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Mild synthesis of enantiomerically pure imidazo-[1,2-*a*]azepines mediated by Yb(OTf)$_3$

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Abstract—The reaction of various chiral 2,2′-diaryldialdehydes with achiral and chiral 1,2-diamines in the presence of Lewis acids to give imidazo[1,2-*a*]azepines was investigated. Best results were achieved with Yb(OTf)$_3$; the reaction outcome is strongly dependent upon the geometric features of both reactants. Kinetic resolution of *rac*-2,2′-dinaphthyldialdehyde with (*R*,*R*)-1,2-diphenyl-1,2-diamminoethane (up to 92% e.e.) was achieved. © 2001 Elsevier Science Ltd. All rights reserved.

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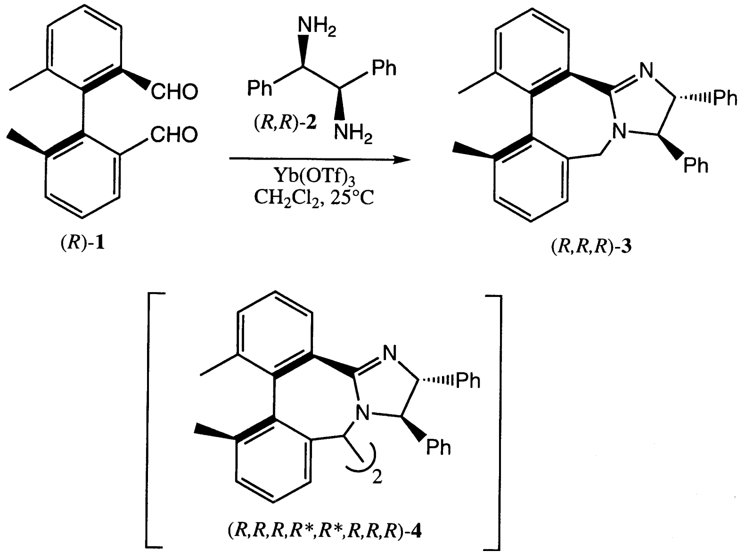
1. Introduction

The biological activity of molecules containing a modified azepinic ring is intensively tested, both in vitro and in vivo, against various diseases (e.g. cancer, AIDS-related dementia, Alzheimer's disease).[1,2] In the course of our studies toward the synthesis of chiral 1,2-diamines,[3] we observed that treatment of (*R*)-6,6′-dimethyldiphenyl-2,2′-dialdehyde **1** with (*R*,*R*)-1,2-diphenyl-1,2-diaminoethane **2** in the presence of Yb(OTf)$_3$ unexpectedly led to the diastereoisomerically pure adduct (*R*,*R*,*R*)-**3** (93% chemical yield; Scheme 1).[†]

Actually, this reaction outcome is not completely unprecedented: inspection of the literature confirmed that in acidic conditions the condensation reaction between diphenyl-2,2′-dialdehydes with 1,2-diamines led to the synthesis of imidazo[1,2-*a*]azepines via formation of an hydroimidazole,



Scheme 1. Synthesis of (*R*,*R*,*R*)-**3** in the presence of Yb(OTf)$_3$.

Keywords: imidazo[1,2-*a*]azepines; ytterbium triflate; imine; kinetic resolution.

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[†] The formation of (*R*,*R*,*R*)-**3** was first observed when the reaction was performed in THF and in the presence of SmI$_2$ together with Yb(OTf)$_3$. However, Sm(II) species did not interfere with the reaction, and only led to traces of a dimeric product **4** (Scheme 1), derived from **3** via hydrogen abstraction and dimerization of the benzylic radical.

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Table 1. Reaction of dialdehyde *rac*-**5** with different 1,2-diamines under acidic conditions. Structures of reactants and adducts are given in Fig. 1 and Scheme 1

Entry	1,2-Diamine	*T* (°C)	Acid	Product	Yield%[a]
1	**6**	25	$Yb(OTf)_3$	*rac*-**7**	47
2	**6**	40	$Yb(OTf)_3$	*rac*-**7**	40
3	**6**	25	$Yb(OTf)_3$[b]	–	–
4	**6**	25	$TiCl_4$	*rac*-**7**	46
5	**6**	25	CF_3COOH	*rac*-**7**	27
6	(*R*,*R*)-**2**	25	$Yb(OTf)_3$	(R^*,*R*,*R*)-**8**	5
7	(*R*,*R*)-**9**	25	$Yb(OTf)_3$	(R^*,*R*,*R*)-**10**	12
8	(*R*,*R*)-**9**	40	$Yb(OTf)_3$	(R^*,*R*,*R*)-**10**	18

[a] Yields refer to products purified by flash chromatography.

[b] 0.2 M equiv.

subsequent intramolecular nucleophilic addition of one of the imidazole nitrogens to the aldehydic carbon, loss of water and 1,3-hydride shift.[4,5] However, the use of $Yb(OTf)_3$ as Lewis acid allows the reaction to be carried on under milder conditions (12 h at room temperature instead of 24 h in refluxing acetic acid).[‡] Moreover, chemical yields seemed to be excellent. We thus undertook more detailed studies, in order to verify the applicability of this improved methodology to a general synthesis of imidazo[1,2-*a*]azepines.

2. Results and discussion

Racemic diphenyl-2,2′-dialdehyde **5** was initially chosen as a substrate, and its reaction with various 1,2-diamines in the presence of different acidic species was examined. All reactions were run in CH_2Cl_2 as solvent for 12 h in the presence of 1 M equiv. of $Yb(OTf)_3$ under a nitrogen atmosphere. Significant results are collected in Table 1. Structures of the reactants and adducts are shown in Fig. 1 and Scheme 1. Adducts were fully characterized by spectroscopic techniques, as discussed later.

Table 2. Reaction of chiral dialdehydes (*R*)-**1** and (*R*)-**13** with different diamines in the presence of $Yb(OTf)_3$. Structures of reactants and adducts are given in Figs. 1 and 2 and Scheme 1

Entry	Dialdehyde	Diamine	*T* (°C)	Product	Yield%[a]
1	(*R*)-**1**	(*R*,*R*)-**2**	25	(*R*,*R*,*R*)-**3**	93
2	(*R*)-**1**	(*R*,*R*)-**9**	25	(*R*,*R*,*R*)-**11**	23[b]
3	(*R*)-**1**	(*R*,*R*)-**9**	40	(*R*,*R*,*R*)-**11**	25[b]
4	(*R*)-**1**	**6**	25	(*R*)-**12**	45
5	(*R*)-**13**	(*R*,*R*)-**2**	25	(*R*,*R*,*R*)-**14**	41
6	(*R*)-**13**	(*S*,*S*)-**2**	25	–	–

[a] Yields refer to products purified by flash chromatography.

[b] Yield was estimated by ^1H NMR (the product decomposed on silica gel).

Surprisingly enough, from the reaction of *rac*-**5** with 1,2-diaminobenzene **6** the expected product **7** was isolated in 47% yield only (entry 1). No improvements were observed upon performing the reaction in refluxing CH_2Cl_2 (entry 2), while the use of catalytic $Yb(OTf)_3$ did not afford reasonable quantities of the adduct (only unreacted **5** and **6** were isolated—entry 3). We turned our attention to the use of other acidic species, in an attempt to increase the chemical yields; however, the results were disappointing. Only in the presence of $TiCl_4$ the reaction proceeded with decent, but not improved, yield (entry 4). The use of strong protic species such as CF_3COOH (1 M equiv.) led to the formation of **7**, but only in 27% yield (entry 5).

Furthermore, diamine (*R*,*R*)-**2**, which gave excellent results in the reaction with dialdehyde (*R*)-**1** (Scheme 1), was almost unreactive with *rac*-**5**: only traces of the corresponding imidazo[1,2-*a*]azepine **8** were isolated (entry 6). The use of (*R*,*R*)-1,2-diaminocyclohexane **9** was also disappointing: adduct **10** was isolated in only 12% yield when the reaction was performed at room temperature, and in slightly higher yields (18%) at 40°C (entries 7 and 8).

Based on these results, we decided to re-examine the reaction of (*R*)-**1** with different diamines; the results are

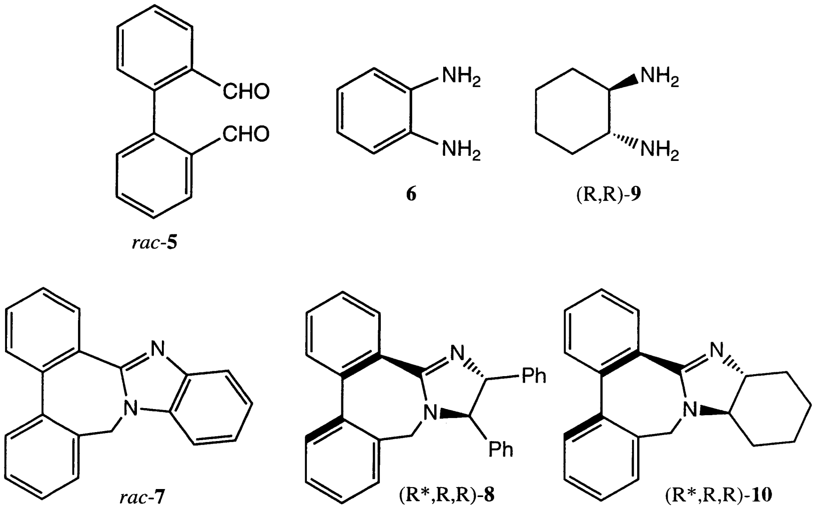
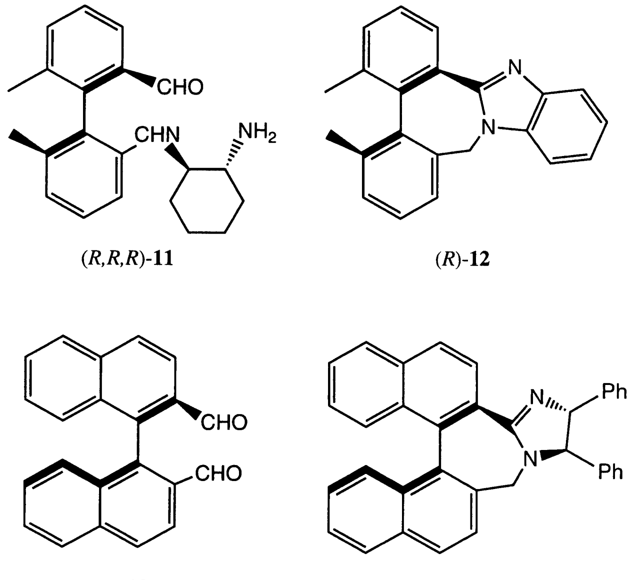


Figure 1. Structures of *rac*-**5**, 1,2-diamines **6**, (*R*,*R*)-**9** and adducts **7**, **8** and **10** (Table 1).

[‡] $Yb(OTf)_3$ was chosen because of its recognized ability to activate imines toward nucleophilic attack at carbon. See Ref. 3 and references therein.



(*R*,*R*,*R*)-**11** (*R*)-**12** (*R*)-**13** (*R*,*R*,*R*)-**14**

Figure 2. Structures of dialdehyde (*R*)-**13** and adducts **11**, **12** and **14** (Table 2).

collected in Table 2, structures of reactants and adducts in Figs. 1 and 2, and Scheme 1.

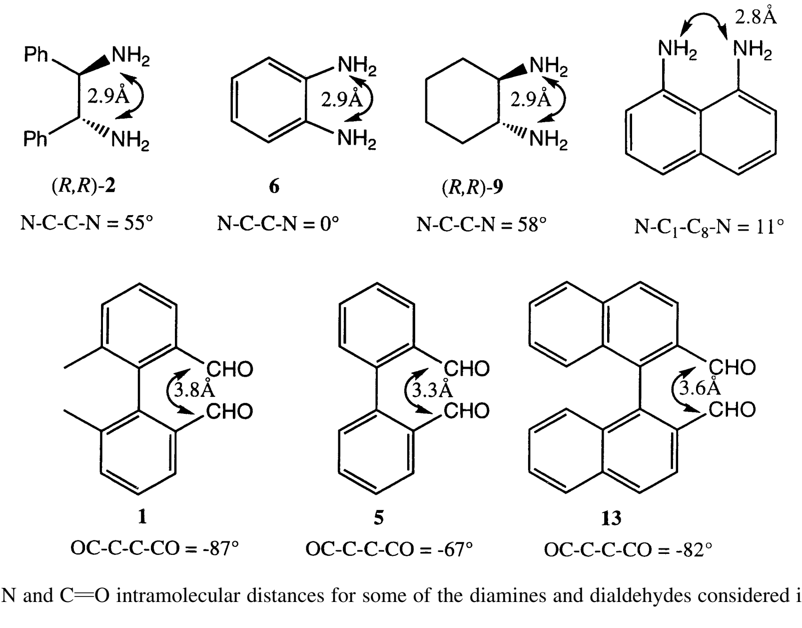
We were pleased to find that the reaction of (*R*)-**1** with (*R*,*R*)-**2** in the presence of $Yb(OTf)_3$ allowed for the formation of (*R*,*R*,*R*)-**3** in excellent chemical yield (entry 1). The use of different diamines led again to disappointing results: with (*R*,*R*)-**9** only the corresponding monoimine **11** was formed, at room temperature as well as in refluxing CH_2Cl_2 (entries 2 and 3); only one diastereoisomer was isolated. In the reaction with 1,2-diaminobenzene **6**, adduct **12** was isolated in 45% yield (entry 4). The reaction of (*R*)-**1** with flexible 1,5-diaminopentane and 1,6-diaminohexane only led to the formation of polymeric imines; on the other hand, with 1,8-diaminonaphthalene (a rigid, planar 1,3-diamine) a complex mixture of products was isolated, with no formation of the expected imidazo[1,2-*a*]azepine.

The reaction of chiral, enantiomerically pure (*R*)-2,2′-dinaphthyldialdehyde **13** with (*R*,*R*)-**2** led to the expected enantiomerically pure imidazo[1,2-*a*]azepine (*R*,*R*,*R*)-**14** as the unique product in 41% chemical yield (entry 5). On the other hand, no reaction occurred between (*R*)-**13** and the mismatching diamine (*S*,*S*)-**2** (entry 6), thus demonstrating the existence of both the matching (*R*)-**13** plus (*R*,*R*)-**2** and the mismatching (*R*)-**13** plus (*S*,*S*)-**2** couples.

2.1. Structural elucidation by ^1H and ^{13}C NMR spectroscopy

A complete spectroscopic investigation was performed to establish the structure of all reaction products depicted in Figs. 1 and 2, and in Scheme 1. A concerted use of several gradient-enhanced experiments such as 2D COSY, $^1H/^{13}C$ 2D HMQC (Heteronuclear Multiple-Quantum Coherence)[6] and $^1H/^{13}C$ 2D HMBC (Heteronuclear Multiple-Bond Correlation)[6–8] provided the sequence-specific assignment of all compounds allowing the structural elucidation of these multi-ring aromatic derivatives. The ^1H and ^{13}C NMR chemical shifts values are reported in Section 4.

From the multiplicity and the $^1H/^1H$ connectivities found in 2D COSY spectra, we were able to distinguish the H8–H10 and H8′–H10′ series of the protons for compounds **3**, **11**, **12**, as H8–H11 and H8′–H11′ protons for **7**, from the other aromatic hydrogens H14–H6 and H17–H19 for **3**, or H12–H15, for **12**, but it was impossible to assign each series of these three (four) protons to the right ring (for the proton and carbon numbering, see Fig. 4). For this purpose we performed the heteronuclear direct- and multiple-bond correlations experiments: the $^1H/^{13}C$ HMQC gave for all protons the direct attachment to carbons, while the $^1H/^{13}C$ HMBC allowed the complete assignments of all protons and quaternary carbons. The correlation of C3 with H8 and C5 with H8′ for all compounds, and of C3 with H7 and C5 with



(*R*,*R*)-**2** N-C-C-N = 55°

6 N-C-C-N = 0°

(*R*,*R*)-**9** N-C-C-N = 58°

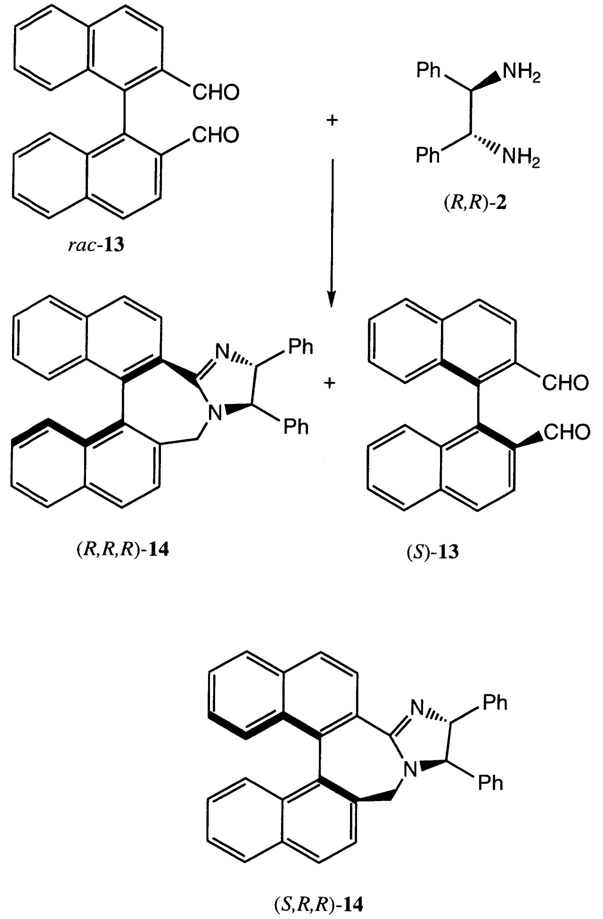
N-C_1-C_8-N = 11°

1 OC-C-C-CO = -87°

5 OC-C-C-CO = -67°

13 OC-C-C-CO = -82°

Figure 3. Dihedral angles, N–N and C=O intramolecular distances for some of the diamines and dialdehydes considered in the present work.



Scheme 2. Kinetic resolution of *rac*-**13** with (*R*,*R*)-**2**.

H6 in the case of **7** and **12**, was the key to assign the hydrogens of the diaryl moiety and, as a consequence, the other set of aromatic protons. This was supported by the correlation of C6 with H14, in compounds **3**, **7**, **12**, **14**, and of C7 with H17 (**3**, **14**) or H13 (**7**, **12**). Moreover, the C2′ carbon showed both long-range couplings with H5 and H8, which allowed us to distinguish C2 from C2′, as the correlation with H8 or H8′ distinguish C1 from C1′. The methylene protons H5 gave an AB system, with a geminal coupling constant of about 14 Hz, in **3**, **7**, **12**, **14**.

2.2. Discussion

Our results allow some interesting considerations: first of all, the structure of the diamine plays the major role in determining the feasibility of the reaction. With planar, aromatic 1,2-diamines, such as 1,2-diaminobenzene **6**, similar chemical yields are observed with both 2,2′-diphenyldialdehyde **5** and 6,6′-dimethyl-2,2′-diphenyldialdehyde **1**.[§] Obviously, a 1,2-planar arrangement of the two reacting nitrogens guarantees a smooth reaction path. Other planar diamines, such as 1,8-diaminonaphthalene, did not react as expected despite a similar N–N distance (2.8 vs 2.9 Å) and an almost planar arrangement (11 vs 0°) in both cases (Fig. 3). A 1,2-relationship between the two amino groups evidently avoids strain in the formation of a fused imidazolinic ring, the first step in the proposed reaction path.[3,4] Some structural data for the diamines and the dialdehydes used in this work, as evaluated in vacuo by molecular mechanic techniques, are shown in Fig. 3.[¶]

Similar considerations apply for aliphatic and alicyclic 1,2-diamines. When reacted with (*R*)-**1**, flexible (*R*,*R*)-**2** can better be accommodated on the forming imidazolinic ring than (*R*,*R*)-**9** (Table 2); in the first case, the imidazo[1,2-*a*]azepinic ring is formed in excellent yields, while in the latter, the equilibria are shifted toward the formation of the corresponding monoimine. Reasonably enough, 1,5- and 1,6-diamines led only to dimeric imines, while formation of intramolecular bis-imines or imidazo[1,2-*a*]azepine is completely disfavored.

Also the differences between the reactivity of dialdehydes **1**, **5** and **13** can be ascribed to their structural differences (Fig. 3). The two *ortho* methyl groups lock the aryl rings of dialdehyde **1** in an almost orthogonal conformation (−87°), while in the less constrained dialdehyde **5** the dihedral angle closes up to −67°. This decreases the distance between the two carbonyls from 3.8 to 3.2 Å. Differences between the conformations of 2,2′-dinaphthyldialdehyde **13** and of 6,6′-dimethyl-2,2′-diphenyldialdehyde **1** are even smaller: both compounds show an almost identical dihedral angle between the two aryl groups, the steric hyndrance of an *ortho*-fused phenyl ring being comparable to the one of an *ortho*-methyl residue. The two carbonyls, however, are slightly closer in 2,2′-dinaphthyldialdehyde **13** (3.6 Å) than in 6,6′-dimethyl-2,2′-diphenyldialdehyde **1** (3.8 Å). The reaction mechanism greatly amplifies these apparently insignificant differences (Tables 1 and 2), thus revealing a strong dependence of the reaction path upon geometrical constrains of both reactants.

Our results, together with literature data,[3,4] clearly indicate the limits of this reaction; however, good to excellent results can be obtained with chiral, enantiomerically pure, matching reactants, as in the case of (*R*)-**1** and (*R*)-**13** with (*R*,*R*)-**2** (Table 2, entries 1 and 5). To further test this point, we undertook an investigation of the feasibility of a kinetic resolution of *rac*-**13**:[11] clearly, only (*R*)-**13** would react in the presence of diamine (*R*,*R*)-**2**, thus allowing for a maximum 50% yield. Indeed, in the reaction of *rac*-**13** with (*R*,*R*)-**2**, we isolated the expected imidazo[1,2-*a*]azepine (*R*,*R*,*R*)-**14** in 13% yield; unreacted (*S*)-**13** (15% yield) showed a 92% optical purity (Scheme 2). The multi-step nature of the reaction mechanism, with formation of several intermediates, can account for the low yield of the process. Attempts to increase the chemical yield by raising the reaction temperature, however, led to the formation of a diastereoisomeric mixture of (*R*,*R*,*R*)- and (*S*,*R*,*R*)-**14** in a 2:1 ratio and 21% yield (Scheme 2), while in the presence of only 0.5 M equiv. of (*R*,*R*)-**2** the reaction did not occur.

[§] Actually, in Refs. 4 and 5, authors employed 4,5-diaminopyrimidine and 2,3-diaminonaphthalene; the results were extremely similar to those obtained by us with 1,2-diaminobenzene **6**.

[¶] Molecular mechanic calculations were run on a SGI O2 workstation, with the MacroModel 5.5 package[9] and the MM2* force field.[10]

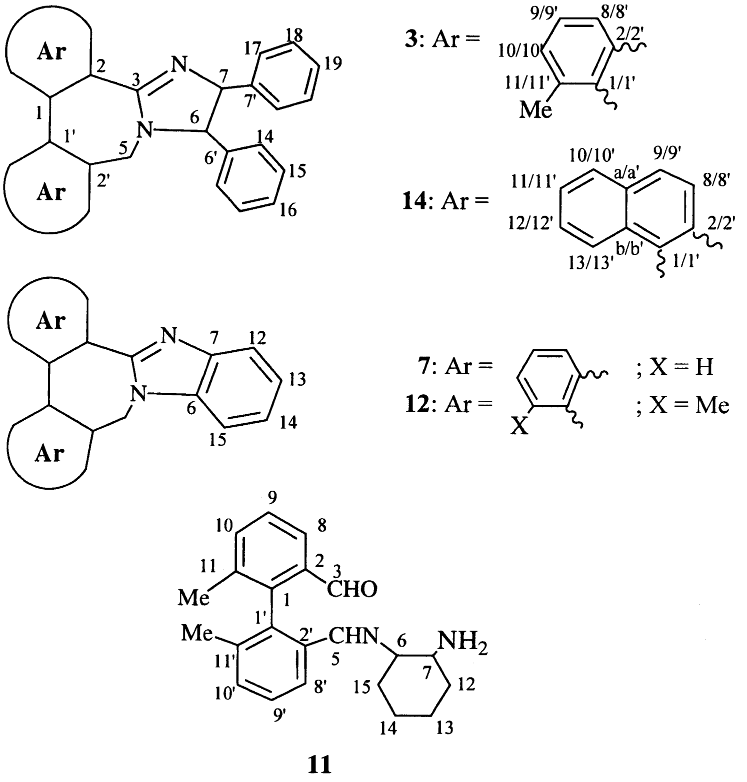


Figure 4. Numbering of imidazo[1,2-*a*]azepinic rings for NMR assignments.

3. Conclusion

The scope and limitations of a mild Lewis acid catalyzed synthesis of imidazo[1,2-*a*]azepines have been studied, and the structure of the products was elucidated by NMR techniques. The outcome of the process and the stereochemistry of the adducts are completely dominated by geometrical parameters of the reactants (as elucidated by molecular mechanics): when the reaction occurs, it is completely stereo- and enantio-selective. Matching and mismatching pairs play a major role when dealing with chiral reagents, to the point that only one enantiomer may lead to the heterocyclization reaction.

4. Experimental

CHN analyses were performed on a Perkin–Elmer 240 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM300 at 300.133 and 75.47 MHz, respectively, in $CDCl_3$ as solvent. ^{1}H chemical shifts are reported in δ relative to TMS; H–H coupling constants and ^{13}C chemical shifts are reported in Hz. IR Spectra were recorded in CH_2Cl_2 solution on a Perkin–Elmer 1725X FTIR spectrometer. Mass spectra were performed on an analytical VG 7070 EQ instrument. Optical activities were measured with a Perkin–Elmer 241 polarimeter. Melting points are uncorrected.

Silica gel (230–400 mesh) was used for flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. Dry CH_2Cl_2 was distilled from CaH_2 and kept under a nitrogen atmosphere.

Compounds (*R*,*R*)-**2**, (*S*,*S*)-**2**, **6**, (*R*,*R*)-**9** were commercially available. (*R*)-**1**,[12] *rac*-**5**,[13] *rac*-[14] and (*R*)-**13**[15] were prepared following known procedures.

4.1. General procedure for the synthesis of imidazo[1,2-*a*]azepines

To a stirred solution (10^{-3} M) of the desired dialdehyde in dry CH_2Cl_2, the required amount of Lewis or protic acid (Tables 1 and 2) and 1 mol of the diamine were added; the reaction was allowed to stir for 12 h either at room temperature (25°C) or at 40°C, in the presence of $MgSO_4$ or molecular sieves (4 Å) as drying agents. The reaction was monitored via TLC (silica gel). The reaction mixture was filtered, and after removal of solvent the organic residue was purified by flash chromatography. Chemical yields are collected in Tables 1 and 2. For the numbering system used in the description of the NMR spectra, see Fig. 4.[‖]

4.1.1. Compound (*R*,*R*,*R*)-3. The compound was a waxy compound; [Found: C, 86.96; H, 6.31; N, 6.73. $C_{30}H_{26}N_2$ requires C, 86.92; H, 6.32; N 6.76%]; R_f (Et_2O) 0.4; $[\alpha]_D^{20}=+70.0$ (*c* 0.3, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3055, 2930, 2360, 2341, 1735, 1602, 1454, 1263 cm^{-1}; δ_H (300.133 MHz, $CDCl_3$) 8.12 (1H, d, *J*=7.5 Hz, *H*-8), 7.51 (1H, d, *J*=7.5 Hz, *H*-10), 7.46 (1H, t, *J*=7.5 Hz, *H*-9), 7.37–7.33

[‖] We were not able to achieve a satisfactory purification of adducts **8** and **10**; thus, no complete spectroscopic and chemical characterization was possible in these two cases.

(4H, m, *H*-16, *H*-18, *H*-19), 7.28 (2H, d, *J*=7.0 Hz, *H*-17), 7.24 (2H, t, *J*=7.0 Hz, *H*-15), 7.20 (1H, d, *J*=7.5 Hz, *H*-10′), 6.97 (2H, d, *J*=7.0 Hz, *H*-14), 6.92 (1H, t, *J*=7.5 Hz, *H*-9′), 6.17 (1H, d, *J*=7.5 Hz, *H*-8′), 5.15 (1H, d, *J*=6.8 Hz, *H*-7), 4.77 (1H, d, *J*=6.8 Hz, *H*-6), 4.31 (1H, B part of an AB system, *J*=14.0 Hz, *H*-5$_B$), 3.73 (1H, A part of an AB system, *J*=14.0 Hz, *H*-5$_A$), 2.19 (3H, s, C*H*$_3$), 2.14 (3H, s, C*H*$_3$); δ_C (75.47 MHz, $CDCl_3$) 165.0 (*C*-3), 140.0 (*C*-2′), 138.5 (*C*-1, *C*-2, *C*-11), 138.2 (*C*-11′), 135.0 (*C*-1′), 134.0 (*C*-10), 130.5 (*C*-10′), 129.4 (*C*-14, *C*-16, *C*-18, *C*-19), 128.7 (*C*-8), 128.5 (*C*-9), 128.1 (*C*-14), 128.0 (*C*-9′), 126.7 (*C*-17), 125.0 (*C*-8′), 77.0 (*C*-6), 73.0 (*C*-7), 48.5 (*C*-5), 20.5, 2.19 (*C*H$_3$); *m*/*z* (FAB$^+$): 415 (MH$^+$).

4.1.2. Compound rac-7. The compound was a white solid, mp 150°C; [Found: C, 85.05; H, 4.98; N, 9.97. $C_{20}H_{14}N_2$ requires C, 85.08; H, 5.00; N, 9.92]; R_f (50% hexane/Et_2O) 0.19; ν_{max} (CH_2Cl_2) 3057, 2982, 2361, 1736, 1692, 1459, 1449, 1266, 1245 cm^{-1}; δ_H (300.133 MHz, $CDCl_3$) 8.31 (1H, dd, *J*=7.1, 2.2 Hz, *H*-8), 7.86 (1H, dd, *J*=7.4, 1.5 Hz, *H*-12), 7.66 (1H, dd, *J*=7.1, 2.2 Hz, *H*-9), 7.62 (3H, m, *H*-10, *H*-11, *H*-11′), 7.57 (1H, dd, *J*=7.4, 1.5 Hz, *H*-15), 7.48 (1H, dd, *J*=7.5, 1.5 Hz, *H*-8′), 7.45 (1H, dt, *J*=7.5, 1.5 Hz, *H*-10′), 7.40 (1H, t, *J*=7.5, 1.5 Hz, *H*-9′), 7.35 (1H, dt, *J*=7.5, 1.5 Hz, *H*-14), 7.27 (1H, dt, *J*=7.5, 1.5 Hz, *H*-13), 5.23 (1H, B part of an AB system, *J*=14.0 Hz, *H*-5$_B$), 5.00 (1H, A part of an AB system, *J*=14.0 Hz, *H*-5$_A$); δ_C (75.47 MHz, $CDCl_3$) 152.1 (*C*-3), 143.5 (*C*-7), 139.2 (*C*-1′), 138.0 (*C*-1), 136.3 (*C*-2, *C*-2′), 134.5 (*C*-6), 130.8 (*C*-11′), 130.6 (*C*-8), 130.2 (*C*-10), 130.0 (*C*-11), 129.0 (*C*-10′), 128.4 (*C*-9), 128.3 (*C*-9′), 127.5 (*C*-8′), 122.5 (*C*-14), 122.2 (*C*-13), 120.0 (*C*-12), 108.7 (*C*-15), 46.8 (*C*-5).

4.1.3. Compound (*R*)-12. The compound was isolated as a waxy compound; [Found: C, 85.17; H, 5.83; N, 9.00. $C_{22}H_{18}N_2$ requires C, 85.13; H, 5.85; N, 9.02]; R_f (Et_2O) 0.45; $[\alpha]_D$=+32.7 (*c* 0.2, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3057, 2935, 2361, 1735, 1658, 1456, 1265 cm^{-1}; δ_H (300.133 MHz, $CDCl_3$) 8.01 (1H, dd, *J*=7.1, 2.2 Hz, *H*-8), 7.81 (1H, dd, *J*=7.0, 1.8 Hz, *H*-12), 7.50–7.49 (2H, m, *H*-9, *H*-15), 7.45 (1H, dd, *J*=7.1, 1.8 Hz, *H*-10), 7.31–7.25 (3H, m, *H*-8′, *H*-13, *H*-14), 7.19 (2H, m, H-9′, *H*-10′), 5.08 (1H, B part of an AB system, *J*=14.2 Hz, *H*-5$_B$), 4.88 (1H, A part of an AB system, *J*=14.2 Hz, *H*-5$_A$), 2.30 (3H, s, C*H*$_3$), 2.10 (3H, s, C*H*$_3$); δ_C (75.47 MHz, $CDCl_3$) 152.0 (*C*-3), 143.5 (*C*-7), 138.8 (*C*-2′, *C*-11′), 137.5 (*C*-2, *C*-11), 136.3 (*C*-1, *C*-1′), 134.5 (*C*-6), 131.3 (*C*-10), 130.5 (*C*-10′), 128.0 (*C*-8), 127.9 (*C*-9), 127.8 (*C*-9′), 124.3 (*C*-8′), 122.4 (*C*-14), 122.1 (*C*-13), 120.1 (*C*-12), 108.6 (*C*-15), 47.2 (*C*-5), 20.2 (*C*H$_3$), 20.0 (*C*H$_3$).

4.1.4. Compound (*R*,*R*,*R*)-14. The compound was a thick oil; [Found: C, 88.91; H, 5.36; N, 5.73. $C_{36}H_{26}N_2$ requires C, 88.86; H, 5.39; N, 5.75]; R_f (Et_2O) 0.25; $[\alpha]_D$=+19.7 (*c* 1.3, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3055, 2986, 2360, 2307, 1734, 1374, 1266, 1246 cm^{-1}; δ_H (300.133 MHz, $CDCl_3$) 8.42 (1H, d, *J*=8.5 Hz, *H*-8), 8.09 (1H, d, *J*=8.5 Hz, *H*-9), 8.01 (1H, t, *J*=8.2 Hz, *H*-10), 7.88 (1H, d, *J*=8.2 Hz, *H*-10′), 7.63 (1H, d, *J*=8.2 Hz, *H*-9′), 7.53 (1H, dt, *J*=8.2, 1.5 Hz, *H*-11), 7.44 (1H, dt, *J*=8.2, 1.0 Hz, *H*-11′), 7.37 (5H, m, *H*-17, *H*-18, *H*-19), 7.30 (1H, t, *J*=7.1 Hz, *H*-16), 7.22 (1H, dt, *J*=8.2, 1.0 Hz, *H*-12), 7.18–7.14 (5H, m, *H*-12′, *H*-13, *H*-13′, *H*-16), 7.00 (2H, d, *J*=7.1 Hz, *H*-14), 6.68 (1H, d, *J*=8.2 Hz, *H*-8′), 5.07 (1H, d, *J*=8.0 Hz, *H*-7), 4.68 (1H, d, *J*=8.0 Hz, *H*-6), 4.53 (1H, B part of an AB system, *J*=14.5 Hz, *H*-5$_B$), 3.84 (1H, A part of an AB system, *J*=14.5 Hz, *H*-5$_A$); δ_C (75.47 MHz, $CDCl_3$) 165.0 (*C*-3), 139.0 (*C*-2′), 135.0 (*C*-2), 134.5 (*C*-1, C-a), 133.4 (*C*-a′), 133.2 (*C*-b′), 132.7 (*C*-1′, *C*-b), 129.05 (*C*-18, *C*-19), 129.0 (*C*-9, *C*-15, *C*-16), 128.9 (*C*-9′), 128.6 (*C*-10), 128.5 (*C*-10′), 128.1 (*C*-13′, *C*-14), 127.6 (*C*-13), 127.3 (*C*-11), 127.1 (*C*-17), 126.5 (*C*-12′), 126.3 (*C*-11′, *C*-12), 125.9 (*C*-8), 125.8 (*C*-8′), 77.6 (*C*-6, *C*-7), 48.3 (*C*-5); *m*/*z* (FAB$^+$): 487 (MH$^+$). From the kinetic resolution experiment, dialdehyde (*S*)-**13** was recovered with 92% optical purity: $[\alpha]_D$=−7.7 vs −8.4 (EtOH).[15]

4.1.5. Compound monoimine (*R*,*R*,*R*)-11. The compound was not chromatographed and was isolated as an oil; [Found: C, 79.07; H, 7.81; N, 8.34. $C_{22}H_{26}N_2O$ requires C, 79.00; H, 7.84; N, 8.38]; ν_{max} (CH_2Cl_2) 3520, 3505, 3055, 2930, 2360, 2342, 1695, 1645, 1602, 1263 cm^{-1}; δ_H (300.133 MHz, $CDCl_3$) 9.63 (1H, s, *H*-3), 8.06 (1H, d, *J*=7.7 Hz, *H*-8′), 7.91 (1H, dd, *J*=7.7, 0.9 Hz, *H*-8), 7.76 (1H, s, *H*-5), 7.61 (1H, d, *J*=7.7 Hz, *H*-10), 7.52 (1H, t, *J*=7.7 Hz, *H*-52), 7.35 (2H, m, *H*-9′, *H*-10′), 3.23 (1H, m, *H*-7), 2.83 (1H, m, *H*-6), 2.17 (2H, m, *H*-12), 1.67 (2H, m, *H*-15), 1.33 (4H, m, *H*-13, *H*-14), 2.00 (3H, s, C*H*$_3$), 1.88 (3H, s, C*H*$_3$).

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References

1. Guzikowski, A. P.; Cai, S. X.; Espitia, S. A.; Hawkinson, J. E.; Huettner, J. E.; Nogales, D. F.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *J. Med. Chem.* **1996**, *39*, 4643–4653 and references therein.
2. Link, A.; Kunick, C. *J. Med. Chem.* **1998**, *41*, 1299–1305 and references therein.
3. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1998**, *39*, 3333–3336.
4. Rabinovitz, M.; Agranat, I.; Shaw, W.-C. *J. Org. Chem.* **1981**, *46*, 3018–3020.
5. Agranat, I.; Rabinovitz, M.; Tang, C.-P.; Shaw, W.-C. *J. Org. Chem.* **1982**, *47*, 1578–1579.
6. Hurd, R. E.; John, B. K. *J. Magn. Reson.* **1991**, *91*, 648.
7. Ruiz-Cabello, J.; Vuister, G. W.; Moonen, C. T. W.; van Gelder, P.; Cohen, J. S.; van Zijl, P. C. M. *J. Magn. Reson.* **1992**, *100*, 282.
8. Wilker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Magn. Reson. Chem.* **1993**, *31*, 287.
9. 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.
10. Burkert, U.; Allinger, N. L. *Molecular Mechanics*; *ACS Monograph*, Vol. 177; American Chemical Society: Washington, DC, 1982.

11. Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26 and references therein.
12. (a) Andrus, M. B.; Asgari, D.; Sclafani, J. A. *J. Org. Chem.* **1997**, *62*, 9365–9368. (b) Tichy, M.; Holanova, J.; Zavada, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3497–3504.
13. Kobayashi, S.; Kihiara, M.; Shizu, S.; Katayama, S.; Ikeda, H.; Kitahiro, K.; Matsumoto, H. *Chem. Pharm. Bull.* **1977**, *25*, 3312–3323.
14. Brunner, H.; Goldbrummer, J. *Chem. Ber.* **1989**, 2005–2010.
15. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Woods, C. R.; Siegel, J. S. *Eur. J. Org. Chem.* **2001**, 173–180.