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Synthesis of new enantiopure γ-aminoalcohols: their use as catalysts in the alkylation of benzaldehyde by diethylzinc

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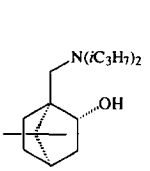
Abstract: The straightforward synthesis of new enantiopure γ-aminoalcohols through 1,3-dipolar cycloadditon to a chiral cyclic nitrone derived from L-malic acid is described. Results of the application of these compounds as chiral catalysts in the alkylation of benzaldehyde with diethylzinc are also reported. © 1997 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure chiral aminoalcohols have found a widespread use in organic chemistry, mainly as catalysts in the alkylation of aldehydes by dialkylzinc derivatives (Scheme 1).[1] β-Aminoalcohols are the most popular compounds of this class, due to their ready availability from the chiral pool[2] and probably also to the good results they provided since the beginning.[3] Nevertheless, the few published examples of chiral γ-aminoalcohols **1–4** showed that they are also able to catalyse the same reaction with good efficiency.[4–6]



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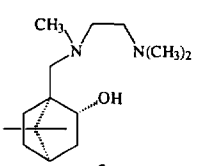

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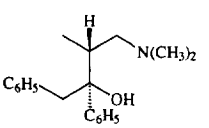

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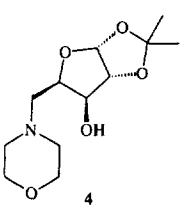
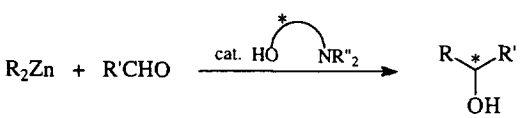


4

The aim of our research is the investigation of γ-aminoalcohols as ligands for metal catalysed organic reactions. In this paper we report the synthesis of a series of ligands belonging to this class and the results of their use as catalysts in the alkylation of benzaldehyde by diethylzinc.

The strategy for the synthesis of the ligands is based on reductive opening of N–O bond in isoxazolidine **7**,[7] which directly delivers the desired γ-aminoalcohols **8**. Since isoxazolidines **7** are, in turn, readily available through cycloaddition of nitrones **5** to olefins **6**,[8] the overall procedure (Scheme 2) represents, by far, the most convenient method for the synthesis of enantiomerically pure chiral γ-aminoalcohols.

Our approach to the ligands took advantage of the recently reported syntheses of enantiomerically pure nitrones derived from tartaric[9] and malic acids.[10] These procedures made the starting nitrones available in large scale and in both enantiomeric configurations, therefore excellent substrates for the



Scheme 1.

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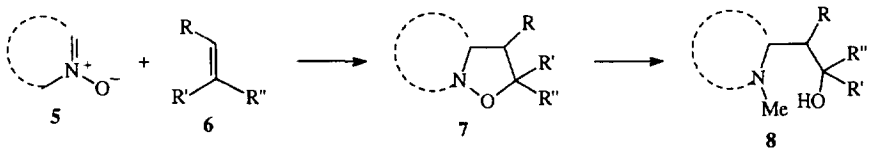
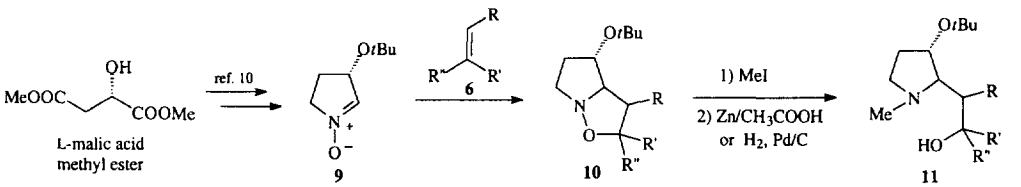


Scheme 2.



Scheme 3.

synthesis of chiral γ-aminoalcohols. The use of the L-malic acid derived nitrone **9**[10] is here reported (Scheme 3).

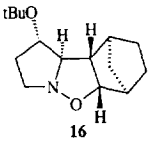
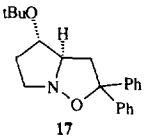
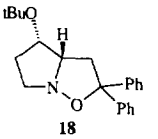
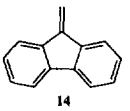
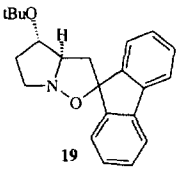
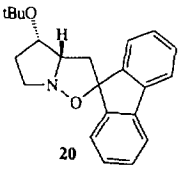
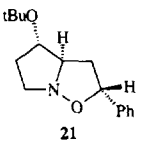
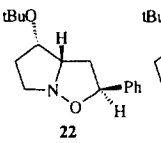
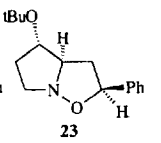
The cycloadditions of nitrone **9** to olefins **12–15** (Table 1) proceed with moderate to good yields (41–89%). The cycloaddition to norbornene **12** gave exclusively the adduct **16**, arising from the approach of both reagents in an *exo* fashion and *anti* to the *tert*-butoxy group. On the contrary, 1,1-diphenylethylene **13** and methylenefluorene **14** gave both the possible diastereoisomers derived from the approaches to the two diastereotopic faces of nitrone **9** with scarce selectivity (2÷3:1) in favor of the *anti* adduct (Figure 1). The low yields of these reactions are related to competitive polymerization of the two dipolarophiles. Finally, styrene **15** gave the same two *anti* and *syn* diastereoisomers **21** and **22** in the *exo* approach, with a larger 5:1 preference for the *anti*. A minor *anti-endo* isomer **23** was also isolated from the reaction mixture (Table 1).

Structural assignment to all compounds **16–23** was secured by ^{1}H NMR and 2D NOESY spectra. Adducts **16**, **17**, **19**, **21**, **23** derived from an *anti* approach (Figure 1) present a *trans* relationship at C3a–C4 stereocenters, in agreement with the observed coupling constants of the corresponding protons (J_{H3a-H4}=3–5 Hz). Higher values of the corresponding coupling constants in compounds **18**, **20**, **22** (J=6–8 Hz) confirm the opposite relative stereochemistry at C3a–C4. The structure of compound **23** has been assigned with the aid of a 2D NOESY spectrum, which showed a NOE effect between protons on C2 and C3a, consistently with the structure reported in Table 1.

The low facial selectivities found in these cycloadditions, unusual for this nitrone,[9] is profitable in this study, allowing the obtainment of stereoisomers, with different arrangement at the stereocenters to be tested as catalysts.

Conversion of isoxazolidines **16–22** to the corresponding *N*-methyl γ-aminoalcohols **24–30** was achieved by methylation with MeI followed by reduction with Zn in acetic acid[7f–g] or hydrogenation over Pd/C[7d–e] (Scheme 3). γ-Aminoalcohols **24–30** were thus obtained in satisfactory yields and high purity.

Table 1. Cycloadditions of nitrone **9** to dipolarophiles **12–15** (in benzene as solvent)

Entry	Dipolarophile	Conditions	Adducts	Yield (%)	Ratio
1	 **12**	4 d, rt	 **16**	89	
2	 **13**	2 d, 60 °C	 **17**  **18**	41	3 : 1
3	 **14**	2 d, 60 °C	 **19**  **20**	54	2 : 1
4	 **15**	1 d, 60 °C	 **21**  **22**  **23**	88	15 : 3 : 1

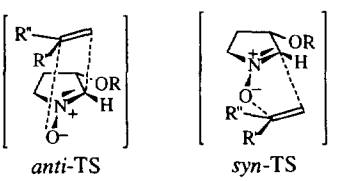
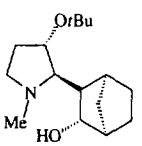
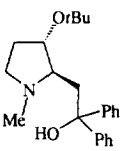
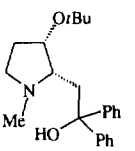
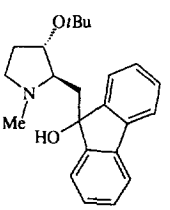

anti-TS *syn*-TS

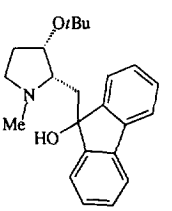
Figure 1. Diastereofacial attacks of dipolarophiles to nitrone **9**.

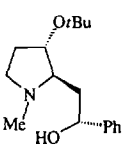

24 (53%)

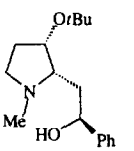

25 (77%)


26 (75%)


27 (59%)

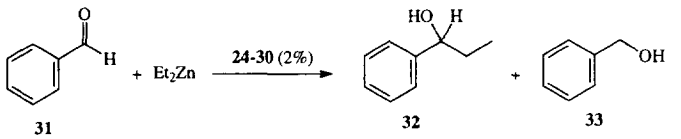

28 (58%)


29 (97%)


30 (93%)

The efficiency of ligands **24–30** in catalysing the alkylation of benzaldehyde **31** by diethylzinc to

Table 2. Distribution of products and enantiomeric excesses of 1-phenylpropanol **32** in the alkylation of benzaldehyde **31** by diethylzinc catalysed by aminoalcohols **24–30**[a]



Entry	Catalyst	Products			
		31[b]	**33**[b]	**32**[b]	E.e.[b,c,d]
1	**24**	57	8	35	7 (*S*)
2	**25**	5	8	87	43 (*S*)
3	**26**	-	-	100	54 (*R*)
4[e]	**26**	-	-	100	48 (*R*)
5	**27**	59	11	30	3 (*R*)
6[f]	**27**	15	28	57	10 (*R*)
7	**28**	24	10	66	20 (*S*)
8	**29**	44	18	38	8 (*R*)
9	**30**	15	7	79	6 (*R*)

[a]Reactions carried out at room temperature in toluene. [b]Values in percent. [c]Obtained by integration of GC peaks using a chiral stationary phase (see Experimental). [d]Absolute configuration of the major isomer reported in parentheses. [e]In diethyl ether. [f]At 50 °C.

give 1-phenylpropanol **32** has been tested and the results are reported in Table 2. The reactions were run in toluene by addition of 2.2 equivalents of diethylzinc (toluene solution) to benzaldehyde **31** and 2% mol of chiral catalyst at 0°C. Then the mixture was reacted at room temperature for 48 h.

The enantiomeric purity of 1-phenylpropanol **32** has been evaluated by GC using a chiral stationary phase column (BETADEX 120) which allows a complete resolution of a racemic mixture (Δr_t=0.4 min). Variation of temperature or solvent did not affect significantly the enantioselectivity of the reaction (*cfr.* entries 3–4 and 5–6), albeit increase of temperature favored a higher conversion. However, the reaction took long times for completion, which might explain the presence of benzyl alcohol as a side-product.

The reported e.e. values, though modest, show that catalyst **26** is the most efficient for both conversion and selectivity, suggesting that two bulky substituents α to the hydroxy group are required. This is confirmed by dropping of efficiency of the catalyst when one phenyl group is removed (entries 8 and 9). The results with the fluorene derivatives (entries 5–7) are more intriguing, since linkage of the phenyl groups in a more rigid structure also leads to a diminished catalyst efficiency. Rationalization of all the substituent effects is hardly accomplishable taking into account the reaction mechanism proposed by Noyori and Kitamura for this reaction,[2] which relays on several equilibria among dimers and monomers where the steric hindrance of substituents might play a determinant and delicate role.

Noteworthy, the diastereomeric couples of aminoalcohols derived from 1,1-diphenylethylene and methylenefluorene act complementarily since catalysts **25** and **28** give preferentially (*S*)-1-phenylpropanol **32** while their epimers **26** and **27** give predominantly the opposite enantiomer (*R*)-**32**. This could be ascribed to the scarce influence on selectivity of the *tert*-butoxy group, which lies away from the reaction centers, so that diastereomeric pairs behave like simple enantiomers. The influence of the absolute configuration of the stereocenter bearing the *tert*-butoxy group is illustrated by difference in catalyst efficiency within a diastereomeric couple.

In conclusion, seven new enantiopure γ-aminoalcohols **24–30** have been synthesized by *N*-

methylation and reductive ring-opening of the corresponding isoxazolidines **16–22**, obtained in turn by cycloaddition of dipolarophiles **12–15** to nitrone **9**. The γ-aminoalcohols have been tested as chiral catalysts in zinc mediated alkylation of benzaldehyde. The results were satisfactory concerning the conversion (entries 2–4, Table 2) but still modest regarding the enantioselectivity induced (entry 3: 54% for the *R* configuration; entry 2: 43% for *S* configuration). The present study evidenced the features which play a major role in determining the selectivity and will be helpful in the design of new and, hopefully, more efficient γ-aminoalcohol catalysts. This purpose will be made possible by the high flexibility of the cycloaddition approach used in our syntheses. The application of γ-aminoalcohol as catalysts in other metal catalysed reactions is currently under study in our laboratory.

Experimental

General procedure for cycloaddition reactions

A 1 M benzene solution of nitrone **9** and 1.5 equivalent of olefin is left under stirring at the time and at the temperature specified in Table 1. The crude material is purified by passage on a short pad of silica gel.

*(1S,6R,9S,9aS,9bR)-Decahydro-1-*tert*-butoxy-6,9-methano-pyrrolo[1,2-b][1,2] benzisoxazole* ***16***

R_f (diethyl ether–petroleum ether 1:1)=0.33; m.p.: 88–89°C; $[\alpha]_D^{20}$: −29.1 (c=1.06, CH_2Cl_2); ^{1}H-NMR: δ 4.12 (d, *J*=6.6 Hz, 1H), 4.01 (ddd, *J*=7.3, 4.4, 2.9 Hz, 1H), 3.23 (ddd, *J*=11.3, 7.3, 5.9 Hz, 1H), 3.08 (dd, *J*=4.3, 2.5 Hz, 1H), 2.94 (dt, *J*=11.3, 7.4 Hz, 1H), 2.27–2.10 (m, 4H), 1.83–1.78 (m, 1H), 1.74–1.58 (m, 1H), 1.51–1.44 (m, 2H), 1.19 (s, 9H), 1.08–0.97 (m, 3H); ^{13}C-NMR: δ 84.8 (d), 78.3 (d), 76.8 (d), 73.6 (s), 58.1 (d), 53.7 (t), 40.7 (d), 40.3 (d), 33.0 (t), 32.5 (t), 28.4 (q), 27.8 (t), 23.3 (t); IR ($CHCl_3$): 2972, 1443, 1390, 1198, 1030 cm^{-1}; MS: m/z 251 (M^+, 19), 195 (22), 194 (100), 152 (32), 138 (23), 57 (66); Anal. calcd for $C_{15}H_{25}NO_2$: C 71.67, H 10.02, N 5.57; found C 71.65, H 10.15, N 5.92.

*(3aR,4S)-Hexahydro-4-*tert*-butoxy-2,2-diphenylpyrrolo[1,2-b]isoxazole* ***17***

R_f (diethyl ether–petroleum ether 1:2)=0.24; m.p.: 122–123°C; $[\alpha]_D^{18}$: −40.1 (c=0.71, CH_2Cl_2);^{1}H-NMR: δ 7.58–7.52 (m, 2H), 7.38–7.20 (m, 8H), 3.96 (dt, *J*=6.2, 3.1 Hz, 1H), 3.63–3.50 (m, 1H), 3.50–3.29 (m, 3H), 2.49 (dd, *J*=12.3, 6.8 Hz, 1H), 2.42–2.20 (m, 1H), 1.78–1.62 (m, 1H), 1.14 (s, 9H); ^{13}C-NMR: δ 145.3 (s), 144.4 (s), 128.2 (d), 127.0 (d), 126.8 (d), 125.8 (d), 87.1 (s), 77.8 (d), 74.1 (d), 73.5 (s), 55.7 (t), 46.6 (t), 33.1 (t), 28.4 (q); IR (CH_2Cl_2): 3055, 2972, 2948, 1362, 1187, 1073 cm^{-1}; MS: m/z 337 (M^+, 3), 280 (100), 264 (22), 191 (22), 180 (48), 179 (23), 165 (31), 105 (27), 91 (23), 77 (25), 57 (46); Anal. calcd for $C_{22}H_{27}NO_2$: C 78.30, H 8.06, N 4.15; found C 78.32, H 7.90, N 4.17.

*(3aS,4S)-Hexahydro-4-*tert*-butoxy-2,2-diphenylpyrrolo[1,2-b]isoxazole* ***18***

R_f (diethyl ether–petroleum ether 1:2)=0.11; m.p.: 147–149°C; $[\alpha]_D^{22}$: +2.1 (c=0.58, $CHCl_3$); ^{1}H-NMR: δ 7.60–7.52 (m, 2H), 7.42–7.16 (m, 8H), 4.19 (q, *J*=7.6 Hz, 1H), 3.66 (q, *J*=7.8 Hz, 1H), 3.43 (ddd, *J*=13.4, 7.3, 3.1 Hz, 1H), 3.14–2.83 (m, 3H), 2.16–1.99 (m, 1H), 1.93–1.78 (dtd, 8.4, 6.6, 3.3 Hz, 1H), 1.19 (s, 9H); ^{13}C-NMR: δ 145.7 (s), 144.7 (s), 128.8 (d), 128.6 (d), 127.6 (d), 127.4 (d), 127.0 (d), 126.6 (d), 88.4 (s), 74.2 (s), 72.9 (d), 68.2 (d), 54.0 (t), 43.3 (t), 32.1 (t), 28.8 (q); IR ($CHCl_3$): 2975, 1446, 1361, 1181, 1101 cm^{-1}; MS: m/z 337 (M^+, 6), 336 (8), 280 (100), 191 (33), 180 (73), 179 (31), 165 (44), 105 (28), 77 (36), 57 (82); Anal. calcd for $C_{22}H_{27}NO_2$: C 78.30, H 8.06, N 4.15; found C 77.94, H 8.21, N 3.86.

*(3′aR,4′S)-Hexahydro-4′-*tert*-butoxyspiro[fluorene-9-2′-pyrrolo[1,2-b]isoxazole]* ***19***

R_f (petroleum ether–ethyl acetate 3:1): 0.47; $[\alpha]_D^{21}$: −59.5 (c=0.77, $CHCl_3$); ^{1}H-NMR: δ 7.94–7.90 (m, 1H), 7.63–7.59 (m, 2H), 7.46–7.30 (m, 5H), 4.27 (dt, *J*=5.9, 2.5 Hz, 1H), 4.08 (m, 1H),

3.58–3.44 (m, 2H), 2.96 (dd, *J*=12.8, 8.8 Hz, 1H), 2.60 (dd, *J*=12.8, 6.8 Hz, 1H), 2.58 (m, 1H), 1.87 (ddt, *J*=12.8, 3.6, 2.5 Hz, 1H); ^{13}C-NMR: ipso carbons not detected, δ 129.5 (d), 128.7 (d), 128.3 (d), 127.8 (d), 124.8 (d), 123.6 (d), 120.0 (d), 119.7 (d), 79.1 (d), 75.1 (d), 73.9 (s), 55.7 (t), 45.1 (t), 33.4 (t), 28.5 (q); IR ($CHCl_3$): 2975, 1447, 1388, 1362, 1169 cm^{-1}; MS: m/z 335 (M^+, 4), 278 (20), 260 (7), 179 (19), 178 (100), 176 (13), 165 (12), 152 (13), 84 (13), 57 (24); Anal. calcd for $C_{22}H_{25}NO_2$: C 78.60, H 8.32, N 3.98; found: C 78.90, H 7.95, N 3.90.

*(3′aS,4′S)-Hexahydro-4′-*tert*-butoxyspiro[fluorene-9-2′-pyrrolo[1,2-b]isoxazole]* ***20***

R_f (petroleum ether–ethyl acetate 3:1): 0.23; $[\alpha]_D^{22}$: −4.92 (c=0.72, $CHCl_3$); ^{1}H–NMR: δ 7.89–7.85 (m, 1H), 7.80–7.75 (m, 1H), 7.63–7.58 (m, 2H), 7.42–7.29 (m, 4H), 4.38 (q, *J*=7.6 Hz, 1H), 4.24 (td, *J*=7.6, 5.5 Hz, 1H), 3.53 (ddd, *J*=13.6, 7.0, 2.2 Hz, 1H), 3.28 (dd, *J*=13.0, 5.6 Hz, 1H), 3.11 (ddd, *J*=6.1, 12.7, 13.6 Hz, 1H), 2.54 (dd, *J*=13.1, 8.6 Hz, 1H), 2.42–2.22 (m, 1H), 2.08 (dtd, *J*=12.8, 6.2, 2.2 Hz, 1H); ^{13}C-NMR: δ 149.3 (s), 144.5 (s), 140.3 (s), 139.0 (s), 129.1 (d), 128.4 (d), 128.0 (d), 127.6 (d), 124.7 (d), 124.3 (d), 119.5 (d), 89.2 (s), 73.7 (s), 72.6 (d), 68.5 (d), 52.9 (t), 40.1 (t), 32.6 (t), 28.1 (q); IR ($CHCl_3$): 2972, 1447, 1362, 1183, 1090 cm^{-1}; MS: m/z 335 (M^+, 2), 278 (11), 179 (15), 178 (100), 176 (12), 165 (9), 152 (10), 84 (16), 57 (26); Anal. calcd for $C_{22}H_{25}NO_2$: C 78.60, H 8.32, N 3.98; found: C 78.85, H 7.95, N 4.06.

*(2R,3aR,4S)-Hexahydro-4-*tert*-butoxy-2-phenylpyrrolo[1,2-b]isoxazole* ***21***

R_f (diethyl ether–petroleum ether 1:1)=0.47; $[\alpha]_D^{18}$: +12.1 (c=0.77, CH_2Cl_2); ^{1}H-NMR: δ 7.40–7.18 (m, 5H), 4.93 (t, *J*=7.7 Hz, 1H), 3.89 (dt, *J*=6.9, 4.7 Hz, 1H), 3.59 (q, *J*=5.2 Hz, 1H), 3.39 (dt, *J*=12.5, 6.9 Hz, 1H), 3.20 (dt, *J*=12.5, 6.4 Hz, 1H), 2.46–2.36 (m, 2H), 2.14 (dq, *J*=12.9, 6.9 Hz, 1H), 1.69 (dtd, *J*=12.9, 6.9, 5.1 Hz, 1H), 1.15 (s, 9H); ^{13}C-NMR: δ 140.3 (s), 128.3 (d), 127.6 (d), 126.2 (d), 78.0 (d), 77.4 (d), 73.5 (s), 72.9 (d), 55.6 (t), 43.1 (t), 33.8 (t), 28.5 (q); IR ($CHCl_3$): 2975, 1361, 1173, 1087 cm^{-1}; MS: m/z 261 (M^+, 5), 205 (22), 204 (66), 77 (34), 57 (100), 55 (35); Anal. calcd for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36; found C 73.38, H 8.95, N 5.15.

*(2S,3aS,4S)-Hexahydro-4-*tert*-butoxy-2-phenylpyrrolo[1,2-b]isoxazole* ***22***

R_f (diethyl ether–petroleum ether 1:1)=0.16; $[\alpha]_D^{18}$: −3.5 (c=1.16, $CHCl_3$); ^{1}H-NMR: δ 7.40–7.18 (m, 5H), 4.96 (dd, *J*=9.1, 6.2 Hz, 1H), 4.06 (dt, *J*=6.3, 5.4 Hz, 1H), 3.79 (ddd, *J*=8.8, 6.8, 2.0 Hz, 1H), 3.19 (t, *J*=6.8 Hz, 2H), 2.71 (ddd, *J*=12.0, 5.8, 2.2 Hz, 1H), 2.07 (dt, *J*=12.0, 8.9 Hz, 1H), 1.84 (td, *J*=7.0, 5.9 Hz, 2H), 1.16 (s, 9H); ^{13}C-NMR: δ 140.3 (s), 128.2 (d), 127.5 (d), 126.4 (d), 79.4 (d), 73.7 (s), 71.3 (d), 68.6 (d), 54.1 (t), 39.6 (t), 33.3 (t), 28.3 (q); IR ($CHCl_3$): 2973, 2877, 1451, 1388, 1362, 1177, 1105 cm^{-1}; MS: m/z 261 (M^+20), 205 (58), 204 (100), 188 (37), 148 (35), 130 (30), 115 (33), 105 (54), 104 (52), 77 (50), 57 (100); Anal. calcd for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36; found C 73.40, H 9.05, N 5.20.

*(2S,3aR,4S)-Hexahydro-4-*tert*-butoxy-2-phenylpyrrolo[1,2-b]isoxazole* ***23***

R_f (diethyl ether–petroleum ether 1:1)=0.25; $[\alpha]_D^{18}$: −13.0 (c=0.40, CH_2Cl_2); ^{1}H-NMR: δ 7.35–7.18 (m, 5H), 4.94 (dd, *J*=9.9, 6.6 Hz, 1H), 3.99 (dt, *J*=6.2, 2.6 Hz, 2H), 3.76–3.64 (ddd, *J*=11.6, 5.6, 2.5 Hz, 1H), 3.49 (ddd, *J*=13.2, 7.7, 2.2 Hz, 1H), 3.32 (td, *J*=13.6, 6.5 Hz, 1H), 2.93 (ddd, *J*=12.4, 9.0, 6.2 Hz, 1H), 2.42 (ddt, *J*=13.1, 10.5, 6.5 Hz, 1H), 1.95 (ddd, *J*=12.6, 9.6, 5.6 Hz, 1H), 1.70 (ddt, *J*=13.1, 6.6, 2.5 Hz, 1H), 1.16 (s, 9H); ^{13}C-NMR: δ 139.1 (s), 128.4 (d), 127.9 (d), 126.3 (d), 79.6 (d), 79.1 (d), 75.0 (d), 73.6 (s), 55.2 (t), 43.2 (t), 33.2 (t), 28.4 (q); IR ($CHCl_3$): 2975, 1449, 1388, 1362, 1176, 1071 cm^{-1}; MS: m/z 261 (M^+, 5), 205 (30), 204 (89), 148 (20), 130 (17), 117 (16), 115 (19), 105 (32), 104 (24), 98 (19), 91 (19), 77 (31), 71 (18), 57 (100), 55 (31); Anal. calcd for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36; found C 73.25, H 9.18, N 5.02.

General procedure for alkylation and reduction of the N–O bond

MeI (3 equivalents) is added to a 1 M benzene solution of the isoxazolidine. The solution is left at r.t. under stirring overnight and concentrated to give the crude isoxazolidinium salt which is directly reduced to the corresponding aminoalcohol using one of the following methods.

Method A (for aminoalcohols **24**, **25**, **26**).[7f-g] The salt (5 mmol) is dissolved in 18 mL of acetic acid /water 9:1 and zinc powder (20 mmol) is added in small portions over 1 h. The mixture is left under stirring at r.t. for 2 h, diluted with water and Na_2CO_3 is added until neutrality is reached. The solution is extracted with methylene chloride (3 × 50 mL), the organic phase is dried over Na_2SO_4 and concentrated to give the crude product, purified by passage on a short pad of silica gel.

Method B (for aminoalcohols **27**, **28**, **29**, **30**).[7d-e] The salt (5 mmol) is dissolved in 10 mL of methanol and 20% Pd/C (600 mg) is added. The suspension is transferred in autoclave and stirred at rt for 12 h in hydrogen atmosphere at 4 atm. The suspension is filtered over a celite pad and passed through a column of Amberlyst 26. The final solution is concentrated and the crude material is purified by passage on a short pad of silica gel.

(2R,3S,1'S,2'S,3'R)-N-*Methyl-3*-tert-*butoxy-2-(3-hydroxy-2-norbornyl)-pyrrolidine* ***24***

R_f (methylene chloride/methanol 18:1)=0.17; $[\alpha]_D^{20}$: +9.0 (c=0.72, $CHCl_3$); ^{1}H-NMR: δ 4.19 (m, 1H), 4.05 (d, *J*=6.6 Hz, 1H), 3.60 (ddd, *J*=11.5, 8.6, 3.0 Hz, 1H), 3.03 (d, *J*=9.5 Hz, 1H), 2.89–2.67 (m, 1H), 2.76 (s, 3H), 2.26–2.02 (m, 3H), 1.91–1.80 (m, 1H), 1.74 (d, *J*=9.9 Hz, 1H), 1.62–1.38 (m, 3H), 1.18 (s, 9H), 1.13–1.00 (m, 3H); ^{13}C-NMR: (quaternary carbon not detected), δ 76.6 (d), 75.6 (d), 74.9 (d), 54.6 (t), 49.5 (d), 45.1 (d), 44.7 (d), 39.6 (q), 33.1 (t), 32.9 (t), 29.6 (t), 28.3 (q), 23.7 (t); IR ($CHCl_3$): 2971, 2876, 1570, 1409, 1390, 1365, 1182 cm^{-1}; MS: m/z 210 (M^+–C_4H_9, 60), 166 (57), 156 (100), 100 (98), 57 (48); Anal. calcd for $C_{16}H_{29}NO_2$: C 71.87, H 10.93, N 5.24; found C 71.52, H 11.27, N 5.13.

(2R,3S)-N-*Methyl-2-(2-hydroxy-2,2-diphenylethyl)-3*-tert-*butoxypyrrolidine* ***25***

R_f (ethyl acetate–petroleum ether 1:1)=0.24; $[\alpha]_D^{20}$: −63.0 (c=0.63, $CHCl_3$); ^{1}H-NMR: δ 7.60–7.53 (m, 4H), 7.38–7.10 (m, 6H), 3.72 (dt, *J*=6.6, 3.1 Hz, 1H), 3.11 (ddd, *J*=10.3, 8.1, 4.2 Hz, 1H), 2.68–2.46 (m, 3H), 2.34–2.17 (m, 1H), 2.21 (s, 3H), 2.08–1.88 (m, 1H), 1.76–1.61 (m, 1H), 1.12 (s, 9H); ^{13}C-NMR: (quaternary carbon not detected), δ 148.6 (s), 148.1 (s), 128.0 (d), 127.9 (d), 126.3 (d), 126.3 (d), 125.9 (d), 125.7 (d), 77.7 (d), 73.8 (s), 72.0 (d), 54.1 (t), 43.1 (q), 40.8 (t), 32.9 (t), 28.4 (q); IR ($CHCl_3$): 3012, 2975, 2870, 1444, 1388, 1362, 1198, 1032 cm^{-1}; MS: m/z 353 (M^+, 3), 183 (79), 156 (79), 114 (100), 105 (80), 100 (46), 77 (50), 70 (52), 57 (63); Anal. calcd for $C_{23}H_{31}NO_2$: C 78.15, H 8.84, N 3.96; found C 78.05, H 9.00, N 3.68.

(2S,3S)-N-*Methyl-2-(2-hydroxy-2,2-diphenylethyl)-3*-tert-*butoxypyrrolidine* ***26***

$[\alpha]_D^{20}$: +4.0 (c=1.20, CH_2Cl_2); ^{1}H-NMR: δ 7.60–7.45 (m, 4H), 7.41–7.12 (m, 6H), 4.15 (q, *J*=7.9 Hz, 1H), 3.23 (ddd, *J*=11.3, 8.9, 3.9 Hz, 1H), 2.80–2.56 (m, 2H), 2.44–2.26 (m, 1H), 2.20–2.00 (m, 2H), 1.82 (dq, *J*=12.7, 8.6 Hz, 1H), 1.27 (s, 9H); ^{13}C-NMR: δ 149.4 (s), 148.6 (s), 128.5 (d), 128.4 (d), 126.8 (d), 126.6 (d), 126.1 (d), 78.4 (s), 74.3 (s), 71.3 (d), 66.2 (d), 51.5 (t), 44.7 (q), 37.4 (t), 32.7 (t), 28.8 (q); IR ($CHCl_3$): 3001, 2971, 1444, 1360, 1184, 1075 cm^{-1}; MS: m/z 183 (67), 156 (100), 114 (96), 105 (58), 100 (26), 77 (28), 70 (54), 57 (37); Anal. calcd for $C_{23}H_{31}NO_2$: C 78.15, H 8.84, N 3.96; found C 78.19, H 9.16, N 3.83.

(2R-3S)-N-*Methyl-3*-tert-*butoxy-2-(9-(9-hydroxy)-fluorenylmethyl)-pyrrolidine* ***27***

M.p.=129–131°C; $[\alpha]_D^{22}$: +8.8 (c=0.93, $CHCl_3$); ^{1}H-NMR: δ 7.66–7.56 (m, 4H), 7.39–7.30 (m, 4H), 3.91 (dt, *J*=7.7, 4.6 Hz, 1H), 3.22 (ddd, *J*=10.9, 8.6, 6.2 Hz, 1H), 3.09 (q, *J*=5.9 Hz, 1H), 2.70 (ddd, *J*=10.8, 9.1, 6.3 Hz, 1H), 2.39 (s, 3H), 2.26–2.08 (m, 1H), 2.04–1.81 (m, 3H), 1.19 (s, 9H); ^{13}C-NMR: δ 150.4 (s), 139.0 (s), 128.3 (d), 127.5 (d), 127.3 (d), 124.2 (d), 123.8 (d), 118.8 (d), 89.8

(s), 77.2 (d), 74.5 (s), 70.1 (d), 54.3 (t), 42.4 (q), 41.5 (t), 32.2 (t), 28.5 (q); IR ($CHCl_3$): 3332, 3065, 2976, 2870, 1448, 1388, 1362, 1176, 1077 cm^{-1}; MS: m/z 351 (M^+, 3), 294 (8), 181 (92), 156 (66), 152 (35), 114 (100), 100 (24), 70 (62), 57 (41); Anal. calcd for $C_{23}H_{29}NO_2$: C 78.60, H 8.32, N 3.98; found C 78.30, H 8.48, N 3.73.

(2S-3S)-N-*Methyl-3*-tert-*butoxy-2-(9-(9-hydroxy)-fluorenylmethyl)-pyrrolidine* ***28***

$[\alpha]_D^{21}$: +22.5 (c=0.94, $CHCl_3$); ^{1}H-NMR: δ 7.67–7.54 (m, 4H), 7.39–7.24 (m, 4H), 4.29 (q, *J*=7.0 Hz, 1H), 3.34–3.15 (m, 2H), 2.44 (q, *J*=6.6 Hz, 1H), 2.40 (s, 3H), 2.28–2.08 (m, 2H), 1.91–1.71 (m, 2H), 1.13 (s, 9H); ^{13}C-NMR: δ 150.6 (s), 150.4 (s), 139.1 (s), 138.8 (s), 128.3 (d), 128.1 (d), 127.4 (d), 127.2 (d), 124.0 (d), 123.8 (d), 119.8 (d), 119.6 (d), 82.0 (s), 73.9 (s), 71.7 (d), 65.9 (d), 52.0 (t), 42.3 (q), 35.4 (t), 32.3 (t), 28.3 (q); IR ($CHCl_3$): 3332, 3070, 2973, 2796, 1447, 1387, 1362, 1181, 1103, 1075 cm^{-1}; MS: m/z 351 (M^+, 1), 294 (5), 181 (65), 156 (34), 152 (22), 114 (100), 70 (55), 57 (20), 47 (33); Anal. calcd for $C_{23}H_{29}NO_2$: C 78.60, H 8.32, N 3.98; found C 78.44, H 8.65, N 4.05.

(2R-3S)-N-*Methyl-2-((2R)-2-hydroxy-2-phenylethyl)-3*-tert-*butoxypyrrolidine* ***29***

$[\alpha]_D^{19}$: +46.7 (c=0.86, CH_2Cl_2); ^{1}H-NMR: δ 7.43–7.25 (m, 5H), 5.08 (dd, *J*=8.3, 4.9 Hz, 1H), 4.29 (m, 1H), 3.14 (t, *J*=9.0 Hz, 1H), 2.59–2.42 (m, 1H), 2.45 (s, 3H), 2.26–2.04 (m, 2H), 1.94 (dd, *J*=8.4, 3.7 Hz, 2H), 1.80–1.63 (m, 1H), 1.24 (s, 9H); ^{13}C-NMR: δ 144.7 (s), 127.8 (d), 126.5 (d), 125.0 (d), 73.3 (s), 73.2 (d), 72.2 (d), 71.6 (d), 54.5 (t), 40.5 (q), 34.9 (t), 32.9 (t), 28.3 (q); IR (CH_2Cl_2): 3032, 2970, 2847, 2795, 1602, 1448, 1388, 1362, 1183, 1125, 1033 cm^{-1}; MS: m/z 277 (M^+17), 220 (10), 156 (98), 114 (100), 107 (30), 105 (11), 100 (48), 98 (14), 96 (15), 82 (22), 79 (17), 78 (12), 77 (30), 70 (100), 57 (71); Anal. calcd for $C_{17}H_{27}NO_2$: C 73.61, H 9.81, N 5.05; found C 73.44, H 9.92, N 4.72.

(2S-3S)-N-*Methyl-2-((2S)-2-hydroxy-2-phenylethyl)-3*-tert-*butoxypyrrolidine* ***30***

$[\alpha]_D^{20}$: −8.8 (c=1.11, CH_2Cl_2); ^{1}H-NMR: δ 7.50−7.18 (m, 5H), 5.27 (t, *J*=6.2 Hz, 1H), 4.25 (q, *J*=8.4 Hz, 1H), 3.09 (t, *J*=7.4 Hz, 1H), 2.68 (dt, *J*=9.1, 4.2 Hz, 1H), 2.41 (s, 3H), 2.31–1.90 (m, 3H), 1.83 (dd, *J*=6.0, 3.9 Hz, 2H), 1.24 (s, 9H); ^{13}C-NMR: δ 146.2 (s), 127.9 (d), 126.4 (d), 125.4 (d), 73.7 (s), 73.5 (d), 72.6 (d), 66.7 (d), 52.6 (t), 41.6 (q), 36.4 (t), 35.1 (t), 28.3 (q); MS: m/z 277 (M^+11), 156 (14), 114 (36), 100 (30), 82 (34), 78 (57), 77 (55), 70 (68), 57 (100); Anal. calcd for $C_{17}H_{27}NO_2$: C 73.61, H 9.81, N 5.05; found C 73.35, H 9.77, N 5.25.

General procedure for catalysis test: alkylation of benzaldehyde with diethyl zinc

A 1.1 M solution of diethyl zinc (2 mL, 2.2 mmol) in toluene is added dropwise to an ice cooled solution of benzaldehyde (100 μL, 1 mmol), and catalyst (0.02 mmol) in 6 mL of toluene. The reaction is left under stirring at r.t. for 48 h. The reaction is quenched by addition of 5 mL of 5% HCl. The aqueous phase is separated and extracted with ethyl ether. The organic phases, collected together and washed with a saturated solution of $NaHCO_3$ and brine, are dried over Na_2SO_4 and concentrated to give the crude reaction mixture which is analyzed by GC.

Column: HP1 (100% methylsilicon, 0.53 mm ID); condition: 40°C for 2 minutes, 15°C up to 270°C. R_t: benzaldehyde 2.95, benzyl alcohol 4.32, 1-phenyl-1-propanol 5.79.

Column: Beta Dex 120^{TM} (30 m, 0.25 mm ID); condition: isotherm at 120°C. R_t: benzaldehyde 2.59, benzyl alcohol 6.18, *R*(+)-1-phenyl-1-propanol 9.95, *S*(−)-1-phenyl-1-propanol 10.35.

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References

1. (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833; (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475; (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551; Corey, E. J.; Bakshi, R. K.; Shibata, S. J.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547.
2. Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 34.
3. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
4. Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645.
5. Muchow, D.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron* **1987**, *28*, 6163.
6. Tae Cho, B.; Kim, N. *Tetrahedron Lett.* **1994**, *35*, 4115.
7. $Mo(CO)_6$ reduction: (a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351; Ni Raney reduction: (b) Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1969**, *101*, 2568; (c) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134; Pd reduction: (d) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048; (e) De Shong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686; Zn reduction: (f) Ito, S.; Narita, S.; Endo, K. *Bull. Chem. Soc. Jpn* **1973**, *46*, 3517; (g) LeBel, N. A.; Ojha, N. D.; Menke, J. R.; Newland, R. J. *J. Org. Chem.* **1972**, *37*, 2896; $LiAlH_4$ reduction: (h) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722; (i) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396.
8. (a) Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, Feuer, H. Ed.; VCH Publisher: 1988 New York; (b) Tufariello, J.J. in *1,3-Dipolar Cycloaddition Chemistry*, vol. 2, 83, Padwa, A., Ed.; J. Wiley & Sons: 1984 New York; (c) Confalone, P.N., Huie, E.M. *Org. React.* **1988**, *36*, 1.
9. Cicchi, S.; Höld, H.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274.
10. Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743.

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