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Study of the regioselectivity and diastereoselectivity in the addition of 3-substituted-2-propenylmetal reagents to *N*,*N*′-di[1(*S*)-phenylethyl]ethanediimine

Claudio Fiorelli, Lucia Maini, Gianluca Martelli, Diego Savoia* and Carla Zazzetta

Dipartimento di Chimica 'G. Ciamician', Università di Bologna, via Selmi 2, 40126 Bologna, Italy

Dedicated to Professor Gianfranco Cainelli on the occasion of his 70th birthday

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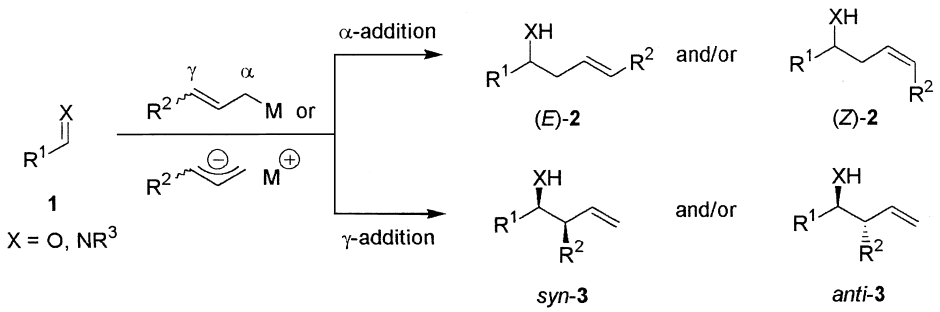
Abstract—The additions of 3-aryl-2-propenyllithium and -zinc reagents to *N*,*N*′-di[1(*S*)-phenylethyl]ethanediimine in THF occurred by α and γ-addition, affording 4,5-diamino-1,7-dienes with linear and branched allylic substituents, respectively. 3-Phenoxy- and 3-alkoxy-2-propenyllithiums reacted with lack of regioselectivity, whereas the corresponding zinc reagents exclusively followed the γ-addition pathway. The (*S*)-configuration of the auxiliaries induced the preferential attack to the Re face of the azomethine groups. In the γ-addition route, four new stereocentres were formed and the simple (*syn*/*anti*) diastereoselectivity was dependent on the alkene geometry in the allylmetal reagents. C_2-symmetric compounds with *syn*–*syn*–*syn* or *anti*–*syn*–*anti* relative stereochemistry were prevalently obtained. In contrast, when 3-ethoxy-2-propenylzinc chloride was prepared by transmetallation of the corresponding titanium reagent, a C_1-symmetric compound (*anti*–*syn*–*syn*) was mainly formed.

1. Introduction

The synthetic utility of the organometallic addition to imines is limited, as compared to carbonyl compounds, by the low reactivity of the imine function towards organometallic reagents,[1] and the occurrence of competitive reaction pathways, such as deprotonation and SET processes. Nevertheless, a number of stereoselective synthesis of amines have been described exploiting the addition of organometallic reagents to chiral imines, particularly those bearing a stereogenic *N*-substituent.[1–3] The use of allylmetal compounds or allyl carbanions can circumvent the aforementioned reactivity problems. However, the use of γ-substituted allylmetal compounds raises the additional problem of regioselectivity, which has been more deeply studied for the addition to carbonyl compounds, alkyl halides or other electrophiles.[4–6] In fact, the α or γ-additions of such reagents to unsaturated electrophiles **1** gives either the linearly substituted (*E*) and/or (*Z*)-homoallylic alcohols and amines **2**, or the branched homoallylic isomers **3** (Scheme 1).

The simple (*syn*/*anti*) diastereoselectivity[7–10] in the formation of branched products **3** is governed by a number of factors: the nature of both the imine and the allylmetal reagent, the substitution pattern and the alkene geometry in the latter compound, the presence of a Lewis acid, which in turn affects the mechanism and/or the transition state



Scheme 1.

Keywords: allylation; amines; diastereoselection; imines; regioselection.

* Corresponding author. Tel.: +39-51-2099571; fax: +39-51-2099456; e-mail: savoia@ciam.unibo.it

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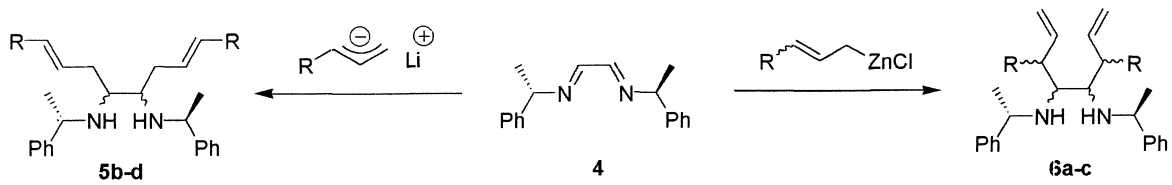


Scheme 2.

structure. Several reactions of chiral imines with γ-substituted allylmetal reagents have been described previously. The addition of crotylmetals (M=MgCl, $SnBu_3-BF_3$) to imines gave low to moderate levels of simple diastereoselectivity,[11,12] but crotyl-9-BBN gave *anti*/*syn* ratios of the γ-addition products ranging from 100:0 to 0:100.[11] Moreover, the *anti*/*syn* ratio 84:16 was obtained in the addition of crotyllithium to the benzaldimine derived from the 2(*S*)-amino-1(*R*)-methoxy-1,2-diphenylethane.[12] The additions of crotyl-9-BBN, -MgCl, $-ZrCp_2Cl$ and -Ti(*i*-PrO)$_3$ to chiral aliphatic imines gave low *syn*/*anti* ratios, but (*E*)-crotyl-9-BBN added the imine derived from butyl glyoxylate and 1(*S*)-phenylethylamine with excellent *syn*- as well as Cram-selectivity.[13] The same glyoxylate imine gave better *anti*-selectivity with 3-phenoxy-, 3-methoxy- (*anti*/*syn* 5:1) and 3-methylthio-2-propenylzinc bromide (*anti*/*syn* 3:1) than with the corresponding titanate, aluminate or boronate reagents.[14] In these reactions, the prevalent formation of the *anti*-isomer was explained by assuming the intramolecular coordination of the heteroatom to the metal, resulting in the (*Z*)-geometry of the allylic double bond; it is also noteworthy that the 1,3-asymmetric induction (auxiliary induced diastereoselectivity) was high for the methoxy-substituted zinc reagent, but absent for the phenoxy-substituted reagent.[14] A remarkably complete stereocontrol was observed in the addition of the geometrically stable (*Z*)-2-ethoxycarbonyl-2-butenylzinc bromide to ethyl *N*-benzylidene (*R*)-phenylglycinate.[15] The intramolecular allylation of a chiral aliphatic aldimine by a terminal (*Z*)-3-alkoxy-2-alkenyl-tributylstannane moiety was promoted by different Lewis acids, which affected also the simple diastereoselectivity: only the *trans*(*anti*)-isomer was obtained in the HCl and $ZrCl_4$ mediated cyclisations.[16]

Finally, it is noteworthy that substituted allyltitanium reagents were quite useful for the stereoselective addition to imines: in fact, the (*E*)-crotyl[17,18] and (*E*)-cinnamyltitanium[17] reagents added to *N*-propylidene-1(*R*)-phenylethylamine to give the homoallyilc amines with prevalent *syn* stereochemistry.† On the other hand, the reaction of (*Z*)-cyclooctenyltitanium reagent with *N*-benzylidenepropylamine gave the *anti*-adduct.[19] Therefore, it is surprising that the 3-benzyloxy-2-propenyltitanium reagent derived from acrolein dibenzyl acetal, presumably having (*Z*)-geometry, gave the *syn*-adduct with an aliphatic imine,[20] perhaps through an open or boat-like six-membered cyclic transition state. Conversely, the reagent prepared from acrolein (*R*,*R*)-1,2-dicyclohexylethylene acetal reacted with the opposite regioselectivity (α-addition), so acting as a chiral homoenolate equivalent.[21]

We have been mostly active during the last decade in allylmetalation reactions of imines and 1,2-diimines carrying stereogenic *N*-substituents.[3] Particularly, we have described that the addition of pentadienyl-, 1-trimethylsilyl-allyl- and cinnamyllithium to the glyoxal diimine **4** in THF at −78 to 0°C gave regioselectively the linear substituted 1,2-diamines **5b–d** with high stereocontrol (Scheme 2).[22] This is in direct contrast with the reported exclusive formation of branched products by the γ-addition of crotyllithium to a chiral benzaldimine.[12] We have also reported that crotyl- and pentadienylzinc halides added to the same diimine with allylic rearrangement to give the branched 1,2-diamines **6a**,**b** with high levels of 1,3-asymmetric induction.[23] However, in this case the *syn*/*anti* diastereoselectivity was not controlled, owing to the geometrical instability of crotylzinc bromide. Consequently, it appeared interesting to us to widen the scope of the allylmetalation reactions of the diimine **4** investigating the reactivity and selectivity of differently substituted allyllithium and-zinc reagents having a stable (*E*) or (*Z*)-geometry. Particularly, the 3-oxy-substituted 2-propenyllithium reagents were expected to behave as homoenolate equivalents, so allowing the preparation of compounds **5**. On the other hand, the preparation of branched oxy-substituted 1,2-diamines **6** using the corresponding zinc reagents would also be interesting. Here we describe the reactions of 3-aryl- and oxygen-substituted 2-propenyllithium and -zinc reagents to the diimine **4**.

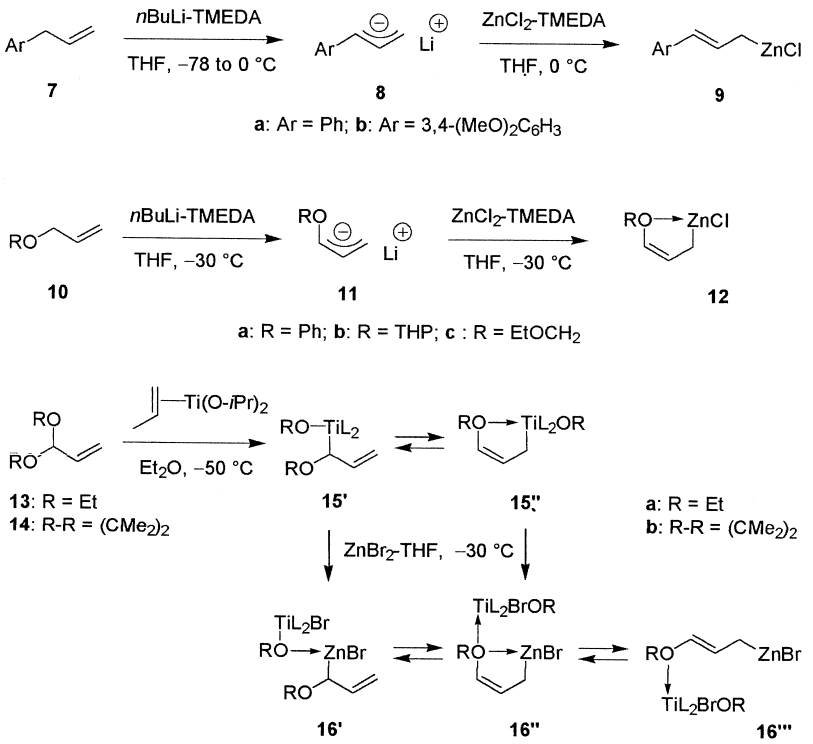
2. Results and discussion

2.1. Preparation of 3-substituted-2-propenylmetal reagents

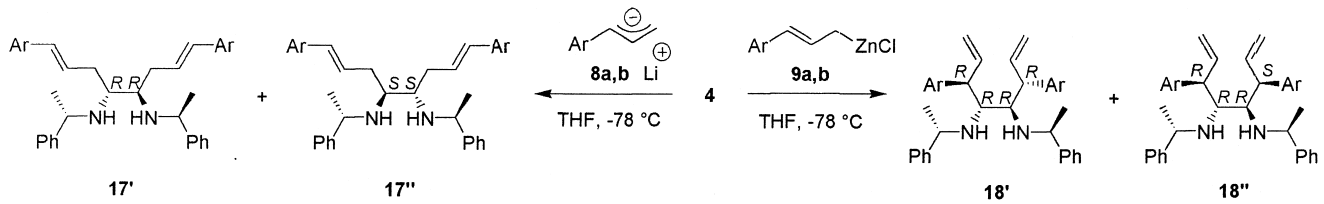
The methods we have used to prepare the γ-substituted allylmetal species are described in Scheme 3. Following the described route to the desired lithium and zinc reagents,[24,25] we have carried out the metalation of allyl-substituted arenes **7** and allyl ethers **10** by *n*BuLi–TMEDA in THF at the proper temperatures to give the lithium reagents **8** and **11**,[24] respectively.‡ Starting from allylarenes **7**, the

† Sato[17] prepared reagents having the structure **15′** from acrolein acetals derived from ethylene glycol, (*R*,*R*)-2,3-butandiol and (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol. In our hands, the titanium reagent prepared from **14** did not react with a 2-pyridylimine, but added to benzaldehyde as expected to give the linear homoallylic alcohols, thus demonstrating the structure **15′**.

‡ We consider the allylic lithium reagents as highly ionic compounds, although crotyllithium has been depicted as a covalent compound reacting with an imine by allylic rearrangement.[12]



Scheme 3.



17'a/17''a = 78:22, **17'a**: 45% after chromatography (ref. 21);
17'b/17''b = 80:20, **17'b**: 42% after crystallisation

18a: ds>90%; **18'a**: 60% after crystallisation;
18b: ds= 80%, **18'b**: 33% after chromatography and crystallisation

Scheme 4.

completeness of the metallation steps was ensured by raising the temperature from −78 to 0°C, and this temperature was maintained in the subsequent transmetallation with the $ZnCl_2$–TMEDA complex, which produced the corresponding zinc reagents **9** and **12**. Although it has been reported that the γ-oxygen-substituted allyllithium compounds must be prepared and maintained at a temperature below −78°C to avoid decomposition by Wittig rearrangement,[6,24,25] we have obtained the best results following the Yamamoto protocol, by which the reagents **11a** and **12a** were prepared at −30°C.[14] It should be underlined that different alkene geometries are present in the allylmetal reagents, i.e. **8**, **9** vs **11**, **12**, depending on the nature of the allyl substituent. The (*Z*)-geometry of the cinnamyl reagents **8** and **9** is dictated by the steric properties of the Ph substituent in the allyl moiety. On the other hand, either the ionic or covalent oxygen-substituted reagents **11** and **12** have the (*Z*)-geometry, which is stabilised by internal coordination.

Acrolein acetals are useful starting materials to prepare alkoxy-substituted allyltitanium reagents by oxidative addition of (η^2-propene)-Ti(O-*i*Pr)$_2$, which is generated in situ from Ti(O-*i*Pr)$_4$ and 2 equiv. of *i*PrMgCl.[18] It is noteworthy that the branched reagents **15′** are formed from the cyclic acetals derived from 1,2-diols,† e.g. **14**, whereas the (*Z*)-linear isomers **15″** are produced from the acyclic acetals, e.g. **13**. The reactivity of the titanium reagents **15′** and **15″** towards imines is only moderate, being almost limited to aliphatic imines.§ Therefore, we have converted them to the corresponding zinc reagents by a transmetallation step, as previously described by Normant to prepare (*Z*)-3-ethoxy-2-propenylzinc chloride.[26] By this way, we envisioned the preparation of either branched products exploiting the reagent **16′**, in turn prepared from the cyclic acetal **14**, or linear products from the alternative structures **16″** and/or **16‴**.

§ The allylic titanium reagents **15′** and **15″** are poorly reactive towards aromatic imines. In our hands, **14** reacted unsatisfactorily with the diimine **4**, presumably the second attack being hampered by steric hindrance.

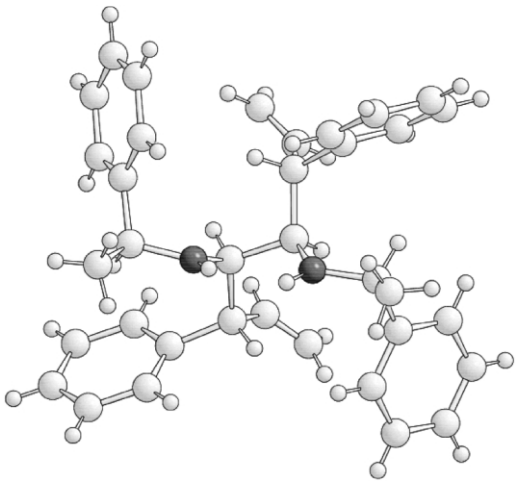
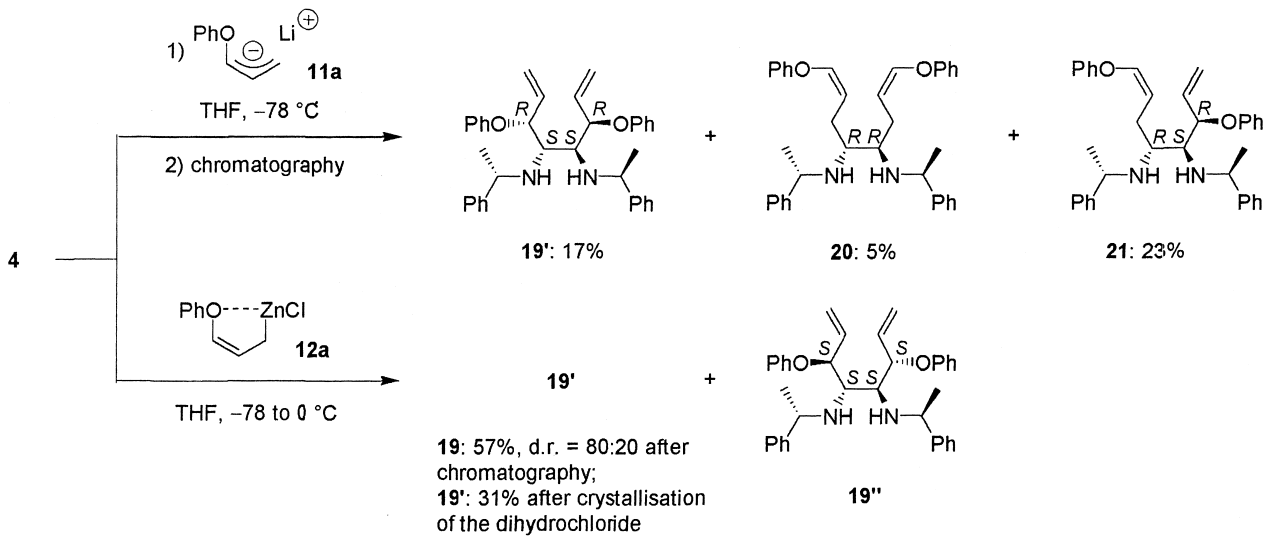


Figure 1. X-Ray structure of compound **18′a**; two independent molecules, which differ very slightly, are present in the crystal, but only one is shown.



Scheme 5.

2.2. Addition of γ-arylallylmetal reagents

The reaction of the diimine **4** with 3 equiv. of the 3,4-dimethoxyphenylallyllithium reagent **8b** was performed in THF at −78°C and followed the same reaction pathway as the cinnamyllithium,[21] affording exclusively the linear 1,2-diamines **17′b** and **17″b**, coming from the double α-addition to the C=N groups (Scheme 4). An 80:20 ratio of diasteromers was determined by ^{1}H NMR analysis of the crude product. The main (*R*,*R*)-diastereomer **17′b** was isolated with 42% yield by crystallisation from methanol, and the *R* configuration of the newly formed stereocentres was assumed by analogy with the previously prepared (*R*,*R*)-**17′a**.[21] Moreover, the (*E*)-geometry of the double bonds was shown from the *J* value of the vinylic protons. The minor diastereomer **17″b** was not isolated.

Conversely, the cinnamyl- and 3,4-dimethoxyphenylallylzinc chloride **9a**,**b**, obtained by transmetallation of the corresponding lithium reagents, reacted with the 1,2-diimine **4** exclusively by γ-attack, giving the branched bis-homoallylic 1,2-diamines **18a**,**b** with high yields and a good level of diastereoselectivity (Scheme 4).[¶] In both reaction mixtures, two diastereomers were evidenced by t.l.c. and ^{1}H NMR spectroscopy. The prevalent ones **18′a**,**b**, having C_2-symmetry, were isolated pure by crystallisation (**18′a**, 60%; **18′b**, 33%). The configuration of **18′a** was determined by X-ray structure analysis, which showed the *R* configuration of all the newly formed stereocentres (Fig. 1). The minor diastereomers **18″a**,**b** were not isolated pure, but their C_1-symmetry was demonstrated by ^{1}H NMR spectroscopy of enriched chromatographic fractions.

2.3. Addition of 3-oxygen-substituted 2-propenylmetal reagents

We first studied the addition of γ-phenoxyallyllithium **11a** and observed that a mixture of isomeric and diastereomeric 1,2-diamines were formed. Column chromatography allowed separation of three main compounds with satisfactory purity, presumably all of them having the *R* configuration of the newly formed stereocentres (α to N). Two of them, **19′** (17%) and **20** (5%), had C_2-symmetry, but differed for having branched or (*Z*)-linear γ-phenoxyallyl substituents, respectively, and the third one, **21** (23%), had one (*Z*)-linear and one branched substituents. This lack of regioselectivity was rather unexpected, considering the outcome of the previously described reaction with cinnamylithium, although we have found no report on the regioselective α-addition of alkoxyallyllithiums to imines. The *anti*,*syn*,*anti*-configuration could be assigned to the branched diamine **19′** when the same compound was obtained as the major product of the reaction of the diimine **4** with 3-phenoxy-2-propenylzinc chloride **12a** (Scheme 5).

[¶] This result is in contrast with the reported formation of the linear homoallylic amine by addition to *N*-benzylidene methylamine at room temperature,[27] however, this likely occurred because of the rapid isomerisation of the initially formed branched homoallylic amine to the most stable linear isomer.

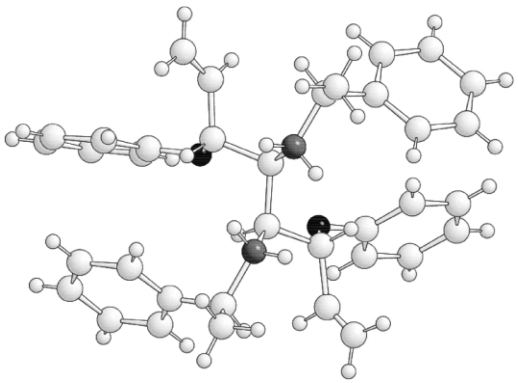


Figure 2. X-Ray structure of compound **19′**-2HCl; chloride ions are omitted.

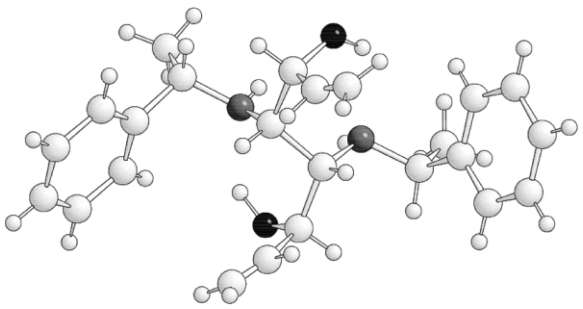
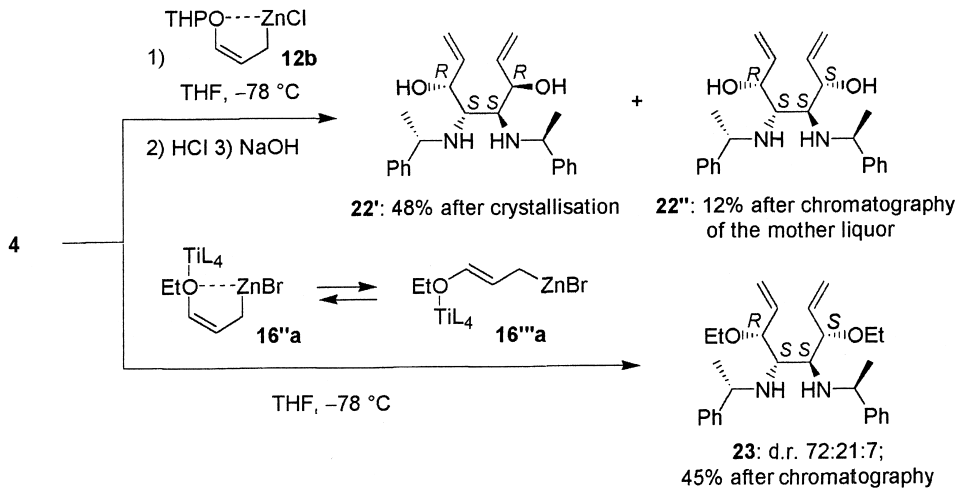


Figure 3. X-Ray structure of compound **22′**.

In this case, compound **19′** could not be separated from an isomer by chromatography, as a 4:1 ratio of isomers was determined by ^{1}H NMR analysis, but crystallisation of the derived dihydrochlorides mixture from methanol, followed by basic treatment gave pure **19′** in 31% yield. Its structure was determined by X-ray crystallographic analysis (Fig. 2). ^{1}H NMR analysis of the diastereomeric mixture allowed assignment of the C_2-symmetry of the minor diastereomer, to which the structure **19″** may be assigned, assuming the same sense of asymmetric induction in the additions to the diimine moiety. Aiming to assess the influence of the *O*-substituent on the regio- and diastereoselectivity, and particularly to find a route to 1,8-dialkoxy-4,5-diamino-1,7-dienes, we carried out the reaction with the THPO-allyllithium **11b**[24] and *O*-ethoxymethyl derivative **11c**, hoping that these reagents would add exclusively by α-addition. Unfortunately, both the reactions gave a complex mixture of at least four relevant products. ^{1}H NMR spectroscopy showed the presence of linear and branched substituents, although with different ratios in the two cases. The crude products were not elaborated further.

On the other hand, a good control of the regio- and diastereoselectivity was obtained using THPO–allylzinc chloride **12b** (Scheme 6). After acidic removal of the OH-protective groups, followed by basic treatment, a solid diamino-diol **22′** was obtained and purified by crystallisation (48% yield). The crystals of **22′** were suitable for X-ray diffraction analysis, and the relative *anti*,*syn*,*anti* relationship of the hydroxy and amino groups was so determined (Fig. 3). The *anti* relationship of the hydroxy and amino groups could be related to the coupling constant J=2.2 Hz measured for the NC*H*CHOH protons in the ^{1}H NMR spectrum, whereas the coupling constant J=6.6 Hz was assigned to the corresponding proton in the *syn*-1,2-aminoalcohol moieties of **19′** (Scheme 5). The C_1-symmetric diastereomer **22″** was also obtained in 12% yield by column chromatography of the mother liquor coming from the crystallisation of the crude reaction product. Surprisingly, the diethoxy-substituted diamine **23** was the main product obtained by the reaction of **4** with the zinc reagent **16‴a** (Scheme 6), which was in turn prepared from the titanium reagent **15′a** (Scheme 3). The C_1-symmetry of **23**, which was isolated pure in 45% yield by chromatography of the crude product, was determined from the ^{1}H NMR spectrum, where the two coupling constants J=2.0, 6.6 Hz for the CHCHN protons proved the *anti* and *syn* relationships of the two 1,2-alkoxy-amine moieties. Moreover, the X-ray structure lacking, the *S* configuration of the NCH*CH*N stereocentres was inferred in the light of the outcome of the reaction of **4** with allylzinc bromide prepared by treatment of (allyl)Ti(*i*PrO)$_2$Br with ZnBr$_2$: as a fact the diallylation product was obtained with almost the same diastereomeric ratio (92:4:4) provided by neat allylzinc bromide.[28] This finding demonstrates that the presence of the Ti(IV) salt did not affect the sense and the degree of the asymmetric induction in the allylzincation reaction.

Finally, we made an attempt to prepare regioselectively a



Scheme 6.

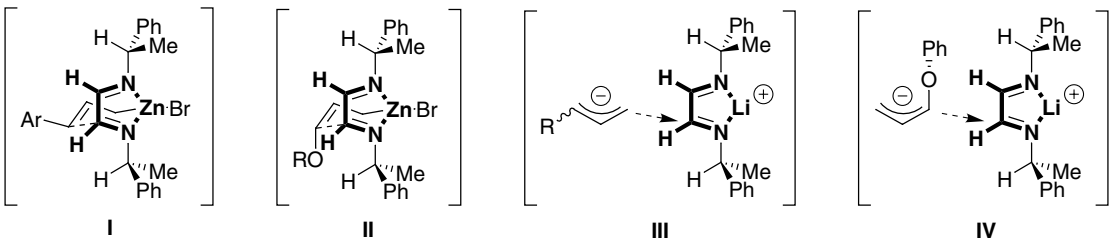


Figure 4.

1,8-dialkoxy-4,5-diamino-1,7-diene by using the zinc reagent **16b** prepared from the cyclic acrolein acetal **14**, through the titanium reagent **15′b** (Scheme 3); however, a mixture of branched diastereomers was instead obtained, which could not be separated by chromatography.

2.4. Origin of the regio- and stereocontrol

Both the regioselectivity and the stereoselectivity were affected by the nature of the organometallic reagent, i.e. either the metal and the allylic substituent. First of all, it should be considered that the carbon–metal bond is largely covalent in allylic zinc compounds, whereas it is borderline between covalent and ionic in allyllithiums. For the addition of allylic zinc reagents to imines a six-membered cyclic transition state is expected for the C–C bond forming step, which follows the preliminary N–Zn coordination. Consequently, branched homoallylic amines are formed with γ-substituted allylzinc species, and the simple (*syn*/*anti*) diastereoselectivity is dictated by the alkene geometry in the reagent. The *syn*-relationship of the phenyl and amino substituents in the compounds **18a**,**b** stems from the preferred (*E*)-geometry of the aryl-substituted reagents **9a**,**b**, which is maintained in the C–C bond forming steps developing through cyclic transition states, e.g. **I**, which is relative to the first organometallic attack to the 1,2-diimine **4** (Fig. 4). Conversely, the *anti*-stereochemistry of the hydroxy and amino substituents in the compounds **19**, **22** and, in part, **23** is rationalised by assuming the (*Z*)-geometry of the zinc reagents **12**, which are stabilised by internal O–Zn coordination and react in the first step through the transition structure **II**.[‖] On the other hand, the formation of the C_1-symmetric product **23**, where both the *syn* and *anti* diastereoselectivity were operating, may have different explanations. We suggest that the oxophilicity of the titanium salt causes the disruption of the intramolecular O–Zn coordination in **16″a** which enter into equilibrium with the linear structure **16‴a** (Scheme 3). Alternatively, but less likely, one can suppose that the Ti–Zn transmetallation, i.e. **15″a** to **16″a**, was incomplete and the consecutive additions of two different organometallic species to the diimine **4** occurred with opposite simple diastereoselectivity, i.e. by *syn* addition of the titanium reagent and *anti*-addition of the zinc reagent. It is worth reminding the reported *syn*-selective addition of a 3-benzyloxy-2-propenyltitanium species to an aliphatic imine.[20] Finally, the observed γ-addition of the zinc reagent **16b** to **4** indicated that the structures **16″b** and **16‴b** were preferred, contrary to the precursory titanium reagent **15b**, which assumes the structure **15′b**.[**]

The regioselectivity of the allylic lithium compounds was dependent on the nature of the allylic substituent and is not easily rationalised. As a matter of fact, the aryl-substituted reagents **8** exclusively reacted by α-addition to give the linear homoallylic products **17**, preserving the (*E*)-geometry of the C=C bond, whereas the behaviour of oxyallyllithiums was affected by the *O*-substituent. A perfect regioselectivity was observed with the THP-protected reagent **11b** which gave exclusive α-addition leading to the (*Z*,*Z*)-linear diamine **22**, while preserving the double bond geometry. Instead, the 3-phenoxy-2-propenyllithium **11a** gave the products **19′**–**21** by competitive α and γ-addition processes. If we assume that all the allylic lithium species are ionic, an acyclic transition state must be considered for their additions to the diimine–lithium cation complex. The α-attack of the carbanion, depicted in model **III** (Fig. 4), is clearly favoured by the reduced non-bonding interactions, with respect to the γ-attack. So, the lack of regioselectivity of 3-phenoxy-2-propenyllithium **11a** is surprising. The formation of the diamines **19** and **21**, having at least one branched substituent, is probably favoured by the (*Z*)-geometry of the reagent, which makes easier the γ-attack with respect to the (*E*)-reagent, as depicted in model **IV**, which is relative to the first addition step. Alternatively, it can be assumed that the reagent **11a** exists (reacts) as a covalent species, as in a previous report,[12] in this case a cyclic transition state analogous to **II** should be involved.

3. Conclusions

In this work, we have investigated the reactivity of γ-substituted allyllithium and -zinc reagents to the glyoxal diimine **4**, and determined the role of the metal and the allylic substituent on the regioselectivity and diastereoselectivity. Particularly, we have found that the γ-aryl-substituted allyllithium reagents gave exclusively α-addition products, whereas the γ-phenoxy and γ-alkoxy-substituted lithium compounds followed both the α and γ-addition pathways. Moreover, the geometry of the (*E*)-aryl- or (*Z*)-oxy-substituted reagents was preserved

[‖] Although the stereochemistry of the compounds **19′** and **23** was not safely determined, the depicted configuration of the N–C*–C*–N stereocentres is highly probable, in view of the high level of diastereoselectivity generally obtained with allylic zinc reagents; consequently, the configuration of the CH*O stereocentres is determined by the C_2 or C_1-symmetry of the compound.

[**] The reagent **15′b** was not described by Sato.[17] In our hands, it did not react with a chiral 2-pyridylimine but added benzaldehyde to give a mixture of (*E*) and (*Z*)-4-alkoxy-1-phenyl-3-propen-1-ol.

in the linear diamines obtained. Only moderate control of 1,3-asymmetric induction was obtained with the lithium reagents.

Most importantly, all the γ-substituted allylzinc halides reacted with the diimine **4** with complete regioselectivity (γ-addition) and high stereocontrol. The auxiliary-induced and simple diastereoselectivity were generally good, however, the latter was dependent on the nature of the allylic substituent, which in turn affects the geometry of the C=C bond. In these reactions ten diastereomers can be formed, but we generally obtained two main diastereomers, accounting for 80–90% of the crude product. The prevalent diastereomer often had C_2-symmetry, and could be isolated as a crystalline compound with satisfactory to good yield. Only from the γ-ethoxyallylzinc reagent which was prepared from the titanium reagent a C_1-symmetric diamine was mainly obtained, presumably owing to the presence of a titanium(IV) salt.

From the synthetic point of view, these reactions widen the accessibility of 1,2-diamines and especially open a new route to 2,3-diamino-1,4-diols. Moreover, it is possible to exploit the presence of the alkene functions in these useful intermediates. For example, the homoallylic amines are synthetic equivalents of β-amino-carbonyl compounds and β-aminoacids and the 1,7-diene skeleton can be converted to cyclohexene and cyclohexane by transition metal-catalysed or -promoted cyclisation procedures. For example, we have described the reductive cyclozirconation[29] and the ring-closing metathesis[30] reactions of the unsubstituted compounds **5** or **6** (R=H) to 1,2-diamino-4,5-dimethylcyclohexane and -4-cyclohexene with good yield. Similarly, aza-heterocyclic compounds can be constructed by electrophile-mediated aminocyclization reactions. For example, Alexakis has recently reported the synthesis of the 2,2′-bis(pyrrolidine) from **6** (R=H), through a sequence involving the hydroboration of the C=C double bonds.[31] The application of several cyclisation procedures to the substituted 1,7-octadienes herein described is currently under investigation in our laboratory.

4. Experimental

4.1. General conditions

Melting points are uncorrected. Solvents were distilled over the appropriate drying agent in N_2 atmosphere before use: THF (sodium benzophenone ketyl, then $LiAlH_4$), Et_2O (Na, then $LiAlH_4$), *n*hexane (Na), CH_2Cl_2 (P_2O_5). Optical rotations were measured on a digital polarimeter in a 1 dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 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 separations were performed on columns of SiO_2 (Merck, 230–400 mesh) at medium pressure. The following compounds were purchased from Aldrich: *n*BuLi, zinc, zinc dichloride–TMEDA complex, titanium tetraisopropoxide, glyoxal trimeric dihydrate, (*S*)-1-phenylethylamine, TMEDA, acrolein, allyl alcohol, 3,4-dihydro-2*H*-pyran, 2,3-dimethyl-2,3-butandiol, **7a**,**b**, **10a**, **13a**. The 1,2-bis-imine **4** was prepared according to the described procedure.[28] All the organometallic reactions were performed in a flame-dried apparatus under a static atmosphere of dry N_2.

4.2. Preparation of the 3-substituted-2-propenylmetal reagents

4.2.1. Lithium reagents 8a,b and 11a,b. *n*BuLi (1.6 M in hexanes, 9.4 mL, 15 mmol) was slowly added to the solution of TMEDA (2.25 mL, 15 mmol) and the substituted propene (15 mmol) in THF (25 mL) at the indicated temperature: allylbenzene **7a** and 4-allyl-1,2-dimethoxybenzene **7b**, −78 to 0°C; allyl phenyl ether **10a** and allyl tetrahydropyranyl ether **10b**, −30°C. The mixture was then stirred for further 30 min.

4.2.2. Zinc reagents 9a,b and 12a–c. These were prepared by the slow addition of a solution of the $ZnCl_2$–TMEDA complex (3.80 g, 15 mmol) in THF (15 mL) to the previously prepared solutions of the corresponding lithium reagents **8a**,**b** and **11a**,**b** at the same temperature used for the metallation step, and the mixture was stirred for further 30 min.

4.3. Addition of the allylic organometallic reagents 11 and 12 to the 1,2-diimine (4)

To the solution of the allylic organometallic reagent (15 mmol), cooled at −78°C under N_2, was added the solution of the 1,2-diimine **4** (1.32 g, 5 mmol) in dry THF (20 mL) during 30 min. After stirring for 1 h, the mixture was quenched with de-aerated H_2O (10 mL), and the organic phase was extracted with Et_2O (3×20 mL). The collected ethereal phase was dried (Na_2SO_4) and concentrated to leave the crude 1,2-diamine, generally as an oil. The pure diastereomers were then obtained by chromatography on an SiO_2 column eluting with cyclohexane–EtOAc mixtures.

4.3.1. (*E*,*E*)-4(*R*),5(*R*)-Di-[1-(*S*)-phenylethylamino]-1,8-di-(3,4-dimethoxyphenyl)-1,7-octadiene (17′b). This was obtained by reaction of **4** with **8b**; the crude semi-solid compound was crystallised from methanol to give a white crystalline solid: 1.30 g (42%); mp 111–113°C; $[\alpha]_D^{20}$=−56.4 (*c* 0.97, $CHCl_3$); ν_{max} (Nujol) 3328, 3050, 2930, 2841, 1628, 1262, 1010, 902 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34 (d, *J*=6.3 Hz, 6H, CH*Me*), 1.40 (broad, 2H, NH), 2.30 (m, 6H, $CH_2CHCHCH_2$), 3.84 and 3.87 (2s, 12H, OMe), 3.86 (q, *J*=6.3 Hz, 2H, C*H*Me), 5.62 (dt, *J*=16.0, 5.4 Hz, 2H, CH_2CH=CH), 5.82 (d, *J*=16.0 Hz, 2H, CH=C*H*Ar), 6.65–6.79 (m, 6H, Ar), 7.25–7.45 (m, 10H, Ph); ^{13}C NMR (300 MHz): δ 25.4, 34.5, 55.7, 55.9, 56.5, 108.6, 111.0, 118.7, 126.4, 126.7, 127.4, 128.2, 131.01, 146.6, 148.1 and 148.8. Found: C 77.42, H 7.81, N 4.50%; $C_{40}H_{48}N_2O_4$ requires: C 77.38, H 7.79, N 4.51%.

4.3.2. 4(*R*),5(*R*)-Di-[1(*S*)-phenylethylamino]-3(*R*),6(*R*)-diphenyl-1,7-octadiene (18′a). This was obtained by the reaction of **4** with **9a**; the crude solid product was

crystallised from MeOH to give a white crystalline solid: 1.50 g (60%); mp 135–136°C; $[\alpha]_D^{20}=-49.1$ (*c* 0.42, $CHCl_3$); ν_{max} (Nujol) 3358, 3061, 3022, 1599, 1491, 1101, 992 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.05 (d, *J*=6.6 Hz, 6H, CH*Me*), 1.56 (broad, 2H, NH), 2.53 (d, *J*=7.2 Hz, 2H, NCHCHN), 3.25 (m and q, *J*=6.6 Hz, 4H, CHC*H*Ph and NC*H*Me), 4.39 (dd, *J*=1.8, 17.1 Hz, 2H, CH=CH_2), 4.86 (dd, *J*=1.8, 10.2 Hz, 2H, CH=CH_2), 5.89 (dt, *J*=17.1, 10.2 Hz, 2H, C*H*=CH_2), 6.57–6.68 (m, 4H, Ph), 6.98–7.08 (m, 6H, Ph), 7.22–7.42 (m, 10H, Ph). Found: C 86.37; H 8.06, N 5.59%; $C_{36}H_{40}N_2$ requires: C 86.35; H 8.05, N 5.60%.

4.3.3. 4(*R*),5(*R*)-Di-[1(*S*)-phenylethylamino]-3(*R*),6(*S*)-diphenyl-1,7-octadiene (18″a). This compound was not obtained pure. The mother liquor from the crystallisation of **18′a** were concentrated and the residue was chromatographed on a SiO_2 column (cyclohexane–ethyl acetate 20:1); a fraction containing a 1:3 mixture of **18′a/18″a** was obtained and analysed by ^1H NMR, from which the signals of the C_1-isomer **18″a** were identified: δ=0.87 and 1.34 (2d, *J*=6.6 Hz, 6H, CH*Me*), 1.56 (broad, 2H, NH), 2.08 and 2.66 (2d, *J*=8.4, 9.6 Hz, 2H, NCHCHN), 2.88 and 3.78 (2 q, *J*=6.6 Hz, 2H, NC*H*Me), 3.01 (m, 2H, C*H*Ph), 3.87 (dd, *J*=1.8, 17.1 Hz, 1H, CH=CH_2), 4.58 (dd, *J*=1.8, 10.2 Hz, 1H, CH=CH_2), 4.95 (dd, *J*=1.8, 10.2 Hz, 1H, CH=CH_2), 5.04 (dd, *J*=1.8, 17.1 Hz, 1H, CH=CH_2), 5.32 (dt, *J*=17.1, 10.2 Hz, 1H, C*H*=CH_2), 6.10 (dt, *J*=17.1, 10.2 Hz, 1H, C*H*=CH_2), 6.16–6.24 and 6.65–6.89 (2m, 4H, Ph), 7.0–7.40 (m, 16H, Ph).

4.3.4. 4(*R*),5(*R*)-Di-[1(*S*)-phenylethylamino]-3(*R*),6(*R*)-di-(3,4-dimethoxyphenyl)-1,7-octadiene (18′b). This was obtained by reaction of **4** with **9b** and chromatography of the crude product on a SiO_2 column (cyclohexane–ethyl acetate 15:1), followed by crystallisation of the main semi-solid product from methanol: white crystalline solid, 1.02 g (33%); mp 118–119°C; $[\alpha]_D^{20}=-51.3$ (*c* 0.83, $CHCl_3$); ν_{max} (Nujol) 3313, 3072, 2922, 1592, 1516, 1464, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.15 (d, *J*=6.6 Hz, 6H, CH*Me*), 1.57 (broad, 2H, NH), 2.49 (d, *J*=6.0 Hz, 2H, NCHCHN), 3.30 (dd, *J*=6.0, 9.6 Hz, 2H, NCHC*H*Ar), 3.51 (q, *J*=6.6 Hz, 2H, C*H*Me), 3.60 and 3.78 (2s, 12H, OMe), 4.60 (dd, *J*=1.5, 17.1 Hz, 2H, CH=CH_2), 4.92 (dd, *J*=2.1, 10.2 Hz, 2H, CH=CH_2), 5.84 (dt, *J*=10.2, 17.1 Hz, 2H, C*H*CH_2), 5.97 (d, *J*=8.1 Hz, 2H, Ar), 6.04 (s, 2H, Ar), 6.41 (d, *J*=8.1 Hz, 2H, Ar), 7.18–7.42 (m, 10H, Ph). Found: C 77.40, H 7.80, N 4.50%; $C_{40}H_{48}N_2O_4$ requires: C 77.38, H 7.79, N 4.51%.

4.3.5. 4(*R*),5(*R*)-Di-[1(*S*)-phenylethylamino]-3(*R*),6(*S*)-di-(3,4-dimethoxyphenyl)-1,7-octadiene (18″b). This compound was not obtained pure; the ^1H NMR spectrum of a chromatographic fraction containing a 1:2 mixture of **18′b** and **18″b** showed the following signals attributed to **18″b**: δ=0.94 and 1.33 (2d, *J*=6.6 Hz, CH*Me*), 2.12 and 2.64 (2 d, *J*=8.5 Hz).

4.3.6. 3(*R*),6(*R*)-Diphenoxy-4(*S*),5(*S*)-di-[1(*S*)-phenylethylamino]-1,7-octadiene (19′). This was obtained by reaction of **4** with **12a**, chromatography of the crude product (SiO_2 column, cyclohexane–ethyl acetate 40:1), formation of the dihydrochloride (gaseous HCl, Et_2O), crystallisation (MeOH) and basic treatment: yellowish oil, 0.82 g (31%); $[\alpha]_D^{20}=-25.4$ (*c* 0.52, $CHCl_3$); ν_{max} (liquid film) 3346, 3026, 2959, 1596, 1494, 1239, 1110, 1002 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.29 (d, *J*=6.6 Hz, 6H, CH*Me*), 1.87 (broad, 2H, NH), 2.89 (d, *J*=5.2 Hz, 2H, NCHCHN), 3.91 (q, *J*=6.6 Hz, 2H, C*H*Me), 4.62 (t, *J*=3.4 Hz, 2H, CHO), 5.14 (dt, *J*=7.6, 1.4 Hz, 2H, CH=CH_2), 5.21 (broad s, 2H, CH=CH_2), 5.79 (ddd, *J*=5.4, 11.1, 16.8 Hz, 2H, C*H*=CH_2), 6.65–6.76 (m, 4H, OPh), 6.85–6.98 (m, 2H, OPh), 7.12–7.35 (m, 14H, Ph and OPh). Found: C 81.18, H 7.56, N 5.25%; $C_{36}H_{40}N_2O_2$ requires: C 81.16, H 7.57, N 5.26%.

19′-2HCl: mp 211–212°C (dec.); $[\alpha]_D^{20}=+59.8$ (*c* 0.54, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.65 (broad, NH), 1.96 (d, *J*=7.0 Hz, 6H, CH*Me*), 3.50 (d, *J*=8.4 Hz, 2H, NCHCHN), 4.67 (q, *J*=7.0 Hz, 2H, C*H*Me), 5.32 (dd, *J*=4.8, 8.2 Hz, 2H, CH=CH_2), 5.67 (dd, *J*=3.0, 8.2 Hz, 2H, CH=CH_2), 5.94 (m, 4H, OC*H*C*H*=CH_2), 6.58 (d, *J*=8.2 Hz, 8H, OPh), 6.79–7.35 (m, 12H, OPh and Ph), 7.52 (d, *J*=7.4 Hz, 4H, Ph), 10.5 and 11.3 (2 broad s, 2H, NH).

A C_2-symmetric isomer, presumably **19″**, was present in the product prior to crystallisation; the ^1H NMR signals differed from those of **19′** only for NCHCHN (δ=3.06: d, *J*=6.6 Hz) and two *ortho*-phenol protons (δ=6.80: d, *J*=7.0 Hz).

4.3.7. (*Z*,*Z*)-1,8-Diphenoxy-4(*R*),5(*R*)-di-[1(*S*)-phenylethylamino]-1,7-octadiene (20). This was obtained by chromatography, being eluted after **19**, and was ca. 90% pure by ^1H NMR analysis, which revealed an unidentified impurity: yellowish oil, 0.132 g (5%); ^1H NMR (300 MHz, $CDCl_3$): δ=1.29 (d, *J*=6.6 Hz, 6H, CH*Me*), 1.62 (broad, 2H, NH), 2.22–2.45 (m, 6H, $CHCH_2$), 3.88 (q, *J*=6.6 Hz, 2H, C*H*Me), 4.39–4.50 (m, 2H, CH_2C*H*=CH), 6.26 (d, *J*=6.0 Hz, 2H, CH=C*H*O), 6.87–6.98 (m, 4H, OPh), 7.0–7,09 (m, 2H, OPh), 7.13–7.37 (m, 14H, OPh and Ph).

4.3.8. (*Z*)-1,6(*R*)-Diphenoxy-4(*R*),5(*S*)-di-[1(*S*)-phenylethylamino]-1,7-octadiene (21). This was eluted after **20**: yellowish oil, 0.61 g (23%), ca. 85% pure by ^1H NMR analysis; ^1H NMR (300 MHz, $CDCl_3$): δ=1.24, 1.28 (2d, *J*=6.6 Hz, 6H, CH*Me*), 1.76 (broad, 2H, NH), 2.22–2.35 and 2.41–2.60 (2m, 2H, $CHCH_2$), 2.85–2.96 (m, 2H, NCHCHN), 3.82 and 3.88 (2 q, *J*=6.6 Hz, 2H, C*H*Me), 4.58–4.68 (m, 1H, CH_2C*H*=CHO), 4.72–4.81 (m, 1H, CH_2=CHC*H*O), 5.11–5.28 (m, 2H, CH=CH_2), 5.71–5.93 (m, 1H, C*H*=CH_2), 6.41 (d, *J*=6.0 Hz, 1H, CH=C*H*OPh), 6.71 (d, *J*=8.4 Hz, 2H, OPh), 6.81–6.98 (m, 4H, OPh), 7.11–7.42 (m, 14H, OPh and Ph).

4.3.9. 3(*R*),6(*R*)-Dihydroxy-4(*S*),5(*S*)-di-[1(*S*)-phenylethylamino]-1,7-octadiene (22′). This was obtained by reaction of **4** with **12b** and crystallisation of the crude product from methanol: white crystalline solid, 0.91 g (48%); mp 153–155°C; $[\alpha]_D^{20}=-184.3$ (*c* 0.73, $CHCl_3$); ν_{max} (Nujol) 3500–3100 (broad), 3324, 2923, 1616, 1456, 1121, 1077 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.47 (d, *J*=6.6 Hz, 6H, CH*Me*), 2.51 (d, *J*=2.2 Hz, 2H, NCHCHN), 3.96 (q, *J*=6.6 Hz, 2H, C*H*Me), 4.40–4.50 (m, 2H, CHO), 4.65–4.88 (3m, 4H, CH=CH_2), 5.09 (ddd, *J*=3.6, 10.2, 14.6 Hz, 2H, C*H*=CH_2), 7.15–7.42 (m, 10H, Ph); ^{13}C

NMR (200 MHz, $CDCl_3$): δ=24.2, 54.6, 55.9, 71.9, 114.8, 127.7, 128.5, 138.8, 142.6. Uncoloured crystals suitable for X-ray analysis were obtained by slow re-crystallisation from MeOH. Found: C 75.23, H 8.50, N 7.35%; $C_{24}H_{23}N_2O_2$ requires: C 75.25, H 8.48, N 7.36%.

4.3.10. 3(*R*),6(*S*)-Dihydroxy-4(*S*),5(*S*)-di-[1(*S*)-phenylethylamino]-1,7-octadiene (22″). This was obtained from the mother liquor coming from the crystallisation of **22′**, by solvent evaporation and chromatography (SiO_2, cyclohexane–ethyl acetate 10:1): yellowish oil, 0.24 g (12%); ca. 95% pure by ^1H NMR analysis; ^1H NMR (200 MHz, $CDCl_3$): δ=1.32, 1.42 (2d, *J*=6.6 Hz, 6H, CH*Me*), 2.18 and 2.80 (2m, 2H, NCHCHN), 3.79–3.84 and 4.22–4.33 (2m, 2H, CHO), 4.0 and 4.07 (2q, *J*=6.6 Hz, 2H, C*H*Me), 4.54–4.68 (m, 2H, CH=CH_2), 4.86 (ddd, *J*=5.6, 11.2, 16.4 Hz, 1H, C*H*=CH_2), 5.11 (dt, *J*=10.6, 2.2 Hz, 1H, CH=CH_2), 5.37 (dt, *J*=17.2, 1.8 Hz, 1H, CH=CH_2), 5.93 (ddd, *J*=4.0, 10.6, 17.2 Hz, 1H, C*H*=CH_2), 7.16–7.42 (m, 10H, Ph); ^{13}C NMR (200 MHz, $CDCl_3$): δ=23.4, 24.5, 54.7, 56.2, 56.3, 61.7, 72.0, 75.5, 126.9, 127.4, 127.5, 127.6, 127.9, 128.1, 128.3, 128.6, 138.8, 139.5, 143.0, 143.4.

4.3.11. Preparation of 3(*R*),6(*R*)-diethoxy-4(*S*),5(*S*)-di-[1(*S*)-phenylethylamino]-1,7-octadiene (23). *i*PrMgCl (2 M in Et_2O, 15 mL, 30 mmol) was slowly added to the stirred solution of acrolein diethyl acetal (1.95 g, 15 mmol) and titanium(IV) isopropoxide (4.16 g, 15 mmol) at −60°C. The mixture was further stirred for 2 h at −50°C, then a solution of anhydrous $ZnBr_2$ (5.06 g, 22.5 mmol) in THF (30 mL) was added. After stirring for 1 h at −50°C, the mixture was cooled to −78°C and the diimine **4** (1.32 g, 5 mmol), dissolved in THF (10 mL) was slowly added. The temperature was allowed to reach 0°C during 2 h, then the mixture was quenched with 30% NH_4OH and 1 M NH_4Cl (1:1, 30 mL). After usual work-up, column chromatography of the crude oily product eluting with cyclohexane–ethyl acetate (20:1) gave **23** as a yellowish oil: 1.00 g (45%); $[\alpha]_D^{20}$=−46.3 (*c* 0.76, $CHCl_3$); ν_{max} (liquid film) 3330, 2972, 1610, 1452, 1368, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=0.92 and 1.17 (2 t, *J*=6.9 Hz, 6H, CH_2CH_3), 1.23 and 1.32 (2d, *J*=6.6 Hz, 6H, $CHCH_3$), 1.69 (broad s, 2H, NH), 2.22 (dd, *J*=2.0, 6.6 Hz, 1H, NCHCHN), 2.52 (m, 2H, OCH and NC*H*CHN), 3.20 (m, 2H, OCH_2), 3.44 (m, 3H, OCH and OCH_2), 3.80 and 4.07 (2q, *J*=6.6 Hz, 2H, C*H*Me), 4.36 (dd, *J*=1.3, 17.1 Hz, 1H, CH=CH_2), 4.86 (dd, *J*=1.3, 10.2 Hz, 1H, CH=CH_2), 5.02–5.20 (m, 2H, CH=CH_2), 5.40 and 5.62 (2ddd, *J*=7.1, 10.2, 17.1 Hz, 2H, C*H*=CH_2), 7.08–7.43 (m, 10H, Ph); MS *m/z* (relative intensity) 105 (100), 218 (M^+/2, 63), 57 (33), 161 (31), 351 (29), 114 (25), 266 (21). Found: C 77.0, H 9.25, N 7.32%; $C_{28}H_{40}N_2O_2$ requires: C 77.02, H 9.23, N 7.33%.

4.4. X-Ray structure determinations

X-Ray diffraction data for **18′a** were collected on a Bruker AXS SMART diffractometer. X-Ray data for **19′**-2HCl and **22′** were carried out on a NONIUS CAD-4 diffractometer. Both diffractometers equipped with a graphite monochromator (Mo Kα radiation, λ=0.71073 Å). SHELXS-97[32] and SHELXL97[32] were used for structure solution and refinement based on F^2. SCHAKAL979[33] was used for the graphical representation of the results. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC no. 186718–186720. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Crystal data for **18′a**: $C_{36}H_{40}N_2$, *T*=293(2) K, *M*=500.70, Monoclinic, $P2_1$, *a*=12.0298(8), *b*=15.0517(10), *c*=17.4652(9) Å, β=104.899(2)°, *V*=3056.1(3) $Å^3$, *Z*=4, μ(Mo Kα)=0.063 mm^{-1}, D_c=1.088 Mg m^{-3}, 19,676 reflections collected, 12,134 independent refections, R_1 ($I>2\sigma(I)$)=0.0695, wR_2 (F^2, all refls.)=0.2230, 587 parameters.

Crystal data for **19′**-2HCl: $C_{36}H_{42}Cl_2N_2O_2$, *T*=293(2) K, *M*=380.52, Monoclinic, $P2_1$, *a*=10.117(4), *b*=9.554(4), *c*=17.591(6) Å, β=95.99(3)°, *V*=1691(1) $Å^3$, *Z*=2, μ(Mo Kα)=0.225 mm^{-1}, D_c=1.189 g cm^{-3}, 3240 reflections collected, 3136 independent refections, R_1 ($I>2\sigma(I)$)=0.0648, wR_2 (F^2, all refls.)=0.2976, 332 parameters.

Crystal data for **22′**: $C_{24}H_{32}N_2O_2$, *T*=293(2) K, *M*=380.52, monoclinic, *C*2, *a*=22.035(6), *b*=6.767(4), *c*=7.636(9) Å, β=97.09(3)°, *V*=1129.9(9) $Å^3$, *Z*=2, μ(Mo Kα)=0.071 mm^{-1}, D_c=1.118 Mg m^{-3}, 1157 reflections collected, 1073 independent reflections, R_1 ($I>2\sigma(I)$)=0.0615, wR_2 (F^2, all refls.)=0.2166, 125 parameters.

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