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# An efficient synthetic approach for N–C bond formation from (*S*)-amino acids: an easy access to *cis*-2,5-disubstituted chiral piperazines†

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An efficient synthetic strategy is described for the construction of amino acids derived enantiomerically pure *cis*-2,5-disubstituted chiral piperazines. Cu-catalyzed spontaneous regioselective ring opening and ring closing of non-activated *N*-tosyl aziridines as well as Pd-mediated N–C bond formation from *N*-tosyl halogenated amino-derivatives are the key steps for accessing disubstituted piperazines.

## Introduction

Piperazines, nitrogen-containing heterocycles and related compounds are of major interest because of their wide spectrum of pharmaceutical importance. They display a variety of biological activities[1,2] including dopamine $D_3$ agents[3] acting on CNS receptor,[4] 5HT-anxiolytics,[5] HIV protease inhibitors[1b] such as indinavir, antimicrobial agents such as pefloxacin and related quinolones,[6] Bcl-2 inhibitors,[7] cytochrome *c* inhibitors,[8] anti-proliferative agents,[9] and antihypertensive agents.[10] Furthermore, there are also a number of bioactive natural products containing chiral piperazine spacer such as ectenaiscidin 743,[11] piperazinomycin[12] and dragmacidins[13] (see Fig. 1).

Piperazinomycin has been isolated from *Streptoverticillium olivoreticuli Neoenacticus*[12] and has antimicrobial and antifungal activity. The group of dragmacidin alkaloids represent a promising class of marine natural products obtained by an exhaustive set of protocols from a number of deep water sponges including *Dragmacidon*, *Halicortex*, *Spongosorites*, *Hexadella and* the tunicate *Didemnum candidum*.[13–15] Although these compounds have been shown to hold a wide array of biological activities, some of their metabolites (piperazine linking dragmacidins) exhibit potent and diverse bioactivities such as cytotoxic,[13,16,18] antitumor,[15a] antiviral,[15a] antifungal,[16,17] and anti-inflammatory activities.[19] Bisindole alkaloids, such as dragmacidins have been reported to inhibit the ligand binding to $\alpha_{1a}$ and $\alpha_{1b}$ adrenergic receptors.[20] The $\alpha_1$ adrenergic antagonists may be considered as potential candidates for the treatment of hypertension and benign prostatic hyperplasia. Also many compounds having the piperazine scaffold find use in asymmetric catalysis as chiral ligands.[21] Traditionally, the asymmetric synthesis of chiral piperazines involves the reduction of substituted mono- and diketopiperazines[22,23] which are again obtained either from chiral building blocks or *via* asymmetric synthesis using a chiral auxiliary. However, this strategy suffers from many drawbacks. Though Lewis acid mediated nucleophilic ring opening of aziridines are well documented,[22] copper acetate catalyzed spontaneous regioselective ring opening and closing of non-activated aziridines are new methods in this arena.

Our group is committed to developing new synthetic methodology for the synthesis of chiral heterocycles and their bioevaluation[24] and in continuation of this project, we have developed an efficient synthetic methodology to synthesize chirally pure *cis*-2,5-disubstituted piperazines utilizing catalytic N–C bond formation.

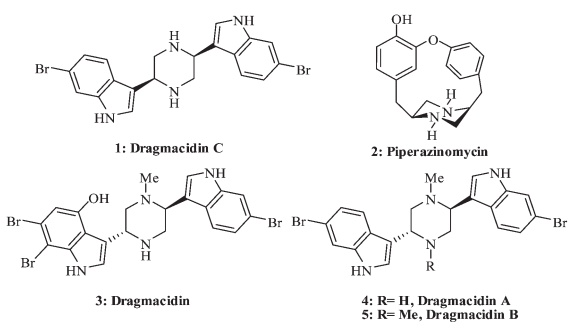


**Fig. 1** Some important representative piperazine core containing natural products.

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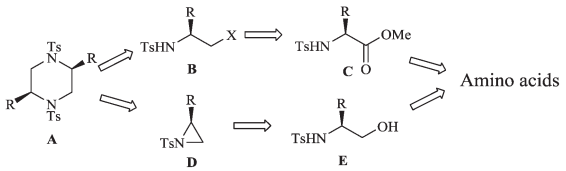



**Scheme 1** Retrosynthetic analysis of piperazine derivatives.

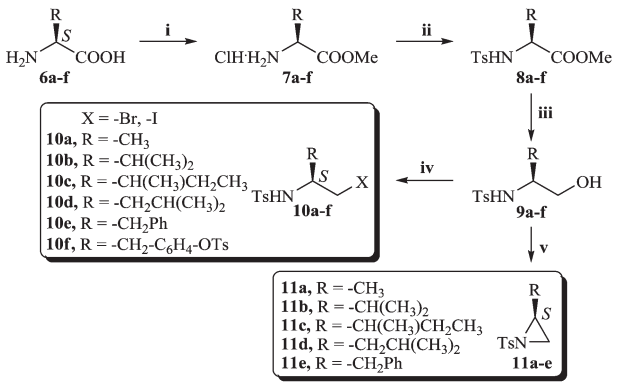
## Result and discussion

### Retrosynthetic analysis

The retrosynthetic analysis of piperazines is illustrated in Scheme 1. We envisioned that the chiral piperazine could be constructed from intermediate B and D through intermolecular catalytic N–C bond formation *via* palladium acetate mediated non-activated *N*-tosyl halogenated amino derivatives (from B) and copper acetate mediated regioselective *N*-tosyl aziridines ring opening (from D) and ring closing among different amino acids counterparts by the synthetic sequences mentioned above.

First, the synthesis of chiral halogenated amino alcohols and aziridines was undertaken. All the compounds were prepared with good yields from different naturally abundant (*S*)-amino acids following four synthetic steps, involving esterification of acids, tosylation of amines, LAH reduction of ester groups followed by Appel[25] reaction (halogenations of amino alcohols) and Mitsunobu[26] cyclization (Scheme 2). Now with chiral halogenated amino alcohols **10a–f** and aziridines **11a–e** in hand, the stage was set to implement the crucial catalytic N–C bond formation towards *cis*-2,5-disubstituted chiral piperazines.

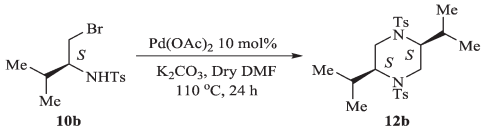
In order to optimise the desired reaction conditions, at first we used (*S*)-*N*-(1-bromo-3-methylbutan-2-yl)-4-methyl-benzenesulfonamide **10b** as a model substrate with different Pd




***Reagents and conditions***: (i) $SOCl_2$, MeOH, 6 h, 85-90%; (ii) TsCl, $Et_3N$, DCM, 2 h, 90-95%; (iii) LAH, dry THF, 1 h, 80-85%; (iv) (a) $PPh_3$, $I_2$, Imidazole, DCM (b;) $PPh_3$, $CBr_4$, DCM, 68-85% after two steps; (v) $PPh_3$, DEAD, THF, 0 °C, 42-45% (overall yield after four steps).

**Scheme 2** Synthesis of chiral halogenated amino derivatives (**10a–f**) and aziridines (**11a–e**).

**Table 1** Optimization studies for the synthesis of **12b** from halogenated amino derivatives




| Entry | Catalyst | Solvent | *T*/°C | Base | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ 5 mol (%) | DMF | 110 | $K_2CO_3$ | 55[c] |
| 2 | $Pd(OAc)_2$ 10 mol (%) | Toluene | 120 | $K_2CO_3$ | NR |
| 3 | $Pd(PPh_3)_4$ 10 mol (%) | Acetonitrile | 110 | $K_2CO_3$ | NR |
| 4 | $Pd(PPh_3)_2Cl_2$ 10 mol (%) | DMSO | 120 | $K_2CO_3$ | 24 |
| 5 | — | DMF | 110 | $K_2CO_3$ | NR |
| 6 | $Pd(OAc)_2$ 10 mol (%) | DMF | 110 | — | Trace |
| 7 | $Pd(MeCN)_2Cl_2$ 10 mol (%) | Toluene | 110 | $K_2CO_3$ | NR |
| 8 | $Pd(PPh_3)_2Cl_2$ 10 mol (%) | DMF | 110 | $K_2CO_3$ | NR |
| 9 | $Pd(OAc)_2$ 10 mol (%) | 1,4-dioxane | 100 | $K_2CO_3$ | NR |
| 10 | $Pd(OAc)_2$ 10 mol (%) | DMSO | 110 | $K_2CO_3$ | 57(47[b]) |
| 11 | $Pd(MeCN)_2Cl_2$ 10 mol (%) | DMF | 120 | $K_2CO_3$ | NR |
| 12 | $Pd(PPh_3)_4$ 10 mol (%) | Toluene | 110 | $K_2CO_3$ | NR |
| 13 | $Pd(OAc)_2$ 10 mol (%) | DMA | 120 | $K_2CO_3$ | 32 |
| 14 | $Pd(MeCN)_2Cl_2$ 5 mol (%) | DMSO | 110 | $K_2CO_3$ | NR |
| 15 | $Pd(OAc)_2$ 10 mol (%) | DMF | 110 | $K_2CO_3$ | 66(59[b])(<55[d]) |
| 16 | $Pd(PPh_3)_2Cl_2$ 10 mol (%) | DMF | 110 | $K_2CO_3$ | NR |
| 17 | $Pd(PPh_3)_2Cl_2$ 10 mol (%) | 1,4-dioxane | 110 | $K_2CO_3$ | NR |
| 18 | $Pd(OAc)_2$ 5 mol (%) | DMSO | 110 | $K_2CO_3$ | 53 |
| 19 | $Pd(OAc)_2$ 10 mol (%) | DMF | 110 | $K_2CO_3$ | 52[e] |

[a] Isolated yield of **12b**. [b] 2 equiv. of $Cs_2CO_3$ instead of $K_2CO_3$. [c] 1.5 equiv. of $K_2CO_3$. [d] Reaction temperature (70–80 °C). [e] When -Br is replaced by -I, NR = no reaction.

sources, solvents, and bases at varied temperatures (Table 1). The reaction occurred through oxidative addition, (cyclic five membered stable transition state) and intra molecular nucleophilic substitution followed by reductive elimination to afford the desired (2*S*,5*S*)-2,5-diisopropyl-1,4-ditosylpiperazine **12b** with 55% yield when the substrate was stirred with 5 mol% $Pd(OAc)_2$ in DMF at 110 °C under an argon atmosphere, Scheme 3.

The catalytic activity of the Pd sources were compared, and $Pd(OAc)_2$ was found to be superior to $Pd(PPh_3)_2Cl_2$, $Pd(MeCN)_2Cl_2$ and $Pd(PPh_3)_4$. Replacing the solvent DMF with DMSO gave a 53% yield of **12b** . The yield of **12b** was further increased to 66% when the substrate was stirred with 10 mol% $Pd(OAc)_2$ in DMF. In contrast, solvents such as toluene, acetonitrile, DMA, and 1,4-dioxane gave inferior results. The reaction was effective with $K_2CO_3$, $Cs_2CO_3$, but $K_2CO_3$ yielded the best results.

Lowering the reaction temperature (below 100 °C) or the base (1.5 equiv.) gave <55% yield of **12b**. Control experiments

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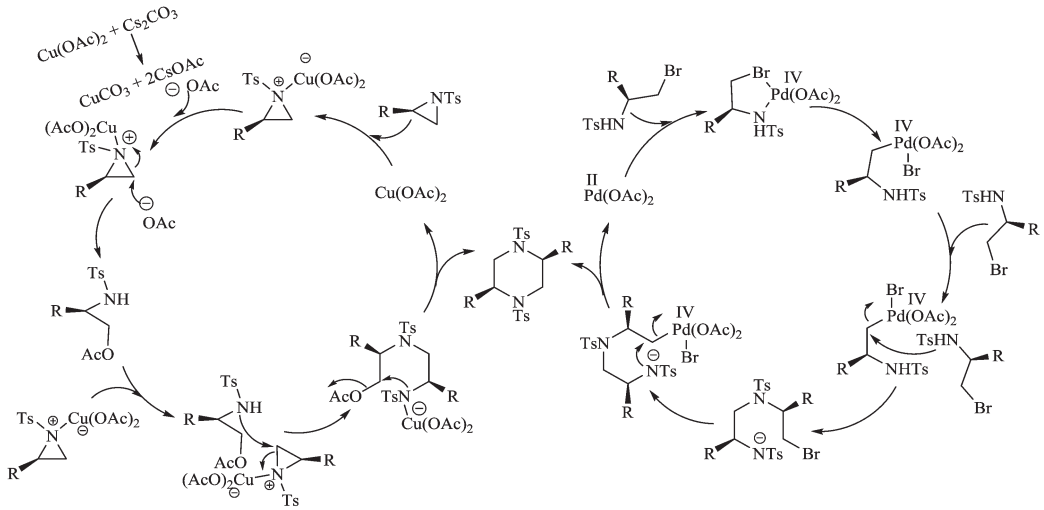


**Scheme 3** Proposed mechanistic pathway for the synthesis of symmetrical and unsymmetrical piperazine derivatives.

confirmed that no product was obtained in the absence of the palladium source. In summary, the optimal conditions in DMF include $Pd(OAc)_2$ (10 mol%) and $K_2CO_3$ (2 equiv.) at 110 °C for 24 h under an argon atmosphere. However, this reaction was performed two times on the gram scale (**10b**: 3.840 mmol, yield: 64% and 4.746 mmol, yield: 63%).

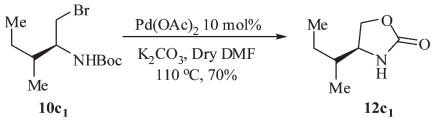
Next, we decided to vary the protecting groups in the final products, so that they could be easily deprotected. But when we subjected *tert*-butyl (2*S*,3*R*)-1-bromo-3-methylpentan-2-ylcarbamate **10c$_1$** to the above optimised condition instead of getting the desired piperazine, we obtained (*S*)-4-*sec*-butyloxazolidin-2-one **12c$_1$** (Scheme 4) as the sole product.

So, we considered other protecting groups such as tosyl chloride, nosyl chloride, mesyl chloride. Finally we detected tosyl chloride as an optimised protecting group on the basis of variation of yields (Table 2).

After successful synthesis of piperazine derivatives from halogenated amino derivatives, we turned our attention to access the chiral piperazine scaffold through copper acetate mediated regioselective ring opening and ring closing of *N*-tosyl aziridines **11a–e**. For ring opening reactions (both nucleophilic as well as pericyclic) of aziridines, it is well documented that the substituents attached to the nitrogen atom play a decisive role. For example, electron withdrawing groups on the nitrogen atom activate the aziridine ring towards the ring opening reaction while the electron releasing group deactivates it.[27] Moreover aziridines can act as marked 1,3 dipoles and thereby take part in Lewis acid (LA) mediated or thermal 1,3 dipolar cycloaddition with alkenes, nitriles and ketones.[28,29] However LA mediated nucleophilic attack primarily occurs at the benzylic position presumably due to the stabilisation of the incipient carbocation by the phenyl ring.[30] Similarly nucleophilic attack on the non-activated 2-phenylaziridines occurs almost exclusively at the benzylic position, while reactivity as a formal 1,3-dipole obtained by a C–N bond cleavage, to the best of our knowledge, has never been reported.[31]

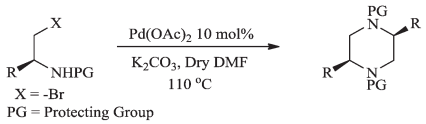
While surveying the literature we found that the formation of piperazinium halides from *N*-alkylaziridines and the formation of C-unsubstituted piperazines from β-chloro- or β-tosyloxyethylamines have been respectively reported by Dick[32] *et al.* and De Kimpe *et al.*[33] Further He *et al.* observed the formation of *N,N′*-diethyl piperazines as a minor side product when *N*-alkyl $C_2$-substituted aziridines were reacted with $CO_2$.[34] Recently it was found that in the presence of metal, some non-activated aziridines underwent dimerization to the corresponding piperazines depending on the reaction conditions.[35]

For the said purpose, we performed a model study on one of the previously prepared piperazines **12b**, the reaction conditions were optimized using (*S*)-2-isopropyl-1-tosylaziridine **11b** as a model substrate with different Cu sources, solvents, and bases at various temperatures (Table 3). To find the most



**Scheme 4** Synthesis of (*S*)-4-*sec*-butyloxazolidin-2-one.

**Table 2** Variation of protecting groups for the synthesis of **12b**



| Entry | *R* | PG | Yield (%)[a] |
|---|---|---|---|
| 1 | $-CH(CH_3)_2$ | -Ts(**10b**) | 66 |
| 2 | $-CH(CH_3)_2$ | -Ns(**10b$_1$**) | 58 |
| 3 | $-CH(CH_3)_2$ | -Ms(**10b$_2$**) | 51 |

[a] Isolated yield of **12b** after silica gel column chromatography.


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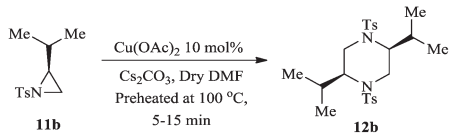
**Table 3** Catalytic scanning of **12b** from aziridines



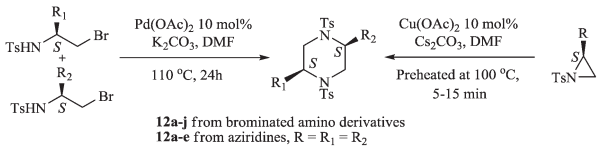

| Entry | Catalyst | Solvent | Base | $T$/°C | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ | DMF | $K_2CO_3$ | 80 | 47 |
| 2 | $Cu(OAc)_2$ | DMF | — | 80 | NR |
| 3 | $Cu(OTf)_2$ | DMF | $K_2CO_3$ | 80 | 43[b] |
| 4 | $Cu(OTf)_2$ | DMF | — | 80 | NR |
| 5 | $Cu(OAc)_2$ | DMSO | $K_2CO_3$ | 80 | 32 |
| 6 | $Cu(OAc)_2$ | DMF | $Cs_2CO_3$ | 100 | 76(54)[c] |
| 7 | $Cu(OAc)_2$ | DMF | — | 100 | NR |
| 8 | $Cu(OAc)_2$ | DMSO | $Cs_2CO_3$ | 100 | 44 |
| 9 | $Cu(OTf)_2$ | DMF | $Cs_2CO_3$ | 100 | 72[b] |
| 10 | $Cu(OAc)_2$ | Toluene | $Cs_2CO_3$ | 100 | NR |
| 11 | $Cu(OAc)_2$ | 1,4-dioxane | $Cs_2CO_3$ | 100 | NR |

[a] Isolated yield of **12b** after silica gel column chromatography. [b] Mixture of diastereoisomers. [c] 5 mol% $Cu(OAc)_2$, NR = no reaction.

advantageous reaction condition for the dimerization of aziridines **11a–e**, we tested two LAs $Cu(OAc)_2$ and $Cu(OTf)_2$ at different reaction conditions (solvent, temperature and LA amount). It was found that, when the substrate was stirred with 10 mol% $Cu(OAc)_2$ and $Cs_2CO_3$ (1.2 equiv.) in DMF preheated at 100 °C under an argon atmosphere, appreciable yields were obtained of the corresponding diastereoselective piperazine **12b** (Table 3). The $Cu(OAc)_2$ was tested in both stoichiometric and catalytic (10 mol%) amounts, only the use of a catalytic amount of the LA gave faster reactions and higher yields. When $Cu(OAc)_2$ was replaced by $Cu(OTf)_2$ under the same conditions, we got a mixture of diastereomers because in the presence of $Cu(OTf)_2$, non-activated aziridine could be highly activated and opening of the ring occurs through nucleophilic attack from both sides. Replacing the solvent DMF with DMSO gave a 44% yield of **12b**. In contrast, solvents such as toluene and 1,4-dioxane gave negative results. The reaction was effective with $K_2CO_3$, $Cs_2CO_3$, but $Cs_2CO_3$ yielded the best results. Lowering of the reaction temperature (below 50 °C), $Cu(OAc)_2$ (5 mol%) or the base (0.5 equiv.) gave a lower yield of **12b**. The role of $Cs_2CO_3$ is very important, it may react with $Cu(OAc)_2$ to generate ionic CsOAc which takes part in spontaneous regioselective aziridine ring opening and finally $Cs_2CO_3$ abstracts the NH-proton and is cyclised through the $S_N2$ pathway (Scheme 3). In this process we frequently monitored the reaction and also isolated the intermediate (*R*)-2-(4-methylphenylsulfonamido)-3-phenylpropyl acetate (**12e$_1$**, see ESI†) thereby indicating the proposed mechanistic path. Control experiments confirmed that no product was obtained in the absence of the copper source. In summary, the optimal conditions in DMF include $Cu(OAc)_2$ (10 mol%) and $Cs_2CO_3$ (1.2 equiv.) preheated at 100 °C for 5–15 min under an argon atmosphere. Moreover, this reaction was also performed on a large scale (**11b**: 3.133 mmol, yield: 74%).

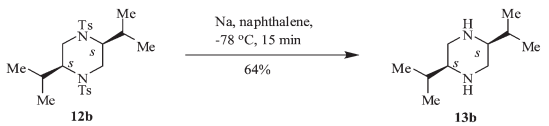
By using the same procedure as in the case of symmetrical piperazines we achieved the synthesis of unsymmetrical ones though trace amounts of symmetrical piperazines corresponding to the halogenated amino alcohols were always obtained (Table 4).

**Table 4** Synthesis of piperazine derivatives from halogenated amino derivatives and aziridines




| Entry | $R_1$ | $R_2$ | Yield (%)[a] |
|---|---|---|---|
| 1(**12a**) | -methyl | -methyl | 57[b](52[c]) |
| 2(**12b**) | -*iso*-propyl | -*iso*-propyl | 66[b](76[c]) |
| 3(**12c**) | -*sec*-butyl | -*sec*-butyl | 76[b](68[c]) |
| 4(**12d**) | -*iso*-butyl | -*iso*-butyl | 69[b](71[c]) |
| 5(**12e**) | -benzyl | -benzyl | 62[b](56[c]) |
| 6(**12f**) | *O*-Tos-benzyl | *O*-Tos-benzyl | 70[b] |
| 7(**12g**) | -*sec*-butyl | -*iso*-butyl | 52[d] |
| 8(**12h**) | -*sec*-butyl | -benzyl | 48[d] |
| 9(**12i**) | *O*-Tos-benzyl | -benzyl | 51[d] |
| 10(**12j**) | *O*-Tos-benzyl | -*iso*-butyl | 47[d] |

[a] Isolated yield of piperazine derivatives after silica gel column chromatography. [b] Isolated yield from chiral halogenated amino derivatives. [c] Isolated yield from chiral aziridines. [d] Trace amount of symmetrical piperazines.




**Scheme 5** Deprotection of the tosyl group of **12b**.

As a representative example, the tosyl group of the *cis*-2,5-disubstituted chiral piperazine **12b** was selectively deprotected by using sodium naphthalenide[24l] as a reducing agent providing **13b** with 64% yield, which gives scope for further structural diversification (Scheme 5).

## Conclusion

In summary, we have developed a scalable synthetic route for piperazine derivatives from readily available (*S*)-amino acids involving catalytic N–C bond formation. Although both routes are effective, the Pd-catalyzed process is more favourable than the Cu-catalyzed process, which furnished both symmetrical as well as unsymmetrical piperazines. Further investigations are underway in order to increase the yield as well as to expand the applicability of this process with controlled stereoselectivity.

## Experimental section

### General

All the dry reactions were carried out under argon in oven-dried glassware using standard gas-light syringes, cannulas

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and septa. All reagents and solvents were dried prior to use according to standard methods. Commercial reagents were used without further purification unless otherwise stated. Amino acids, tosyl chloride, nosyl chloride, mesyl chloride, palladium acetate, copper acetate and LAH were purchased from Aldrich Milwaukee, WI. Organic solvents were dried by standard methods. All the final products were characterized by $^1$H, $^{13}$C, IR, ESI-MS, HRMS. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was accomplished with iodine under a UV lamp. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). $^1$H NMR and $^{13}$C NMR spectra were recorded with a Brucker DPX-200 (operating at 200 MHz for $^1$H and 50 MHz for $^{13}$C) or DPX-300 (operating at 300 MHz for $^1$H and 75 MHz for $^{13}$C) spectrometer. $^1$H NMR splitting patterns were designated as singlet (s), doublet (d), double dublet (dd), triplet (t), quartet (q) or multiplet (m). Experiments were recorded in $CDCl_3$ at 25 °C. Chemical shifts were given in the $\delta$ scale and were referenced to TMS at 0.00 expressed in parts per million (ppm) for protons. For the $^{13}$C NMR reference $CDCl_3$ appeared at 77.00 ppm. IR spectra were recorded with Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded with a JEOL JMS-600H high resolution spectrometer using the EI mode at 70 eV. Optical rotations were determined with Autopol III polarimeters using a 1 dm cell at 25 °C in chloroform and methanol as the solvents, the concentrations mentioned are in g/100 mL. The enantiomeric excess was determined using a Lichro CART Chiradex column (250 × 4 mm) and an *R*,*R*-Whelk-01 column with an eluent of 5% *iso*-propanol and 95% acetonitrile and a flow rate of 0.50 mL min$^{-1}$ at 25 °C. The retention time range was 0 to 30 min.

### Experimental procedures and characterization data

**Procedure for the synthesis of chiral aziridines (11a–e).** The chiral aziridines were prepared using our previously reported procedure.[36]

**Synthesis of *cis*-2,5-disubstituted chiral piperazines (symmetrical) (12a–f) from *N*-tosyl halogenated amino alcohols.** $Pd(OAc)_2$ (10 mol%), $K_2CO_3$ (2 mmol) and *N*-tosyl halogenated amino alcohols **10a–f** (1 mmol) were stirred at 110 °C in DMF (10 mL) for 24 h under an argon atmosphere. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed successively with brine (1 × 3 mL) and water (3 × 5 mL). Drying ($Na_2SO_4$) and vaporation of the solvent gave a residue that was purified by silica gel column chromatography using 1 : 9 ethyl acetate and hexane as the eluent.

**Synthesis of *cis*-2,5-disubstituted chiral piperazines (symmerical) (12a–e) from aziridines.** $Cu(OAc)_2$ (10 mol%), $Cs_2CO_3$ (1.2 mmol) and aziredines **10a–e** (1 mmol) were preheated to 100 °C and stirred for 5–15 min in DMF (10 mL) under an argon atmosphere. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The usual work-up was carried out (as described above), the residue obtained was purified by silica gel column chromatography using 1 : 9 ethyl acetate and hexane as the eluent to obtain **12a–e**.

**(2*S*,5*S*)-2,5-diisopropyl-1,4-ditosylpiperazine (12b).** A colorless oily liquid, yield = 66% (from **10b**), 76% (from **11b**). This reaction was performed two times at the gram scale (from **10b**: 3.840 mmol, yield: 64% and 4.746 mmol, yield: 63%) and the yield varied from 63–64% (from **11b**: 3.133 mmol, yield: 74%). $[\acute{a}]_D^{25}$= +78.231 (*c* = 0.110, $CH_3OH$). HPLC analysis: ee > 99 ($t_R$ = 5.268 min, *iso*-propanol/acetonitrile). $R_f$ 0.62 (20% EtOAc/hexane). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\ddot{a}_H$ 7.66 (d, *J* = 8.28 Hz, 4H), 7.28 (d, *J* = 8.04 Hz, 4H), 3.62–3.54 (m, 4H), 3.09–3.00 (m, 2H), 2.42 (s, 6H), 2.21–2.10 (m, 2H), 0.82 (dd, $J_1$ = 7.05, $J_1$ = 14.7 Hz, 12H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\ddot{a}_C$ 143.4, 137.5, 129.7, 127.0, 58.4, 40.8, 30.7, 21.5, 18.6, 15.6 ppm. IR (Neat, cm$^{-1}$): 3460, 3241, 2964, 1637, 1460, 1339, 1158, 1094, 929, 761. Mass (ESI-MS): *m*/*z* 479.1 (80, [M + 1]+), 501.1 (30, [M + Na]+), 323.1 (35, [M-Ts]+), 168.1 (50, [M-2Ts]+). ESI-HRMS: *m*/*z* [M + H]+ calcd for $C_{24}H_{35}N_2O_4S_2$ 479.2038, found 479.2040.

**Synthesis of *cis*-2,5-disubstituted chiral piperazines (unsymmetrical) (12g–j) from *N*-tosyl halogenated amino alcohols.** $Pd(OAc)_2$ (10 mol%), $K_2CO_3$ (2 mmol) and *N*-tosyl halogenated amino alcohols **10c–f** (1 mmol) (1 mmol of each *N*-tosyl halogenated amino alcohol) were stirred at 110 °C in DMF (10 mL) for 24 h under an argon atmosphere. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The usual work-up was carried out (as described above), the residue obtained was purified by silica gel column chromatography using 1 : 9 ethyl acetate and hexane as the eluent to obtain **12g–j**.

**Experimental procedure for the synthesis of (2*S*,5*S*)-2,5-diisopropylpiperazine (13b).** Finely chopped sodium metal (87 mg, 3.760 mmol) and naphthalene (531 mg, 4.136 mmol) were dissolved in 10 mL dry THF and stirred for 2 h, until a dark green colour appeared. The desired THF solution of **12b** (90 mg, 0.188 mmol) was cooled to −78 °C and then Na-napthalenide solution was added dropwise to the reaction mixture *via* a syringe, until a dark green colour persisted followed by stirring for 15 min at −78 °C. The reaction was quenched by adding 1–2 drops water to discharge the green colour and the usual work-up was carried out followed by column chromatography. A light brown oily liquid was obtained, yield = 64%. $R_f$ 0.46 (15% methanol/chloroform). $[\alpha]_D^{25}$ = +18.243 (*c* = 0.030, $CH_3OH$). HPLC analysis: ee > 99 ($t_R$ = 5.549 min, *iso*-propanol/acetonitrile). $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ 4.76 (s, 2H), 3.21 (d, *J* = 12.12 Hz, 2H), 3.02–2.96 (m, 2H), 2.85 (s, 2H), 2.03 (s, 2H), 0.98 (d, *J* = 6.48, 6H), 0.95 (d, *J* = 6.27, 6H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C$ 58.5, 43.3, 27.4, 19.0, 18.7 ppm. IR (Neat, cm$^{-1}$): 3298, 3024, 2964, 1463, 1321, 1158, 758. Mass (ESI-MS): *m*/*z* 171.2 (90, [M + H]+). ESI-HRMS: *m*/*z* [M + H]+ calcd for $C_{10}H_{23}N_2$ 171.1861, found 171.1860.

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