Regioselective and diastereoselective addition of organometallic reagents to (*S*)-*N*-[(2-pyridyl)methylene]-*O*-(trimethylsilyl)valinol. Synthesis of (*S*)-1-(2-pyridyl)alkylamines

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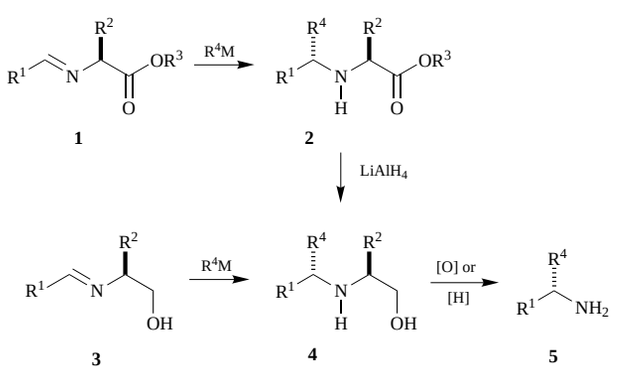
The imine prepared by condensation of pyridine-2-carbaldehyde and (*S*)-valinol, followed by protection of the hydroxy group as its trimethylsilyl ether, undergoes addition of organometallic reagents at either the carbon and/or nitrogen atom of the C=N double bond. Primary alkylmagnesium halides (R = Et, Bu, cyclohexylmethyl) add preferentially at 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 is obtained. Other Grignard reagents RMgX (R = Me, Pr^i, Bn, allyl, vinyl, Ph) and organolithium and zincate reagents add at the carbon atom to give the secondary amines as the main or exclusive regioisomers. Ketimines are 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 are also observed, presumably coming from C,N-dialkylation of the C=N double bond and attack on the pyridine ring. The C-alkylation products are formed with excellent or perfect diastereoselectivity (*si* face attack), apart from the *tert*-butyl and benzyl reagents; then, after acidic work-up, the (*S*,*S*)-amino alcohols are converted to (*S*)-1-(2-pyridyl)alkylamines by oxidative cleavage of the auxiliary. The superior asymmetric induction provided by *O*-(trimethylsilyl)valinol as auxiliary, with respect to valine esters, is rationalized on the basis of the lower basicity of the oxygen atom. Polar and radical mechanisms, explaining the formation of regioisomeric products and by-products, are discussed.

Introduction

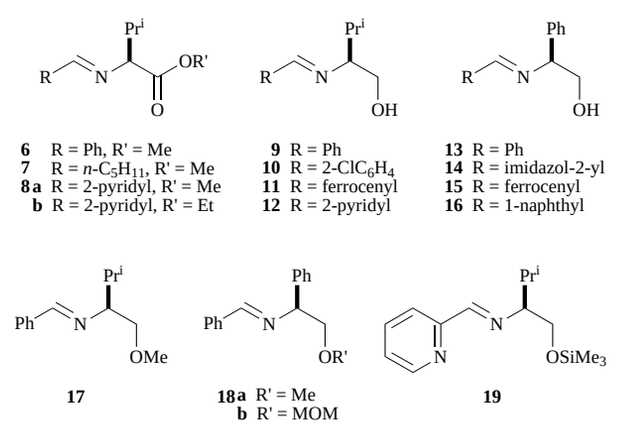
Amines carrying an α-stereocentre can be easily prepared by adding organometallic reagents to imines. The routes feasible for the asymmetric synthesis of these amines have been recently reviewed.[1] For example, chirality information can be incorporated in the nitrogen substituent (auxiliary-induced diastereoselectivity). Amines derived from α-amino acids have been exploited as auxiliaries, *e.g.* α-amino acid esters,[1–3] especially valine esters,[3] and β-amino alcohols, such as valinol[1,4] and phenylglycinol,[1,5] since they allow a highly effective stereocontrol in the nucleophilic addition to the derived imines, due to the presence of a bulky substituent in the resident stereocentre.[1]

The sequence of steps necessary to prepare optically active amines by this route is showed in Scheme 1. Organometallic



Scheme 1 Auxiliary-induced asymmetric syntheses of primary amines from imines derived from α-amino acid ester and β-amino alcohols

addition to the imine **1**, derived from an α-amino acid ester, produces the secondary amine **2**, whereas the analogous reaction performed on the imine **3**, derived from a β-amino alcohol, gives the amine **4**. Cleavage of the auxiliary in compound **4** to obtain the primary amine **5** is generally achieved by oxidation or hydrogenolysis, depending on the nature of the substituent R^2, but other procedures have been occasionally applied.[1] Starting from substrate **1**, a supplementary step is necessary to convert ester **2** to the intermediate **4**; therefore the route from the imino alcohol **3** allows a shorter sequence, provided that the hydroxy group is not protected before the organometallic step is undertaken. Moreover, the different auxiliaries allow a different range of organometallic reagents to be applied, and sometimes provide variable levels of stereocontrol. Hence, significant results reported up to now for the organometallic additions to selected imines **6**–**18** need to be discussed.



Imines derived from (*S*)-valine esters, (*S*)-valinol and (*S*)-phenylglycinol

α-Amino esters have been infrequently used. In addition to the poor reactivity of the C=N double bond towards Grignard reagents, imines carrying these auxiliaries suffer from competing attack on the ester group by organolithium compounds, apart for esters having bulky α-substituents and *tert*-butyl

esters.[2] However, perfluorohexyllithium–boron trifluoride complex[2b] and allylic derivatives of several metals (Zn, Cu, Ti, Al, Pb, Bi, In), more electronegative than lithium and magnesium, added to aromatic and aliphatic imines, *e.g.* **6** and **7**, with excellent or complete chemoselectivity and diastereoselectivity.[1,3a,b]

The 2-pyridylimines **8a**,**b** were particularly reactive and underwent attack by organometallic reagents which were incapable of adding to imine **6**. For example, homoallylic secondary amines were obtained from compound **8a** and allyllead bromide and allyltin trihalides with high but opposite diastereoselectivities [diastereomeric excess (de) 92–94%].[3c] Moreover, mixed triorganozincate reagents $Me_2RZnMgX$ and Me_2RZnLi selectively transferred the R group (Et, Bu, Pr^i, Bu^t, allyl, Bn, vinyl) to imine **8b**, and the stereocontrol was very high (de 90 to >99%), apart from allyl, benzyl and *tert*-butyl groups.[3d] Unfortunately, the methyl group could not be efficiently transferred from trimethylzincates, and mixed zincates prepared by the addition of phenylmagnesium bromide, hept-1-ynyllithium and 2-furyllithium to dimethylzinc were unreactive.[3d]

As concerns the use of valinol and phenylglycinol, we noticed that protection of the hydroxy group was generally avoided, but an excess of the organometallic reagent, typically 3 to 5 mol equiv., and sometimes drastic experimental conditions were necessary, especially for the addition of Grignard reagents, which often required high temperatures (40–66 °C).[1] In these conditions, complete stereocontrol was achieved in the addition of benzylic Grignard reagents and aryllithium compounds to several valinol-derived aliphatic and aromatic imines, but not in the addition of ethylmagnesium bromide to the phenylimine **9** (de 56%),[4a] of aryllithiums to the 2-chlorophenylimine **10** (de 74–80%),[4b] of methyllithium to the ferrocenylimine **11** (de 80%)[4c] and of cyclohexylmethylmagnesium bromide to the 2-pyridylimine **12** (de 74%).[4d]

Similarly, high levels of stereocontrol were obtained in the addition of Grignard, organolithium and especially organocerium reagents to phenylglycinol-derived imines, *e.g.* phenylimine **13** (de 90–98%),[1] imidazol-2-ylimine **14** (de >99%),[5a] and ferrocenylimine **15** (de 84 to >98%),[4c] but lower diastereoselectivities were claimed for the addition of benzylmagnesium chloride to unspecified arylimines (de 70%)[5b] and of butyllithium to 1-naphthylimine **16** (de 26%).[5c]

In some cases valinol proved to be superior to phenylglycinol, presumably because the isopropyl group is more sterically demanding than phenyl.[6] In the synthesis of the homoallylic amine from imine **9** by a Barbier reaction (allyl bromide, Zn) only one diastereomer was formed,[3a] but a mixture of diastereomers were obtained from the analogous imine **13** in the corresponding reaction (de 73%),† as well as by the addition of allylcerium reagents to compound **13** and analogous imines (de 80–90%).[5e] Moreover, primary ferrocenylalkylamines were prepared with superior optical purity from isopropyl compound **11** than from phenyl analogue **15**, and this was attributed to partial metallation at the benzylic stereocentre of substrate **15** in the organometallic step.[4c]

Only a few studies have been reported on the organometallic addition to imines derived from valinol and phenylglycinol, where the hydroxy group was previously protected, generally as its methyl ether.[1,4a,7] Ethylmagnesium bromide attacked compound **17** with good stereocontrol (de 83%).[4a] On the other hand, organo-lithium and -cerium compounds were the reagents of choice for the phenyl analogue **18a** and analogous imines derived from phenylglycinol (de 90–99%),[7a,b] and dialkylcuprate–boron trifluoride reagents added with the opposite sense of asymmetric induction (de 64–96%).[7b] Notably, protection of the hydroxy group as a methoxymethyl (MOM) ether can be detrimental to the diastereoselectivity, as observed in the reaction of MOM ether **18b** with 2-(alkoxycarbonyl)allylzinc bromides.[7c]

Aiming to expand the synthetic scope and to improve the diastereoselectivity of the organometallic addition to 2-pyridylimines,[3d,4d] we decided to test (*S*)-*O*-(trimethylsilyl)valinol as an auxiliary, and so we prepared the imine **19**. We envisaged that the trimethylsilyl protection of the hydroxy group would allow us to use milder experimental conditions and, consequently, to achieve better stereocontrol. We also considered that the economy of the planned synthetic route would not be significantly affected by the supplementary protection step, as the trimethylsilyl group is easily introduced, allows basic organometallic (Li, Mg) reagents to be used even in only small excess, and is easily removed by acidic work-up.

Results and discussion

The imine **12** was first prepared by mixing pyridine-2-carbaldehyde and (*S*)-valinol in dichloromethane in the presence of magnesium sulfate, and was immediately converted to compound **19** by treatment with an equimolar amount of chlorotrimethylsilane and triethylamine. The protected imine **19** was obtained with almost quantitative yield and purification was unnecessary.‡ The organometallic reactions were performed by adding 2 mol equiv. of Grignard and triorganozincate reagents and 1.2 mol equiv. of organolithium reagents to siloxane **19** in tetrahydrofuran (THF) (Scheme 2), generally at −78 °C, resulting in almost complete consumption of the imine within 0.5–1 h. However, the addition of the least reactive methyl-, vinyl- and phenyl-magnesium halides occurred only partially under these conditions, or required higher temperature to be complete.

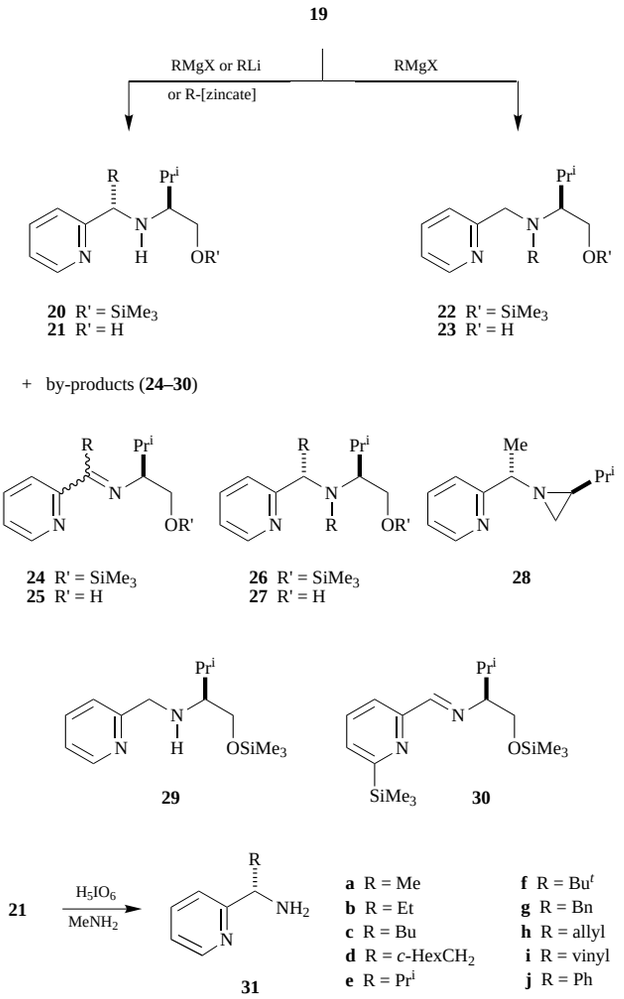
Basic quenching of the reaction mixtures preserved the siloxy group in the products and allowed an easy determination, by GLC-MS analysis, of the composition of the reaction mixtures and the diastereomeric ratios (dr) of the C-alkylation products **20**. The diastereoselectivity was not affected by the nature of the metal and was generally excellent (dr > 97:3), a single diastereomer often being detected by GLC-MS analysis, apart from the addition of benzyl reagents and, especially, *tert*-butyl reagents.

The composition of the reaction mixtures was dependent on the nature of the organometallic reagent. Most importantly, attack at the nitrogen atom of the imine was a competitive pathway in Grignard reactions, and the regioselectivity was dependent on the nature of the reagent, as described in the following sub-section. On the other hand, organolithium and zincate compounds generally gave the expected C-alkylation products with complete regioselectivity, apart from butyllithium and dimethyl(isopropyl)zincate, which gave the N-alkylation products **22c** and **22e**, respectively, as well, in trace amounts (Table 1, entries 5 and 10). Moreover, the C-alkylation process was often accompanied by side-reactions leading to one or more by-products **24**–**30**.

The O-silylated ketimines **24** could not be isolated, since they decomposed during column chromatography of the crude reaction products obtained by basic quenching, or were hydrolyzed during the acidic work-up. Hence most of them could be identified only by their relative molecular mass or mass-spectral fragmentation patterns. An indirect proof of their presence in the reaction mixtures was their disappearance after acidic

† Unpublished result from our laboratory.

‡ The equilibrium between these imines and their ring tautomers, *i.e.* oxazolidines, is affected by the solvent; for example, in the case of compound **12** the imine form is predominant in THF, but not in $CHCl_3$.[4d] We determined, by ^{1}H NMR spectroscopy, the presence of both *cis* and *trans* oxazolidines in the $CDCl_3$ solution of compound **12**, but only open-chain product **19** was obtained by silylation of the mixture; moreover, the NMR non-equivalence of the CH_2OSi protons in compound **19** suggests a rigid structure, due to nitrogen–silicon coordination.



Scheme 2 Addition of organometallic reagents to the 2-pyridylimine **19** and synthesis of (*S*)-1-(2-pyridyl)alkylamines **31**

hydrolysis of the reaction mixtures, with concomitant formation of the corresponding 2-pyridyl ketones, in turn identified by their GLC-MS spectrum, and valinol. Only the ketimine **24a** and its hydrolysis product, 2-acetylpyridine, were identified by comparison (GLC-retention times, mass spectra and ^{1}H NMR absorptions for the CH_3–C=N groups of the crude products) with authentic compounds. Similarly, the presence of N-(2-pyridylmethyl)-*O*-(trimethylsilyl)valinol **29** in the crude reaction mixtures was assessed by comparison with the GLC-MS properties of the authentic compound prepared by Pd/C-catalyzed hydrogenation of the imine **19**. The C,N-dialkylation by-products **27e**,**f** as well as the aziridine **28** and the imine **30**, could neither be isolated by column chromatography, nor compared with authentic compounds, and their structure is only presumed on the basis of the fragmentation patterns observed in their mass spectra (GLC-MS).

Methylmagnesium chloride reacted very slowly with the siloxy imine **19** at −20 °C and gave prevalently the C-alkylation product **21a** (dr 97 : 3) together with the ketimine **24a** (<7%) after basic quenching, but a small amount (2%) of the aziridine **28** was observed after acidic quenching. Moreover, if the reaction mixture was stirred overnight while the temperature was allowed to reach 20 °C before quenching, the diastereomeric ratio of product **21a** was considerably lowered (dr 70 : 30) and *N*-benzyl-*O*-(trimethylsilyl)valinol **29** was also detected (2%). The N-methylation product **23a** was absent. However, the regioselectivity of the Grignard reagents RMgX was dependent on the nature of the R group (Table 1). The secondary amines **20e**–**j** were prevalently or exclusively obtained when R was Pr^i, Bu^t, Bn, allyl, Ph, and vinyl (entries 9, 13, 14, 16, 17 and 20), but the tertiary amines **22b**–**d** were the prevalent products with primary alkylmagnesium halides, *i.e.* when R was Et, Bu, *c*-HexCH_2 (entries 3, 6, 7). Notably, the addition of cyclohexylmethylmagnesium bromide to the unprotected imine **12** gave mainly the C-alkylation product **21d**, together with the N-alkylation product **23d** (10–20% yield).[4d]

To avoid the N-alkylation pathway, we converted these Grignard reagents to mixed triorganozincate reagents, mimicking our previously described application of such reagents for the addition to the imine **8b**.[3d] The mixed zincates were generally prepared *in situ*, taking advantage of the lack of reactivity of MeMgCl and R_2Zn towards the imine **19** at −78 °C. In a single experiment, first MeMgCl was added to imine **19**, followed by Et_2Zn (entry 4), but generally Me_2Zn was added to imine **19** prior to RMgX (entries 8, 10, 15 and 18). In this way, the preferential or selective transfer of Et and R groups, rather than Me, was observed, and the N-alkylation was suppressed or reduced to a large extent. Moreover, these results demonstrate that the imine-zincate complexation was preliminary to the bond-forming step.§ Vinylzincate gave a superior yield of product **20i** with respect to vinylmagnesium bromide (entries 17 and 18), but in both cases the ketimine **24b** was partially formed (2–3%), through metallation of compound **20i** at the benzylic position.

The formation of the ketimines **24** and the C,N-dialkylation products **26** was relevant in the reactions of hindered organometallic compounds, *i.e.* isopropyl and *tert*-butyl reagents (entries 9–13).¶ However, we discovered later that the relative amount of compound **24e** was significantly reduced by adding the imine to the preformed isopropylzincate (entry 11; footnote g), suggesting that the inverse addition procedure could be usefully applied to any organometallic reagents. Reduction of the imine was generally not observed, apart from the reactions with vinylmagnesium bromide, where compound **29** was formed in 2% yield. Moreover, we suppose that phenylmagnesium bromide partially metallates the pyridine ring at C-6, since a by-product, presumably having the imine structure **30**, was formed in almost 4% yield.

Acidic quenching of the reaction mixtures allowed us to obtain directly the secondary and tertiary amines **21** and **23** by concomitant deprotection of hydroxy groups of the intermediates **20** and **22**, and caused, at the same time, hydrolytic cleavage of the ketimines **24** and, in part, of the by-products **27f**. Most of the crude products contained the C- or N-alkylation compound in almost pure state (>95% by ^{1}H NMR analysis), which also confirmed the high stereochemical purity of the secondary amines **21a**–**j**: in fact, the diastereomers of these and analogous amines have different absorptions, particularly of the Ar-C*H*-N or pyridyl protons.[3,4d] Only compounds **21d**,**e**,**f** were purified by column chromatography, but partial loss of amine **21f** occurred, apparently owing to decomposition on SiO_2.

The auxiliary was easily removed from the secondary amines **21a**,**d**,**j** by oxidative cleavage with periodic acid in the presence of methylamine,[3] giving the primary amines **31a**,**d**,**j** (Scheme 2) in good yields (90, 83 and 94%, respectively). It should be noted that compounds **31a**,**j** could not be prepared by the route starting from the imine **8b**,[3d] due to the low reactivity and diastereoselectivity of the required zincates. Moreover, the route to amines **31d** and **31h** starting from compound **19**, despite the incomplete group-transfer selectivity of dimethyl(cyclohexylmethyl)zincate, is preferable in terms of diastereoselectivity and/or overall yield to the previously reported syntheses from **8a**,**b** [3c,d] and **12**.[4d]

§ Similarly, sequential addition of diethylzinc (no reaction) and methyllithium to the imine derived from pyridine-2-carbaldehyde and (*S*)-1-phenylethylamine gave the C-alkylation product by selective transfer of the ethyl group to the C=N double bond.[3d]

¶ By-products analogous to compounds **24** and **26** were formed in the reactions of organolithium reagents with aromatic imines derived from (*S*)-1-phenylethylamine.[8]

Table 1 Addition of organometallic reagents to the imine **19**[a]

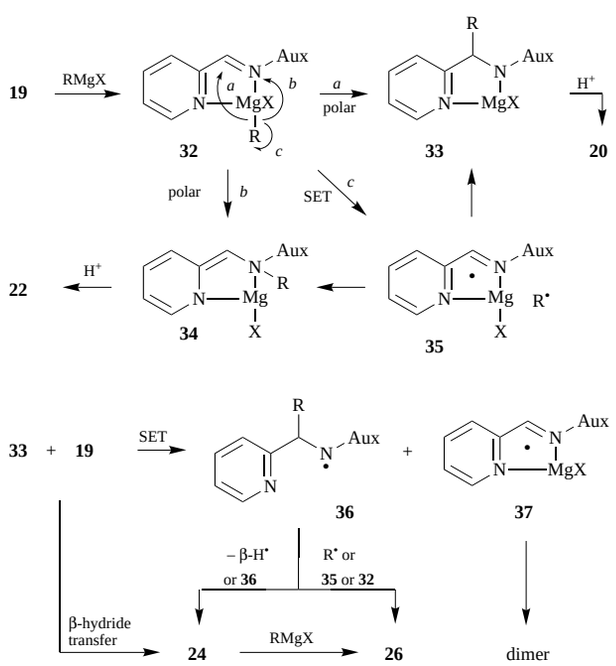
Entry	RM	Temp. (°C), time (h)	Intermediate products and main by-products (%)[b,c]	dr of compound **20**[b]	Isolated product (yield %)[d]
1	MeLi	−78, 0.5	**20a** (97)	>97:3	**21a** (93)
2	MeMgCl	−20, 4	**20a** (81), **24a** (9)	>97:3	**21a** (90)[e]
3	EtMgBr	−78, 0.5	**20b** (28), **22b** (67)	>99:1	
4	(i) MeMgCl; (ii) Et_2Zn	−78, 0.5	**20a** (<2), **20b** (94)	>99:1	**21b** (95)
5	BuLi	−78, 0.5	**20c** (92), **22c** (2), **24c** (<1)[f]	>99:1	**21c** (90)
6	BuMgCl	−78, 0.5	**20c** (5), **22c** (90)	>99:1	**23c** (85)
7	*c*-HexCH_2MgBr	−78, 0.5	**20d** (2), **22d** (91)		**23d** (84)
8	(i) Me_2Zn; (ii) *c*-HexCH_2MgBr[g]	−78, to −50, 1	**20a** (7), **20d** (88)	99:1	**21d** (83)[h]
9	Pr^iMgCl	−78, 0.5	**20e** (82), **22e** (<4), **24e** (6), **26e** (1)	>99:1	**21e** (76)[h]
10	(i) Me_2Zn; (ii) Pr^iMgCl	−78, 1	**20e** (86), **22e** (1), **24e** (<8)	>99:1	**21e** (74)[h]
11	$Me_2Pr^iZnMgCl$[i]	−78, 1	**20e** (92), **24e** (6)	>99:1	**21e** (91)
12	Bu^tLi	−78, 0.5	**20f** (73), **24f** (8), **26f** (5)[j]	70:30	**21f** (51)[h]
13	Bu^tMgCl[k]	−78, 0.5	**20f** (71), **24f** (17), **26f** (3)	63:37	
14	BnMgCl	−78, 1	**20g** (92)	81:19	**21g** (91)
15	(i) Me_2Zn; (ii) BnMgCl	−78, 1	**20g** (90)	87:13	**21g** (90)
16	allyl-MgCl	−78, 0.5	**20h** (96)	>99:1	**21h** (87)
17	vinyl-MgBr	−78, to −50, 1	**20i** (54), **24b** (3%), **29** (2%)	>99:1	
18	(i) Me_2Zn; (ii) vinyl-MgBr	−78, to −50, 1	**20i** (92), **24b** (3%)	>99:1	**21i** (93)
19	PhLi	−78, to −50, 1	**20j** (96)[l]	>98:2	**21j** (95)
20	PhMgBr	−78 to 20, 12	**20j** (87), **30** (4)[l]	>99:1	**21j** (80)

[a] The reactions were carried out on 3 mmol imine in THF, to which was added 1.2 mol equiv. RLi, or 2 mol equiv. RMgX, or 2 mol equiv. zincate formed *in situ*. [b] Approximate conversions and dr determined by GLC-MS analysis of reaction samples obtained by quenching with aq. $NaHCO_3$ [c] Trace amounts of starting imine and/or other unidentified by-products were sometimes present in the reaction mixtures. [d] Yield of crude products, generally >95% pure by ^1H NMR analysis, obtained by acidic quenching of the reaction mixtures, followed by extraction of neutral compounds with Et_2O, and treatment with base. [e] The crude reaction product, obtained by quenching with base, contained also the ketimine **24a** and 2-acetylpyridine, (GLC-MS and ^1H NMR analyses). When the reaction mixture was quenched after 12 h at 20 °C, the dr of compound **21a** was 70:30, and the amine **29** (2%) was also observed (GLC-MS). On the other hand, acidic quenching gave also the aziridine **28** (2%). [f] Higher-boiling impurities (~ 5%) were present but were not identified. [g] The same regioisomeric and diastereomeric ratios were obtained by adding the preformed zincate to the imine. [h] The products were purified by column chromatography on SiO_2. [i] By the inverse-addition procedure, *i.e.* by adding the imine to the zincate, we obtained compound **20e** in better yield but lower diastereoselectivity (95%; dr 97:3), together with compound **24e** (<4%). [j] In repeated runs, the relative amounts of compounds **20f**, **24f** and **26f** varied slightly and other by-products were always formed, some of them probably coming from attack on the pyridine ring. [k] The sequential addition of Me_2Zn and Bu^tMgCl to the imine gave similar results. [l] Trace amounts of unidentified lower boiling by-products and some diphenyl, already present in the organometallic reagent, were observed in the reaction mixture.

Since we had previously described the conversion of the secondary amines **21b**,**c**,**e**,**g**–**i** to the primary amines **31b**,**c**, **e**,**g**,**i**[3d] and **31h**,[3c] we did not worry about having to repeat those transformations, despite compound **21** having been obtained in this work with improved diastereoselectivity. We also made no attempt to separate isomers (*S*,*S*)- and (*R*,*S*)-**21f**, or to prepare the primary amine **31f** from the diastereomeric mixture (dr 68:32).

The optical purity of the primary amine **31a** was assessed by comparing the specific optical rotation with the value reported for the authentic compound,[9] while the optical rotation of the known amine **31d** has not been reported,[4d] and, to our knowledge, the amine **31j** has never been prepared before. However, the optically purity of amines **31d**,**j** is presumed, since we never experienced epimerization or racemization in the oxidative cleavage of chiral β-amino alcohols by periodic acid.

Our route to 1-(2-pyridyl)alkylamines favourably compares with previous syntheses. The amine **31d** was prepared not only by Grignard addition to the imine **12**, but even through reduction of a ketimine prepared in three steps from phenylglycinol.[4d] The enolates of *N*-(2-pyridyl)methyl ketimines derived from 2-hydroxypinan-3-one, 3-hydroxycaran-2-one and camphor underwent alkylation by alkyl halides with high diastereoselectivity.[10] Moreover, in syntheses starting from α-amino and α-hydroxy acids, the pyridine ring was built by cobalt(I)-catalyzed cyclotrimerization of the intermediate α-heterosubstituted nitriles with alkynes.[11]



Scheme 3 Polar and radical pathways for the reactions of Grignard reagents with the imine **19**

Mechanisms, regioselectivity and diastereoselectivity

The possible mechanisms by which the regioisomeric products **20** and **22** as well as the by-products **24** and **26** can be formed are showed in Scheme 3. We assume that the complex **32** is preliminary formed from the imine and the organometallic reagent, *e.g.* a Grignard reagent. Then, a polar attack can occur at either the carbon or nitrogen atom of the C=N double bond (arrows *a* and *b*) to give the adducts **33** and **34**, which are precursors of the products **20** and **22**. However, a single-electron transfer (SET) from the R–Mg bond to the lowest unoccupied molecular orbital (LUMO) of the pyridylimine moiety (arrow *c*) can be envisaged, affording the radical-pair **35**, followed by coupling steps leading to adduct(s) **33** and/or **34**.

Similarly, the ketimine **24** and the amine **26** might be formed by radical processes involving the preliminary SET step from the metal amide **33** to the imine **19**, giving the aminyl radical **36** and imine radical anion **37**. Then, the aminyl radical **36** can lose a β-hydrogen atom to give the ketimine **24**, or undergo disproportionation to products **24** and **20**.

The ability of lithium dialkylamides to act as a SET reducing agent is well documented.[12] For example a large percentage of ketyl radical anion was detected in the reaction of lithium diisopropylamide (LDA) with benzophenone;[12a] however, kinetic and mechanistic probe studies supported a more complex pathway to the ketyl, initiated by β-hydride transfer to the carbonyl group, leading to lithium benzhydrolate and a ketimine.[12b] An analogous mechanism can explain the formation of the ketimine **24**, together with the metal amide of compound **29**, from adduct **33** and compound **19** (in Scheme 3 the steps leading to structure **37** are not reported for sake of simplicity). Moreover, the observed decrease of the dr of compound **20a** with increasing time at 20 °C before quenching of the reaction mixture (Table 1, entry 2, footnote e) can be due to the reaction of the intermediate amide **33a** (Scheme 3) with the ketimine **24a**, present as by-product: in fact, compounds **33a** and **24a** can undergo interconversion by hydride transfer, and/or by a more complex mechanism involving a SET step.

On the other hand, the tertiary amine **26** (almost exclusively the *tert*-butyl-substituted amine **26f**) can derive from coupling of the aminyl radical **36** with a free radical R· or, more probably, with the radical pair **35** or the complex **32** (in these cases the imine radical-anion **37** is concomitantly formed). However, it cannot be excluded that amine **26f** is produced by attack of the *tert*-butylmetal reagent (by polar and/or SET mechanism) at the nitrogen atom of imine **24** (Scheme 3), despite the fact that the *N*-*tert*-butylamine **22f** was never formed in the reactions of *tert*-butylmetal reagents with the aldimine **19**. Finally, the reductive–dimerization of the imine **19** is expected to occur through the imine radical anion **37**, but the diastereomeric dimers were not be detected by GLC-MS analysis, perhaps owing to their high relative molecular masses.

In our opinion, both the C- and N-alkylation products **20** and **22** can be formed by a composite mechanism, where either the polar or the radical pathway prevails depending on the nature of the organometallic reagent. The chelate-binding mode lowers the barrier to the inner-sphere electron-transfer process, but also increases the nucleophilicity of the organometallic reagent and the electrophilicity of the imine at both the carbon and nitrogen atoms. Moreover, both the intermediate benzylic 'carbanions' and radicals are stabilized by resonance and intramolecular chelation.

A thorough literature search indicated that the mechanism and the regioselectivity of the organometallic addition to activated C=N bonds are dependent on a confusing combination of steric and electronic factors of both reaction partners.

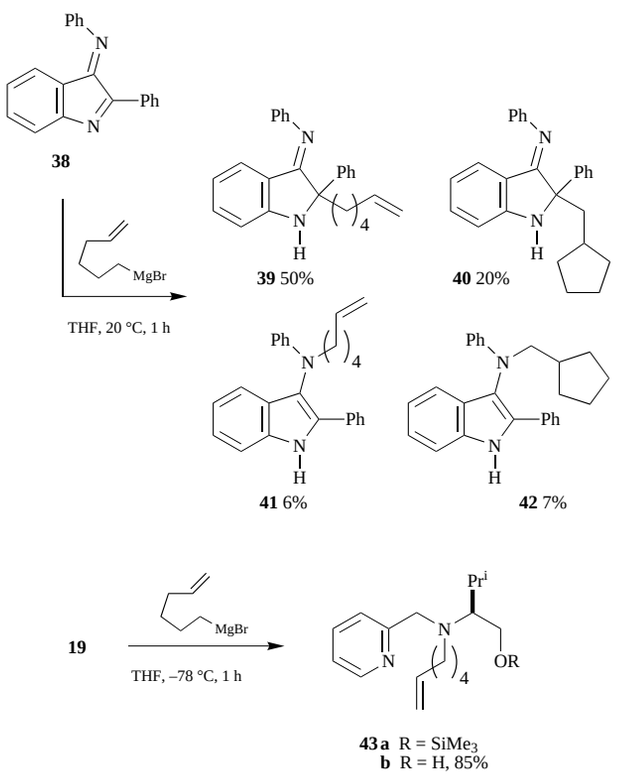
Organometallic reagents (Li, Mg, Cu) attacked oxime *O*-tosyl esters to give imines,[13] and particularly the oxime *O*-tosyl ester of 2,3,4,5-tetraphenylcyclopentadienone to give *N*,*N*-dialkylamines (double attack at nitrogen), presumably owing to the stability of the intermediate carbanion.[13b] Conversely, *p*-benzoquinone-*N*,*N*′-diphenyl diimine underwent N-alkylation by Grignard and organolithium reagents by a presumed radical mechanism,[14a] whereas 3,5-di-*tert*-butyl-4-iminocyclohexa-2,5-dienone was attacked at nitrogen by isopropylmagnesium bromide, but at the C=O carbon by other Grignard reagents.[14b]

A radical pathway took place in the addition of dialkylzinc compounds to *N*,*N*′-di-*tert*-butyl-1,4-diazabutadiene (DAD), which underwent N-alkylation by primary and *sec*-alkyl reagents, and C-alkylation by methyl, neopentyl, *tert*-alkyl, benzyl and aryl reagents.[15] The SET character was demonstrated by the presence of persistent [EtZn-DAD]· radical, and the regioselectivity was explained by considering the different nucleophilicity and 'radical activity' of R· (from R_2Zn), defined by the strength of the C–H bond in the radical centre. Notably, RZnX did not add to DAD, and the double addition of allylzinc bromide, phenylmagnesium bromide and methylmagnesium chloride to the carbon atoms of a chiral 1,4-diazabutadiene has been reported.[16]

Similarly, 1,2-imino ketones[17] underwent N-alkylation by dialkylzinc reagents through a presumed radical mechanism, but carbonyl C-alkylation by dimethyl- and diaryl-zinc reagents, and a polar (ionic) mechanism was considered possible for the latter reagents, since they are weaker reducing agents in the electron-transfer sense.‖

In the addition of organometallic reagents (RM) to the C=N group of 1,2-imino esters the regioselectivity was dependent on the nature of R and M,[2b,20] but the mechanism was not discussed. As a matter of fact, Grignard reagents gave C-alkylation (R = Me, Bu^t, allyl), N-alkylation (R = Et, Pr, Bu^i, Bn) or both reactions (R = Pr^i), Et_2Zn attacked nitrogen, but $Bu^t{}_2Zn$, RZnX, BuLi and $R_2Cd(MgX_2)_2$ attacked carbon, and benzylmetal halides gave N-alkylation (Mg, Cu, Ti, B, Al) or C-alkylation (Zn, Cd).

3-Arylimino-2-phenyl-3*H*-indoles, *e.g.* compound **38**, underwent attack by organolithium[21a] and Grignard reagents[21b] at both carbon and nitrogen atoms (Scheme 4), and the occurrence of a SET mechanism was demonstrated by the observation of an electron-spin resonance (ESR) signal[21a] and by using hex-5-enylmagnesium bromide as a 'radical probe.'[21b] In fact, owing to rapid cyclization of the hex-5-enyl radical to cyclopentylmethyl radical, mixtures of C- and N-alkylation



Scheme 4 Addition of hex-5-enylmagnesium bromide to the imines **38** and **19**

‖ In fact, the reversible redox potential $E°$ for the carbanions or organometallic reagents decreases in the order: Ph < vinyl < Me < Bu < Et < Bn < Pr^i < Bu^t, allyl.[18] However, vinylic magnesium halides attacked the oxygen atom of di(benzothiazolyl) ketone to give vinyl ethers, contrary to the case with alkyl, allyl and acetylenic Grignard reagents, which gave only C-alkylation;[19] this regioselectivity is not consistent with a radical pathway related to the reducing power of the Grignard reagent.

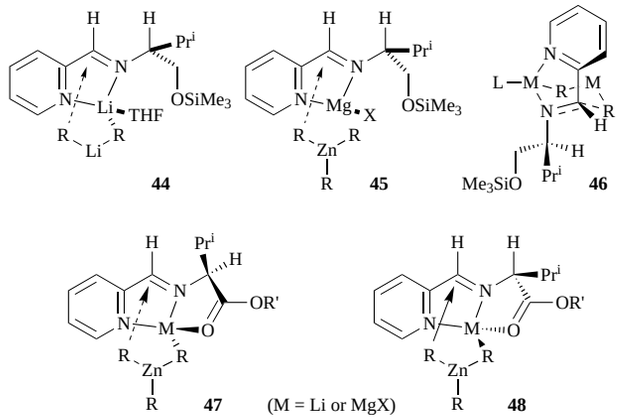


Fig. 1 Stereochemical models and transition states for the polar addition of organometallic reagents to the imines **19** and **8**

products, either linear or rearranged, *i.e.* products **39**–**42**, were obtained.

Prompted by this report, and aiming to get further mechanistic information, we added hex-5-enylmagnesium bromide to imine **19** (Scheme 4). Only one N-alkylation product, compound **43a**, was observed by GLC-MS analysis and the linear structure of the N-substituent was assessed by ^{1}H NMR analysis of the crude β-amino alcohol **43b**, isolated by acidic quenching. This result suggests a prevalent or exclusive polar pathway. However, in the absence of kinetic studies, it cannot be excluded that, after the first SET step, the tightly bound radical pair underwent coupling at a rate largely exceeding the cyclization rate of the cyclohexylmethyl radical.

We consider a polar mechanism plausible for the addition of organolithium and zincate compounds to the 2-pyridylimine **19**. Moreover, we suppose that substrate **19** acts as an N,N-bidentate rather than an N,N,O-tridentate ligand, owing to the weaker basicity of the silicon-bound oxygen atom with respect to the nitrogen atoms and the oxygen atom of THF. The associated structure of the organometallic compounds should be disrupted by this chelation, and the complexes **44** should be formed with dimeric methyllithium and phenyllithium, since these organometallic compounds are tetrameric in THF.[22] Similarly, bidentate chelation of lithium or magnesium triorganozincates[3d] should afford the complexes **45** (Fig. 1).

The diastereoselectivity of the organometallic additions to imine **19** can be rationalized by assuming early transition states for the C–C bond-forming step, so that the stereochemistry is governed by the ground-state conformation of the imine, *i.e.* the orientation of the auxiliary, which in turn controls the configuration of the metal stereocentre in the complexes **44** or **45**. We previously reported that in 2-pyridylimines the auxiliaries (*S*)-1-phenylethylamine[8] and methyl (*S*)-valinate[3c] preferentially take the orientation with eclipsed H–C=N and H–C* hydrogens. Moreover, ^{1}H NMR nuclear Overhauser effect (NOE) studies showed that no appreciable modification occurred by complexing the imine with diethylzinc, zinc dibromide and tin dichloride, whereas a remarkable rotation along the N–C* axis occurred with bulky tin tetrachloride (this provides an explanation for the reversal of diastereoselectivity observed with bulky organometallic reagents).

By analogy, we prepared the complex between the imine **19** and an equimolar amount of $ZnBr_2$ in $CDCl_3$ solution and observed that two species were apparently formed, since two partially overimposed singlets were observed for the azomethyne proton. However, irradiation of this proton resulted in a positive NOE for both the pyridine H–C(3) (+9%) and the H–C* (+11%) protons. So, we assume that in the organometallic complexes, *e.g.* **44** and **45** in Fig. 1, the auxiliary has the eclipsed orientation and that the metal stereocentre is formed with the configuration having the organometallic chain *anti* to Pr^i. Thus, the C–C bond-forming step is forced to occur at the *si* face of the imine through the six-membered chair transition state **46**. The particularly low stereocontrol obtained with *tert*-butylzincate reagent can be attributed to the reduced stability of species **46**, due to steric interactions of R = Bu^t, with respect to alternative transition states involving *re* face addition.

tert-Butyllithium, phenyllithium and Grignard reagents, which are dimeric or monomeric in THF,[22e] will form bidentate chelation complexes with monomeric organometallic species, *e.g.* **32** in Scheme 3, and the C-alkylation step must proceed *via* a four-membered cyclic transition state. In this case, N-alkylation may be competitive, occurring through a three-membered cyclic transition state, and the regioselectivity should be governed by steric and/or electronic properties of the organic group.

We wish to underline that the excellent level of diastereoselectivity obtained in the formation of C-alkylated product **20** by any organometallic reagent is not a proof in favour of a polar mechanism. First of all, nucleophilic carbon radicals added to chiral imines[23] and electron-poor alkenes[24] with comparable or better diastereoselectivities with respect to organometallic reagents.[24b,c] However, since the outcome of the reaction of imine **19** with hex-5-enylmagnesium bromide indicated that free radicals were not involved, tightly bound radical pairs **35** (Scheme 3) should be considered as intermediates, which would collapse to product **20** *via* four-membered cyclic transition states, closely resembling those involved in the polar pathway.

A further point of interest is the higher level of asymmetric induction obtained with *O*-(trimethylsilyl)valinol as auxiliary, with respect to valine esters and valinol, as evinced by comparing the results obtained in the addition of organometallic reagents to the corresponding 2-pyridylimines, *i.e.* **19** *vs.* **8a**,**b**[3c,d] and **12**.[4d] We believe that this is due to the weaker basicity of the siloxy group. The imine **8b**, for example, can form with a triorganozincate compound a complex analogous to species **45**, but can also act as a tridentate ligand. In the latter case, the fused bicyclic structures **47** and **48** (Fig. 1) should be considered. At first glance, complexes **47** and **48** have comparable stability, because in *S*-isomer **47** the Pr^i group has the unfavourable *endo* orientation, but is disposed *trans* to the metal substituent R, whereas in *R*-isomer **48** the *cis* disposition of Pr^i and R is attained. Most importantly, complexes **47** and **48** differ in their configuration at the metal stereocentre and lead to the opposite diastereomers. Consequently, the minor (*R*,*S*)-diastereomer can be produced to a certain degree from isomer **48**. An analogous tridentate chelation, together with a temperature effect, can explain the incomplete stereocontrol obtained with substrate **12**.**,[4d]

Experimental

General conditions

Solvents were distilled in N_2 prior to use: Et_2O and THF over sodium benzophenone ketyl and successively over $LiAlH_4$, and CH_2Cl_2 over P_2O_5. Optical rotations were measured on a digital polarimeter for samples in methanol solution in a 1-dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded on a Varian Gemini instrument at 300 or 200 MHz for samples in $CDCl_3$ which was stored over Mg. ^{1}H Chemical shifts are reported in ppm relative to $CHCl_3$ (δ_H 7.27) and *J*-values are given in Hz. MS spectra were taken at an ionizing voltage of 70 eV on a Hewlett-Packard 5970 or 5890 spectrometer with GLC injection. Chromatographic purifications

** In a recent paper, which appeared when this work had been completed, the addition of Grignard reagents to the ketimines derived from 2-acylpyridines and (*S*)-*O*-(*tert*-butyldimethylsilyl)phenylglycinol was performed in dichloromethane in the presence of an excess of magnesium bromide: in particular, ethylmagnesium bromide attacked only the carbon atom of the imine (60% yield, 97% de).[25]

were carried on columns of silica gel (Merck, 230–400 mesh) at medium pressure. MeLi (1.6 M in Et_2O), *n*-BuLi (2.5 M in hexanes), *tert*-BuLi (1.7 M in pentane), PhLi (2 M in 70 : 30 benzene–Et_2O), MeMgCl (3 M in THF), EtMgBr (1 M in THF), BuMgCl (2 M in THF), Pr^iMgCl (2 M in THF), BnMgCl (2 M in THF), allyl-MgCl (2 M in THF), PhMgCl (2 M in THF), and vinyl-MgBr (1 M in THF) were purchased from Aldrich. Cyclohexylmethylmagnesium bromide and hex-5-enylmagnesium bromide were prepared as ~ 1 M solutions in THF from the corresponding bromides and magnesium turnings and were titrated prior to use. (*S*)-Valinol was prepared by reduction of (*S*)-valine with sodium borohydride and iodine.[26] Aldehydes were distilled before use. All organometallic reactions were performed in flame-dried apparatus under a static atmosphere of dry N_2.

Preparation of the imine (*S*)-*N*-[(2-pyridyl)methylene]-*O*-(trimethylsilyl)valinol 19

Anhydrous $MgSO_4$ (5 g) and pyridine-2-carbaldehyde (1.07 g, 10 mmol) were added to a solution of (*S*)-valinol (1.03 g, 10 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C, and the mixture was stirred by a magnetic bar for 2 h. The solid phase was filtered off and the organic solvent was evaporated off under reduced pressure to leave the crude imine **12** (1.92 g, 100%). The imine was dissolved in anhydrous CH_2Cl_2 (10 cm^3) and triethylamine (1.12 g, 11 mmol) and chlorotrimethylsilane (1.16 g, 11 mmol) were added to the magnetically stirred solution. The mixture was stirred during 3 h, then the solvent was removed *in vacuo*, the residue was taken up in anhydrous Et_2O–cyclohexane (1 : 1; 50 cm^3) and the solid phase was filtered off. The organic solution was concentrated *in vacuo* to leave the imine **19** as an oil (2.51 g, 95%), which was used in subsequent reactions without purification: $[\alpha]_D^{20}$ −15.9 (*c* 1.1 in $CHCl_3$); δ_H(300 MHz) 8.77 (1 H, m, pyridine), 8.33 (1 H, s, CH=N), 8.05 (1 H, m, pyridine), 7.76 (1 H, m, pyridine), 7.33 (1 H, m, pyridine), 3.93 and 3.90 (1 H, dd, *J* 4.1 and 10.3, CH_2O), 3.73 and 3.69 (1 H, dd, *J* 7.9 and 10.3, CH_2O), 3.10 (1 H, m, CHN), 2.00 (1 H, m, C*H*Me_2), 0.97 (3 H, d, *J* 6.1, CH*Me*$_2$), 0.95 (3 H, d, *J* 6.7, CH*Me*$_2$) and 0.07 (9 H, s, $SiMe_3$); *m*/*z* 161 (100%, $M^+ - CH_2OSiMe_3$), 119 (30), 92 (25), 73 (23, $SiMe_3$), 131 (19), 191 (8, $M^+ - SiMe_3$), 221 (8, $M^+ - Pr^i$) and 249 (8, $M^+ - Me$).

The complex **19**·$ZnBr_2$ was prepared by adding the imine **19** to an equimolar amount of anhydrous $ZnBr_2$ suspended in $CDCl_3$, resulting in the dissolution of the salt. The ^1H NMR spectrum apparently suggested the existence of two species, since the absorption of the azomethine proton appeared as two partially overlapping singlets: δ_H(300 MHz) 8.78 (1 H, m, pyridine), 8.49 (1 H, 2 s, CH=N), 8.18 (1 H, 2 t, pyridine), 7.92 (1 H, m, pyridine), 7.79 (1 H, m, pyridine), 4.05–3.88 (2 H, m, CH_2O), 3.46 (1 H, m, CHN), 2.40 (1 H, m, C*H*Me_2), 1.07 and 1.00 (6 H, 2 m, CH*Me*$_2$) and 0.17 (9 H, s, $SiMe_3$). Irradiation of the azomethine proton at δ 8.49 gave a positive response at δ 7.92 (+9%) and 3.46 (+11%).

Organometallic reactions of the imine 19

Different procedures were followed, as described below, according to the nature of the organometallic reagent. The structure of the intermediates **20** and **43a** and of the by-products **24**–**30** was deduced exclusively from their relative molecular mass and/or mass-spectral fragmentation pattern determined by GLC-MS analysis of the crude reaction mixtures. The amines **21b**,**c**,**e**,**g**–**i** were previously prepared and fully characterized.[3c,d] No attempt was made to separate C-alkyl amine **21b** from the N-alkyl regioisomer **23b**.

Addition of Grignard and organolithium reagents. The imine (3 mmol) was dissolved in THF (10 cm^3) and the solution was cooled at −78 °C, then the organometallic reagent (mol equiv.: 1.2 RLi, 2 RMgX) was added while the mixture was stirred by a magnetic bar. The mixture was further stirred at the temperature and for the time indicated in Table 1. A sample of the reaction mixture was quenched with aq. $NaHCO_3$ and analyzed by GLC-MS to detect the O-silylated products. When the reaction was complete the mixture was quenched with 1 M HCl (10–15 cm^3) and the mixture was stirred at 20 °C until the desilylation was complete (TLC or GLC analysis). Extended reaction time or lower pH sometimes led to partially epimerized β-amino alcohols **21**. The aqueous phase was washed with cyclohexane–Et_2O (2 : 1; 10 $cm^3 \times 2$), then made basic with NaOH pellets at 0 °C, and the organic bases were extracted with Et_2O (20 $cm^3 \times 3$), dried ($MgSO_4$) and concentrated to give the β-amino alcohols **21** and/or **23**.

Addition of mixed triorganozincate reagents. The imine **19** (0.792 g, 3 mmol) was dissolved in THF (10 cm^3) and the solution was cooled at −78 °C, then Me_2Zn (2 M in toluene; 4.5 mmol, 2.25 cm^3) and, after 5 min, the Grignard reagent (4.5 mmol) were added to the magnetically stirred solution. The reaction was followed and then quenched by the same procedures described above.

(*S*)-*N*-[(1*S*)-1-(2-Pyridyl)ethyl]-*O*-(trimethylsilyl)valinol 20a: *m*/*z* 106 (100%, ArCHMe), 177 (85, $M^+ - CH_2OSiMe_3$), 73 (22, $SiMe_3$), 237 (9, $M^+ - Pr^i$) and 265 (1, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-1-(2-Pyridyl)propyl]-*O*-(trimethylsilyl)valinol 20b: *m*/*z* 191 (100%, $M^+ - CH_2OSiMe_3$), 120 (59, ArCHEt), 251 (19, $M^+ - Pr^i$), 73 (10, $SiMe_3$), 265 (4, $M^+ - Et$) and 279 (2, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-1-(2-Pyridyl)pentyl]-*O*-(trimethylsilyl)valinol 20c: *m*/*z* 219 (100%, $M^+ - CH_2OSiMe_3$), 148 (96, ArCHBu), 106 (35), 73 (30, $SiMe_3$), 93 (28), 279 (16, $M^+ - Pr^i$), 265 (5, $M^+ - Bu$) and 307 (<2, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-2-Cyclohexyl-1-(2-pyridyl)ethyl]-*O*-(trimethylsilyl)valinol 20d: *m*/*z* 259 (100%, $M^+ - CH_2OSiMe_3$), 188 (63), 106 (28), 319 (24, $M^+ - Pr^i$), 73 (15, $SiMe_3$), 265 (10, $M^+ - C_6H_{11}CH_2$) and 347 (3, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-2-Methyl-1-(2-pyridyl)propyl]-*O*-(trimethylsilyl)-valinol 20e: *m*/*z* 205 (100%, $M^+ - CH_2OSiMe_3$), 134 (95, ArCHPr^i), 265 (55, $M^+ - Pr^i$), 73 (25, $SiMe_3$) and 293 (4, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-2,2-Dimethyl-1-(2-pyridyl)propyl]-*O*-(trimethylsilyl)valinol 20f: *m*/*z* 265 (100%, $M^+ - Bu^t$), 148 (94, ArCHBu^t), 219 (84, $M^+ - CH_2OSiMe_3$), 107 (28), 73 (28, $SiMe_3$), 279 (8, $M^+ - Pr^i$), 321 (6, $M^+ - H$) and 322 (2, M^+).

(*S*)-*N*-[(1*S*)-2-Phenyl-1-(2-pyridyl)ethyl]-*O*-(trimethylsilyl)-valinol 20g: *m*/*z* 265 (100%, $M^+ - Bn$), 182 (96, ArCHBn), 253 (81, $M^+ - CH_2OSiMe_3$), 73 (27, $SiMe_3$), 313 (8, $M^+ - Pr^i$) and 341 (3, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-1-(2-Pyridyl)but-3-enyl]-*O*-(trimethylsilyl)valinol 20h: *m*/*z* 203 (100%, $M^+ - CH_2OSiMe_3$), 265 (63, $M^+ -$ allyl), 132 (51, $ArCHC_3H_5$), 107 (33), 117 (30), 73 (28, $SiMe_3$) and 291 (3, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-1-(2-Pyridyl)prop-2-enyl]-*O*-(trimethylsilyl)-valinol 20i: *m*/*z* 189 (100%, $M^+ - CH_2OSiMe_3$), 118 (68, ArCHCH=CH_2), 117 (29), 73 (21, $SiMe_3$), 172 (20), 159 (14), 249 (10, $M^+ - Pr^i$) and 277 (3, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-α-(2-Pyridyl)benzyl]-*O*-(trimethylsilyl)valinol 20j: *m*/*z* 168 (100%, ArCHPh), 167 (40), 239 (36, $M^+ - CH_2OSiMe_3$), 299 (9, $M^+ - Pr^i$) and 73 (5, $SiMe_3$).

(*S*)-*N*-[(1*S*)-1-(2-Pyridyl)ethyl]valinol 21a: $[\alpha]_D^{20}$ −47.5 (*c* 0.84, $CHCl_3$); δ_H(300 MHz) 8.59 (1 H, m, pyridine), 7.67 (1 H, m, pyridine), 7.32–7.16 (2 H, m, pyridine), 3.94 (1 H, q, C*H*Me), 3.67 and 3.63 (1 H, dd, *J* 4.1 and 10.7, CH_2O), 3.41 and 3.38 (1 H, dd, *J* 5.1 and 10.7, CH_2O), 2.26 (1 H, m, OCH_2CHN), 1.71 (1 H, m, C*H*Me_2), 2.1–1.8 (2 H, br, OH and NH), 1.42 (3 H, d, *J* 6.7, CH*Me*) and 0.89 and 0.87 (6 H, 2 d, *J* 6.8, CH*Me*$_2$); *m*/*z* 106 (100%, ArCHMe), 177 (41, $M^+ - CH_2OH$), 107 (38), 165 (18, $M^+ - Pr^i$) and 193 (1, $M^+ - Me$).

(*S*)-*N*-[(1*S*)-2-Cyclohexyl-1-(2-pyridyl)ethyl]valinol 21d: mp 53–55 °C; $[\alpha]_D^{20}$ −27.8 (*c* 0.58, $CHCl_3$); δ_H(200 MHz) 8.57 (1 H, m, pyridine), 7.59 (1 H, m, pyridine), 7.14 (2 H, m, pyridine), 3.77 (1 H, t, ArC*H*N), 3.63 and 3.57 (1 H, dd, *J* 3.9 and 10.6, CH_2O), 3.41 and 3.36 (1 H, dd, *J* 3.8 and 10.6, CH_2O), 2.05 (1 H, m, NC*H*CH_2O), 1.95–1.40 (8 H, m, OH, NH, C*H*Me_2 and

C_6H_{11}), 1.35–0.80 (6 H, m, C_6H_{11}), 0.77 and 0.74 (6 H, 2 d, *J* 6.8, CH*Me*$_2$); *m*/*z* 259 (100%, $M^+ - CH_2OH$), 188 (94, ArCH-$CH_2C_6H_{11}$), 106 (82), 193 (40, $M^+ - C_6H_{11}CH_2$), 247 (35, $M^+ - Pr^i$), 189 (34) and 107 (33).

(*S*)-*N*-[(1*S*)-2,2-Dimethyl-1-(2-pyridyl)propyl]valinol 21f: δ_H(300 MHz) 8.58 (1 H, m, pyridine), 7.59 (1 H, m, pyridine), 7.15 (2 H, m, pyridine), 3.62 and 3.58 (1 H, dd, *J* 3.7 and 10.5, CH_2O), 3.44 and 3.40 (1 H, dd, *J* 3.7 and 10.5, CH_2O), 3.34 (1 H, s, Bu^{t}C*H*), 3.15 (1 H, br, OH), 2.0 (1 H, m, OCH_2CHN), 1.8 (1 H, br, NH), 1.61 (1 H, m, C*H*Me$_2$), 0.94 (9 H, s, Bu^t), 0.80 and 0.74 (6 H, 2 d, *J* 6.8, CH*Me*$_2$); (*R*,*S*)-**21f** gave different absorptions at δ 7.25 (2 H, m, pyridine), 3.60 (1 H, s, Bu^{t}C*H*), 2.19 (m, 1 H, CHN) and 1.85 (1 H, m, C*H*Me$_2$); *m*/*z* 193 (100%, $M^+ - Bu^t$), 107 (53), 148 (50, ArCHBu^t), 92 (24), 119 (22), 132 (15), 219 (14, $M^+ - CH_2OH$) and 207 (7, $M^+ - Pr^i$).

(*S*)-*N*-[(1*S*)-α-(2-Pyridyl)benzyl]valinol 21j: $[\alpha]_D^{20}$ +64.8 (*c* 1.0, $CHCl_3$); δ_H(300 MHz) 8.58 (1 H, m, pyridine), 7.59 (1 H, m, pyridine), 7.45–7.22 (5 H, m, Ph), 7.15 (2 H, m, pyridine), 5.02 (1 H, s, PhC*H*N), 3.59 and 3.54 (1 H, dd, *J* 4.1 and 10.8, CH_2O), 3.44 and 3.38 (1 H, dd, *J* 6.8 and 10.8, CH_2O), 2.7 (2 H, br, OH and NH), 2.45 (1 H, m, NC*H*CH_2O), 1.91 (1 H, m, C*H*Me$_2$) and 0.95 and 0.92 (6 H, 2 d, *J* 6.8, CH*Me*$_2$).

(*S*)-*N*-Ethyl-*N*-[(2-pyridyl)methyl]-*O*-(trimethylsilyl)valinol 22b: *m*/*z* 191 (100%, $M^+ - CH_2OSiMe_3$), 202 (35, $M^+ - ArCH_2$), 93 (33), 73 (13, $SiMe_3$), 251 (12, $M^+ - Pr^i$) and 279 (3, $M^+ - Me$).

(*S*)-*N*-Butyl-*N*-[(2-pyridyl)methyl]-*O*-(trimethylsilyl)valinol 22c: *m*/*z* 219 (100%, $M^+ - CH_2OSiMe_3$), 230 (40, $M^+ - ArCH_2$), 93 (38), 73 (20, $SiMe_3$), 92 (18), 279 (14, $M^+ - Pr^i$) and 307 (3, $M^+ - Me$).

(*S*)-*N*-Cyclohexylmethyl-*N*-[(2-pyridyl)methyl]-*O*-(trimethylsilyl)valinol 22d: *m*/*z* 259 (100%, $M^+ - CH_2OSiMe_3$), 270 (55, $M^+ - ArCH_2$), 93 (23), 73 (15, $SiMe_3$), 319 (11, $M^+ - Pr^i$), 279 ($M^+ - C_6H_{11}$) and 347 (2, $M^+ - Me$).

(*S*)-*N*-Isopropyl-*N*-[(2-pyridyl)methyl]-*O*-(trimethylsilyl)-valinol 22e: *m*/*z* 205 (100%, $M^+ - CH_2OSiMe_3$), 163 (40), 93 (36), 216 (35, $M^+ - ArCH_2$), 73 (22, $SiMe_3$), 92 (20), 206 (16), 265 (15, $M^+ - Pr^i$), 293 (3, $M^+ - Me$) and 308 (<1, M^+).

(*S*)-*N*-Butyl-*N*-[(2-pyridyl)methyl]valinol 23c: (Found: C, 72.06; H, 10.42; N, 11.39. $C_{15}H_{26}N_2O$ requires C, 71.95; H, 10.47; N, 11.19%); δ_H(300 MHz) 8.55 (1 H, m, pyridine), 7.62 (1 H, m, pyridine), 7.30–7.10 (2 H, m, pyridine), 4.08 and 3.85 (2 H, 2 d, *J* 15.6, ArC*H*$_2$N), 3.65 and 3.35 (2 H, 2 m, C*H*$_2$OH), 2.72 (2 H, m, NC*H*$_2$CH$_2$), 2.55 (1 H, m, C*H*CH$_2$OH), 1.82 (1 H, m, C*H*Me$_2$), 1.65 (1 H, br, OH), 1.20 (4 H, m, CH_2CH_2), 1.05 and 0.89 (6 H, 2 d, *J* 6.7, CH*Me*$_2$) and 0.75 (3 H, t, CH_2Me); *m*/*z* 93 (100%), 219 (70, $M^+ - CH_2OH$), 158 (60, $M^+ - ArCH_2$), 92 (44), 94 (33) and 207 (25, $M^+ - Pr^i$).

(*S*)-*N*-Cyclohexylmethyl-*N*-[(2-pyridyl)methyl]valinol 23d: (Found: C, 74.56; H, 10.35; N, 9.69. $C_{18}H_{30}N_2O$ requires C, 74.43; H, 10.41; N, 9.65%); δ_H(300 MHz) 8.55 (1 H, m, pyridine), 7.60 (1 H, m, pyridine), 7.30–7.10 (2 H, m, pyridine), 4.03 and 3.88 (2 H, 2 d, *J* 15.6, ArC*H*$_2$N), 3.65 and 3.50 (2 H, 2 m, C*H*$_2$OH), 2.50 (3 H, m, C*H*CH$_2$OH and C_6H_{11}-C*H*$_2$N), 1.95–1.45 (7 H, m, OH, C*H*Me$_2$ and C_6H_{11}), 1.20–0.80 (6 H, m, C_6H_{11}) and 1.06 and 0.80 (6 H, 2 d, *J* 6.7, CH*Me*$_2$); *m*/*z* 198 (100%, $M^+ - ArCH_2$), 93 (97), 259 (86, $M^+ - CH_2OH$), 121 (42), 92 (42), 207 (27, $M^+ - C_6H_{11}$) and 247 (25, $M^+ - Pr^i$).

(*S*)-*N*-[1-(2-Pyridyl)ethylidene]-*O*-(trimethylsilyl)valinol 24a: *m*/*z* 175 (100%, $M^+ - CH_2OSiMe_3$), 106 (42), 73 (36, $SiMe_3$), 133 (24), 145 (19), 176 (17), 78 (11), 263 (8, $M^+ - Me$) and 235 (5, $M^+ - Pr^i$); the mass spectrum and the GLC retention time were identical with those of the authentic compound prepared by condensation of 2-acetylpyridine with valinol (CH_2Cl_2, $MgSO_4$) and hydroxy-group protection (Me_3SiCl, Et_3N). Moreover, the ^1H NMR spectrum of the crude reaction product obtained by quenching of the reaction of imine **19** with methylmagnesium chloride with aq. $NaHCO_3$ showed singlets at δ 2.37 (s) and at 2.73 (s) that we attributed to compound **24a** (CH_3C=N) and 2-acetylpyridine (CH_3C=O), the latter coming from hydrolysis of compound **24a**. Only the former absorption disappeared after acidic hydrolysis. The other ketimines **24b–f** were identified on the basis of their mass spectra, since the same fragmentation patterns were observed for compound **24a**.

(*S*)-*N*-[1-(2-Pyridyl)propylidene]-*O*-(trimethylsilyl)valinol 24b: *m*/*z* 189 (100%, $M^+ - CH_2OSiMe_3$), 73 (25, $SiMe_3$), 159 (23), 118 (20), 77 (13, $M^+ - Me$) and 249 (6, $M^+ - Pr^i$).

(*S*)-*N*-[1-(2-Pyridyl)pentylidene]-*O*-(trimethylsilyl)valinol 24c: *m*/*z* 217 (100%, $M^+ - CH_2OSiMe_3$), 73 (38, $SiMe_3$), 106 (28), 187 (18), 179 (14), 148 (13), 132 (10), 291 (7, $M^+ - Et$), 277 (9, $M^+ - Pr^i$) and 305 (6, $M^+ - Me$).

(*S*)-*N*-[2-Methyl-1-(2-pyridyl)propylidene]-*O*-(trimethylsilyl)-valinol 24e: *m*/*z* 203 (100%, $M^+ - CH_2OSiMe_3$), 134 (17), 73 (16, $SiMe_3$), 173 (13), 291 (8, $M^+ - Me$) and 263 (7, $M^+ - Pr^i$).

(*S*)-*N*-[2,2-Dimethyl-1-(2-pyridyl)propylidene]-*O*-(trimethylsilyl)valinol 24f: *m*/*z* 217 (100%, $M^+ - CH_2OSiMe_3$), 187 (20), 73 (14, $SiMe_3$), 175 (9), 277 (8, $M^+ - Pr^i$), 148 (7) and 305 (6, $M^+ - Me$).

Apart from the amine **29**, we assigned the following structures to the by-products **26**–**30** on the basis of their relative molecular mass and/or fragmentation patterns observed in GLC-MS, since they could neither be isolated nor compared by GLC-MS analysis with authentic compounds.

(*S*)-*N*-Isopropyl-*N*-[(1*S*)-2-methyl-1-(2-pyridyl)propyl]-*O*-(trimethylsilyl)valinol 26e: *m*/*z* 176 (100%), 203 (70), 247 (58, $M^+ - CH_2OSiMe_3$), 73 (52, $SiMe_3$), 307 (50, $M^+ - Pr^i$), 161 (23), 103 (21) and 134 (19, ArCHPr^i).

(*S*)-*N*-*tert*-Butyl-*N*-[(1*S*)-2,2-dimethyl-1-(2-pyridyl)propyl]-*O*-(trimethylsilyl)valinol 26f: *m*/*z* 321 (100%, $M^+ - Bu^t$), 204 (70), 275 (48, $M^+ - CH_2OSiMe_3$), 217 (32), 322 (24), 73 (16, $SiMe_3$), 163 (15), 188 (14), 175 (13), 363 (6, $M^+ - Me$), 148 (5, ArCHBu^t), 231 (4, $M^+ - ArCHC_4H_8$) and 335 (4, $M^+ - Pr^i$).

(*S*)-*N*-*tert*-Butyl-*N*-[(1*S*)-2,2-dimethyl-1-(2-pyridyl)propyl]-valinol 27f: *m*/*z* 249 (100%, $M^+ - Bu^t$), 204 (34), 163 (26), 231 (19), 250 (18), 179 (17), 148 (15, ArCHBu^t), 164 (15), 190 (12), 275 (11, $M^+ - CH_2OH$) and 291 (1, $M^+ - Me$).

(2*S*)-2-Isopropyl-1-[(1*S*)-1-(2-pyridyl)ethyl]aziridine 28: *m*/*z* 84 (100%, $M^+ - ArCHMe$), 107 (73), 106 (55, ArCHMe), 55 (35), 68 (30), 147 (8, $M^+ - Pr^i$), 175 (6, $M^+ - Me$) and 190 (<1, M^+). The most abundant fragment at *m*/*z* 84, coming from loss of the N-substituent, was indicative of the aziridine moiety, and was also observed in the mass spectrum of (2*S*)-2-isopropyl-1-[(1*S*)-1-phenylethyl]aziridine, previously prepared by us (unpublished work).

(*S*)-*N*-[(2-Pyridyl)methyl]-*O*-(trimethylsilyl)valinol 29: *m*/*z* 163 (100%, $M^+ - CH_2OSiMe_3$), 93 (16), 161 (15), 92 (14), 164 (12), 73 (11, $SiMe_3$), 223 (9, $M^+ - Pr^i$) and 131 (9); the mass spectrum and the GLC retention time were identical with those of the authentic compound prepared by Pd/C-catalyzed hydrogenation of compound **19**.

(*S*)-*O*-(Trimethylsilyl)-*N*-[2-(6-trimethylsilyl)pyridylmethylene]valinol 30: *m*/*z* 265 (100%, $M^+ - 71$), 233 (97, $M^+ - CH_2OSiMe_3$), 162 (26), 266 (20), 73 (19, $SiMe_3$), 92 (17), 234 (15), 119 (14), 293 (6, $M^+ - Pr^i$), 321 (2, $M^+ - Me$) and 336 (~0.3, M^+).

(*S*)-*N*-(Hex-5-enyl)-*N*-[(2-pyridyl)methyl]-*O*-(trimethylsilyl)-valinol 43a: *m*/*z* 245 (100%, $M^+ - CH_2OSiMe_3$), 93 (48), 256 (41, $M^+ - ArCH_2$), 73 (28, $SiMe_3$), 92 (22, $ArCH_2$), 305 (12, $M^+ - Pr^i$) and 279 (2, $M^+ - C_5H_9$).

(*S*)-*N*-(Hex-5-enyl)-*N*-[(2-pyridyl)methyl]valinol 43b: δ_H(300 MHz) 8.55 (1 H, m, pyridine), 7.63 (1 H, m, pyridine), 7.24–7.13 (2 H, m, pyridine), 5.75–5.10 (1 H, m, C*H*=CH$_2$), 4.93–4.83 (2 H, m, CH=C*H*$_2$), 4.08 and 3.84 (2 H, 2 d, *J* 15.4, ArC*H*$_2$N), 3.68 and 3.36 (2 H, 2 m, CH_2O), 2.74 (2 H, t, $C_5H_9CH_2N$), 2.56 (1 H, m, NC*H*CH_2O), 1.94–1.75 (3 H, m, C*H*$_2$CH=CH$_2$ and C*H*Me$_2$), 1.35–1.15 (4 H, m, CH_2CH_2), 1.04 and 0.90 (6 H, 2 d, *J* 6.7, CH*Me*$_2$); the product underwent decomposition during GLC-MS analysis.

Preparation of primary amines 31

To the solution of the β-amino alcohol **21** (2 mmol) in MeOH–THF (9 : 1; 5 cm^3) was added 40% aq. $MeNH_2$ (2 cm^3), then aq. H_5IO_6 (1.64 g in 5 cm^3) was added slowly, while the mixture was stirred magnetically. The progress of the reaction was monitored by TLC (EtOAc–MeOH, 95 : 5), then water (5 cm^3) was added and the solid phase was filtered off. The solution was extracted with Et_2O (15 $cm^3 \times 3$) and the collected organic layers were thoroughly dried over $MgSO_4$, then concentrated under reduced pressure to leave the primary amine in a pure state as an oily residue. The amines **31b**,**c**,**e**,**g**–**i** were previously prepared from the precursors **21b**,**c**,**e**,**g**–**i** and were fully characterized.[3b–d]

(*S*)-1-(2-Pyridyl)ethylamine 31a: 90% $[\alpha]_D^{20}$ −22.6 (*c* 0.76, $CHCl_3$); $[\alpha]_D^{20}$ −25.6 (*c* 0.39, EtOH); a sample purified by column chromatography on a SiO_2 column (EtOAc) gave $[\alpha]_D^{20}$ −28.1 (*c* 1, EtOH); lit.,[9] $[\alpha]_D^{20}$ −28.5 (EtOH); δ_H(300 MHz) 8.67 (1 H, m, pyridine), 7.65 (1 H, m, pyridine), 7.30 (1 H, m, pyridine), 7.15 (1 H, m, pyridine), 4.15 (1 H, q, C*H*Me), 1.95–1.75 (2 H, br, NH_2) and 1.43 (3 H, d, *J* 6.8, CH*Me*); δ_C(300 MHz) 165.8, 149.1, 136.5, 121.8, 120.0, 52.5 and 24.5; *m*/*z* 107 (100%), 80 (26), 108 (12), 78 (11), 52 (10), 51 (9), 104 (8), 105 (7), 121 (5) and 122 (3, M^+).

(*S*)-2-Cyclohexyl-1-(2-pyridyl)ethylamine 31d:[4d] 83%; $[\alpha]_D^{20}$ +6.4 (*c* 1.6, $CHCl_3$); δ_H(300 MHz) 8.57 (1 H, m, pyridine), 7.63 (1 H, m, pyridine), 7.26 (1 H, m, pyridine), 7.14 (1 H, m, pyridine), 4.04 (1 H, t, CHN), 1.82–1.55 (9 H, m, NH_2, CH_2, C_6H_{11}) and 1.40–0.85 (6 H, m, C_6H_{11}); δ_C(300 MHz) 165.4, 149.0, 136.2, 121.6, 120.7, 54.4, 46.4, 34.3, 33.7, 32.8, 26.4, 26.1 and 26.0; *m*/*z* 107 (100%), 108 (14), 80 (8), 160 (7), 106 (5), 121 (4) and 204 (2, M^+).

(*S*)-α-(2-Pyridyl)benzylamine 31j: 94% (Found: C, 78.06; H, 6.55; N, 15.39. $C_{12}H_{12}N_2$ requires C, 78.23; H, 6.57; N, 15.21%); $[\alpha]_D^{20}$ +67.1 (*c* 1.9, $CHCl_3$); δ_H(300 MHz) 8.56 (1 H, m, pyridine), 7.59 (1 H, m, pyridine), 7.45–7.23 (6 H, m, Ph and pyridine), 7.13 (1 H, m, pyridine), 5.25 (1 H, s, CHN), and 2.15 (2 H, br, NH_2); δ_C(300 MHz) 163.4, 149.0, 144.7, 136.5, 128.5, 127.1, 127.0, 121.9, 121.6 and 61.1; *m*/*z* 106 (100%), 184 (46, M^+), 79 (28), 107 (27), 77 (18), 80 (15), 107 (14), 78 (14), 51 (13) and 183 (12).

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