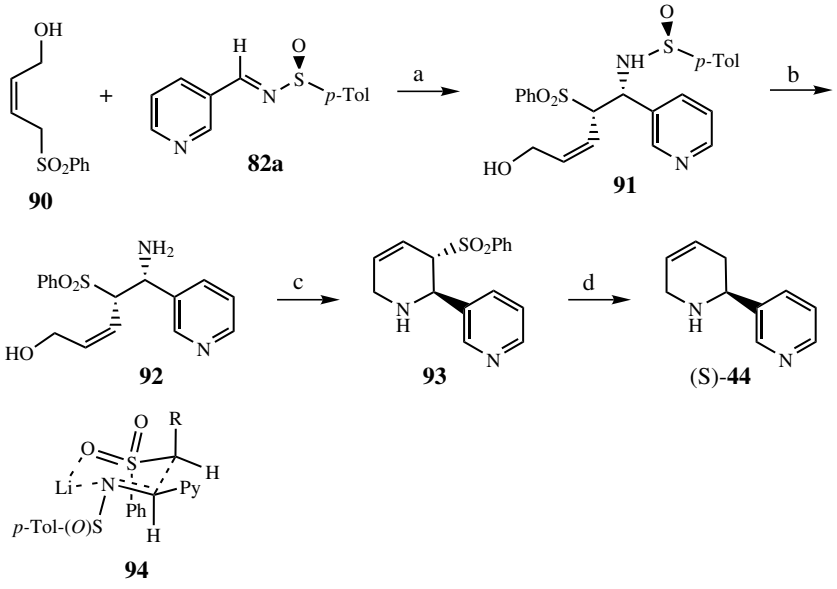
Nucleophile	Temp (°C)	Ratio (R_s,*R*)-**88**:(R_s,*S*)-**89**	Yield (%)
MeMgCl	−78	14:1	85
AllylMgCl	−40	8:1	74
PropynylMgCl	−20	15:1	90
PhMgCl	−40	28:1	70
i-PrMgCl	−40	15:1	70
VinylMgCl	−78	2:1	>99

[a] Only the best results are reported.

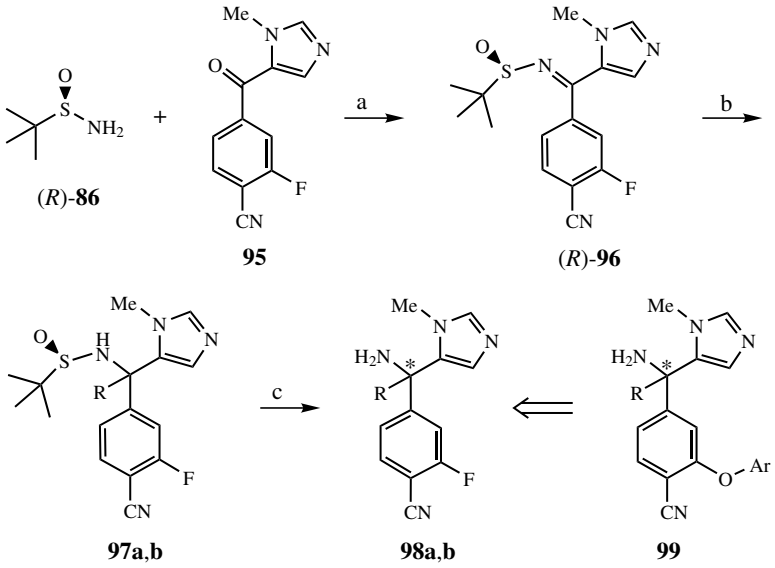
removed by treatment with trifluoroacetic acid to give **92**, which was converted into the piperidine derivative **93** under Mitsunobu conditions[35] (properly modified in the mode of addition) (70% yield). Finally, treatment of **93** with Na(Hg) in MeOH under buffered conditions afforded (*S*)-anatabine **44** in 70% yield and 70% ee. The observed diastereoselectivity was tentatively attributed to Li^+ chelation between the sulfonyl oxygen and the sulfinimine nitrogen forming a six-membered chair-like transition state **94**, which directs the pyridyl group to the equatorial position due to 1,3-diaxial Py/Ph(SO_2) repulsion (Scheme 20).

Show et al., in order to obtain the bioactive compound **99** (Scheme 21), envisaged that the diastereoselective 1,2-addition of organometallic reagents to the *N*-*tert*-butanesulfinyl ketimines of diaryl ketones could be an appropriate method for the preparation of its intermediates.[36] Among various organometallic reagents, the addition of 3-pyridyllithium and 2-methoxy-5-pyridyllithium to *N*-*tert*-butanesulfinyl ketimine (*R*)-**96**, obtained in turn by $Ti(OEt)_4$ mediated condensation of the ketone **95** with (*R*)-(+)-2-methyl-2-propanesulfinamide **86**, was examined (Scheme 21). The reaction was carried out in THF at −78 °C, followed by cleavage of the *N*-*tert*-butanesulfinyl group with 4 M HCl in dioxane and methanol. Amines **98a** and **98b** were obtained with good stereoselectivities (94% and 92% ee, respectively), but the yields proved unsatisfactory (35–57%), presumably due to the instability of the pyridyllithium reagents. The addition was selective for the ketimine over the nitrile when the organometallic reagent was added to the substrate, but not under inverse conditions.

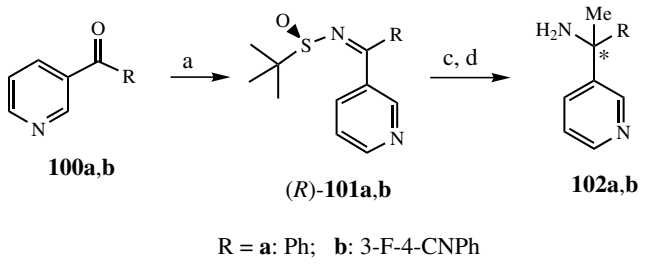
To determine whether the facile and diastereoselective addition of ketimine (*R*)-**96** was unique for this particular compound, the addition of MeMgBr and MeLi to pyridyl-aryl ketimines **101a** and **101b** was examined (Scheme 22). Both organometallic reagents gave amines **102a** and **102b** with good yields (88–100%), but low diastereoselectivities (dr = 60:40 and 73:27 for the Grignard reagent, respectively; dr = 36:64 and 45:55 'for the organolithium, respectively).



Scheme 20. Reagents and conditions: (a) **90**, LiHMDS, −78 °C, 0.5 h, then **82a**, −100/−60 °C, 1.5 h, 57%; (b) CF_3CO_2H, 68%; (c) Mitsunobu reaction, 70%; (d) Na(Hg), MeOH, 70%.



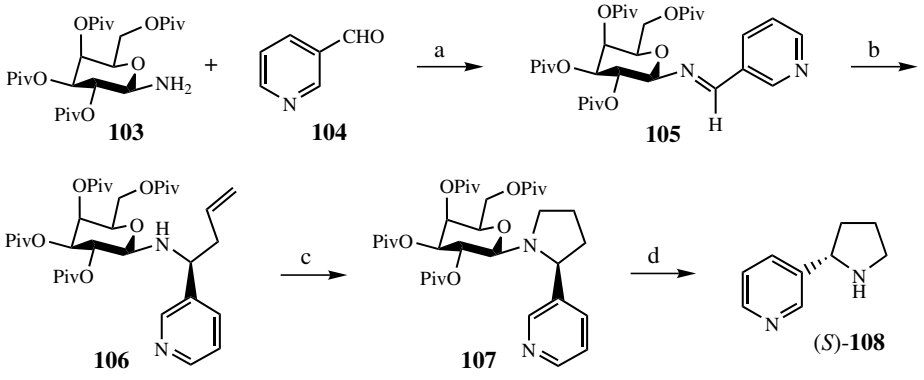
Scheme 21. Reagents and conditions: (a) $Ti(OEt)_4$, THF, reflux, 72 h, 76%; (b) R–Li, THF, −78 °C; (c) HCl (4 M), MeOH.



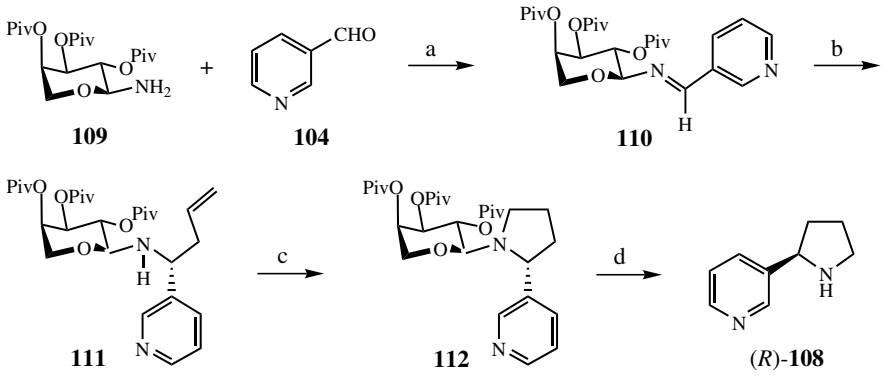
Scheme 22. Reagents and conditions: (a) (*R*)-**86**, $Ti(OEt)_4$, THF, reflux; (b) MeMgBr, 0 °C or MeLi, THF, −78 °C; (c) 4 M HCl, MeOH.

Both enantiomers of nornicotine **108** have been synthesized with good ee through a reaction sequence in which the key step is the diastereoselective addition of allyltributylstannate to aldimines derived from *O*-pivaloyl protected D-galactopyranosylamine and D-arabinopyranosylamine (Schemes 23 and 24).[37] Accordingly, when aldimine **105** prepared by condensation of pyridine-3-carboxaldehyde and 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **103** (pentane, 4 Å molecular sieves, 95%) was treated with allyltributylstannate and $SnCl_4$ (THF, −78 °C to room temperature), the imine **106** was obtained in 74% yield and high diastereoselectivity (dr >25:1) (Scheme 23). Electrophilic-induced cyclization of **105** with mercury(II) trifluoroacetate (MeCN, 0 °C) and subsequent reductive demercuration ($NaBH_4$, NaOH, H_2O) gave (*S*)-pyrrolidine **107** in high yield (74%). (*S*)-Nornicotine was finally obtained almost quantitatively by removal of the chiral auxiliary with 0.1 M HCl in aqueous MeOH, followed by Na_2CO_3. The enantiomeric excess of (*S*)-**108** was estimated to be 84%, indicating that 12% of racemization occurred during the conversion of **106**–**108**.

(*R*)-Nornicotine **108** was obtained following the same protocol using 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine **109** as the chiral auxiliary (Scheme 24).[36] However, the yields of all the single steps were lower than



Scheme 23. Reagents and conditions: (a) pentane, 1.4 Å molecular sieves, 95%; (b) $CH_2{=}CHCH_2SnBu_3$, $SnCl_4$, THF, −78 °C to rt, 74%; (c) (i) $Hg(OOCCF_3)_2$, MeCN, (ii) $NaBH_4$, NaOH, H_2O, 74%; (d) 0.1 M HCl, aqueous MeOH, then Na_2CO_3, 100%.



Scheme 24. Reagents and conditions: (a) pentane, 1.4 Å molecular sieves, 44%; (b) $CH_2{=}CHCH_2SnBu_3$, $SnCl_4$, THF, −78 to <10 °C, 45%; (c) (i) $Hg(OOCCF_3)_2$, MeCN, (ii) $NaBH_4$, NaOH, H_2O, 44%; (d) 0.1 M HCl, aqueous MeOH, then Na_2CO_3, 84%.

those observed in the *N*-galactosyl series. Also, a worse diastereoselectivity was obtained in the addition of allyltributylstannate to imine **110** (dr >20:1).

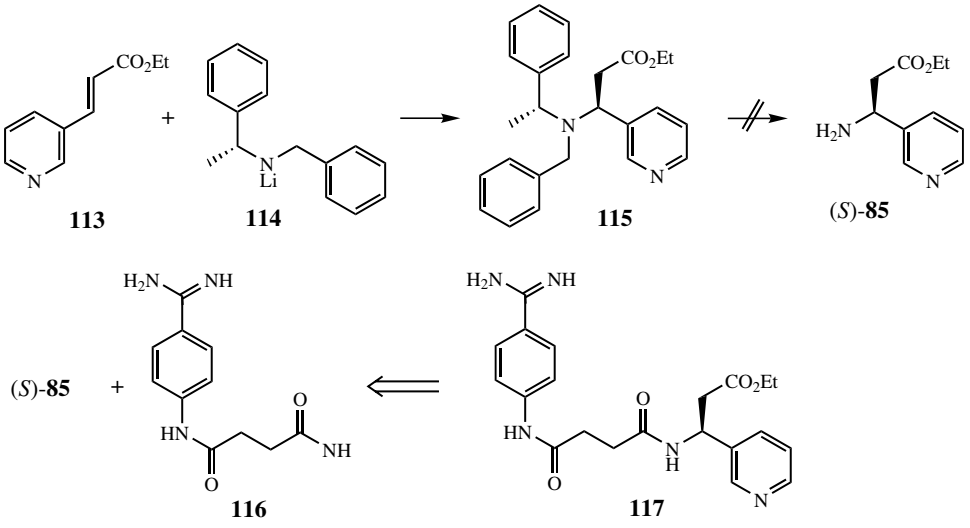
2.3. Addition of chiral amines to pyridyl acrylates

Bovy et al. who required easy access to amino ester (*S*)-**85** (Scheme 25), a key intermediate in the synthesis of the orally active antiplatelet agent **117**, examined the Davies method involving the Michael addition of lithium (*R*)-*N*-(1-phenylethyl)benzylamide **114** to ethyl *trans*-(pyridin-3-yl)acrylate **117** (Scheme 25).[38] Excellent diastereoselectivity was observed in the conjugate addition, but the resulting tertiary amine **116** resisted several attempts to debenzylate with H_2 and $Pd(OH)_2$ under a variety of conditions.

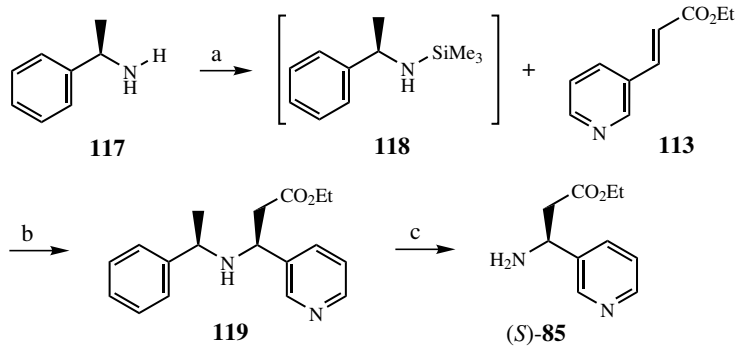
A parallel investigation with the chiral lithium silylamide generated from *N*-(trimethylsilyl)-(*R*)-1-phenylethylamine **118** gave in the nucleophilic addition a good yield (64%) and high diastereoselectivity (>95% de) (Scheme 26).[38] Since in this case a single benzylic bond needed to be removed, an easier deprotection of the adduct **119** to the desired amino acid was expected. Thus, although the debenzylation of **119** still afforded very low yield using H_2 and $Pd(OH)_2$, catalytic transfer hydrogenation using Pd/C and ammonium formate or, better, 1,4-cyclohexanediene gave the desired product (*S*)-**85** in 65% isolated yield. Unfortunately, the removal of the stereodirecting α-methylbenzyl protecting group occurred with partial racemization to give the amino ester with 90% ee.

In order to obtain β-amino ester (*S*)-**124** (Scheme 27), Davies et al.[39] utilized their oxidative deprotection of tertiary benzylamines with ceric ammonium nitrate (CAN). Thus, the addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide **121** to *tert*-butyl 3-(pyridin-3-yl)prop-2-enoate **120** afforded the addition product **122** in good yield (83%) and diastereoselectivity (84% de), which was readily increased to homogeneity by recrystallization (97% de) (Scheme 27).[39] Two consecutive oxidative *N*-deprotections with CAN (2 and 4 equiv, respectively) afforded (*S*)-**124** in 50% yield and 97% ee.

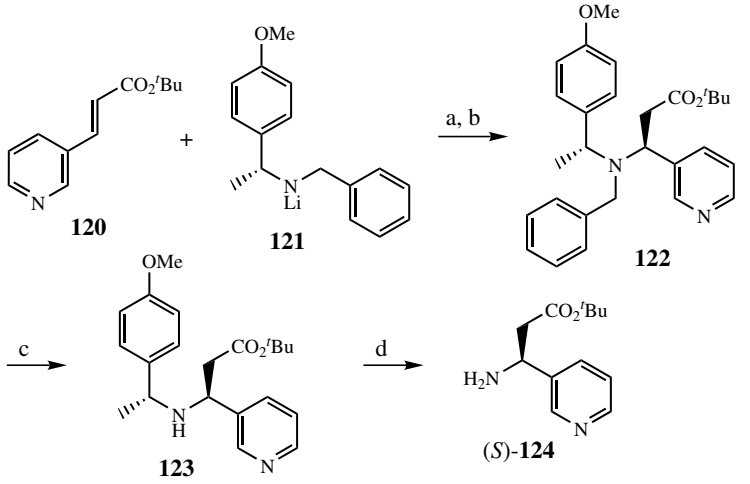
Similar yields and stereoselectivities were obtained using this protocol in the preparation of *tert*-butyl 3-amino-3-



Scheme 25.



Scheme 26. Reagents and conditions: (a) NEt_3 TMSCI, THF; (b) *n*-BuLi, THF, 0 °C, −78 °C to rt, 64%; (c) Pd/C, NH_4COOH (38%) or Pd/C/l,3-cyclohexadiene (65%).

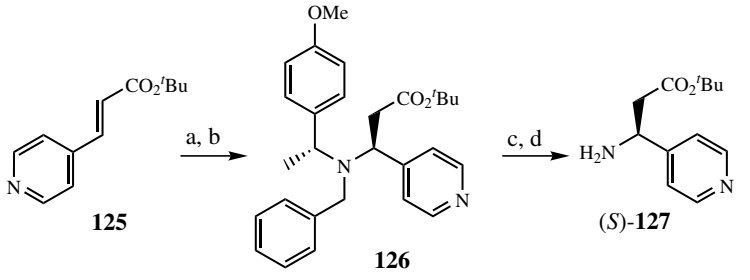


Scheme 27. Reagents and conditions: (a) THF, −78 °C, 83%; (b) recrystallization (hexane–Et_2O); (c) CAN (2 equiv), MeCN/H_2O (5:1), rt, 80%; (d) CAN (4 equiv), MeCN/H_2O (5:1), rt, 63%.

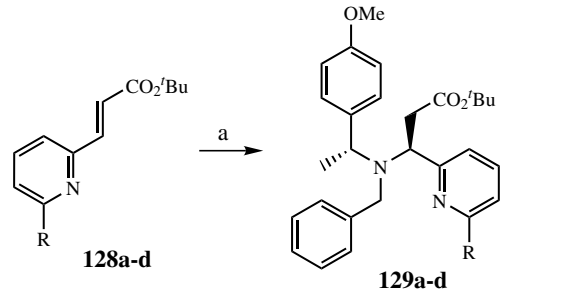
(pyridin-4-yl)propanoate (*S*)-**127** from the α,β-unsaturated ester **125** (Scheme 28).

The application of this methodology to the β-2-pyridyl system afforded very low levels of stereoselectivity unless the acrylate was substituted at the 6-position of the pyridine ring (Scheme 29). The diastereoselectivity in the conjugate addition increased in the series $SiMe_3$ (83%) > Br (81%) > Me (61%) > H (5%), but no products could be purified to homogeneity by chromatography or fractional crystallization. The low levels of observed diastereoselectivity were attributed to the disruption of the normal chelation controlled lithium amide transition state by chelation of the pyridyl nitrogen to a lithium amide complex, affording a competing non-stereoselective pathway for conjugate addition. On the other hand, the introduction of a substituent at the 6-position of the pyridine ring serves to sterically impede the coordination ability of the pyridyl nitrogen.

Finally, the protocol allowed the asymmetric synthesis of (*R*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxypyr-



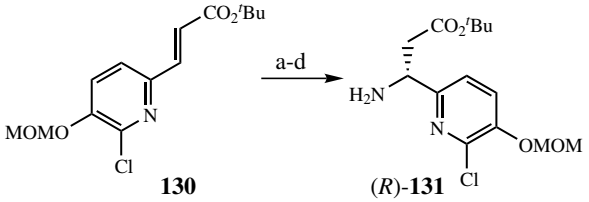
Scheme 28. Reagents and conditions: (a) **121**, THF, −78 °C, 54%; (b) recrystallization (hexane–Et_2O); (c) CAN (2 equiv), MeCN/H_2O (5:1), rt, 86%; (d) CAN (4 equiv), MeCN/H_2O (5:1), 41%.



a: R = H; **b**: R = Me;
c: R = Br; **d**: R = $SiMe_3$

129a: 72% yield, 5% de
129b: 81% yield, 61% de
129c: 45% yield, 81% de
129d: 86% yield, 83% de

Scheme 29. Reagents and conditions: (a) **121**, THF, −78 °C.



Scheme 30. Reagents and conditions: (a) lithium (*S*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide, THF, −78 °C, 69%, 80% de; (c) CAN (2.1 equiv), $MeCN/H_2O$ (5:1), rt, 68%; (b) recrystallization (hexane–Et_2O), 97% de; (d) CAN (4 equiv), $MeCN/H_2O$ (5:1), 49%, 97% ee.

idin-6-yl)-3-aminopropanoate (*R*)-**131**, the protected β-amino ester component of kedarcidin, a potent antitumour antibiotic, in 97% ee (Scheme 30).

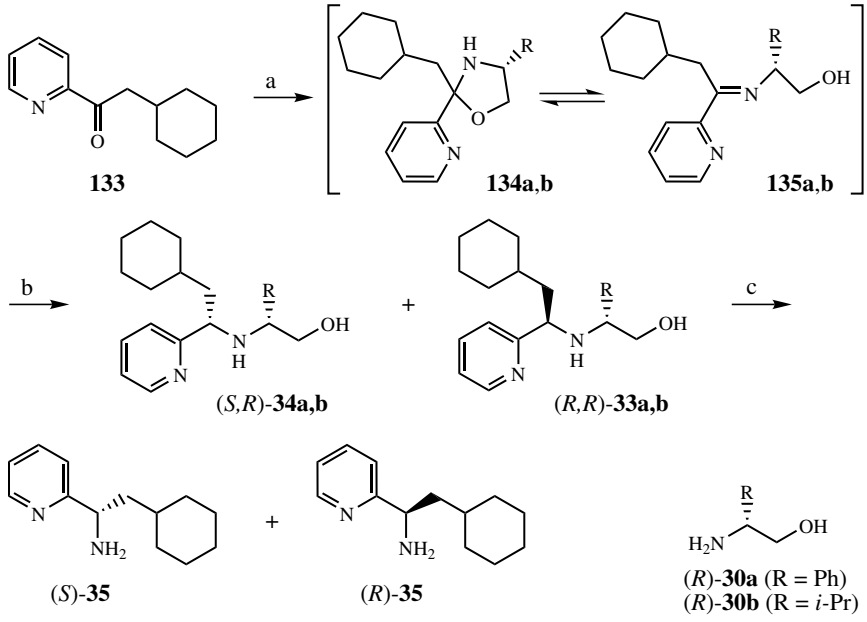
2.4. Reduction of chiral pyridyl imines and enamines

Miao et al. investigated the preparation of the (*S*)-2-cyclohexyl-1-(pyridin-2-yl)-ethylamine (*S*)-**35** (Scheme 31).[22] Among the various approaches (see also Scheme 7), the diastereoselective reduction of a mixture of chiral 2-(pyridin-2-yl)-1,3-oxazolines **134a** and **134b** and 2-pyridyl imines **135a** and **135b** obtained by coupling of ketone **133** with the (*R*)-amino alcohols **30a** and **30b** (Scheme 31) was examined. This mixture was catalytically hydrogenated (Pd/C, room temperature, 85–90%) giving high diastereomeric selectivity for **34** [R = Ph, (*SR*)-**34a**: (*RR*)-**33a** = 98:2; R = *i*-Pr, (*SR*)-**34b**:(*RR*)-**33b** = 90:10]. Oxidative cleavage of diastereomers **34a** and **34b** (a: 96% de, b: 80% de) with $NaIO_4$ provided the desired amine (*S*)-**35** with 96% ee when R = Ph and 80% ee when R = *i*-Pr, but in low yield (35–40%). The diastereomeric distribution in Scheme 31, in which the major diastereomer is the (*S*,*R*)-**34** instead of the (*R*,*R*)-**33** as compared to Scheme 7 where (*S*,*S*)-**33** is predominant, is particularly noteworthy.

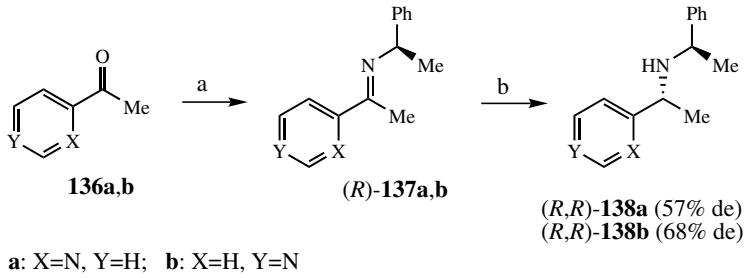
The zinc borohydride reduction of enantiopure imines derived from (*R*)-α-methylbenzylamine and 2- and 4-acetylpyridine **136a** and **136b** has recently been carried out (Scheme 32).[40] The secondary amines **138a** and **138b** were obtained in moderate yield (52% and 53%, respectively) and diastereoselectivity (57% and 68% de, respectively) with the (*R*,*R*)-diastereomer prevailing.

Zhong et al. in research aimed at the preparation of the drug RWJ-53308 (Fig. 1) addressed their interest to (*S*)-3-amino-3-(pyridin-3-yl)propanoate **143** (Scheme 33), a key starting material in its synthesis.[41]

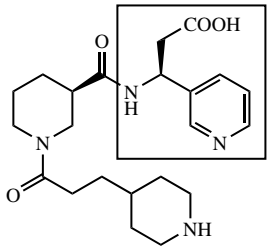
For the synthesis of **143**, the diastereoselective reduction of enamine **141a**, obtained by reaction of (*S*)-α-methyl-



Scheme 31. Reagents and conditions: (a) (*R*)-**30a** or (*R*)-**30b**, $MgSO_4$, $CHCl_3$ reflux, 2 d, 95%; (b) 10% Pd/C, H_2, THF, rt, 4 h, 85–90%; (c) $NaIO_4$, $THF/H_2O/HCl$, rt, overnight, 35–40%.



Scheme 32. Reagents and conditions: (a) (*R*)-1-phenyl-ethylamine; (b) $Zn(BH_4)_2$, THF, 0 °C, 25–30 min, 52–53%.



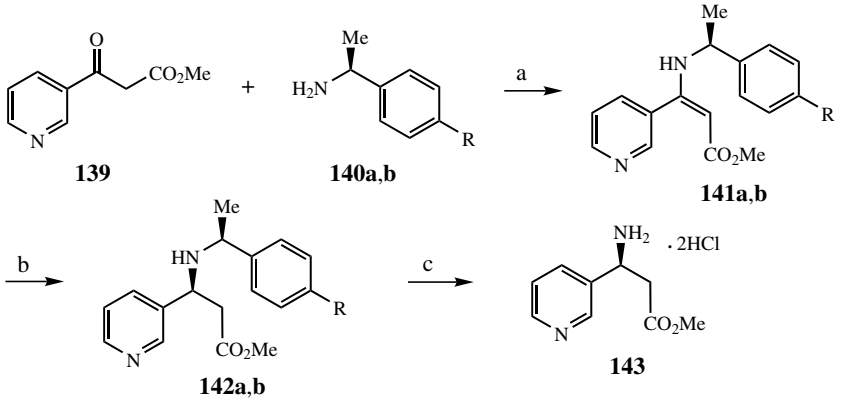
RWJ-53308

Figure 1.

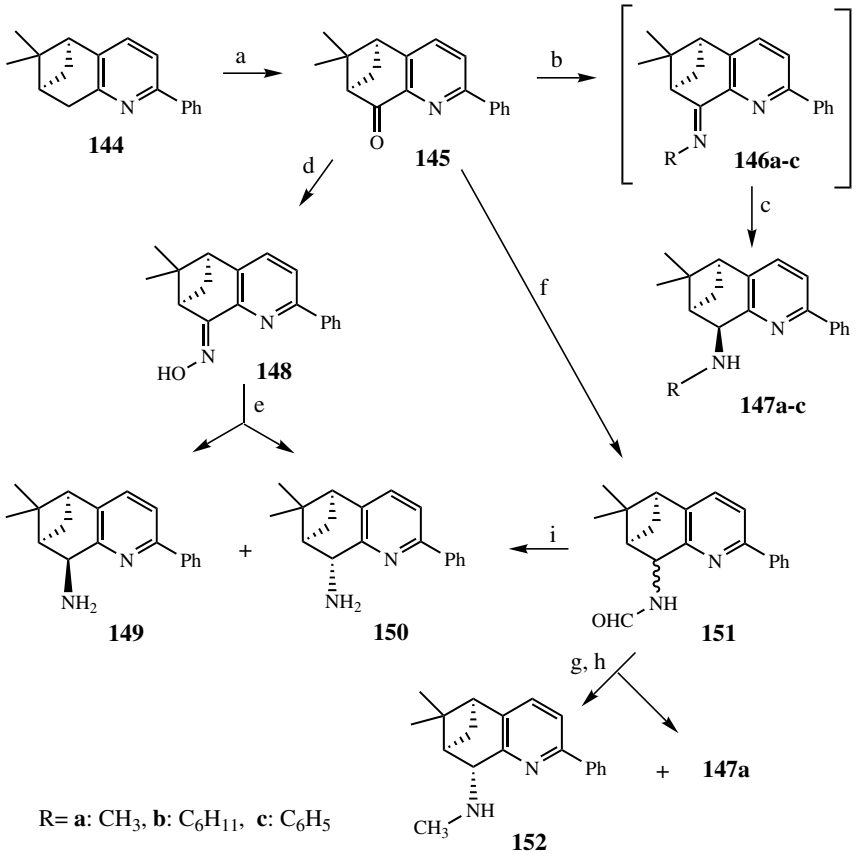
benzylamine **140a** with ketone **139**, was examined. The reduction of **141a** was carried out under various conditions. While the reduction with $NaBH_4$ or $NaB(OAc)_3H$ gave poor to moderate diastereoselectivity (up to 46% de), the palladium catalyzed hydrogenation [H_2 (1 atm), 10% $Pd(OH)_2$ (20% on C), MeOH/AcOH, 79% yield] gave the best diastereoselectivity (76% de). The desired diastereomer was later isolated in >98% de by crystallization of its HCl salt. However, because the removal of the α-methylbenzyl group from **142a** was quite difficult (best conditions: 100% $Pd(OH)_2$ (20% on C), 1,4-cyclohexadiene, AcOH, 50% yield), this amine was substituted with (*S*)-1-(4-methoxyphenyl)ethylamine **140b** hoping that the higher electronic density on the aromatic ring should have facilitated the removal of the chiral auxiliary. Thus, under the optimized conditions used for **141a**, diastereomer **142b** was obtained in 66–88% diastereomeric excess, which was increased to >99% by crystallization. Finally, removal of the chiral auxiliary was successfully accomplished without compromising the enantiomeric purity using the $HCOOH/Et_3SiH$ system (90–100 °C, 1 h, 94% yield).

Chelucci et al., among several ways followed to obtain some diastereomerically pure 8-amino substituted 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-6-7-methanoquinolines, evaluated the diastereoselective reduction of imines and oximes[42] (see also Scheme 42). The synthesis started from the 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-6,7-methano-8-quinolone **145**,[43] which was easily accessible from tetrahydroquinoline **144** (Scheme 34). Thus, the reaction of the appropriate amine with ketone **145**, followed by sodium borohydride reduction of the corresponding unisolated imines, gave secondary amines **147a–c** in satisfactory overall yields (52–76%). The reduction was highly diastereoselective and in all cases the stereoisomer with an (*S*)-configuration at C8 of the tetrahydroquinoline ring was obtained.

In order to prepare both epimeric primary amines, required to obtain the desired *N*-alkylamino derivative, the synthesis of primary amines **149** and **150** was accomplished in two ways. Treatment of ketone **145** with hydroxylamine hydrochloride afforded the corresponding oxime **148**, which by reduction with lithium



Scheme 33. Reagents and conditions: (a) AcOH, toluene, 65 °C, reduced pressure; (b) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 22 h, 60%; (c) $HCOOH/Et_3SiH$, then HCl/EtOAc/MeOH, 90–95%.



Scheme 34. Reagents and conditions: (a) several steps; (b) R–NH_2 catalytic BF_3, benzene, reflux; (c) $NaBH_4$, EtOH, rt; (d) NH_2OH, EtOH; (e) $LiAlH_4$, Et_2O, reflux; (f) $HCOOH/HCONH_2$, 120 °C, 7 h; (g) $LiAlH_4$, THF, reflux; (h) chromatographic separation; (i) KOH, EtOH, reflux, 4 h.

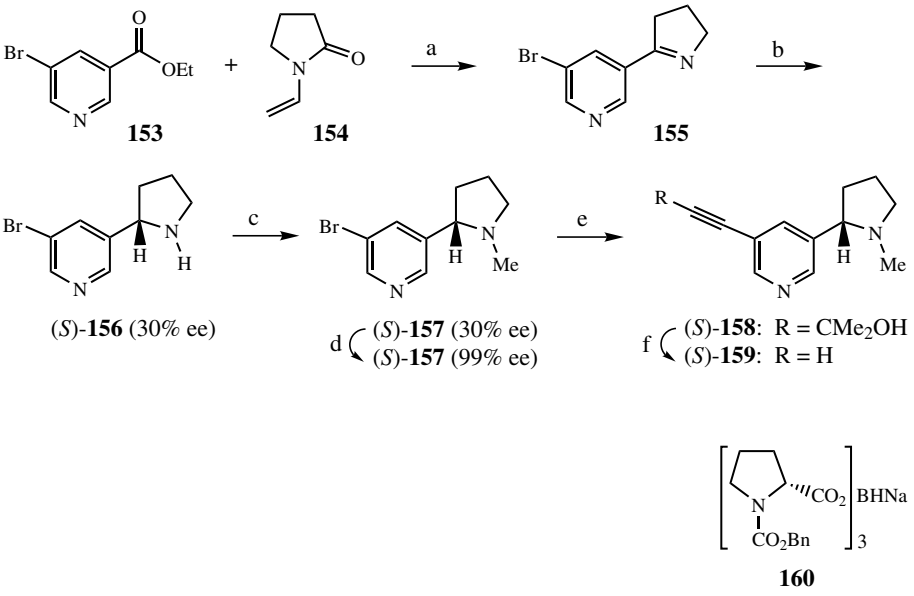
aluminium hydride gave an 8:2 mixture of the *cis*- and *trans*-amines **149** and **150**, respectively. This mixture was separated by column chromatography on silica gel to give the diastereomerically pure amines **149** and **150** in overall yield of 48% and 12%, respectively. Also in this case the *cis*-epimer was prevalent. In the latter approach, ketone **145** was transformed with formic acid and formamide (Leuckart reaction) in a 8:2 diastereomeric mixture of formamides **151** (51% yield). This mixture was not separable but was used in the next step without further characterization. Hydrolysis of **151** under basic conditions, to remove the *N*-formyl group, afforded primary amines **149** and **150** in about a 2:8 diastereomeric ratio, but in very poor yield (7% and 27%, respectively). Although this route does not appear useful for obtaining the primary amines **149** and **150**, it does give ready access to the *trans*-*N*-methylamine **152**, which was not possible to obtain through the above described reductive amination procedure. In fact, lithium aluminium hydride reduction of **151** gave methylamine **152** along with its epimer **147a**. The ratio of **152**:**147a** was 65:35, which was fairly different from that of formamides **151**. Most likely, the equilibration of amides **151**, via their enol tautomers, occurred during the basic conditions of the lithium aluminium hydride reduction.

During a study aimed at the synthesis of the neuronal acetylcholine-gated ion channel agonist (*S*)-(−)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate [(*S*)-**159**, SIB-1508Y], Cosford et al. developed an efficient synthesis of its precursor (*S*)-**157** (Scheme 35).[44] The key steps in the process were the combination of an enantioselective reduction of imine **155** and crystallization of the enantiomerically enriched (*S*)-5-bromo-3-(1-methylpyrrolidin-2-yl)pyridine **157** as the dibenzoyl-L-tartaric acid salt.

Lithium bis(trimethylsilyl)amide-mediated acylation of the *N*-methylpyrrolidone **154** with ethyl 5-bromonicotinate **153**, followed by removal of the *N*-vinyl group, afforded imine **155** in high yield. The enantioselective reduction of **155** was accomplished employing the (acyloxy)borohydride reagent formed from sodium borohydride (1 equiv) with carbobenzyloxy-D-proline (3 equiv).[45] The reaction afforded secondary amine **156** in 98% yield and 30% ee. The enantiomerically enriched **156** was firstly *N*-methylated and then converted into the related dibenzoyl-L-tartaric acid salt, which by two crystallizations afforded (*S*)-**157** in >99% ee. Cross-coupling of (*S*)-**157** with 2-methyl-3-butyn-2-ol (K_2CO_3, CuI, 10% Pd/C, PPh_3, DME–H_2O, 92–98%), followed by deprotection (NaH, toluene, 111 °C) of the intermediate ethynylpyridine (*S*)-**158**, gave (*S*)-**159** in 97% yield.

2.5. Reduction and transformation of azides

Primary amines can be easily prepared by the reduction of azides, which in turn can be obtained from the corresponding alcohols. This strategy was first used by Chelucci for the synthesis of some 1-(pyridin-2-yl)meth-



Scheme 35. Reagents and conditions: (a) (i) **154**, LiHMDS, THF, −22 °C; (ii) **153**, *t*-BuOMe, rt, 18 h, 94–99%; (iii) HCl (12 M), H_2O, charcoal, 98 °C, 2 h, 71%; (b) **160**, CH_2Cl_2, 25 °C, 48 h, 98%; (c) HCO_2H, HCHO–H_2O, 80 °C, 3 h, 71%; (d) dibenzoyl-L-tartaric acid, EtOH–EtOAc, then crystallization; (e) K_2CO_3, CuI, 10% Pd/C, PPh_3, DME–H_2O, 25 °C, 30 min, then 2-methyl-3-butyn-2-ol, reflux, 16 h, 92%; (f) NaH, toluene, 111 °C, distillation, 97%.

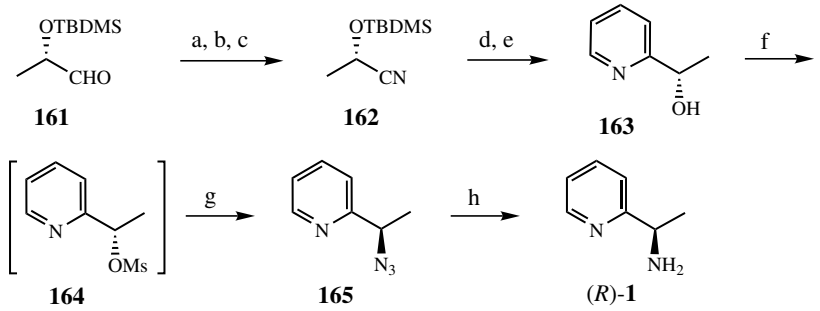
ylamines using natural occurring chiral compounds as starting points (Schemes 36–38).[46] For the preparation of (*R*)-1-(pyridin-2-yl)ethylamine **1** and (*R*)-2-hydroxy-1-(pyridin-2-yl)ethylamine **29a** (Schemes 36 and 37, respectively), chiral alcohols **163** and **169** were obtained by cobalt(I)-catalyzed cyclotrimerization[15,16] of the corresponding chiral *O*-protected α-hydroxynitriles **162** and **167**, easily accessible from the (2*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propanal **161**[47a] and 2,3-*O*-(isopropylidene)-D-glyceraldehyde **166**,[47b] respectively.

Alcohol **163** (100% ee) was converted into azide **165** by treatment of the unisolated mesylate **164** (MsCl, Et_3N, DMPA, CH_2Cl_2) with sodium azide in DMF (room temperature, 24 h, 85% yield) (Scheme 36). The azide was reduced by hydrogen on Pd/C to give amine (*R*)-**1** in 71% overall yield based on **163** and 66% ee.

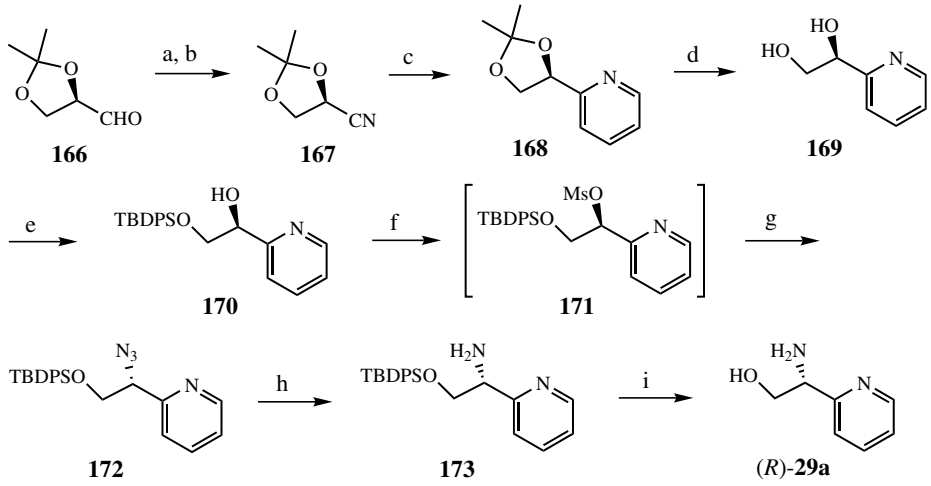
For the transformation of glycol **169** (98% ee) into hydroxy amine (*R*)-**29a**, the selective protection of the primary hydroxy group was necessary (Scheme 37). Next, starting from monoprotected alcohol **170** and following the above procedure, amine **173** was obtained. Removal of the protecting group by 10% hydrofluoric acid gave amine (*R*)-**29a** in 66% overall yield based on **169** and 92% ee.

The application of the same procedure to chiral alcohol **175**, obtained in 85% enantiomeric excess by asymmetric reduction of ketone **174** using (−)-β-chlorodiisopinocampheylborane, led to amine **178** in 85% overall yield based on **175** and 77% enantiomeric excess (Scheme 38).

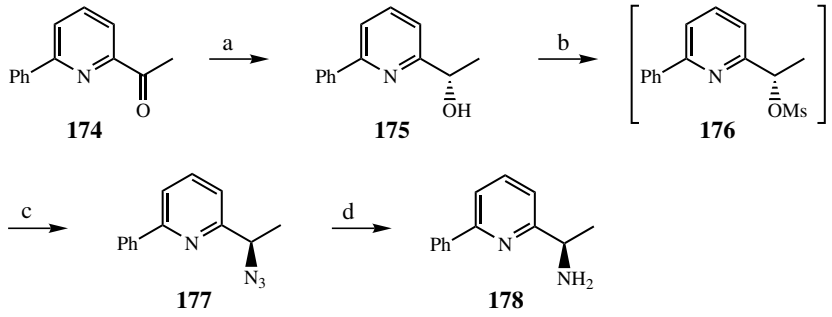
In all the examined cases, a variable loss of the enantiomeric purity during the reaction processes was observed. Uenishi et al.[48] recently re-examined the reaction of the conversion of **163** to **1** and found that the racemization process occurs when the substitution of the mesylate with the azide anion is performed without purification of the intermediate mesylate. In fact, the product after mesylation contains (*R*)-2-(1-cholоromethyl)pyridine



Scheme 36. Reagents and conditions: (a) DIBAL, hexane; (b) $NH_2OH{\cdot}HCl$, 10% K_2CO_3, MeOH; (c) *N*,*N*-carbonyldiimidazole, CH_2Cl_2, 2 h, rt, 92%; (d) CpCo(COD), acetylene, toluene, 14 atm, 140 °C, 82%; (e) 10% HCl; (f) MsCl, Et_3N, DMPA, CH_2Cl_2; (g) NaN_3; DMF, rt, 24 h, 85%; (h) Pd/C, H_2, 95%.



Scheme 37. Reagents and conditions: (a) NH_2OH–HCl, 10% K_2CO_3, MeOH; (b) *N*,*N*-carbonyldiimidazole, CH_2Cl_2, 2 h, rt, 87%; (c) CpCo(COD), acetylene, toluene, 14 atm, 140 °C, 85%; (d) 6% HCl, 95%; (e) (*t*-Bu)Ph_2SiCl, Et_3N, DMPA, CH_2Cl_2, 89%; (f) MsCl, Et_3N, DMPA, CH_2Cl_2; (g) NaN_3, DMF, rt, 24 h, 92%; (h) Pd/C, H_2, 95%; (i) 10% HF, 85%.

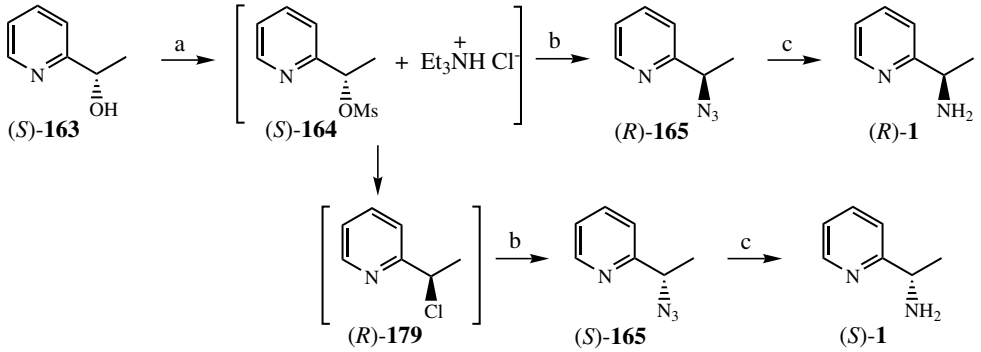


Scheme 38. Reagents and conditions: (a) (−)-β-chlorodiisopinocampheylborane, neat, rt, 2 d then iminodiethanol, Et_2O, 3 h; (b) MsCl, Et_3N, DMPA, CH_2Cl_2; (g) NaN_3, DMF, rt, 24 h, 90%; (h) H_2, Pd/C, 95%.

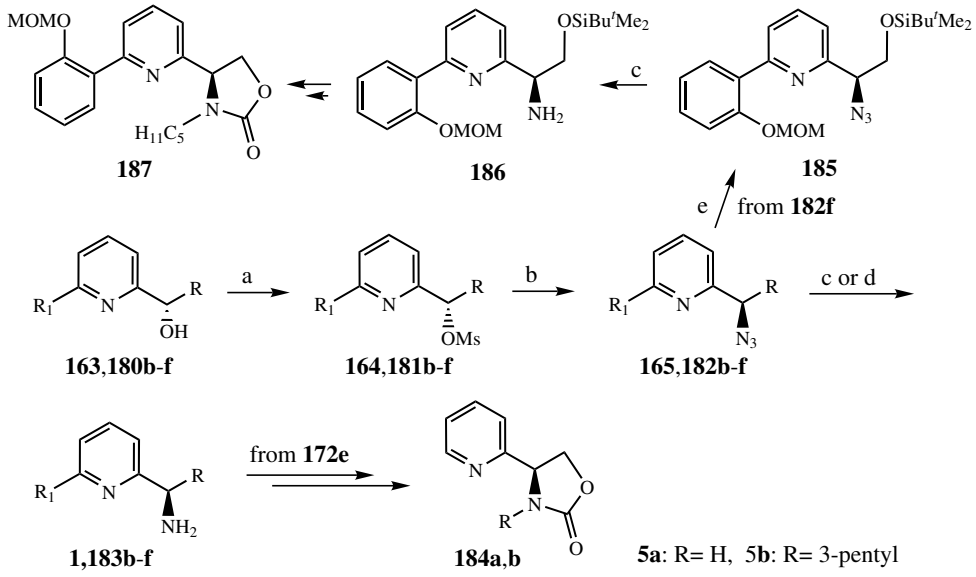
(*R*)-**179** formed in turn by the reaction of the mesylate with triethylamine hydrochloride produced by the mesylation reaction (Scheme 39). Therefore, azide formation through a chloride intermediate decreases the enantiomeric purity of the final azide **1** (Scheme 39).

Taking into account these findings, Uenishi prepared a number of amines (Scheme 40) with complete retention of the enantiomeric purity of the starting alcohols. The optically active alcohols were obtained by lipase-catalyzed enantioselective acetylation. It should be noted that in the case of **181b**, the reduction of the azide function was performed using triphenylphosphine[49] to avoid the hydrogenolysis of bromine on the pyridine ring (77% yield).

On the other hand, azide **182f** was cross-coupled with 2-(methoxymethyloxy)-phenylboronic acid under the Suzuki coupling conditions to give azide **185**, which was reduced by palladium-catalyzed hydrogenation to



Scheme 39. Reagents and conditions: (a) MsCl, Et_3N, DMPA, CH_2Cl_2; (b) NaN_3, DMF, rt, 24 h, 90%; (c) H_2, Pd/C, 95%.



a: R = Me, R_1 = H; **b**: R = Me, R_1 = Br; **c**: R = Me, R_1 = $CH_2OSiBu^tMe_2$; **d**: R = Me, R_1 = 2-pyridyl; **e**: R = $CH_2OSiBu^tMe_2$, R_1 = H; **f**: R = $CH_2OSiBu^tMe_2$, R_1 = Br

Scheme 40. Reagents and conditions: (a) MsCl, DMPA, CH_2Cl_2, rt; (b) NaN_3, DMF, rt; (c) Pd/C, H_2, 95%; (d) Ph_3P, H_2O, THF, rt; (e) $Pd(PPh_3)_4$, 2-(methoxymethyloxy)phenylboronic acid, Na_2CO_3, benzene/EtOH, reflux, 36 h.

amine **186** (100% yield). This compound was converted in a three step sequence to 1,3-oxazolidin-2-one **187** in 64% overall yield. In the same manner, **183e** was transformed into **184a** and **184b** in 92% overall yield.

Shin et al.,[50,51] as part of the total synthesis of antibiotic cyclothiazomycin, prepared the two pyridines **188** and **189** as a diastereomeric mixture, which was separated by chromatography (Fig. 2). In order to determine the configuration of the 2-(1-aminoethyl)-moiety of these diastereomers, both (*R*)- and (*S*)-2-[1-(*N*-Boc)-aminoethyl]pyridines **191** were independently synthesized and their CD spectra recorded. Reduction of 2-acetylpyridine with Baker's yeast afforded alcohol (*S*)-**163**, which was converted into the (*R*)-isomer by treatment with sodium acetate followed by hydrolysis with sodium carbonate (Scheme 41). In the usual way, these alcohols were converted into the *N*-Boc amines (*S*)- and (*R*)-

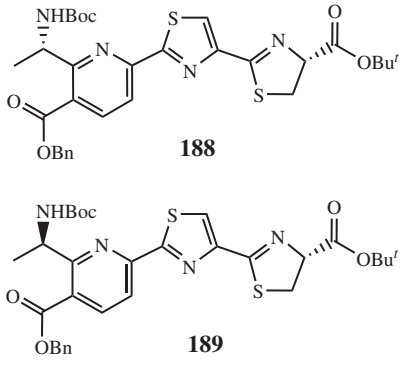
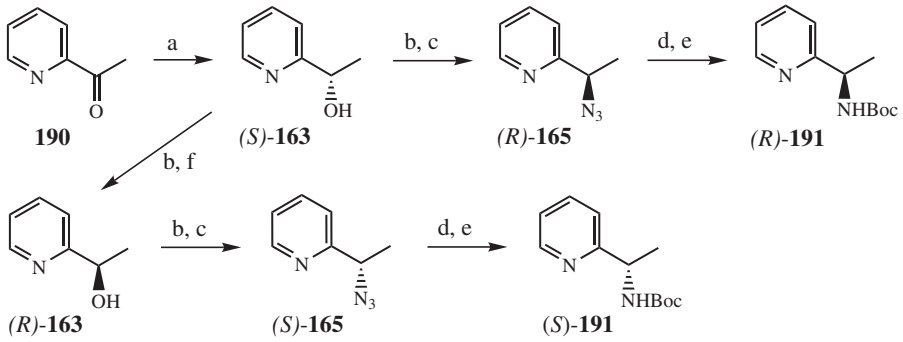


Figure 2.

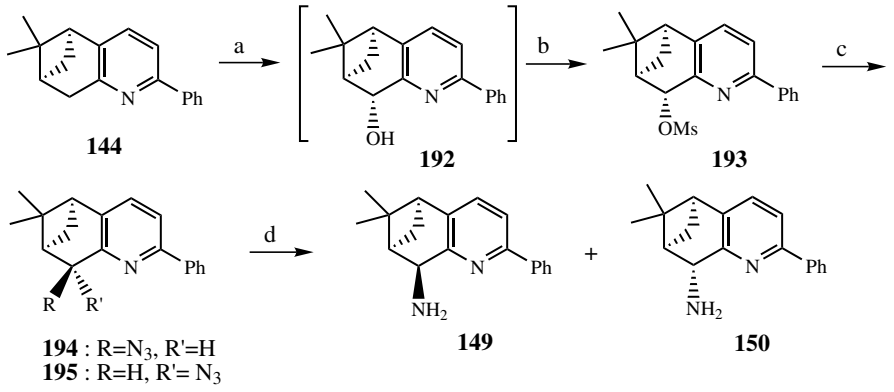
191. Comparison of their CD spectra with those of **188** and **189** allowed the assignment of the absolute structure to these compounds.

Chelucci et al., amongst various methods to obtain some diastereomerically pure 8-amino substituted 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethylmethanoquinolines, evaluated (see Scheme 34) the sequence alcohol-mesylate-azide-amine[42] (Scheme 42). Thus, (5*S*,7*S*,8*R*)-8-hydroxy-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-5,7-methanoquinoline **144** was converted into the corresponding mesylate **193**, which was not isolated but treated directly with sodium azide in DMF (Scheme 41). The reaction occurred only at 90 °C (24 h) to afford azide **194** and its unexpected epimer **195** in an 85:15 ratio, respectively (32% overall yield from the alcohol). The formation of an intermediate carbocation, which probably occurs during the nucleophilic displacement of the mesyloxy group by the azido group, explains the stereochemical outcome (formation of the mixture of epimeric azides) and the low yield (owing to isomerization phenomena). Reduction of this inseparable mixture of azides by hydrogen on Pd/C gave the expected amines **149** and **150** in very poor yield and in a 73:27 ratio.

Lebreton et al. described in a series of papers the preparation of a number of pyridine alkaloids, the syntheses of which led to the formation of chiral azides as the key step.[52] The route followed to obtain the six piperidine and pyrrolidine alkaloids **108**, **199**, **44** and **204**–**206** is described in Scheme 43. The synthesis started from the chiral homoallylic alcohol **196**, which was obtained in 94% yield and >94% enantiomeric excess by treatment of the (+)-*B*-allyldiisopinocampheylborane with



Scheme 41. Reagents and conditions: (a) Baker's yeast, D-Glucose, H_2O, 48 h, 48%; (b) MsCl, Et_3N, DMPA, $CHCl_3$, 0 °C, 30 min; (c) NaN_3, DMF, rt, 24 h, 75%; (h) Pd/C, H_2, EtOH, rt, 30 min; (d) Boc_2O, Et_3N, $CHCl_3$, 0 °C, 30 min, then rt, 3 h, 81%; (f) NaOAc, 15-crown-5-ether, DMF, rt, 24 h then K_2CO_3, MeOH, H_2O, 0 °C, 30 min, rt, 3h, 46%.

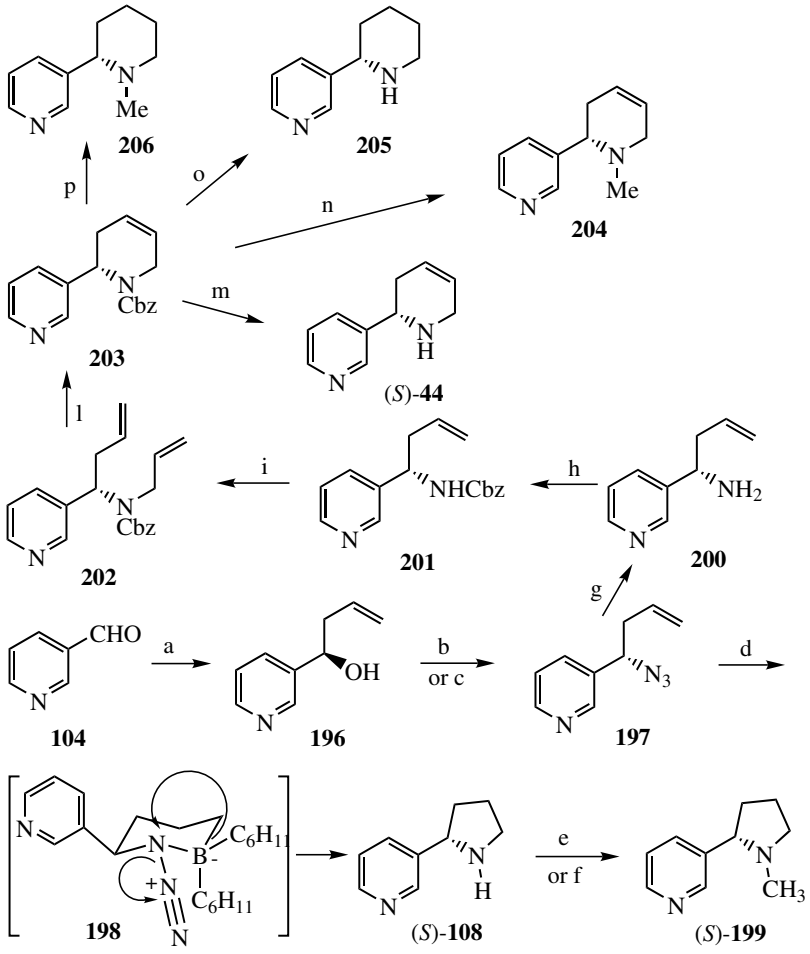


Scheme 42. Reagents and conditions: (a) several steps; (b) MsCl, Et_3N, DMAP, CH_2Cl_2, 24 h; (c) NaN_3, DMF, rt, 24 h; (d) Pd/C, H_2, MeOH, 24 h.

pyridine-3-carboxaldehyde. The next step involved replacing the alcohol at the benzylic position of **196** with the azide group, resulting in an inversion of configuration. This transformation was carried out following two procedures. First, the chiral homoallylic alcohol **196** was treated with diphenyl phosphoroazidedate (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry toluene; the corresponding phosphate formed in situ was displaced by the azide anion to afford azide **197** in good yield (90%) and 94% ee. Later, azide **197** was prepared in two steps by the nucleophilic displacement of the mesylate of **196** with an azide anion. The overall yield was 97% and the enantiomeric excess 94%. With the chiral azide **197** in hand, Lebreton paid attention to the construction of the pyrrolidine ring, which was obtained by treating the azide **197** with freshly prepared dicyclohexylborane followed by hydrolysis with methanol (85% yield). This one-pot sequence proceeds by hydroboration of the double bond of **197** and subsequent formation of a boron–nitrogen bond between the azide and the trialkylborane, to afford the cyclic azide borane complex intermediate **198**. Finally, migration of the borane methylidene group to *N*-1 of **198** proceeds with ring contraction and a concomitant loss of nitrogen. The transformation of the (*S*)-nornicotine **108** to (*S*)-nicotine **199** was achieved using the usual procedure. The enantiomeric excess of both compounds was determined to be 94%.

For the synthesis of piperidine (*S*)-**44** (Scheme 42), azide **197** was reduced to the related amine **200** with an excess of hydrated tin chloride in 98% yield. Amine **200** was then protected as the benzyl carbamate **201**, which was treated with an excess of sodium hydride in the presence of allyl bromide to provide the *N*-allylamine **202** in good yield (76%). A ring closing metathesis reaction was carried out on the pyridine hydrochloride of **202** using 10 mol % of the Grubbs' ruthenium benzylidene catalyst (79%). Having obtained good access to the chiral building **203**, the completion of the synthesis of the four piperidine alkaloids **44** and **204**–**206** proved to be straightforward and could be achieved using either a single-, two- or three-step one-pot procedure, depending on the target piperidine alkaloid, as depicted in Scheme 42.

Lebreton et al.[52c] applied their strategy to the synthesis of the pyrrolidine ring to obtain the (*S*)-SIB-1508Y **159** (Scheme 44), an important nAChR agonist in clinical trial for the treatment of Parkinson's disease. The synthesis started from aldehyde **207**, which was converted into the homoallylic alcohol **209** by the enantioselective reduction with (+)-chlorodiisopinocamphenylborane of the ketone **208** (79% yield, 94% ee). This alternative route was necessary because the direct enantioselective allylboration of aldehyde **207** gave alcohol **209** in 66% ee instead of 94% as in the case of aldehyde **206** (Scheme 43). In the usual way, the homoallylic alcohol **209** was



Scheme 43. Reagents and conditions: (a) *B*-allyldiisopinocamphenylborane (2.2 equiv), Et_2O, −100 °C, 94%; (b) DBU (1.2 equiv), $(PhO)_2P(O)–N_3$ (1.2 equiv), toluene, rt, 90%; (c) MsCl (1.1 equiv), Et_3N (1.2 equiv), CH_2Cl_2, 0 °C, then NaN_3 (2.2 equiv), DMF, 60 °C, 97%; (d) C_6H_{10}, $BH_3–Me_2S$, (2.2 equiv), THF, rt, 85%; (e) LiHMDS (2 equiv), MeI (2 equiv), THF, −78 °C to rt, 78%; (f) EtOCOCl (1.2 equiv), Et_3N (1.3 equiv), Et_2O, rt, then $LiAlH_4$ (1.2 equiv), THF, 0 °C, 90%; (g) $SnCl_2·H_2O$, MeOH, 98%; (h) CbzCl, K_2CO_3, CH_2Cl_2 76%; (i) CH_2=CH–CH_2Br, NaH, DMF, 76%; (l) HCl (gas), CH_2Cl_2, then $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, 79%; (m) $BF_3·Et_2O$, Me_2S, CH_2Cl_2, 67%; (n) $LiAlH_4$, THF, 71%; (o) H_2, Pd/C, EtOH, 82%; (p) H_2, Pd/C, MeOH, HCHO, 88%.

transformed into pyridine **157** with complete retention of enantiomeric excess (94%). Cross-coupling of **157** with 2-methyl-3-butyn-2-ol in the presence of 10% Pd/C, CuI (cat), Ph_3P and K_2CO_3 afforded **158** in high yield (83%). Finally, deprotection provided **159** in 92% yield and 94% ee.

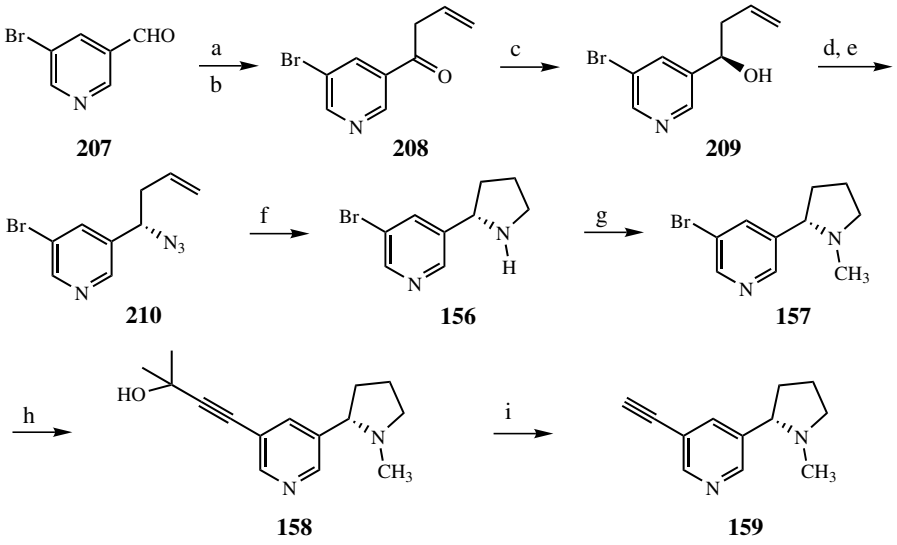
2.6. Alkylation of chiral iminomethylpyridines

Yaozhong et al. reported the synthesis of (*R*)- or (*S*)-1-substituted-1-(pyridin-2-yl)methylamines from (+)- or (−)-2-hydroxy-3-pinanone **211** (Scheme 45).[29] The condensation of (+)-**211** with 2-aminomethylpyridine **212** in the presence of $BF_3–Et_2O$ in benzene afforded ketimine **202** in 90% yield. The deprotonation of **213** with *n*-butyllithium at −78 °C followed by treatment with a number of alkyl halides (MeI, *i*-PrI, CH_2=CH–CH_2Br, $C_6H_5CH_2Br$ and $CH_3OC_5H_4CH_2Cl$) gave the alkylated products **214a–e**, which were not separated, but directly treated with hydroxylamine acetate to give the amines **1**, **5**, **51**, **59f** and **215e** in 30–56% overall yield from **213** and 89–98% enantiomeric excess.

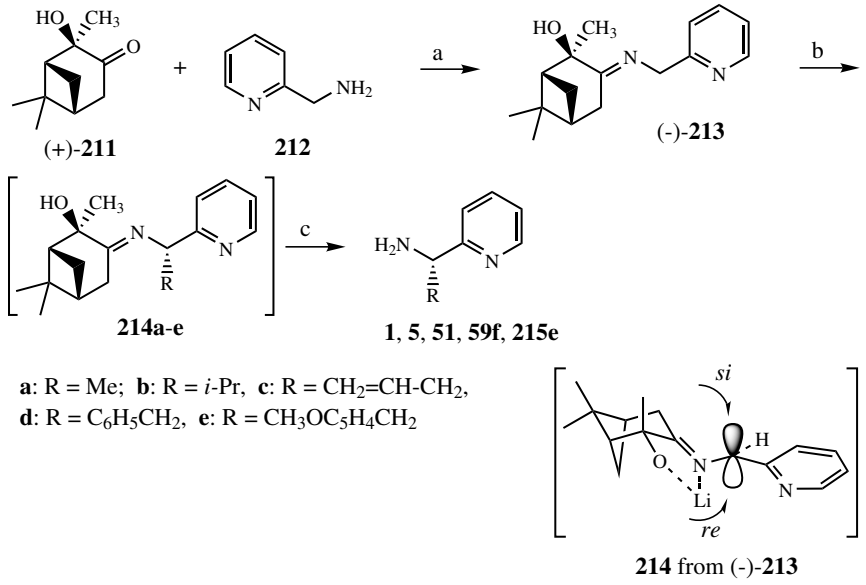
The authors explained the selectivity considering that the alkyl halide should attack from the *si*-face of the anion derived from the (−)-ketimine because of the strong cyclic chelation of the π-lithium association to give the product with an (*S*)-configuration (Scheme 45).

More recently, (*S*)-2-methyl-1-(pyridin-2-yl)propylamine (**5**), (*S*)-2-phenyl-1-(pyridin-2-yl)ethylamine **59f** and (*S*)-1-(pyridin-2-yl)propylamine **59b** have been synthesized following the above procedure from the appropriate pinanone.[12] The obtained ee was typically around 85%, but a single recrystallization of the amine hydrochloric acid salt gave the amines with >95% ee.

Crooks et al. prepared both enantiomers of nornicotine adapting the above method.[53] Condensation of 3-aminomethylpyridine **216** with (+)-**211** in the presence of $BF_3–Et_2O$ in benzene formed the corresponding ketimine **217** in 67% yield (Scheme 46). Treatment of **217** with LDA at −78 °C, followed by C-alkylation with 3-bromopropan-1-ol gave **218**, which by hydrolysis of the ketimino group with hydroxylamine hydrochloride



Scheme 44. Reagents and conditions: (a) Zn (2 equiv), allyl bromide (2 equiv), THF, rt, 1 h, 97%; (b) DMP (1.2 equiv), CH_2Cl_2, rt, 15 min, 100%; (c) (+)-chlorodiisopinocamphenylborane (2.2 equiv), Et_2O, −30 °C, 20 h; 79%; (d) MsCl (1.1 equiv), Et_3N, CH_2Cl_2, 0 °C, 5 min, 100%; (e) then NaN_3 (1.5 equiv), DMF, 60 °C, 4 h, 83%; (f) $B(C_6H_{11})H$ (2 equiv), THF, rt, 1 h then reflux 3 h, 62%; (g) HCHO (37% aqueous), HCO_2H, 80 °C, 3 h, 94%; (h) 2-methyl-3-butyn-2-ol, CuI (cat), 10% Pd/C, Ph_3P, K_2CO_3, DME, rt, then reflux, 16 h, 83%; (i) NaH (10 mol %), toluene, reflux, 2 h, 92%.



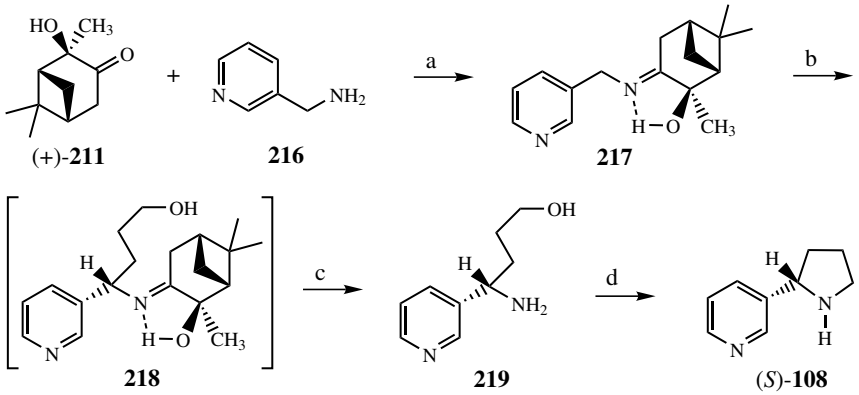
Scheme 45. Reagents and conditions: (a) BF_3–Et_2O, benzene, reflux, 2.5 h, 90%; (b) *n*-BuLi, THF, −78 °C, 2–3 h, then RX (MeI, *i*-PrI, CH_2=CH–CH_2Br, $C_6H_5CH_2Br$, $CH_3OC_5H_4CH_2Cl$); (c) NH_2OH·HOAc, EtOH, reflux, 24 h.

in absolute ethanol afforded the primary amine **219** (73% overall yield from **217**). Compound **219** could then be converted into (*S*)-nornicotine **108** with moderately high enantiomeric excess (81% ee) by initial treatment with HBr under pressure, followed by base-catalyzed intramolecular cyclization (85% yield).

2.7. Diels–Alder reactions

The synthesis of the tobacco alkaloid (*S*)-anabasine **205** and its derivatives has been performed by both diastereo- and enantioselective aza-Diels–Alder reactions between 3-pyridylaldimines and dienophiles.

Kunz et al. reported that the diastereoselective aza-Diels–Alder reaction using the 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine as the chiral template afforded piperidine derivatives (Scheme 47).[54] Thus, the reaction of aldimine **105** with 2-methylbutadiene **222** in the presence of zinc chloride etherate (2 equiv) (CH_2Cl_2, 0–20 °C, 96 h) gave the cycloaddition product **220** as a mixture of diastereomers, from which the more abundant was separated in 48% yield. The absolute configuration of this diastereomer was not determined, but the (*S*)-configuration was attributed by analogy to a related reaction. When Danishefsky's diene **223** was used in the cycloaddition with **105** in

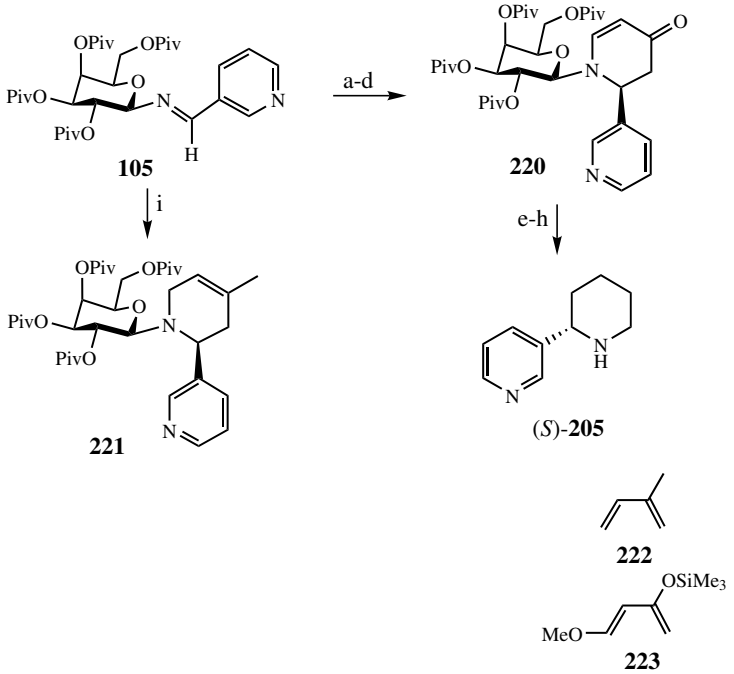


Scheme 46. Reagents and conditions: (a) BF_3–Et_2O, benzene, reflux, 2.5 h, 67%; (b) LDA, THF, 0 °C, 2–3 h, then 3-bromopropan-l-ol, −40 °C, overnight; (c) NH_2OH–HCl, EtOH, rt, 36 h, 73%; (d) HBr, sealed tube, 175–200 °C, overnight, then Et_2O, K_2CO_3, 80%.

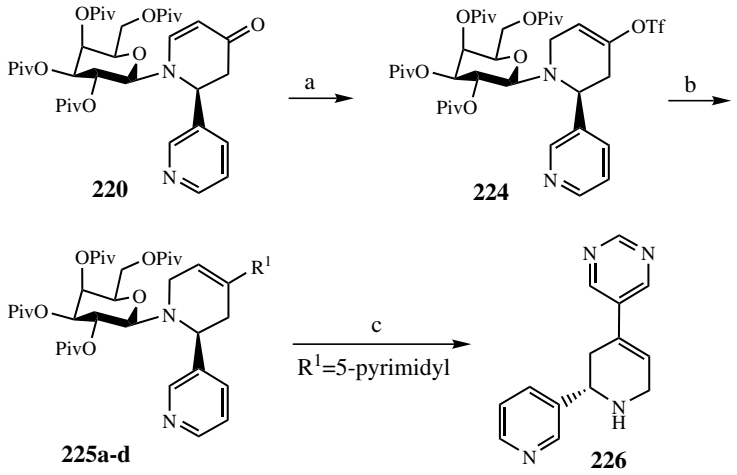
the presence of zinc chloride (2 equiv) (THF, −20 °C, 12 h), followed by the addition of 1 M HCl, neutralization with an $NaHCO_3$ solution, piperidinone **220** was obtained in high yield (92%) showing a diastereomeric ratio of more than 20:1. Pure diastereomer (*S*)-**220** was isolated by chromatography in 86% yield and then converted into the hydrochloride salt of *N*-galactosyl-anabasine by reduction of its double bond with L-selectride, formation of the dithiolane derivative and its desulfurization with Raney nickel. The final release of (*S*)-anabasine **205** from the carbohydrate template was achieved almost quantitatively with HCl–methanol (Scheme 47).

Very recently, Kunz was able to install a functional group at the 4-position of the piperidine ring of **220** (Scheme 48).[55] Chemoselective hydride transfer to the C=C double bond was carried out using the sterically demanding boron hydride reagent L-selectride. Subsequent trapping of the generated enolate with *N*,*N*-bis(trifluoromethanesulfonyl)aniline ($PhNTf_2$) led to the regioselective formation of *N*-galactosyl 4-triflyl 4,5-dehydropiperidine **224**. Cross-coupling of **224** with phenyl and heteroaryl boronic acids (R^1–$B(OH)_2$, R^1 = phenyl, 5-pyrimidyl, 8-quinolyl, 3-pyridyl) in the presence of bis(triphenylphosphine)palladium(II) chloride [$Pd(PPh_3)_2Cl_2$], aqueous caesium carbonate as base and THF as solvent, gave products **225a**–**d** in good yields (71–90%). Cleavage of the *N*-glycosidic bond of compound **225a** afforded 2,4-disubstituted piperidine **226** in 91% yield.

(*S*)-Anabasine was also obtained by a synthesis in which the key step is the enantioselective aza-Diels–Alder



Scheme 47. Reagents and conditions: (a) **223**, THF, $ZnCl_2$ (2 equiv), Et_2O, −20 °C, 12 h; (c) 1 N HCl; (d) $NaHCO_3$, 92%; (e) L-selectride, 96%; (f) $(HS–CH_2)_2$, BF_3–Et_2O, 92%; (g) Raney Ni, 75%; (h) HCl/MeOH, 97%; (i) **222**, $ZnCl_2$–Et_2O (2 equiv), CH_2Cl_2, 0–20 °C, 96 h, 48%.



a: R^1 = 5-pyrimidyl; **b**: R^1 = 8-quinolyl; **c**: R^1 = 3-pyridyl; **d**: R^1 = Ph

Scheme 48. Reagents and conditions: (a) L-selectride, $PhNTf_2$, THF, −78 °C to rt, 66–84%; (b) R^1–$B(OH)_2$, aq Cs_2CO_3, $Pd(PPh_3)_2Cl_2$ or $Pd(dppf)Cl_2$–CH_2Cl_2, THF, reflux, 71–90%; (c) aq HCl, MeOH, rt, 91%.

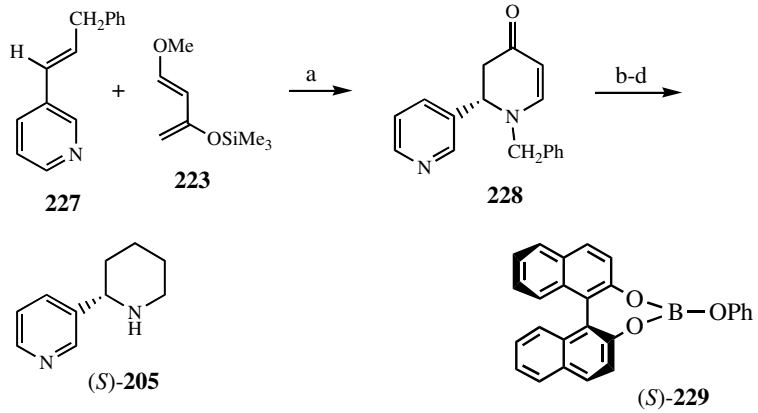
reaction between 3-pyridylaldimine **227** and diene **223**, mediated by the chiral Lewis acid (*S*)-**229** [generated in situ by mixing equimolecular amount of (*S*)-binaphthol and triphenyl borate in CH_2Cl_2 at room temperature for 1 h] (Scheme 49).[56] When a mixture of **227** and **223** was exposed at −78 °C with (*S*)-**229**, dihydropyridone **228** was obtained in 55% yield and essentially enantiomerically pure after recrystallization. Reduction of **228** with L-selectride at −78 °C afforded quantitatively the conjugated reduction product, which was converted to the corresponding *N*-benzylanabasine derivative by tosylhydrazone formation, followed by $NaBH_3CN$ reduction. Removal of the benzyl group by hydrogenation over palladium catalyst gave (*S*)-anabasine **205** in 49% overall yield from **228**.

2.8. Other syntheses

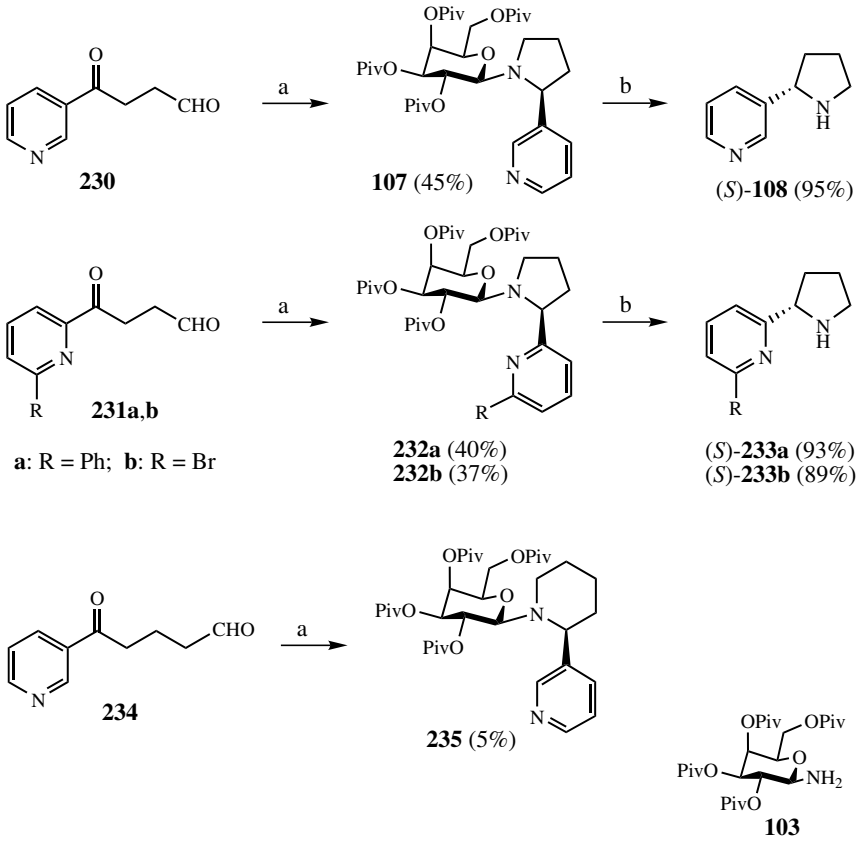
Loh et al.[57] have described the preparation of (*S*)-nornicotine **108** and two other related compounds by reductive aminocyclization reaction of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine **103**[58] with some dicarbonyl compounds (Scheme 50). Thus, when the reductive aminocyclization of **230** and **103** was carried out with 1 equiv of $NaBH_4$ in the presence of 0.5 equiv of acetic acid, the desired product **107** was obtained as a single diastereomer in 45% isolated yield. Acid hydrolysis of **107** afforded enantiomerically pure (*S*)-nornicotine (95% yield).

When the same protocol was applied to 1,4-ketoaldehydes **231a** and **231b**, the related pyrrolidines (*S*)-**233a** and **233b** were obtained enantiomerically pure and in moderate overall yields (37% and 32%, respectively). On the other hand, the 1,5-ketoaldehyde **234** only gave rise to a trace amount of the piperidine product **235**. This result has been ascribed to the difficulty in the formation of the six-membered-ring iminium intermediate, which leads to the piperidine. (see Fig. 3 for the formation of the analogous five membered ring iminium intermediate).

The (*S*)-configuration observed for **107** can be explained using steric considerations (Fig. 3). The reaction involves two subsequent reductive amination steps, first with the aldehyde group and then intramolecularly with



Scheme 49. Reagents and conditions: (a) (*S*)-**229**, CH_2Cl_2, −78 °C, 81%; (b) L-selectride, THF, −78 °C, 99%; (c) $TolSO_2NHNH_2$, $TolSO_3H$, $NaBH_3CN$, 100 °C, 1 h, 69%; (d) H_2, $Pd(OH)_2$, MeOH, rt, 72%.



Scheme 50. Reagents and conditions: (a) **103**, 4 Å molecular sieves, $NaCNBH_3$, AcOH; (b) 1 M HCl/MeOH.

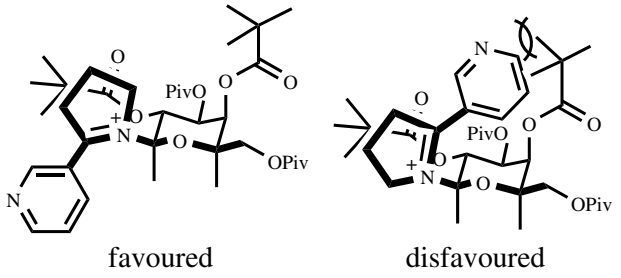
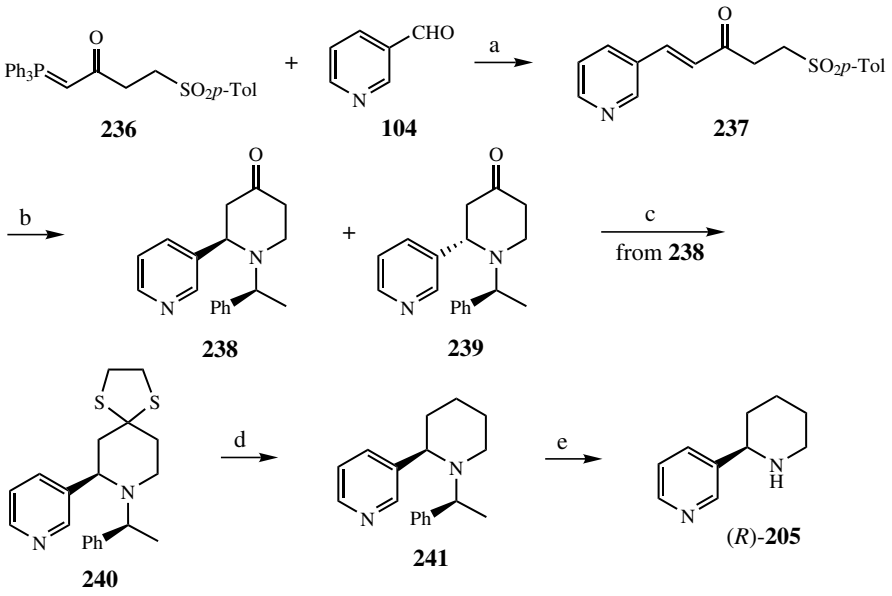


Figure 3.

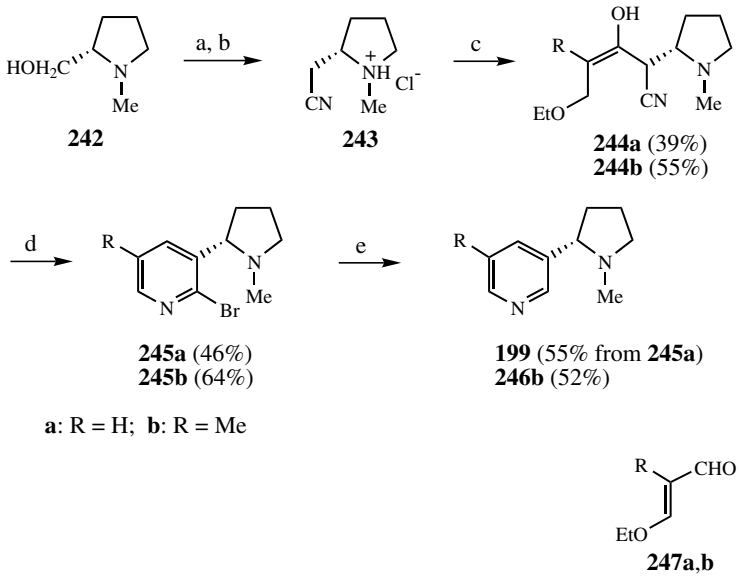
the ketone group. Hydride transfer to the iminium intermediate determines the chirality on the pyrrolidine ring. The aromatic group preferentially points downward to avoid close contact with the axial pivaloyl group. Since the bulky pivaloyl group on the galactopyranosyl ring shields the back *si*-face of the iminium group, the aldehyde is preferentially transferred from the front *re*-face to afford (*S*)-nornicotine.

Pollini et al., in a study aimed at highlighting 4-[(4′-methylphenyl)sulfonyl]-1-(triphenylphosphoranilidene)-2-butanone **236** as a four-carbon synthon for substituted divinyl ketones, reported the stereoselective synthesis of (*R*)-anabasine **205** (Scheme 51).[59] Reaction of the stabilized ylide of **236** with pyridine-3-carboxaldehyde produced enone **237** (benzene, reflux, 12 h, 81%), which by treatment with (*S*)-phenylethylamine (THF, rt, 15–20 h) gave in 70% yield a 3:1 mixture of diastereomers **238** and **239**, which were separated by chromatography. The most abundant isomer **238** was then transformed through conventional reductive steps into (*R*)-anabasine. These involved the removal of the carbonyl group by Raney Ni desulfurization (EtOH, reflux, 12 h, 75%) of the corresponding dithiane **240** [HS–$(CH_2)_2$–SH, BF_3–Et_2O, 0–25 °C, 12 h, 100%] and of the chiral auxiliary of derivate **241** by hydrogenolysis [H_2, $Pd(OH)_2$, MeOH].

In 1982, Chavdarian et al. reported the first synthesis of enantiomerically enriched (*S*)-nicotine **199** and (*S*)-5-methylnicotine **246b** by building up the pyridine ring onto an optically active pyrrolidine (Scheme 52).[60] Accordingly, (*S*)-(1-methylpyrrolidin-2-yl)-methanol **242**, obtained from L-proline, was converted into the (−)-1-methyl-2-(chloromethyl)pyrrolidine ($SOCl_2$, $CHCl_3$, 0 °C to reflux, 88%), which by treatment with potassium cyanide ($NaHCO_3$, 0 °C, 80% aq EtOH, then NaCN, 0 °C to reflux, 51%) gave (−)-1-methyl-2-(cyanomethyl)pyrrolidine **243**. The key steps involved the condensation of the anion of **243** (LDA, THF, −70 °C) with the 3-ethoxyacrolein **247a** to give the hydroxy compound **244** as a mixture of several stereoisomers (40% yield), followed by cyclization of **244** with 30% HBr/AcOH (55 °C, 1 h, 46%) to bromopyridine **245**. This compound was finally hydrogenated [H_2 (50 psi)/$PdCl_2$, NaOAc, EtOH] to remove the halogen, affording (*S*)-nicotine in 55% yield.



Scheme 51. Reagents and conditions: (a) benzene, reflux, 12 h, 81%; (b) (*S*)-phenylethylamine, THF, rt, 15–20 h, 70%; (c) HS–$(CH_2)_2$–SH, BF_3–Et_2O, 0–25 °C, 12 h, 100%; (d) Raney Ni, EtOH, reflux, 12 h, 75%; (e) H_2, $Pd(OH)_2$, MeOH.



Scheme 52. Reagents and conditions: (a) $SOCl_2$, $CHCl_3$, 0 °C to reflux, 88%; (b) (i) $NaHCO_3$, 0 °C, 80% aq EtOH, (ii) NaCN, 0 °C to reflux, 51%; (c) LDA, THF, −70 °C, then **247**; (d) 30% HBr/AcOH, 55 °C, 1 h; (e) H_2 (50 psi)/$PdCl_2$, NaOAc, EtOH.

(*S*)-5-Methylnicotine **246b** was also obtained in slightly better overall yield following the sequences outlined above, but using 2-methyl-3-ethoxylacrolein **247b** in the condensation with **243**. The process provided nicotinoids in enantiomeric excesses up to 56%, indicating that partial racemization occurred in one or more steps of the synthetic route.

3. Conclusions

This report outlines the stereoselective syntheses of a wide range of chiral non-racemic 1-substituted-1-(pyridyl)methylamines. Notwithstanding the many routes towards the asymmetric syntheses to these compounds with comparably simple structures that have been developed, new opportunities are yet to be explored. For instance, since no effective asymmetric route to the 2,2-dimethyl-1-(pyridin-2-yl)propylamine **72f** has been reported so far,[27] we are currently investigating the diastereoselective reduction of enantiopure pyridyl sulfinimines, obtaining **72f** and some of its derivatives substituted on the pyridine ring with enantiomeric excesses up to 99%.[61]

On the other hand, the widescale utility of chiral 1-substituted-1-(pyridyl)methylamines as ligands in metal-catalyzed asymmetric reactions is yet to be

demonstrated, though sparing but fruitful cases have been reported.[3]

Some recent reports have pointed out that ruthenium(II) complexes, which have achiral 1-substituted-1-(pyridyl)methylamines as co-ligands, namely RuCl[(2-CH_2-6-MeC_6H_3)PPh_2](CO)(L) (L = 1-(pyridin-2-yl)methylamine)[62] and RuCl(C*NN*)[$Ph_2P(CH_2)_4PPh_2$] (HC*NN* = 1-(6-phenylpyridin-2-yl)methylamine),[63] exhibit high activity in transfer hydrogenation of ketones in 2-propanol. Therefore, it is tempting to predict that the substitution of achiral with chiral non-racemic 1-substituted-1-(pyridyl)methylamines will open access to the chiral version of these catalysts.

It is hoped that this review will stimulate further research on this subject so that new chiral 1-substituted-1-(pyridyl)methylamine metal complexes can be prepared and applied in many areas of organic chemistry.

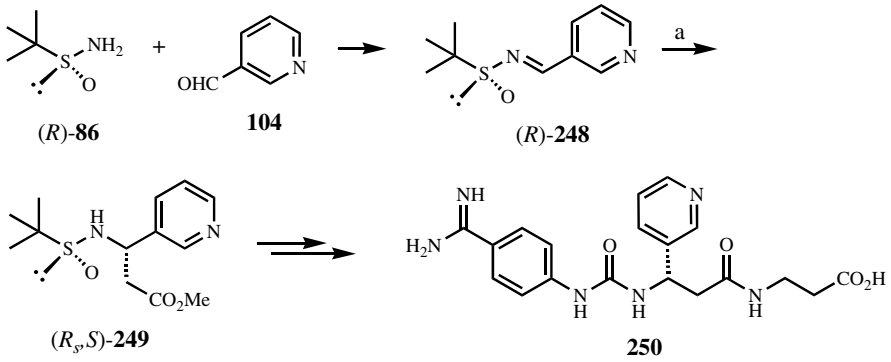
4. Note added in proof

Ellman et al. in a study aimed at the synthesis of β-amino acids incorporating a broad range of substitution patterns by enolate additions to *tert*-butylsulfinyl imines,[64] examined the diastereoselective addition of the lithium enolate of methyl acetate to chiral imine (*R*)-**248** derived from pyridine-3-carboxaldehyde and (*R*)-*tert*-butyl sulfinamide **86** (Scheme 53). Under optimized conditions [LDA, ClTi(O-*i*-Pr)$_3$ (2 equiv), THF, −78 °C] the 3-pyridyl amine (R_s,*S*)-**249** was obtained in good yield (70%) and with high diastereoselectivity (90% de). This result improved that achieved by Davis et al.[30] with the *N*-2-methoxynaphthylsulfinyl group (see Scheme 17). Compound (R_s,*S*)-**249** was used as a starting point for the preparation of the GPIIbIIIa antagonist **250**.[64]

Spero et al. reported an efficient method for the asymmetric synthesis of α,α-disubstitued diakylamines where one of the α-substituents is a 2-pyridyl group (Scheme 54).[65] The method utilized the diastereoselective addition of a Grignard reagent to ketimines (*S*)-**251** derived from (*S*)-phenylglycinol and 2-pyridyl ketones, followed by oxidative cleavage of the chiral auxiliary to afford the amines (*S*)-**252** in high enantiomeric excess (up to 96%). A series of experiments varying temperature, solvent, additives, etc., were carried out and the results obtained under optimized conditions are reported in Table 6. A model involving chelation of the imine and the

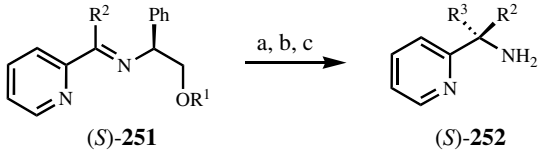
Table 6. Addition of Grignard reagents to imines (*S*)-**251** (Scheme 54)

R^1	R^2	R^3	X	Yield (%)	de (%)
H	Me	*o*-F-Benzyl	Cl	70	96
H	Et	*o*-F-Benzyl	Br	23	92
H	Ph	Benzyl	Cl	72	21
H	Me	Benzyl	Cl	48	93
TBS	Me	Benzyl	Cl	50	97
Me	Me	*o*-F-Benzyl	Cl	73	92
TBS	Me	Et	Br	60	97
TBS	Me	C_6H_{11}	Br	65	76
TBS	Me	Allyl	Br	74	89



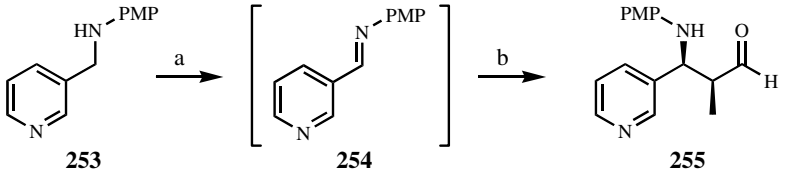
a: CH_3COOCH_3, LDA, ClTi(O-*i*-Pr)$_3$ (2 equiv), THF, -78 °C, 70%.

Scheme 53.



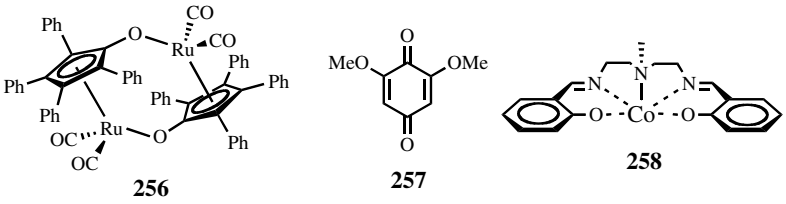
a: R^3MgX, $MgBr_2$, CH_2Cl_2; b: TBAF for R^1= TBS, BBr_3 for R^1= Me;
c: $Pb(OAc)_4$, CH_2Cl_2/MeOH

Scheme 54.



a: **256**, **257**, **258**, toluene, 1/2 O_2, 110 °C, 24 h; b: *N*-methylpyrrolidinone, *L*-proline (30%), propionaldehyde, DMF, -20 C

PMP: benzyl-*p*-methoxyphenyl



Scheme 55.

heterocyclic nitrogen with Mg was proposed to rationalize the observed diastereoselectivity.

The biomimetic catalytic enantioselective addition of aldehydes to amines has been very recently reported. This has been accomplished by the one-pot combination of catalytic linked aerobic oxidations of PMP *N*-protected amines (PMP = benzyl-*p*-methoxyphenyl) involving ruthenium-induced dehydrogenation and organocatalytic enantioselective Mannich reactions. Amongst a variety of amines used in this study, the 3-pyridylmethylamine **253** was converted into the β-amino aldehyde **254** in very high yield (>95%), diastereoselectivity (>95% de) and enantioselectivity (>99% ee) (Scheme 55).[66]

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