Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2727–2734

TETRAHEDRON: *ASYMMETRY*

# Synthesis of enantiomerically pure $C_2$-symmetric acyclic and cyclic 1,2-diamines via pinacol coupling of imines

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Received 17 October 2002; revised 6 November 2002; accepted 8 November 2002

**Abstract**—The inter- and intramolecular coupling of imines promoted by samarium diiodide and Lewis acids or by Zn/MsOH was extensively studied. The intramolecular reaction of chiral, enantiomerically pure bis-imines was also considered, and allowed the efficient, stereoselective synthesis of 1,2-diamines with $C_2$-symmetry. 

## 1. Introduction

The pinacol coupling of imines is one of the most straightforward procedures for the synthesis of 1,2-diamines,[1–3] a class of compounds that have found widespread applications in medicinal[1,4] and analytical chemistry,[1] as well as in the field of stereoselective organic synthesis.[1] In its intermolecular version, the coupling methodology is generally limited to the preparation of symmetrical 1,2-diamines,[1–3,5–20] although significant achievements were recently reported for the synthesis of unsymmetrical diamines and amino alcohols.[6,19,21,22] A few years ago, we started a project aimed at the study of the samarium diiodide-mediated intermolecular coupling of imines,[23] and we now wish to report herein our final results concerning both the inter- and intramolecular version of this reaction.

## 2. Intermolecular coupling reactions

Samarium diiodide has been exploited extensively for the pinacol coupling of carbonyl compounds.[2,24] The extension of the procedure to azacarbonyl derivatives, such as imines, generally requires stronger reaction conditions due to the lower reactivity of these substrates. Our previous studies focused on the combined use of $SmI_2$ and $Yb(OTf)_3$ to promote an efficient and stereoselective coupling of imines to give chiral 1,2-diamines in mild reaction conditions.[23] For instance, while the homocoupling of *N*-benzyl-benzaldimine **1** in the presence of $SmI_2$ required refluxing in THF for 15 h to give a 57/43 *syn*/*anti* mixture of the corresponding 1,2-diphenyl-1,2-dibenzylaminoethane in 53% yield, the reaction proceeded smoothly at room temperature with both $SmI_2$ and $Yb(OTf)_3$ in 81% yield, affording the *syn* diastereoisomer exclusively (Table 1, entries 1, 2). This effect was attributed to the high capability of $Yb(OTf)_3$ to coordinate imines, aiding nucleophilic attack at the carbon atom.[25] We extended the homocoupling reaction to various imines bearing different *C*- and *N*-residues, and the results obtained for different *N*-benzylimines are collected in Table 1.

As was the case with *N*-benzyl-benzaldimine **1**, the *N*-benzylimines of different aromatic aldehydes underwent the coupling reaction in the presence of $SmI_2$ and $Yb(OTf)_3$ at room temperature, with variable results. In particular, derivatives of aldehydes bearing an electron-withdrawing group, such as *N*-benzyl-4-fluorobenzaldimine **2**, reacted in good chemical yields, but with low *syn* selectivity (entry 3). On the other hand, 4-methoxy-substituted imine **3** gave a 70/30 mixture of the corresponding *syn* and *anti* 1,2-diamines **10a**,**b** in extremely low chemical yields (entry 4).† The *N*-benzylimines of heteroaromatic aldehydes displayed more erratic behavior: in the case of *N*-benzyl-2-(6-methyl)pyridylimine **4**, only the *syn* isomer **11a** was formed in the coupling reaction, although in poor yields (entry 5). *N*-Benzyl-2-thiophenylimine **5** reacted in fair yields but with low stereoselection; not unexpectedly, the reaction of furylimine **6** gave a complex mixture of

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† Unexpectedly,[6,7,16,24] the corresponding 2-methoxy derivative was also completely unreactive in these conditions.

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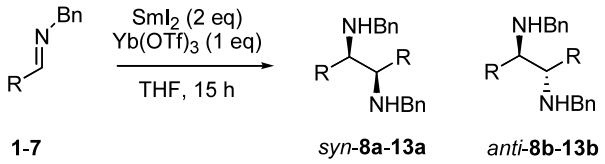
PII: S0957-4166(02)00748-6

**Table 1.** Homocoupling reactions of *N*-benzylimines **1**–**7**




**1-7** *syn*-**8a-13a** *anti*-**8b-13b**

| | Imine | R | T (°C) | Yield (%) | Product | *syn*/*anti* |
|---|---|---|---|---|---|---|
| 1 | **1** | Ph | 65 | 53[a,b] | **8a**,**b** | 57/43[a,b] |
| 2 | **1** | Ph | 20 | 81[a] | **8a** | ≥98/2[a] |
| 3 | **2** | 4-F-Ph | 20 | 95[a] | **9a**,**b** | 60/40[a] |
| 4 | **3** | 4-MeO-Ph | 20 | 20[a] | **10a**,**b** | 70/30[a] |
| 5 | **4** | 2-(6Me)-Py | 20 | 12[c] | **11a** | ≥98/2[c] |
| 6 | **5** | 2-Thiophenyl | 20 | 55 | **12a**,**b** | 67/33 |
| 7 | **6** | 2-Furyl | 20 | [d] | – | – |
| 8 | **7** | Cy | 65[e] | [b,d] | – | – |
| 9 | **7** | Cy | 20 | 14 | **13a**,**b** | 70/30 |

[a] See Ref. 23.
[b] In the absence of $Yb(OTf)_3$.
[c] The use of 2 equiv. of $Yb(OTf)_3$ led to impressive decreases of both chemical yield (<10%) and stereoselectivity (50/50).
[d] A complex mixture of coupling products was obtained.
[e] Lowering the reaction temperature to 20°C was not effective.

different coupling products, due to the radical nature of the reaction and the high reactivity of the furan moiety (entries 6, 7).

The use of imines derived from aliphatic aldehydes (such as cyclohexanecarboxaldehyde) was seriously hampered by isomerization of the imine moiety: the resulting mixture of imines underwent the coupling reaction, affording a regio- and diastereoisomeric mixture of 1,2-diamines (entry 8). Only when the reaction was performed in the presence of both $SmI_2$ and $Yb(OTf)_3$ at room temperature the desired products **13a**,**b** were isolated in poor chemical yield and in a 70/30 diastereoisomeric ratio (entry 9). The yields and stereoselectivities seem to be mainly affected by the stereoelectronic nature of the substituent, that influence the redox potential of the imine.

This procedure appears to be more effective with *N*-benzylimines of aromatic (and sometimes heterocyclic) aldehydes, the worst results being obtained with benzaldimine and electron-rich aromatic aldehyde derivatives.

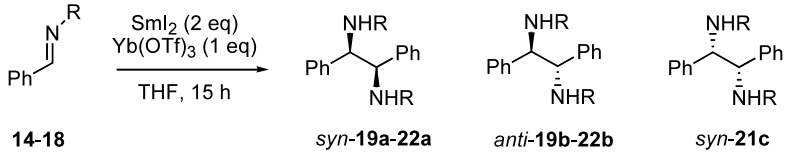
We also investigated the behavior of various benzaldimines bearing different *N*-substituents; the results are collected in Table 2. Imines derived from aromatic amines are not good substrates for this reaction: *N*-phenylbenzaldimine **14** underwent the pinacol coupling in the presence of $SmI_2$ in good chemical yields, but with low stereoselectivity; addition of $Yb(OTf)_3$ was detrimental to the chemical yield and did not improve the *syn*/*anti* ratio (entries 1, 2). 4-*N*-methoxyphenylbenzaldimine **15** was unreactive in these conditions (entry 3).[‡] Better results were obtained with *N*-*t*-butylbenzaldimine **16**, which reacted smoothly with $SmI_2$ to give the corresponding 1,2-diamine **20a**,**b** in good yield but low stereoselectivity; in this case, addition of $Yb(OTf)_3$ lowered the yield but led exclusively to the *syn* isomer **20a** (entries 4, 5). Therefore, it seems that the presence of an $sp^3$ carbon atom directly bound to the imine nitrogen is essential to ensure both good chemical yields and *syn* stereoselectivities.

The coupling procedure is highly effective with imines of aliphatic amines with benzaldehyde or aromatic aldehydes with an electron-withdrawing group on the benzene ring. The use of aliphatic aldehydes is hampered by the tendency of the corresponding imine to isomerize under the reaction conditions. We also tested the reaction of the non-isomerizable *N*-*t*-butyl-cyclohexanecarboxyimine, but in all cases (with or without $Yb(OTf)_3$, and independently of the temperature) only the corresponding reduction product (*N*-*t*-butyl-*N*-(cyclohexylmethyl)amine) was isolated.

In our previous studies, we considered the possibility of controlling both the relative and absolute configuration of the coupling products by using imines derived from chiral, enantiomerically pure amines.[23] Interesting results were obtained in the reaction of imines **17** and **18**, derived from (*R*)-1-phenylethylamine and (*R*)-1-naphthylethylamine. Imine **17** coupled in fair yields with $SmI_2$ only at 65°C, with low relative (*syn*/*anti* = 61/

[‡] Also in this case, the chelating capability of the imine residue has no effect on the course of the $SmI_2$-promoted coupling reaction. More activated compounds, such as *N*-tosylbenzaldimine, were also unreactive.

**Table 2.** Homocoupling reactions of benzaldimines **14**–**18**




**14-18** *syn*-**19a-22a** *anti*-**19b-22b** *syn*-**21c**

| | Imine | R | T (°C) | Yield (%) | Product | *syn*/*anti* |
|---|---|---|---|---|---|---|
| 1 | **14** | Ph | 65 | 88[a] | **19a**,**b** | 65/35 |
| 2 | **14** | Ph | 20 | 23 | **19a**,**b** | 66/34 |
| 3 | **15** | 4-MeO-Ph | [b] | [b] | – | – |
| 4 | **16** | *t*-Bu | 65 | 75[a] | **20a**,**b** | 55/45 |
| 5 | **16** | *t*-Bu | 20 | 40 | **20a** | ≥98/2 |
| 6 | **17** | (*R*)CHMePh | 65 | 53[a] | **21a**–**c** | 61/39[c] |
| 7 | **17** | (*R*)CHMePh | 20 | 86[d] | **21a**–**c** | 62/38[e] |
| 8 | **17** | (*R*)CHMePh | −20 | 85[d] | **21a**–**c** | 64/36[f] |
| 9 | **18** | (*R*)CHMeNaph | 20 | 23[d] | **22a**,**b** | 65/35[g] |

[a] Without addition of $Yb(OTf)_3$.
[b] The presence of $Yb(OTf)_3$ and the reaction temperature were ineffective: no coupling products were obtained in any case.
[c] Two *syn* diastereoisomers were isolated in a 77/23 ratio.
[d] See Ref. 23.
[e] Two *syn* diastereoisomers were isolated in a 75/25 ratio.
[f] Two *syn* diastereoisomers were isolated in a 89/11 ratio.
[g] A single *syn* diastereoisomer was isolated.

39) and absolute (*syn1*/*syn2*=77/23) stereocontrol (entry 6). The presence of $Yb(OTf)_3$ allowed for better yields (86%), without significant effect on the stereoselectivity (entry 7). Lowering the reaction temperature to −20°C gave diamines **21a**–**c** with unchanged yield and *syn*-selectivity, while the ratio of the two *syn* isomers **21a** and **21c** slightly improved (89/11; entry 8). The use of the more hindered imine **18** did not significantly improve the *syn*/*anti* ratio of the corresponding 1,2-diamines. Although these products were obtained in low chemical yields (entry 9), only one *syn* isomer (**22a**) was produced in this case.[§] The *syn*/*anti* ratio achieved with chiral *N*-(*R*)-arylethylimines is thus limited to the value of 65/35 at best.[¶]

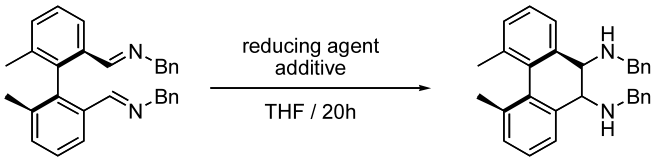
## 3. Intramolecular coupling reactions

We also explored the intramolecular coupling reaction of chiral bis-imines, with the aim of obtaining enantiomerically pure $C_2$-symmetric 1,2-diamines in good chemical yields. Bis-imine **23**, derived from benzylamine and (*R*)-6,6′-dimethyldiphenyl-2,2′-dialdehyde, easily obtainable as a single enantiomer with standard reactions,[26,27] was selected as a model substrate. The results are collected in Table 3. The use of $SmI_2$ alone required refluxing in THF for the coupling reaction to occur in decent yields; only a single diastereoisomer (*R*)-**24a** was isolated from the reaction mixture, the $C_2$-symmetric, *trans* configuration being easily assigned on the basis of the $^1H$ NMR spectrum (entries 1, 2). Unexpectedly, addition of $Yb(OTf)_3$ was detrimental to the reaction stereoselectivity, since a second $C_1$-symmetric *cis* diamine was obtained as the minor stereoisomer (*trans*/*cis*=70/30; entry 3). The use of $BF_3{\cdot}Et_2O$, a Lewis acid incapable of chelation, led to complete *trans* selectivity, although in low chemical yields (entry 4).[28] The use of other additives commonly employed in combination with $SmI_2$, such as HMPA[29] and LiCl,[30] was detrimental to both chemical yields and stereoselectivity.[‖] In a further effort to achieve the synthesis of the $C_2$-symmetric *trans*-1,2-diamine in good yield, we turned to a different coupling approach, namely the one promoted by metallic zinc in the presence of a protic species such as methanesulphonic acid.[31] Under these conditions reaction occurred to afford (*R*)-**24a** in 51% yield with complete *trans* stereoselectivity (entry 6).

Since both *trans* isomers possess $C_2$-symmetry, they can be easily distinguished from their $C_1$-symmetric *cis* counterparts via NMR spectroscopy, and the *trans*/*cis* ratio readily determined. By no means, however, were we able to assign the absolute configuration to the newly formed stereocenters in **24a** and **24b**. Both compounds are waxy solids, and are thus unsuitable for crystallographic analysis. Inspection of molecular models and computational techniques (MM3*),[32] on the other hand, were inconclusive. In fact, *trans*-(*R*,*R*,*R*)-**24a** (Fig. 1) was calculated to be more stable than its

[§] The absolute configuration of compounds **21a**–**c** and **22a**,**b** was assigned on the basis of NMR evidence and literature data.[23]
[¶] Unexpectedly,[7] the coupling of imines derived from benzaldehyde and chiral, enantiomerically pure amino alcohols such as (1*S*,2*R*)-norephedrine did not give satisfactory yields of the corresponding 1,2-diamines.
[‖] Traces of diamine **26** were observed only with HMPA (entry 5).

**Table 3.** Intramolecular coupling reactions of chiral, enantiomerically pure (*R*)-**23**




(*R*)-**23** (*R*)-**24a**,**b**

| | Reducing agent | Additive | T (°C) | Yield (%) | *trans*/*cis* |
|---|---|---|---|---|---|
| 1 | $SmI_2$ (4) | – | 20 | 8 | – |
| 2 | $SmI_2$ (4) | – | 65 | 31 | ≥98/2 |
| 3 | $SmI_2$ (4) | $Yb(OTf)_3$ (2) | 20[a] | 37 | 70/30 |
| 4 | $SmI_2$ (4) | $BF_3{\cdot}Et_2O$ (2) | 65[b] | 18 | ≥98/2 |
| 5 | $SmI_2$ (4) | HMPA (12) | 65 | 5 | – |
| 6 | Zn (5) | MsOH (5) | 0–20 | 51 | ≥98/2 |

[a] Refluxing in THF worsened both yield and stereoselectivity.
[b] At 20°C no reaction was observed.

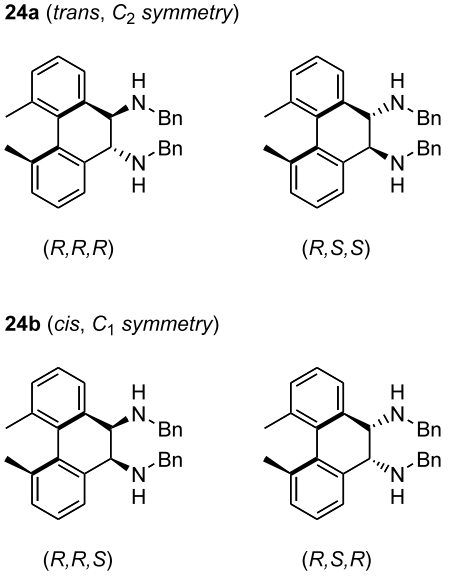
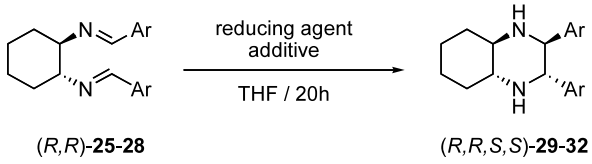



**Figure 1.** Possible diastereoisomeric structures for compounds **24a** and **24b**.

(*R*,*S*,*S*) isomer of ca. 3 kcal/mol. However, the starting imine (*R*)-**23** exists in a unique conformation (with both C=N bonds having *E* geometry), and can react with the formation of (*R*,*S*,*S*)-isomer only. The presence of a single, $C_2$-symmetric *trans* isomer can thus derive either from a complete thermodynamic control (with the formation of (*R*,*R*,*R*)-**24a**) or from a complete kinetic control (leading exclusively to (*R*,*S*,*S*)-**24a**). Formation of the $C_1$-symmetric *cis* isomer **24b** was observed only in the presence of $Yb(OTf)_3$: intramolecular chelation of both nitrogens by ytterbium, with the formation of a flexible nine-membered ring, probably stabilizes other configurations for the imine moieties and, as a consequence, allows the formation of the minor *cis*-1,2-diamine. Even if the two possible isomers for *cis*-**24b** were calculated to be isoenergetic, only one was observed experimentally, suggesting that the reaction is under kinetic control. By analogy, the (*R*,*S*,*S*) configuration can be tentatively assigned to *trans* **24a**.

With the aim of finding more reactive substrates for the synthesis of enantiomerically pure $C_2$-symmetric 1,2-diamines, bis-imines derived from (*R*,*R*)-1,2-diaminocyclohexane and aromatic aldehydes were considered. Both the procedures employed in the case of (*R*)-**23**, i.e. the use of $SmI_2$ in conjunction with various additives, and the procedure employing zinc and methanesulphonic acid, were tested. Significant results are collected in Table 4. Since the use of $Yb(OTf)_3$ in the intramolecular coupling reaction of imines promoted by $SmI_2$ was ineffective, $BF_3{\cdot}Et_2O$ was employed as the Lewis acid.[28] Dibenzaldimine (*R*,*R*)-**25** readily coupled intramolecularly in the presence of $SmI_2$ in refluxing THF; under these conditions, we achieved the synthesis of the enantiomerically pure $C_2$-symmetric, *trans* 1,2-diamine **29** in good chemical yields and with complete stereoselectivity (entry 1), to which the (*R*,*R*,*S*,*S*) absolute configuration was assigned.[33] At room temperature, the reaction was completely stereoselective, but **29** was recovered in only 22% yield. In the presence of other additives, such as HMPA,[29] $NiI_2$,[6] $Me_3SiCl$,[34] or LiCl,[30] no pinacol reaction occurred. Also in the reaction of (*R*,*R*)-**25**, the coupling promoted by zinc and methanesulphonic acid was more efficient, allowing recovery of (*R*,*R*,*S*,*S*)-**29** in 82% yield (entry 3). The better performance of the Zn/MsOH procedure were confirmed also in the reaction of other arylimines, such as (*R*,*R*)-**26**–**28** (entries 4–8): a single isomer was always obtained in good chemical yields. As previously observed for the intermolecular coupling, the imines derived from aromatic aldehydes bearing electron-withdrawing groups, such as

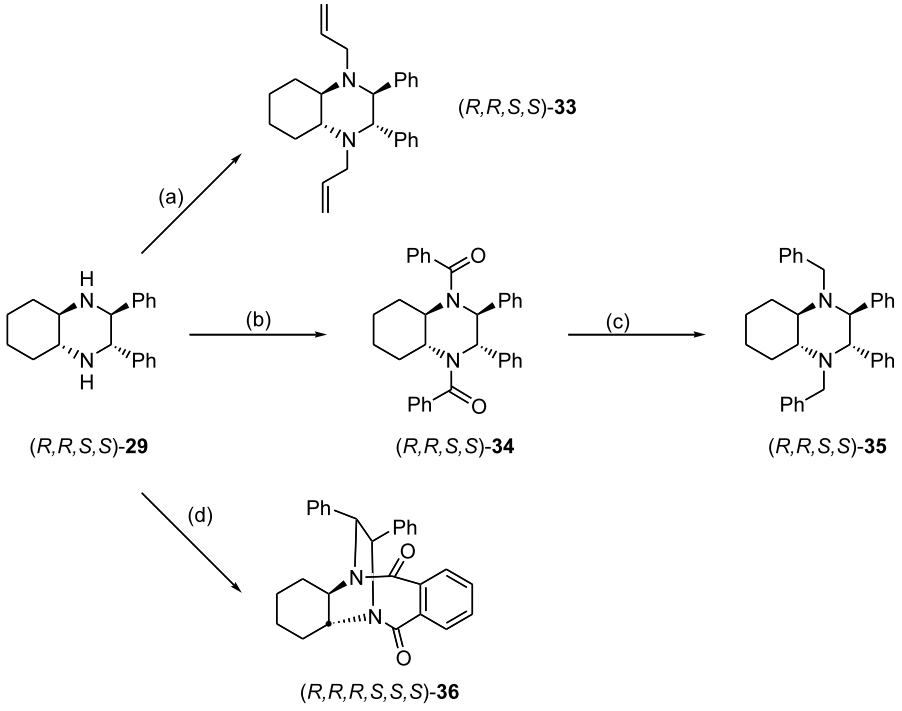
**Table 4.** Intramolecular coupling reactions of chiral, enantiomerically pure (*R*,*R*)-**25**–**28**




| | Imine | Ar | Reducing agent (eq.) | Additive (eq.) | T (°C) | Yield (%) | Product |
|---|---|---|---|---|---|---|---|
| 1 | **25** | Ph | $SmI_2$ (4) | $BF_3{\cdot}Et_2O$ (2) | 65 | 60 | **29** |
| 2 | **25** | Ph | $SmI_2$ (4) | $BF_3{\cdot}Et_2O$ (2) | 20 | 22 | **29** |
| 3 | **25** | Ph | Zn (5) | MsOH (5) | 0–20 | 82 | **29** |
| 4 | **26** | 4-F-Ph | $SmI_2$ (4) | $BF_3{\cdot}Et_2O$ (2) | 65 | 42 | **30** |
| 5 | **26** | 4-F-Ph | Zn (5) | MsOH (5) | 0–20 | 84 | **30** |
| 6 | **27** | 4-MeO-Ph | $SmI_2$ (4) | $BF_3{\cdot}Et_2O$ (2) | 65 | 44 | **31** |
| 7 | **27** | 4-MeO-Ph | Zn (5) | MsOH (5) | 0–20 | 41 | **31** |
| 8 | **28** | 2-TBSO-Ph | Zn (5) | MsOH (5) | 0–20 | 42[a] | **32**[a] |

[a] Only the desilylated product was isolated.

4-fluorobenzaldehyde, were more reactive: (*R*,*R*)-**26** reacted with $SmI_2$ and $BF_3{\cdot}Et_2O$ in 42% yield only, but in 84% yield with the Zn/MsOH couple (entries 4, 5). The 4-methoxyphenyl derivative (*R*,*R*)-**27**, on the other hand, gave, under all reaction conditions, compound (*R*,*R*,*S*,*S*)-**31** in less than 50% yield (entries 6, 7). Bis-imines derived from hydroxyaldehydes decomposed under all reaction conditions; however, the corresponding *t*-butyldimethylsilyl derivative (imine **28**) smoothly reacted in the presence of Zn/MsOH to afford desilylated (*R*,*R*,*S*,*S*)-**32** in 42% yield (entry 8).** We can conclude that the procedure featuring metallic zinc and methanesulphonic acid allows the synthesis of enantiomerically pure $C_2$-symmetric 1,2-diamines more efficiently than when the reaction was promoted by $SmI_2$ and Lewis acids.




**Scheme 1.** *Reagents and conditions*: (a) allyl bromide, NaH, THF, 65°C, 18 h, 52%; (b) PhCOCl, TEA, $CH_2Cl_2$, 0–20°C, 20 h, 90%; (c) LAH, THF, 65°C, 8 h, 64%; (d) phthaloyl chloride, NaH, THF, 65°C, 27 h, 56%.

** The absolute configuration of $C_2$-symmetric diamines **30**–**32** was assigned by analogy with **29** on the basis of the NMR spectra.

Further functionalization of **29** is under investigation (Scheme 1): direct allylation to give the corresponding tertiary diamine **33** was easily achieved using standard conditions, while no direct benzylation occurred; to synthesize **35**, benzoylation of **29** and subsequent reduction of the bis-amide **34** was necessary. Interestingly, tetracyclic compound **36**, which can be converted to a sort of chiral DABCO, was easily obtained by reaction of **29** with phthaloyl chloride. Further reduction of the amide groups, however, was not easily achieved, since breaking of the strained C(O)–N bond occurred preferentially, with formation of decomposition products. Derivatives **34** and **36** may find interesting applications as chiral ligands,[35] while amines **29**–**32** represent a good starting material for the preparation of chiral organic catalysts.[36]

## 4. Conclusions

In conclusion, the scope and limitation of the homocoupling pinacol-type reaction of imines in the presence of $SmI_2$ and $Yb(OTf)_3$ or $BF_3{\cdot}Et_2O$ were investigated. This procedure was extended to the synthesis of $C_2$-symmetric enantiomerically pure 1,2-diamines via intramolecular coupling: in these cases, a different methodology employing metallic zinc and methanesulphonic acid was found to be more convenient. The synthesis of some chiral, enantiomerically pure $C_2$-symmetric 1,2-diamines and their derivatives was thus achieved in good chemical yields and with complete stereoselectivity.

## 5. Experimental

Elemental analyses were performed on a Perkin–Elmer 240 instrument. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM300 spectrometer at 300.133 and 75.47 MHz, respectively, in $CDCl_3$ as solvent; $^1H$ chemical shifts are reported in $\delta$ relative to TMS; $^{13}C$ chemical shifts are reported in Hz. IR spectra were recorded in $CH_2Cl_2$ solution on a Perkin–Elmer 1725 FTIR spectrometer. Optical activities were measured with a Perkin–Elmer 241 polarimeter. Melting points are uncorrected.

Silica gel (230–400 mesh) was used for flash chromatography. Dry solvents were distilled as follows: THF from Na and benzophenone (twice); $CH_2Cl_2$ from $CaH_2$; dry solvents were kept under a nitrogen atmosphere. HMPA was distilled from $CaH_2$ (in vacuo) and stored under a nitrogen atmosphere over 4 Å molecular sieves. All reactions employing dry solvents were run under a nitrogen atmosphere. Commercially available (Aldrich) 0.1 M solution of $SmI_2$ in dry THF was used in the coupling procedure.

All imines were prepared as previously described,[37] and used without further purification.

### 5.1. General procedure for the synthesis of 1,2-diamines promoted by $SmI_2$

To a stirred 0.1 M solution of the required imine in dry THF, kept under a argon atmosphere at the desired temperature, the required amounts of additive and of 0.1 M $SmI_2$ in THF were added (see Tables 1–4); the reaction was allowed to stand at the desired temperature for 15–20 h, then quenched with saturated aqueous $NaHCO_3$ and filtered through a Celite pad. The two phases were separated, and the aqueous layers extracted twice with $CH_2Cl_2$. The organic extracts were then washed with saturated aqueous $Na_2SO_3$, dried over $Na_2SO_4$ and filtered before removal of the solvent under reduced pressure. The crude products were purified by flash chromatography; reaction conditions, chemical yields and diastereoisomeric ratios are collected in Tables 1–4.

### 5.2. General procedure for the intramolecular coupling of 1,2-bis-imines promoted by Zn and MsOH

To a stirred 0.1 M solution of the required bis-imine in dry THF, kept under a argon atmosphere at 0°C, 5 equiv. of metallic Zn and 5 equiv. of methanesulphonic acid were added. The reaction was allowed to stand at rt for 20 h, then quenched with saturated aqueous $NaHCO_3$ and filtered; the salts were washed with $Et_2O$. The two phases were separated, and the aqueous layers extracted twice with $CH_2Cl_2$. Organic phases were dried over $Na_2SO_4$ and filtered before removal of the solvent under reduced pressure. The crude products were purified by flash chromatography; reaction conditions, chemical yields and diastereoisomeric ratios are collected in Tables 3 and 4.

Diamines **8**,[38] **9**,[23] **10**,[23,39] **19**,[40] **20**,[13] **21**,[23] **22**,[23] **29**,[33] are known compounds.

**Compound 11a** was purified with hexanes/$Et_2O$ 50/50 as eluents. Found: C, 79.65; H, 7.10; N, 13.31%; $C_{28}H_{30}N_4$ requires C, 79.59; H, 7.16; N, 13.26; $^1H$ NMR: $\delta=7.43$ (t, $J=7.0$ Hz, 2H), 7.27–7.13 (m, 10H), 6.97 (d, $J=7.0$ Hz, 2H), 7.00 (d, $J=7.0$ Hz, 2H), 4.05 (s, 2H), 3.60 (B part of an AB system, $J=10.0$ Hz, 2H), 3.40 (B part of an AB system, $J=10.0$ Hz, 2H), 2.49 (s, 6H).

**Compounds 12a,b** were purified with hexanes/$Et_2O$ 50/50 as eluents. Found: C, 71.17; H, 5.96; N, 6.99; $C_{24}H_{24}N_2S_2$ requires C, 71.25; H, 5.98; N, 6.93%. **12a**: $^1H$ NMR: $\delta=7.27$–$7.00$ (m, 8H), 7.33 (dd, $J=7.0$, 1.0 Hz, 4H), 7.00 (m, 4H), 4.05 (s, 2H), 3.67 (B part of an AB system, $J=13.5$ Hz, 2H), 3.40 (B part of an AB system, $J=13.5$ Hz, 2H). **12b**: $^1H$ NMR: $\delta=7.37$–$7.23$ (m, 12H), 6.87 (dd, $J=6.5$, 4.5 Hz, 2H), 6.73 (d, $J=6.5$ Hz, 2H), 4.04 (s, 2H), 3.80 (B part of an AB system, $J=8.0$ Hz, 2H), 3.60 (B part of an AB system, $J=8.0$ Hz, 2H).

**Compounds 13a,b** were purified with hexanes/$Et_2O$ 50/50 as eluents. Found: C, 83.20; H, 9.92; N, 6.89; $C_{28}H_{40}N_2$ requires C, 83.11; H, 9.96; N, 6.92%. **13a**: $^1H$ NMR: $\delta=7.40$–$7.20$ (m, 10H), 3.72 (AB system, $J=$

12.0, 4H), 2.43 (d, $J=4.0$ Hz, 2H), 1.90 (m, 2H), 1.87–1.00 (m, 20H). **13b**: $^1$H NMR: $\delta=7.40$–7.20 (m, 10H), 3.67 (AB system, $J=6.0$, 4H), 2.10 (d, $J=7.0$ Hz, 2H), 1.92 (m, 2H), 1.87–1.00 (m, 20H).

**Compounds 24a,b** were purified with $CH_2Cl_2$/MeOH 95/5 as eluents. Found: C, 86.14; H, 7.19; N, 6.64; $C_{30}H_{30}N_2$ requires C, 86.08; H, 7.22; N, 6.69%. **24a**: $[\alpha]_D^{20}=+152°$ ($c$ 0.548, $CH_2Cl_2$); $^1$H NMR: $\delta=7.33$–7.20 (m, 16H), 3.90 (s, 2H), 3.75 (s, 4H), 2.32 ( s, 6H); $^{13}$C NMR: $\delta=130.8$, 128.2, 128.0, 127.8, 126.7, 61.1, 51.05, 20.8. **24b**: $^1$H NMR: $\delta=7.38$–7.10 (m, 16H), 3.96 (B part of an AB system, $J=13.5$ Hz, 2H), 3.75 (m, 4H), 2.31 (s, 3H), 2.28 (s, 3H).

**Compound 30** was purified with $CH_2Cl_2$/MeOH 95/5 as eluents. Found: C, 73.15; H, 6.75; N, 8.53; $C_{20}H_{22}N_2F_2$ requires C, 73.08; H, 6.79; N, 8.61%; mp 85–88°C; $[\alpha]_D^{20}=-61.0°$ ($c$ 0.384, $CH_2Cl_2$); $^1$H NMR: $\delta=7.07$ (dd, $J=5.5$, 8.6 Hz, 4H), 6.83 (t, $J=8.6$ Hz, 4H), 3.77 (s, 2H), 2.65 (m, 2H), 1.78 (m, 4H), 1.43 (m, 4H); $^{13}$C NMR: $\delta=163.6$, 160.3, 136.6, 129.6, 129.5, 114.8, 114.5, 113.3, 67.7, 61.3, 31.5, 24.75.

**Compound 31**: the compound was purified with $CH_2Cl_2$/MeOH 95/5 as eluents. Found: C, 75.02; H, 7.97; N, 8.00; $C_{22}H_{28}N_2O_2$ requires C, 74.97; H, 8.01; N, 7.95%; mp 108–125°C; $[\alpha]_D^{20}=-114.7°$ ($c$ 0.204, $CH_2Cl_2$); $^1$H NMR: $\delta=7.08$ (d, $J=8.2$ Hz, 4H), 7.00 (d, $J=8.2$ Hz, 4H), 3.84 (s, 2H), 3.73 (s, 6H), 2.67 (m, 2H), 1.78 (m, 4H), 1.43 (m, 4H); $^{13}$C NMR: $\delta=158.7$, 153.9, 129.3, 113.3, 67.1, 61.1, 55.05, 31.2, 24.65.

**Compound 32**: the compound was purified with $CH_2Cl_2$/MeOH 95/5 as eluents. Found: C, 74.01; H, 7.49; N, 8.67; $C_{20}H_{24}N_2O_2$ requires C, 74.05; H, 7.46; N, 8.64%; mp 205–210°C; $[\alpha]_D^{20}=-20.5°$ ($c$ 1.186, $CH_2Cl_2$); $^1$H NMR: $\delta=7.09$ (dt, $J=7.8$, 1.6 Hz, 2H), 6.87 (d, $J=7.8$ Hz, 2H), 6.45 (dt, $J=7.8$, 1.0 Hz, 2H), 6.15 (dd, $J=7.8$,1.6 Hz, 2H), 4.20 (s, 2H), 2.73 (m, 2H), 1.83 (m, 4H), 1.43(m, 4H); $^{13}$C NMR: $\delta=156.8$, 130.15, 129.0, 123.0, 118.65, 116.6, 63.3, 59.7, 31.4, 24.3.

**Synthesis of 33**: NaH (2.2 equiv.) was washed with pentane and suspended in dry THF (10 ml) in a nitrogen atmosphere. A solution of (*R*,*R*,*S*,*S*)-**29** (1 equiv.) in dry THF (5 ml) was then added at rt. After 1 h, allyl bromide (3.3 equiv.) was added dropwise; the reaction was refluxed for 27 h and then quenched with saturated aqueous $NH_4Cl$. The two phases were separated, and the aqueous layers extracted twice with $Et_2O$ and twice with $CH_2Cl_2$. Organic phases were dried over $Na_2SO_4$ and filtered before removal of the solvent under reduced pressure. The compound was purified by flash chromatography with hexanes/$Et_2O$ 50/50 as eluents (52%). Found: C, 83.78; H, 8.64; N, 7.57; $C_{26}H_{32}N_2$ requires C, 83.82; H, 8.66; N, 7.52%; mp 110–116°C; $[\alpha]_D^{20}=-73.8°$ ($c$ 0.336, $CH_2Cl_2$); $^1$H NMR: $\delta=7.07$–6.93 (m, 10H), 5.91 (m, 2H), 5.07 (dd, $J=10.5$, 1.2 Hz, 2H), 4.90 (dd, $J=17.2$, 1.4 Hz, 2H), 3.63 (s, 2H), 3.33 (B part of an AB system, $J=16.0$, 6.3 Hz, 2H), 2.91 (A part of an AB system, $J=16.0$, 6.8 Hz, 2H), 2.54 (bd, $J=8.5$ Hz, 2H), 2.27 (d, $J=8.5$ Hz, 2H), 1.80 (m, 2H), 1.32 (m, 4H).

**Synthesis of 34**: to a solution of benzoyl chloride (3 equiv.) and triethylamine (4 equiv.) in dry $CH_2Cl_2$ (5 ml) kept at 0°C under a nitrogen atmosphere, a solution of (*R*,*R*,*S*,*S*)-**29** (1 equiv.) in 5 ml of dry $CH_2Cl_2$ was added. The reaction was kept at rt for 20 h, and then quenched with $H_2O$. The two phases were separated, and the aqueous layers extracted twice with $CH_2Cl_2$. Organic phases were dried over $Na_2SO_4$ and filtered before removal of the solvent under reduced pressure. The compound was purified by flash chromatography with hexanes/$Et_2O$ 50/50 as eluents (90%) Found: C, 81.52; H, 6.49; N, 5.53; $C_{34}H_{32}N_2O_2$ requires C, 81.57; H, 6.44; N, 5.60%; mp 228–230°C; $[\alpha]_D^{20}=+43.0°$ ($c$ 0.360, $CH_2Cl_2$); $\nu$ 1695 cm$^{-1}$; $^1$H NMR: $\delta=7.50$–7.15 (m, 20H), 5.51 (s, 2H), 3.80 (m, 2H), 1.78 (m, 4H), 1.53 (m, 4H); $^{13}$C NMR: $\delta=173.9$, 135.9, 133.4, 130.1, 129.1, 128.4, 127.3, 126.0, 65.45, 56.6, 32.1, 25.1.

**Synthesis of 35**: $LiAlH_4$ (5 equiv.) was suspended in 20 ml of dry THF and kept under a nitrogen atmosphere. (*R*,*R*,*S*,*S*)-**34** dissolved in dry THF (10 ml) was added, and the reaction mixture refluxed for 3.5 h, then quenched with $H_2O$ (86.4 ml). Salts were filtered and washed with $Et_2O$; organics were then dried over $Na_2SO_4$ and filtered before removal of the solvent under reduced pressure. The compound was purified by flash chromatography with hexanes/$Et_2O$ 50/50 as eluents (64%). Found: C, 86.31; H, 7.72; N, 5.98; $C_{34}H_{36}N_2$ requires C, 86.40; H, 7.68; N, 5.93%; mp 149–151°C; $[\alpha]_D^{20}=-156.0°$ ($c$ 0.442, $CH_2Cl_2$); $^1$H NMR: $\delta=7.23$ (m, 12H), 6.98 (s, 8H), 3.85 (B part of an AB system, $J=16.5$ Hz, 2H), 3.65 (s, 2H), 3.37 (A part of an AB system, $J=13.5$ Hz, 2H), 3.00 (m, 2H), 1.60 (m, 2H), 1.27–1.07 (m, 4H); $^{13}$C NMR: $\delta=141.6$, 129.2, 127.6, 127.5, 127.4, 126.5, 125.7, 75.0, 67.9, 56.1, 31.7, 25.1.

**Synthesis of 36**: NaH (2.2 equiv.) was washed with pentane and suspended in dry THF (10 ml) in a nitrogen atmosphere. A solution of (*R*,*R*,*S*,*S*)-**29** (1 equiv.) in dry THF (5 ml) was then added at rt. After 1 h, phthaloyl chloride (1 equiv.) was added; the reaction was refluxed for 27 h, and then quenched with saturated aqueous $NH_4Cl$. The two phases were separated, and the aqueous layers extracted twice with $Et_2O$ and twice with $CH_2Cl_2$. Organic phases were dried over $Na_2SO_4$ and filtered before removal of the solvent under reduced pressure. The compound was purified by flash chromatography with $CH_2Cl_2$/MeOH 95/5 as eluents (56%). Found: C, 79.67; H, 6.24; N, 6.59; $C_{28}H_{26}N_2O_2$ requires C, 79.60; H, 6.20; N, 6.63%; mp >250°C; $[\alpha]_D^{20}=+248.0°$ ($c$ 0.364, $CH_2Cl_2$); $\nu$ 1695 cm$^{-1}$; $^1$H NMR: $\delta=7.65$ (bs, 4H), 7.30 (bs, 8H), 7.03 (bs, 2H), 6.65 (bs, 2H), 6.07 (bs, 2H), 3.37 (bs, 2H), 1.86 (m, 2H), 1.33–1.13 (m, 6H); $^{13}$C NMR: $\delta=171.1$, 139.8, 128.9, 127.1, 126.1, 124.1, 59.0, 33.5, 24.4.

## Acknowledgements

We thank Sara Nemfardi and Andrea Tam for their helpful collaboration. Partial financial support by MIUR and CNR-ISTM is gratefully acknowledged.

## References


1. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.
2. Robertson, G. M. In *Comprehensive Organic Synthesis*; Trosi, B. M.; Fleming, I., Eds. Pinacol coupling reactionsin; Pergamon Press: Oxford, 1991; Vol. 3, pp. 563–611.
3. Benaglia, M.; Raimondi, L. In *Seminars in Organic Synthesis*; Cozzi, F., Ed. Stereoselection in Pinacol Coupling Reactions of C=O and C=N Double Bonds; Società Chimica Italiana, 1998; pp. 225–250.
4. Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug Res.* **1989**, *33*, 135–149.
5. Taniguchi, N.; Uemura, M. *Tetrahedron* **1998**, *54*, 12775–12788.
6. Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315–1318.
7. Yanada, R.; Okaniwa, M.; Kaieda, A.; Ibuka, T.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 1283–1286.
8. Dutta, M. P.; Baruah, B.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Synlett* **1998**, 857–858.
9. Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873–874.
10. Kise, N.; Ueda, N. *Tetrahedron Lett.* **2001**, *42*, 2365–2368.
11. Sergeeva, E. V.; Rozenberg, V. I.; Antonov, D. Y.; Vorontsov, E. V.; Starikova, Z. A.; Hopf, H. *Tetrahedron: Asymmetry* **2002**, *13*, 1121–1123.
12. Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421–9424.
13. Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577–7580.
14. Selvakumar, K.; Harrod, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 2129–2131.
15. Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* **2001**, *66*, 2990–2994.
16. Rieke, R. D.; Kim, S.-H. *J. Org. Chem.* **1998**, *63*, 5235–5239.
17. Jin, W.-S.; Makioka, Y.; Taniguchi, Y.; Kitamura, T.; Fujiwara, Y. *Chem. Commun.* **1998**, 1101–1102.
18. Shimizu, M.; Niwa, Y. *Tetrahedron Lett.* **2001**, *42*, 2829–2832.
19. Jeevanandam, A.; Cartwright, C.; Ling, Y.-C. *Synth. Commun.* **2000**, *30*, 3153–3160.
20. Campos, P. J.; Arranz, J.; Rodríguez, M. A. *Tetrahedron* **2000**, *56*, 7285–7289.
21. Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2002**, *4*, 835–838.
22. Masson, G.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772–1775.
23. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1998**, *39*, 3333–3336.
24. Molander, G. A.; Harris, C. *Chem. Rev.* **1996**, *96*, 307–338.
25. Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049–10053.
26. Tichy, M.; Holanova, J.; Zavada, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3497–3504.
27. Andrus, M. B.; Asgari, D.; Sclafani, J. A. *J. Org. Chem.* **1997**, *62*, 9365–9368.
28. For the use of different Lewis acids with $SmI_2$ in coupling reactions of aldehydes, see: Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L. *Eur. J. Org. Chem.* **1999**, 3369–3374.
29. Enemærke, R. J.; Herz, T.; Skrydstrup, T.; Daasbjerg, K. *Chem. Eur. J.* **2000**, *6*, 3747–3754.
30. Fuchs, J. R.; Mitchell, M. L.; Shabangi, N.; Flowers, R. A., III *Tetrahedron Lett.* **1997**, *38*, 8157–8158.
31. Kise, N.; Oike, H.; Okazaki, E.; Yoshimoto, M.; Shono, T. *J. Org. Chem.* **1995**, *60*, 3980–3992.
32. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.
33. Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.* **1991**, *56*, 3063–3067.
34. Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666–11667.
35. Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 1555–1558.
36. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
37. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 2939–2948 and references cited therein.
38. Cabanal-Duvillard, I.; Mangeney, P. *Tetrahedron Lett.* **1999**, *40*, 3877–3880.
39. Tanaka, H.; Dhimane, H.; Fujita, H.; Ikemoto, Y. *Tetrahedron Lett.* **1988**, *29*, 3811–3814.
40. Kanemasa, S.; Hayashi, T.; Tanaka, J.; Yamamoto, H.; Sakurai, T. *J. Org. Chem.* **1991**, *56*, 4473–4481.