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Stereoselective synthesis of substituted 1,2-ethylenediaziridines and their use as ligands in palladium-catalyzed asymmetric allylic alkylation

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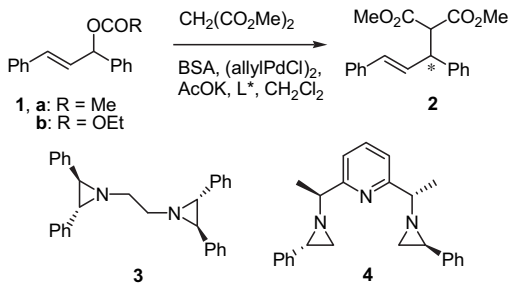
ABSTRACT

The double addition of organometallic reagents to fused oxazino-oxazines prepared from glyoxal and (*S*)-phenylglycinol afforded C_2- or C_1-symmetric 1,2-ethylenebis(β-aminoalcohols), depending on the nature of the organometallic reagent. This route was modified by the use of (*S*)-valinol and phenylglyoxal as starting materials, and by reduction of the oxazino-oxazines by diborane. Cyclization of the β-aminoalcohol moieties gave 1,2-ethylenediaziridines bearing one substituent/stereocenter on the ring carbon and one, two or no substituents/stereocenters in the ethylene tether. These bis(aziridines) were used as ligands in the Pd-catalyzed allylic alkylation of dimethyl malonate. It was established that the substituent(s) in the carbon tether and the configuration of the corresponding stereocenters have limited influence on the enantioselectivity.

1. Introduction

Chiral non-racemic 1,2-diamines are valuable auxiliaries and ligands in asymmetric synthesis and metal-mediated enantioselective catalysis.[1] Among them, bis(aziridines) have found only a limited number of applications. Tanner and Andersson reported the preparation of bis(aziridines) starting from enantiopure stilbene epoxide and used them in a number of asymmetric transformations.[2] The best results were obtained in the palladium-catalyzed asymmetric allylic alkylation (AAA) of dimethyl malonate with the allylic acetate **1a**, affording the product (*S*)-**2** with complete stereocontrol when the bis(aziridine) **3** was used in a sub-stoichiometric amount (Scheme 1).[3] Less satisfactory results were obtained in cyclopropanation, aziridination, and dihydroxylation of alkenes and in the addition of organolithium reagents to imines.[2] More recently, we have described the diastereoselective synthesis of pyridine-aziridines and pyridine-diaziridines by a short route involving: (a) organometallic additions to the imines derived from 2-pyridinecarboxyaldehyde and 2,6-pyridinedicarboxyaldehyde and enantiopure β-amino-alcohols; (b) Mitsunobu cyclization of the two β-aminoalcohol moieties.[4] In particular, we obtained the compound (*R*)-**2** with 99% ee from the allylic carbonate **1b** using the bis(aziridine) **4** as the ligand.[4d]



Scheme 1. Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate using bis(aziridines) as ligands.

The ligands **3** and **4** differ for their skeleton and the substitution pattern either in the aziridine rings and the tether linking the nitrogen atoms. Whereas the ligand **3** has C_2-symmetric 2,3-disubstituted aziridine rings and no substituent/stereocenter in the ethylene tether, the ligand **4**, although being C_2-symmetric, features mono-substituted aziridine rings and two substituents/stereocenters in the 2,6-dimethynepyridine tether. The lack of C_2-symmetry of the aziridine rings in **4** can affect the configuration of the nitrogen atoms in the catalytically active (η3-allylic)L*Pd$^+$ species, where the metal is involved in bidentate chelation to the pyridine and one of the aziridine nitrogen atoms. However, homochirality was observed in all the crystal structures of the cationic η3-allylic complexes we prepared from several ligands analogous to **4**: as a matter of fact, all the Pd-coordinated aziridine nitrogen atoms had the same configuration, the one allowing to reduce the steric interactions of the benzylic and

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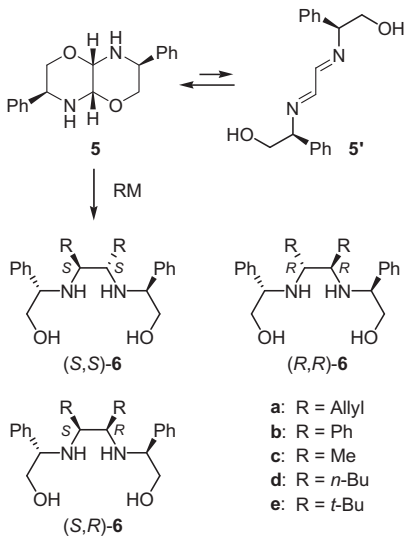
aziridine substituents. Moreover, the aziridine analogous to **4** but lacking a substituent at the tether methine carbons displayed minor enantioselectivity. From this stereochemical outcome, we deduced that the substituents/stereocenters in the tether were necessary to achieve the best level of stereocontrol.

Considering the simplicity and the convenience of the synthetic route to bis(aziridines) from di(aldimines), we envisioned the possibility to prepare C_2-symmetric ligands analogous to **3**, i.e., having the same skeleton but a different substitution pattern, and then investigate their enantioselectivity in the AAA reaction.

Glyoxal and optically pure β-aminoalcohols are the required starting material for the envisioned route.[5,6] The reactions of 1,2-dicarbonyl compounds including glyoxal with diversely *C*- and *N*-substituted β-aminoalcohols gave fused oxazino-oxazines or 2,2′-bis(oxazolidines) or other products, depending on the solvent and experimental conditions used.[5] In particular, the reaction with phenylglycinol afforded a fused oxazino-oxazine **5**, rather than the open chain, 1,2-diimine tautomer **5′**, as confirmed by X-ray crystal diffraction studies.[7] Our first studies were directed to the addition of organometallic reagents to compound **5** (Scheme 2).[8,9]



Scheme 2. Addition of organometallic reagents to the oxazino-oxazine **5** derived from glyoxal and (*S*)-phenylglycinol.

2. Results and discussion

We prepared the known compound **5**[7] by a modified procedure, i.e., by treatment of glyoxal trimer dihydrate with a stoichiometric amount of (*S*)-phenylglycinol in dichloromethane at room temperature in the presence of magnesium sulfate. ^{1}H NMR spectroscopic analysis of the crude compound showed the presence of only one diastereomer and some unreacted (*S*)-phenylglycinol. The compound **5** was then obtained pure by crystallization from methanol. Then, we carried out the addition of different organometallic reagents in order to check their reactivity and diastereoselectivity. In principle, three diastereomers could be formed by the double organometallic addition, having *S*,*S*-, *R*,*R*- and *R*,*S*-configuration of the newly formed stereocenters. The results of the performed reactions are reported in Table 1. In the first experiment carried out with allylzinc bromide, the desired 1,2-diallylated 1,2-diamine **6a** was obtained with high yield and high diastereoselectivity (entry 1). The main diastereomer was easily isolated from the crude reaction mixture by crystallization from methanol, and its C_2-symmetry was apparent in the ^{1}H NMR spectrum. Recrystallization from methanol allowed the separation of crystals suitable for X-ray structure determination (Fig. 1), which showed the *S* configuration of the newly formed stereocenters. The

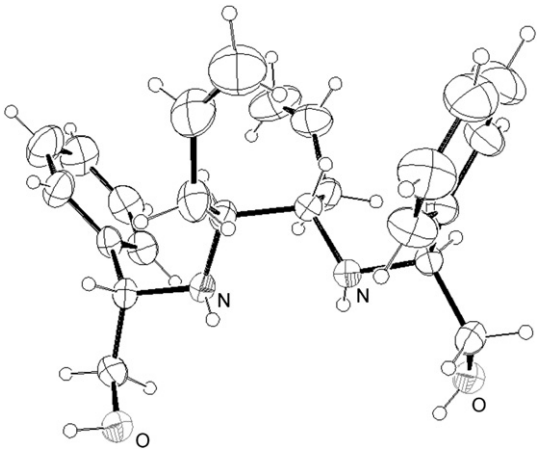


Figure 1.

Table 1
Organometallic reactions[a] and borane-dimethylsulfide reduction[b] of oxazino-oxazines and preparation of 1,2-ethylenediaziridines from bis(β-aminoalcohols)[c]

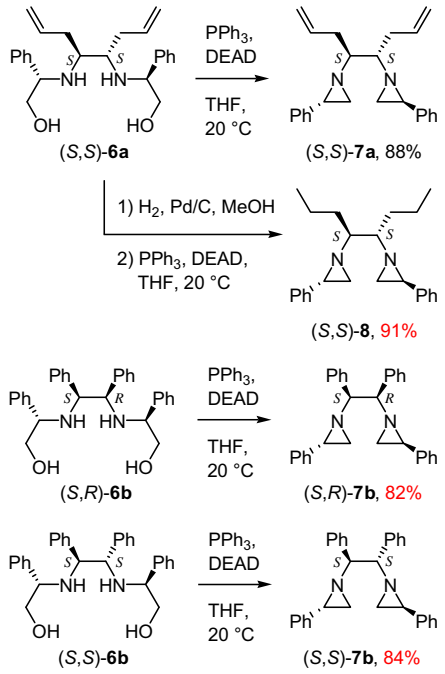
Entry	Starting compound	Reagent	Crude product	Yield (%), dr[d] (%)	Pure products, Yield (%)[e]	Bis(aziridines), Yield (%)[e]
1	**5**	AllylZnBr	**6a**	91, 80:20	(*S*,*S*)-**6a**, 68	(*S*,*S*)-**7a**, 88 (*S*,*S*)-**8**, 91[f]
2	**5**	PhMgBr	**6b**	87, 85:15	(*S*,*R*)-**6b**, 72 (*S*,*S*)-**6b**, 9	(*S*,*R*)-**7b**, 82
3	**5**	PhLi[g]	**6b**	95, 73:27	(*S*,*R*)-**6b**, 64 (*S*,*S*)-**6b**, 22	(*S*,*R*)-**7b**, 82 (*S*,*S*)-**7b**, 84
4	**5**	MeLi	**6c**	91[h]		
5	**5**	*n*-BuLi	**6d**	90, 54:46[i]		
6	**5**	*t*-BuLi	**6e**	97[h]		
7	**5**	BH3-SMe2	**9**[j]	74		**10**, 68
8	**11**	BH3-SMe2	**12**[j]	88, 100:0		(*R*)-**13**, 78
9	**14**	PhMgBr	**15**	93, 95:5	(*S*,*S*)-**15**, 69	(*S*,*S*)-**16**, 81

[a] The reactions were performed by adding the organometallic reagent (6 M equiv) to the compound **5** dissolved in THF at −78 °C while stirring and allowing the temperature to reach 20 °C overnight.
[b] Borane-dimethylsulfide (4 M equiv) was added to the stirred solution of compound **5** in THF and the mixture was stirred at the reflux temperature during 8 h.
[c] Compound **6** dissolved in THF was treated with a 40% toluene solution of DEAD and then with triphenylphosphine (2.2 M equiv each).
[d] The dr was determined by GC–MS or ^{1}H NMR spectroscopic analysis of the crude product.
[e] After column chromatography.
[f] Overall yield after hydrogenation and cyclization steps.
[g] The reaction was performed in Et_2O.
[h] A complex mixture of products was obtained and no compound could be isolated in a pure state by column chromatography.
[i] The diastereomers could not be separated by column chromatography (SiO_2).
[j] The compound was not purified.

stereochemical outcome is in agreement with the sense of asymmetric induction observed in the allylation of the 2-pyridineimines derived from (*S*)-valinol and (*S*)-phenylglycinol.

Surprisingly, much lower diastereoselectivity was observed in the addition of either phenylmagnesium chloride and phenyllithium to **5**. Two main diastereomers were observed by ^{1}H NMR spectroscopy of the crude products coming from both reactions and the prevalent one lacked C_2-symmetry. Consequently the (*R*,*S*)-configuration of the tether stereocenters was assigned. This was surprising since in all the organometallic reactions of chiral 1,2-diimines reported so far, the (*R*,*S*)-diastereomer was by far the less abundant one, if ever observed.[5] Moreover, poor diastereoselectivities and/or complex reaction mixtures were obtained in the addition of methyl-, *n*-butyllithium and *t*-butyllithium to compound **5**.

The 1,2-disubstituted-1,2-ethylenediaziridines (*S*,*S*)-**7a**, (*S*,*R*)-**7b**, and (*S*,*S*)-**7b** were prepared with good yields from the corresponding bis(β-aminoalcohols) (*S*,*S*)-**6a**, (*S*,*R*)-**6b**, and (*S*,*S*)-**6b**, respectively, by treatment with triphenylphosphine and diethyl azodicarboxylate (DEAD) and were purified by column chromatography (Scheme 3). The dipropyl-substituted bis(aziridine) (*S*,*S*)-**8** was similarly obtained by hydrogenation of the unsaturated chains of the precursor (*S*,*S*)-**6a**.



Scheme 3. Synthesis of C_2- and C_1-symmetric 1,2-ethylenediaziridines from bis(β-aminoalcohols).

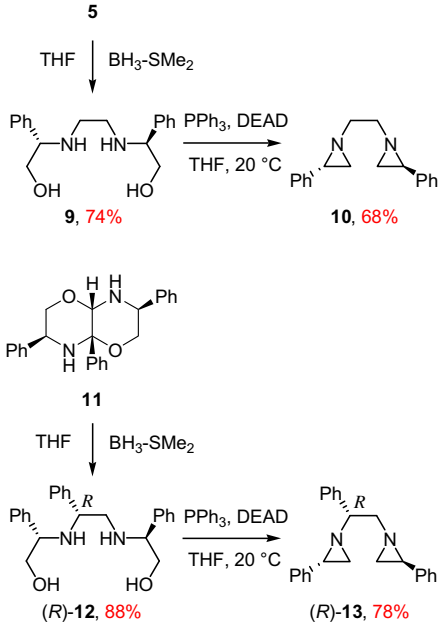
The bis(aziridine) bearing different substituents and stereochemistry in the tether were used as ligands[10] in the standard Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate with ethyl 1,3-diphenyl-3-propen-1-yl carbonate **1b** leading to compound **2**. When the allyl-substituted ligand (*S*,*S*)-**7a** was used, the product **2** was obtained with moderate yield (69%) and enantiomeric excess (55%) (Table 2, entry 1). The corresponding saturated compound (*S*,*S*)-**8** gave better performance (70% ee, entry 2). Then, the ee of **2** raised to 91% when the reaction was carried out with the phenyl-substituted ligand (*S*,*S*)-**7b** (entry 3). On the other hand, using (*S*,*R*)-**7b** a lower level of enantioselectivity (85% ee, entry 4) was obtained. This outcome is in agreement with the hypothesis that the C_2-symmetry of the chiral tether enables a better/complete control of the configuration of the nitrogen stereocenters in the intermediate Pd cationic complexes when the aziridine rings are mono-substituted.

Table 2
Asymmetric allylic alkylation of dimethyl malonate using bis(aziridines) as ligands.[a]

Entry	Bis(aziridine)	Yield (%) of **2**	Configuration	ee[b] (%)
1	(*S*,*S*)-**7a**	69	*R*	55
2	(*S*,*S*)-**8**	88	*R*	70
3	(*S*,*S*)-**7b**	86	*R*	91
4	(*S*,*R*)-**7b**		*R*	85
5	**10**	76	*R*	92
6	(*R*)-**13**	86	*R*	82
7	(*S*,*S*)-**16**	91	*R*	86

[a] The reactions were performed in CH_2Cl_2 at room temperature: 0.24 mmol of carbonate **1b**, 0.60 mmol of dimethyl malonate, 0.72 mmol of BSA and 0.01 mmol of $[(allyl)PdCl]_2$.
[b] The ee was determined by HPLC analysis of the crude product on Chiralpak AD column (*n*-hexane:*i*-PrOH 90:10, 1 mL/min, λ 254 nm).

That supposition was later confirmed by the experiments carried out with two newly synthesized aziridines (Scheme 4). The first one, **10**, lacking substituents in the tether, was easily prepared with 50% overall yield by borane reduction of **5** to give **9**, followed by Mitsunobu cyclization. The other one, (*R*)-**13**, was obtained as a single diastereomer by a similar sequence starting from the oxazino-oxazine **11** derived from phenylglyoxal and (*S*)-phenylglycinol through the intermediate (*R*)-**12**. The structure and hence the configuration of the newly formed stereocenters in compound **11** was determined by X-ray crystallography (Fig. 2). The (*R*)-configuration of compound **13** was assumed considering that the reduction of chiral ketimines generally occurs with opposite diastereoselectivity with respect to the organometallic addition to the corresponding chiral aldimines. Successively, we confirmed the correctness of this hypothesis by an alternative synthesis of (*R*)-**13** exploiting (*R*)- and (*S*)-phenylglycinol without affecting the configuration of the stereocenters .[11] Unexpectedly, the ligand **10**, despite lacking stereocenters in the tether, gave the best level of enantioselectively (92% ee, Table 2, entry 5) in the formation of the substituted malonate **2**, and also the ligand (*R*)-**13**, having the opposite configuration of the phenyl-substituted stereocenter in the tether with respect to (*S*,*S*)-**5b**, gave a good performance maintaining the same sense of asymmetric induction (82% ee, entry 6).



Scheme 4. Synthesis of 1,2-ethylenediaziridines unsubstituted and mono-substituted in the ethylene tether linking the nitrogen atoms.

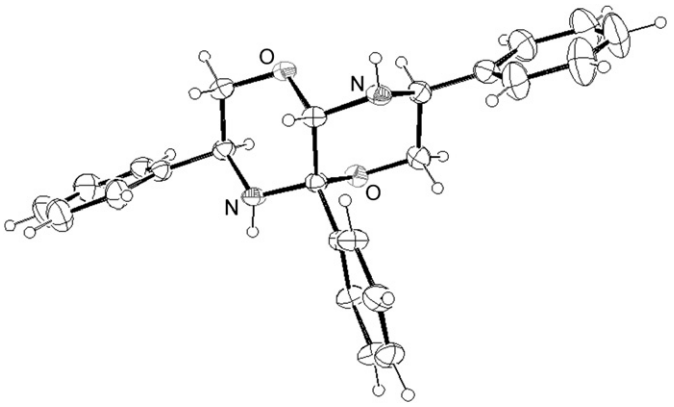
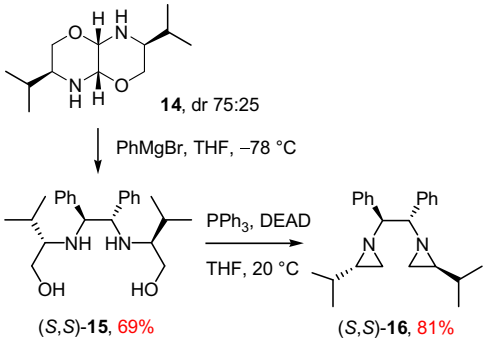


Figure 2.

Finally, we investigated the importance of steric properties of the aziridine substituent on the enantioselectivity of the AAA reaction. This was achieved by using a different 2-aminoalcohol in the initial step. Eventually, we prepared the diaziridine (*S*,*S*)-**16** by the same reactions sequence previously described, from the fused oxazino-oxazine **14** derived from glyoxal trimer dihydrate and (*S*)-valinol (Scheme 5).



Scheme 5. Synthesis of the C_2-symmetric bis(aziridine) (*S*,*S*)-**16** from the oxazino-oxazine **14** derived from (*S*)-valinol.

The ^{1}H NMR spectroscopy and GC–MS analyses of the crude product showed it was a 3:1 mixture of two diastereoisomers, both having C_2-symmetry, as was shown by the absorptions of the aminoacetal (*N*–CH–O) protons, which appeared as a singlet for both diastereoisomers. Separation of the diastereomers proved to be difficult, so that their mixture was used in reaction with phenylmagnesium chloride. Surprisingly, this reaction cleanly afforded the C_2-symmetric product (*S*,*S*)-**17** with very high diastereoselectivity (dr 95:5 by ^{1}H NMR spectroscopy), in marked contrast to the corresponding reaction of oxazino-oxazine **5**. Avoiding separation of the diastereomers, the ring-closure to bis(aziridine) occurred without event by the routine procedure, and the pure diastereomer (*S*,*S*)-**16** was isolated by column chromatography. The AAA of dimethyl malonate with the carbonate **1b** and the ligand (*S*,*S*)-**16** again gave compound **2** with an enantioselectivity falling in the usual range (86% ee), although slightly lower to that displayed by (*S*,*S*)-**7b** (entry 7).

3. Conclusions

The study herein described on the AAA of dimethyl malonate using a number of 1,2-ethylenediaziridines has demonstrated that the sense of asymmetric induction and the degree of enantioselectivity is mainly controlled by the chirality and the substitution pattern of the aziridine rings, and only to a limited extent by the presence of substituents and the relative chirality in the ethylene tether linking the nitrogen atoms. Up to 92% ee has been achieved using the bis(aziridine) bearing only one phenyl substituents in both the aziridine rings, that is, only slightly inferior to the optimum enantioselectivity displayed by the previously described analogous ligands. The shortness, simplicity and convenience of the described route make it worth investigating the new ligands in other asymmetric catalytic reactions.

4. Experimental section

4.1. General information

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 Varian Mercury and Gemini instruments 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), *J*-values are given in Hertz. Infrared spectra were recorded on a Nicolet FT-380 spectrometer and IR assignments are reported in wave numbers (cm^{-1}). MS spectra were taken at an ionizing voltage of 70 eV on a Hewlett-Packard 5975 spectrometer with GLC injection (using HP-5 column, 30 m, ID 0.25 mm). Molecular weights were determined on an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck, 230–400 mesh) at medium pressure. All the organic, inorganic and organometallic reagents and anhydrous solvents were purchased from Aldrich. Compounds **5** and **9** were previously described.[7]

4.1.1. Preparation of oxazino-oxazines: general procedure. To a solution of (*S*)-phenylglycinol (0.600 g, 4.4 mmol) in dry CH_2Cl_2 (40 mL) was added anhydrous $MgSO_4$ (3.0 g) and phenylglyoxal monohydrate (0.333 g, 2.2 mmol) and the mixture was stirred overnight. The solid was filtered off through a pad of Celite and the organic phase was concentrated at reduced pressure to leave a pink solid, which was crystallized from Et_2O to give **11** as white powder: 0.781 g (96%): mp=145.8–146.5 °C; $[\alpha]_D^{25}$+100.6 (*c* 1.0, $CHCl_3$); IR (KBr): *v*=3461, 3342, 3023, 2962, 2904, 2860, 1450, 1336, 1176, 1070, 956, 923, 743, 698, 530; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.66–7.69 (m, 2H), 7.25–7.50 (m, 13H), 5.20 (s, 1H), 4.70 m (2H), 4.04 (dd, *J*=3.4, *J*=11.0 Hz, 1H), 3.78 (dd, *J*=3.8, *J*=11.3 Hz, 1H), 3.73 (app. t, *J*=11.0 Hz, 1H), 3.50 (app. t, *J*=11.3 Hz, 1H), 2.21 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=141.8, 140.1, 139.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.4, 125.9, 83.5, 83.0, 72.5, 70.1, 53.8, 52.2; MS (ES) *m*/*z*=373.1 $[M+H]^+$; Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found C, 77.75; H, 6.51; N, 7.50.

Compound **14** was obtained starting from glyoxal trimer dihydrate and (*S*)-valinol in 65% yield: colorless oil; dr 75:25 (GC–MS, ^{1}H NMR); IR (neat): *v*=3335, 2960, 2873, 1466, 1339, 1288, 1184, 1085, 905, 798, 765, 601; MS (ES) *m*/*z*=229.1 $[M+H]^+$; MS (EI) *m*/*z*=114 (100), 127 (58), 84 (45), 69 (27), 185 (13), 197 (9), 167 (6), 228 (1). Major diastereoisomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.26 (s, 2H), 3.92 (dd, *J*=3.1, *J*=10.9, 2H), 3.39 (app t, *J*=10.9, 2H), 2.97 (m, 2H), 2.12 (br s, 2H), 1.44 (m, 2H), 0.92 (d, *J*=6.9, 3H), 0.88 (d, *J*=6.9, 3H). Minor diastereoisomer: ^{1}H NMR (200 MHz, $CDCl_3$), relative signals: δ=4.64 (s, 2H), 3.22 (app t, *J*=10.5, 2H), 1.63 (m, 2H), 1.08 (d, *J*=6.6, 3H). This compound was not purified.

4.1.2. Organometallic additions to oxazino-oxazines: typical procedure. Phenyllithium (0.5 M in Et_2O, 16 mL, 8.0 mmol) was added to a magnetically stirred solution of the oxazino-oxazine **3** (0.918 g, 3.1 mmol) in THF (10 mL) cooled at −78 °C. After 30 min the reaction mixture was slowly warmed up until room temperature was reached and stirring was continued for 24 h. The mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and 30% NH_4OH (10 mL) at 0 °C, then the organic material was extracted with diethyl

ether (3×20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the crude product as yellow oil. Flash column chromatography (SiO_2) eluting with cyclohexane to cyclohexane/ethyl acetate 8:2 mixtures gave the products (*S*,*R*)-**6b** (0.897 g, 64%) and then (*S*,*S*)-**6b** (0.308 g, 22%) as yellow oils.

Compound (*S*,*R*)-**6b**: $[\alpha]D^{25}$ +158.3 (*c* 1.0, $CHCl_3$); IR (neat): *ν*=3425, 3327, 3284, 3074, 3021, 2908, 1455, 1348, 1104, 1027, 918, 756, 699; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.37–7.14 (m, 14H), 7.00 (dd, *J*=1.3, *J*=7.4 Hz, 2H), 6.92 (dd, *J*=3.9, *J*=7.5 Hz, 2H), 6.84 (dd, *J*=2.0, *J*=3.8 Hz, 2H), 3.76 (d, *J*=7.7 Hz, 1H), 3.66 (d, *J*=7.7 Hz, 1H), 3.55–3.43 (m, 3H), 3.40–3.26 (m, 3H), 2.19 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=141.1, 140.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.3, 127.3, 127.1, 66.4, 66.1, 65.3, 64.1, 61.7, 60.9; MS (ES) *m*/*z*=453.2 $[M+H]^+$; Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19. Found C, 79.98; H, 7.15; N, 6.17.

Compound (*S*,*S*)-**6b**: $[\alpha]_D^{25}$ +178.2 (*c* 1.0, $CHCl_3$); IR (neat): *ν*=3428, 3318, 3278, 3079, 3028, 2915, 1451, 1340, 1109, 1028, 915, 758, 699; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.35–7.25 (m, 6H), 7.15–7.10 (m, 10H), 6.91 (dd, *J*=3.6, *J*=7.3 Hz, 4H), 3.64–3.50 (m, 8H), 2.76 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=140.3, 140.0, 128.6, 128.1, 127.9, 127.6, 127.4, 127.1, 67.3, 65.2, 61.3; MS (ES): *m*/*z*=453.2 $[M+H]^+$; Anal. Calcd for $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19. Found C, 79.81; H, 7.15; N, 6.17.

Compound (*S*,*S*)-**6a**: Colorless crystals; mp=93.0–93.9 °C (MeOH); $[\alpha]_D^{25}$ +145.7 (*c* 1.0, $CHCl_3$); IR (KBr): *ν*=3432, 3324, 3264, 3076, 3030, 2928, 1453, 1348, 1106, 1022, 915, 756, 699; ^{1}H NMR (200 MHz, $CDCl_3$): *δ*=7.46–7.23 (m, 10H), 5.66–5.43 (m, 2H), 5.00–4.82 (m, 4H), 3.80 (dd, *J*=4.1, *J*=9.0 Hz, 2H), 3.66 (dd, *J*=4.3, *J*=10.4 Hz, 2H), 3.51 (dd, *J*=9.0, *J*=10.4 Hz, 2H), 2.37 (m, 2H), 2.27–2.03 (m, 4H), 2.01 (br s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ*=140.8, 134.9, 128.6, 127.6, 117.0, 67.1, 62.3, 56.0, 34.2; MS (ES): *m*/*z*=381.2 $[M+H]^+$; Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found C, 75.70; H, 8.50; N, 7.33.

Compound (*S*,*S*)-**15**: $[\alpha]_D^{25}$ +198.6 (*c* 1.0, $CHCl_3$); IR (neat): *ν* 3412, 3305, 3081, 3056, 3023, 2954, 2921, 2868, 1467, 1454, 1389, 1364, 1103, 1042, 907, 731, 691; ^{1}H NMR (200 MHz, $CDCl_3$): *δ*=7.30–7.39 (m, 2H), 7.02–7.18 (m, 8H), 3.75 (s, 2H), 3.40 (dd, *J*=4.3, *J*=10.6 Hz, 2H), 3.27 (dd, *J*=8.0, *J*=10.6 Hz, 2H), 2.56 (br s, 4H), 2.36 (dd, *J*=4.0, *J*=4.3, *J*=8.0 Hz, 2H), 1.86–2.01 (m, 2H), 0.91 (d, *J*=7.0 Hz, 12H); ^{13}C NMR (50 MHz, $CDCl_3$); *δ*=141.4, 128.0, 127.7, 126.9, 67.3, 61.4, 61.2, 28.2, 19.2, 17.3; MS (ES): *m*/*z*=385.1 $[M+H]^+$; Anal. Calcd for $C_{24}H_{36}N_2O_2$: C, 74.96; H, 9.44; N, 7.28. Found C, 75.11; H, 9.40; N, 7.26.

4.1.3. Reduction of oxazino-oxazines by $BH_3 \cdot SMe_2$. To a solution of **11** (0.150 g, 0.4 mmol) in dry THF (15 mL) was added BH_3–SMe_2 (0.153 μL, 0.123 g, 1.6 mmol) and the mixture was heated at the reflux temperature for 8 h. Water (5 mL), was slowly added at 0 °C and the solvent was removed at reduce pressure. Water (10 mL) was again added and the organic material was extracted with CH_2Cl_2 (3×20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to leave (*R*)-**12** as a yellow oil: 0.132 g (88%). Similarly, **9** was prepared from **5** in 74% yield. The β-aminoalcohols **9** and (*R*)-**12** were used in the next step avoiding purification.

Compound (*R*)-**12**: ^{1}H NMR (200 MHz, $CDCl_3$): *δ*=7.05–7.20 (m, 15H), 3.61–3.84 (m, 7H), 3.01 (br s, 4H), 2.82 (m, 2H).

4.1.4. Preparation of 1,2-ethylenediaziridines: typical procedure. To a solution of the aminoalcohol (*S*,*R*)-**6b** (0.150 g, 0.3 mmol) in THF (20 mL) was added PPh_3 (0.191 g, 0.73 mmol) and then DEAD (40% solution of in toluene, 0.668 mL, 0.73 mmol) dropwise. After stirring for 24 h, 2 M aq KOH (10 mL) was added and the mixture was stirred for 1 h. The organic material was extracted with diethyl ether (3×20 mL) and the collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a yellow oil. Flash column chromatography (SiO_2) eluting with cyclohexane to cyclohexane/ethyl acetate 9:1 mixtures gave the product (*S*,*R*)-**7b** as a white powder: 0.102 g (82%); mp=139.4–140.1 °C; $[\alpha]_D^{25}$ +76.1 (*c* 4.0, $CHCl_3$); IR (KBr): *ν*=3084, 3060, 3029, 2956, 2926, 2851, 1452, 1261, 1105, 1028, 759, 698; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.63–6.93 (m, 20H), 3.14 (d, *J*=6.7 Hz, 1H), 2.98 (d, *J*=6.7 Hz, 1H), 2.32–2.16 (m, 2H), 1.70 (d, *J*=2.2 Hz, 1H), 1.67 (d, *J*=8.7 Hz, 1H), 1.57 (d, *J*=6.4 Hz, 1H), 1.42 (d, *J*=6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=141.0, 140.7, 128.5, 128.5, 128.4, 128.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.3, 127.2, 127.1, 66.4, 66.1, 65.3, 64.1, 61.7, 61.0; MS (ES): *m*/*z*=417.5 $[M+H]^+$; Anal. Calcd for $C_{30}H_{28}N_2$: C, 86.50; H, 6.78; N, 6.72. Found C, 86.48; H, 6.80; N, 6.71.

Compound (*S*,*S*)-**7a**: White solid; mp=49.7–50.8 °C; $[\alpha]_D^{25}$ +227.3 (*c* 1.0, $CHCl_3$); IR (KBr): *ν*=3062, 2976, 2912, 2814, 1497, 1450, 1438, 1313, 1207, 1088, 1028, 999, 741, 696; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.34–7.20 (m, 10H), 5.98–5.84 (m, 2H), 4.98 (m, 4H), 2.78 (dd, *J*=6.36, *J*=13.9 Hz, 2H), 2.50–2.39 (m, 2H), 2.25 (dd, *J*=3.3, *J*=6.3 Hz, 2H), 1.94 (d, *J*=3.3, 2H), 1.82 (d, *J*=6.3 Hz, 2H), 1.76 (d, *J*=9.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ*=140.2, 137.5, 128.2, 126.7, 126.2, 116.1, 73.6, 39.1, 38.7, 34.9; MS (ES): *m*/*z*=345.2 $[M+H]^+$. Anal. Calcd for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found C, 83.81; H, 8.18; N, 8.10.

Compound (*S*,*S*)-**7b**: White solid; mp=139.1–139.8 °C; $[\alpha]_D^{25}$ +97.4 (*c* 1.0, $CHCl_3$); IR (KBr): *ν*=3085, 3058, 3021, 2958, 2921, 2842, 1451, 1269, 1100, 1024, 759, 697; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.38–7.26 (m, 16H), 7.08 (t, *J*=14.7 Hz, 2H), 7.01 (d, *J*=7.5 Hz, 2H), 3.07 (s, 2H), 2.64 (dd, *J*=2.6, *J*=6.2 Hz, 2H), 1.72 (d, *J*=2.6 Hz, 2H), 1.60 (d, *J*=6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=140.5, 139.3, 129.3, 128.2, 126.8, 126.7, 126.1, 79.2, 43.1, 38.1; MS (ES): *m*/*z*=417.2 $[M+H]^+$; Anal. Calcd for $C_{30}H_{28}N_2$: C, 86.50; H, 6.78; N, 6.72. Found C, 86.71; H, 6.76; N, 6.69.

Compound **10**: Colorless oil; $[\alpha]_D^{25}$ +24.1 (*c* 1.0, $CHCl_3$); IR (neat): *ν*=3065, 3038, 2926, 2924, 2852, 1561, 1501, 1459, 1259, 974; ^{1}H NMR (200 MHz, $CDCl_3$): *δ*=7.18–7.25 (m, 10H), 2.73 (s, 4H), 2.38 (dd, *J*=3.2, *J*=6.6 Hz, 2H), 1.94 (d, *J*=3.2 Hz, 2H), 1.76 (d, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ*=140.2, 128.2, 126.8, 126.1, 61.0, 41.0, 38.3; MS (ES): *m*/*z*=265.1 $[M+H]^+$; Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found C, 81.72; H, 7.58; N, 10.57.

Compound (*R*)-**13**: Colorless oil; $[\alpha]_D^{25}$ +39.2 (*c* 1.0, $CHCl_3$); IR (neat): *ν*=3068, 3035, 2927, 2922, 2858, 1560, 1547, 1451, 1268, 972; ^{1}H NMR (200 MHz, $CDCl_3$): 7.13–7.37 (m, 15H), 3.19 (dd, *J*=7.4, *J*=11.7 Hz, 1H), 2.97 (dd, *J*=5.1, *J*=7.4 Hz, 1H), 2.59 (dd, *J*=5.1, *J*=11.7 Hz, 1H), 2.38 (dd, *J*=3.5, *J*=6.5 Hz, 1H), 2.20 (dd, *J*=3.3, *J*=6.5 Hz, 1H), 2.17 (d, *J*=3.5 Hz, 1H), 2.11 (d, *J*=6.5 Hz, 1H), 2.04 (d, *J*=3.3 Hz, 1H), 1.91 (d, *J*=6.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ*=141.8, 141.2, 140.0, 128.1, 128.1, 127.9, 127.5, 127.1, 126.7, 126.5, 126.2, 126.0, 75.1, 68.6, 41.5, 39.8, 39.2, 38.5; MS (ES): *m*/*z*=341.1 $[M+H]^+$; Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23. Found C, 84.75; H, 7.13; N, 8.20.

Compound (*S*,*S*)-**16**: Colorless oil; $[\alpha]_D^{25}$ +72.8 (*c* 1.0, $CHCl_3$); IR (neat): *ν* 3062, 3032, 2956, 2871, 2833, 1469, 1452, 1353, 1285, 1162, 1040, 699; ^{1}H NMR (200 MHz, $CDCl_3$): *δ*=7.14 (m, 10H), 2.85 (s, 2H), 1.62 (ddd, *J*=5.4, *J*=6.6, *J*=7.0 Hz, 2H), 1.45 (m, 2H), 1.31 (d, *J*=7.0 Hz, 2H), 1.27 (d, *J*=7.0 Hz, 6H), 1.17 (d, *J*=6.6 Hz, 2H), 1.07 (d, *J*=7.0 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ*=139.6, 128.7, 126.8, 126.4, 79.6, 49.2, 32.0, 31.0, 21.3, 19.7; MS (ES): *m*/*z*=349.2 $[M+H]^+$; Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found C, 82.93; H, 9.26; N, 8.01.

*4.1.5. Preparation of diaziridine (S,S)-**8**.* To a solution of (*S*,*S*)-**6a** (0.200 g, 0.5 mmol) in MeOH (5 mL) and Et_2O (5 mL) was added anhydrous 10% Pd/C (0.020 g) and the mixture was stirred under an atmosphere of H_2 (1 atm, ballon) for 1 h. The solid was filtered off through a pad of Celite and the organic phase was concentrated at reduced pressure to leave the saturated compound as a white solid (0.198 g, 98%). To this compound (0.190 g, 0.5 mmol) dissolved in THF (20 mL) was added PPh_3 (0.574 g, 2.19 mmol) and then DEAD (40% in toluene, 1.0 mL, 2.19 mmol) dropwise. After stirring for 24 h, 2 M aq KOH (10 mL) was added and the mixture was stirred for 1 h. The organic material was extracted with diethyl ether (3×20 mL) and the collected ethereal layers were dried over Na_2SO_4 and

concentrated to leave a yellow oil. Flash column chromatography (SiO_2) eluting with cyclohexane to cyclohexane/ethyl acetate 9:1 mixtures gave (*S*,*S*)-**8** as a white powder: 0.182 g (91%); mp=91.8–92.4 °C; $[\alpha]_D^{25}$ +231.1 (*c* 1.0, $CHCl_3$); IR (KBr): *ν* 3063, 3038, 2955, 2925, 2863, 2815, 1497, 1466, 1347, 1315, 1204, 1089, 1028, 753, 727, 694; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*=7.19–7.31 (m, 10H), 2.24 (dd, *J*=3.3, *J*=6.5 Hz, 2H), 1.96 (d, *J*=3.3 Hz, 2H), 1.94–1.93 (m, 2H), 1.80 (d, *J*=6.5 Hz, 2H), 1.63–1.73 (m, 4H), 1.52–1.6 (m, 2H), 1.27–1.36 (m, 2H), 0.82 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): *δ*=140.2, 128.2, 126.7, 126.2, 73.3, 39.1, 39.0, 32.6, 20.8, 14.5; MS (ES): *m*/*z*=349.2 $[M+H]^+$; Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found C, 82.39; H, 9.28; N, 8.02.

4.1.6. Palladium-catalyzed allylic alkylation: typical procedure. To a solution of aziridine (*S*,*S*)-**4b** (0.010 g, 0.02 mmol) in CH_2Cl_2 (2 mL) was added $(allylPdCl)_2$ (0.004 g, 0.01 mmol) and the solution was deaerated by a slow stream of Ar and then stirred for 1 h. 1,3-Diphenyl-2-propenyl ethyl carbonate **1b** (0.068 g, 0.24 mmol) was added to the mixture, followed by dimethyl malonate (0.069 mL, 0.60 mmol), BSA (0.176 mL, 0.721 mmol), and KOAc (0.002 g, 0.02 mmol). The reaction was monitored by TLC analysis and, when complete, quenched with 1 N HCl solution (1 mL) and the organic phase was extracted with diethyl ether (3×10 mL). The organic layer was dried over Na_2SO_4 and the solvents were evaporated to dryness. Column chromatography (SiO_2, cyclohexane/AcOEt, 75:5) gave (*R*)-**2**: 0.071 g (91%); ee 91% as determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 1:9, 1.0 mL/min; 250 nm): retention times 10.7 min (major enantiomer) and 14.9 min (minor enantiomer).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2009.11.062.

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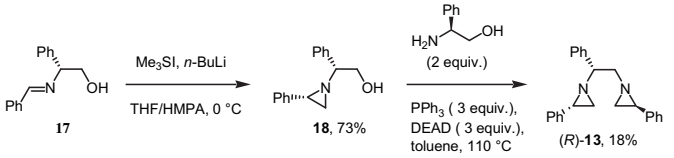
10. 1-Phenylpropanol was produced with low enantiomeric excess (ee 20%) in the addition of diethylzinc to benzaldehyde in the presence of a catalytic amount of (*S*,*S*)- **7a**.
11. The addition of dimethylsulfonium methylide to (*R*)- *N*-benzylidenephenylglycinol **17** gave the aziridine **18** by Re-face attack at the imine group, by analogy with the stereochemical outcomes of the analogous reaction of the corresponding imine-methyl ether[12] and the organometallic reactions of the same imine.[9] In the successive step, the double intermolecular–intramolecular Mitsunobu reaction using (*S*)-phenylglycinol afforded in low yield the desired bis(aziridine), which was identical to the previously prepared (*R*)-**13**.



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