Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1235–1239

TETRAHEDRON: *ASYMMETRY*

1,1′-Binaphthylazepine-based ligands for asymmetric catalysis. Part 2: New aminoalcohols as chiral ligands in the enantioselective addition of $ZnEt_2$ to aromatic aldehydes

Stefano Superchi, Tommaso Mecca, Egidio Giorgio and Carlo Rosini*

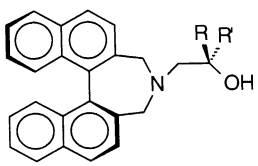
Dipartimento di Chimica, Università della Basilicata, Via Nazario Sauro 85, 85100 Potenza, Italy

Received 6 April 2001; accepted 2 May 2001

Abstract—The new enantiopure 1,2-aminoalcohols **1b**–**1h** having 1,1′-binaphthylazepine skeleton have been tested as catalytic precursors in the enantioselective addition of $ZnEt_2$ to benzaldehyde. The best results were seen with ligand **1d**, which owes its chirality only to the atropisomerism of the binaphthyl nucleus and does not have any stereogenic carbon atom. In the presence of **1d** benzaldehyde was quickly and cleanly transformed to (*S*)-1-phenylpropanol in 99% yield and 87% e.e. The same ligand was also used in the asymmetric $ZnEt_2$ addition to other aryl aldehydes giving rise to (*S*)-1-arylpropanols in almost quantitative yields and e.e.s up to 90%.

1. Introduction

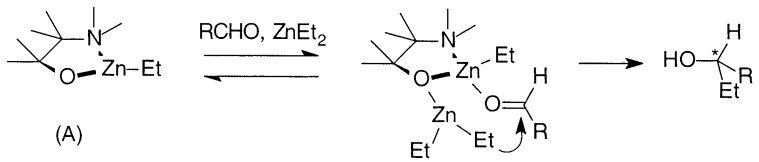
Enantiopure natural[1] and synthetic[2] aminoalcohols have found widespread application in asymmetric synthesis. In general, these systems owe their chirality to the presence of stereogenic carbon atoms, and only recently aminoalcohols having either planar[3,4] or atropisomeric[5,6d,m] chirality have been employed. Taking into account the high efficiency shown by atropisomeric ligands having a 1,1′-binaphthylazepine skeleton in asymmetric catalysis,[6] we decided to evaluate the scope and limitations, as chiral catalysts, of 1,2-aminoalcohols having the general formula reported in Fig. 1.



(*S*)-**1a** R = R' = H
(*S*)-**1b** R = R = CH_3
(*S*)-**1c** R, R' = -$(CH_2)_5$-
(*S*)-**1d** R = R' = Ph
(*S*)-**1e** R = R' = *tert*-Bu
(*S,R*)-**1f** R = Ph, R' = H
(*S,S*)-**1g** R = H, R' = Ph
(*S,S*)-**1h** R = H, R' = cyclohexyl

Figure 1.

To test the efficiency of these ligands we evaluated their behavior in the enantioselective addition of $ZnEt_2$ to aldehydes,[7] taken as a benchmark reaction. As a matter of fact, only a single report by Noyori et al.[6d] concerns the use of the parent aminoalcohol of this family, (*S*)-**1a**, in the $ZnEt_2$ addition to benzaldehyde, leading to (*S*)-1-phenylpropanol in 49% e.e. In the commonly accepted mechanism[7] for this reaction (Scheme 1) the reaction between the aminoalcohol and a molecule of $ZnEt_2$ firstly gives rise to the formation of the chelated ethylzinc–alkoxide intermediate (A), which then coordinates with both the aldehyde and a second molecule of $ZnEt_2$, allowing the stereoselective addition of the ethyl group to the aldehyde carbonyl. Recently, Goldfuss



Scheme 1.

* Corresponding author. Tel.: +39-0971-202241; fax: +39-0971-202223; e-mail: rosini@unibas.it

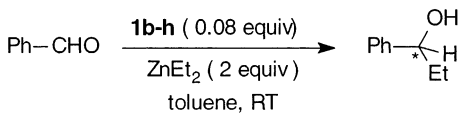
0957-4166/01/$ - see front matter
PII: S0957-4166(01)00200-2

and Houk[8] attempted a theoretical analysis aimed at clarifying the relationship between the stereoselectivity of this reaction and the structural features of several aminoalcohols used as chiral ligands.[9] They calculated the relative energies of the possible transition states for each ligand and explained the moderate enantioselectivity obtained with (*S*)-**1a**, pointing out that in this ligand '…the binaphthyl substituent at N does not efficiently distinguish the faces of the five-membered Zn–chelate ring. The lack of a substituent at C(O) eliminates significant repulsive interactions with the bulky $ZnEt_2$ moieties'.

This conclusion prompted us to carry out an investigation aimed at verifying whether the introduction of substituents of increasing size at the C(O) center of the ligand and the resultant increases in steric demand would lead to higher enantioselectivity.

2. Results and discussion

We prepared[10] aminoalcohols **1b**–**1e** having, respectively, two methyl groups, a cyclohexyl ring, two phenyl, and two *tert*-butyl groups on the C(O). Additionally we prepared the aminoalcohols **1f**–**1h**, where the C(O) atom is stereogenic, in order to evaluate the role on the enantioselectivity of ligands bearing two different types of chirality. The β-aminoalcohols **1b**–**1h** were tested in the enantioselective addition of diethylzinc to benzaldehyde under standard conditions (Scheme 2) in which the reaction was carried out in dry toluene at 20°C in the presence of 8 mol% of the chiral ligand. The reaction mixture was monitored by TLC and GC–MS and when complete conversion of the aldehyde was detected the mixture was quenched with 10% aqueous HCl. After extraction with Et_2O, drying and evaporation of solvent, the product ratio was directly determined on the crude mixture by GC–MS and the e.e. of the 1-phenyl-1-propanol product was measured by HPLC on a chiral stationary phase.



Scheme 2.

The results collected in Table 1 show that, in the presence of catalytic amounts of compounds **1b**–**1h**, diethylzinc adds cleanly to benzaldehyde providing 1-phenyl-1-propanol (with complete conversion and without any trace of benzyl alcohol, a common byproduct of this reaction). Only in run 8, where ligand (*aS*,*R*)-**1f** was used, the reaction was slower and a significant amount of benzyl alcohol (10%) was detected. Reducing the reaction temperature (from 20 to 0°C) slowed down the reaction but did not increase the enantioselectivity (compare runs 2 and 3), while reducing the amount of ligand from 8 to 3% led to only a small decrease in the enantioselectivity, giving product with e.e.s of 81 and 75%, respectively (compare runs 2 and 4). With all the only-atropisomerically chiral ligands **1b**–**1e**, the (*S*)-configuration of the binaphthyl moiety always induced predominant formation of the (*S*)-alcohol product (runs 1–7). Interestingly, higher e.e.s were obtained with increasing bulk of the R groups, the lowest selectivity being seen with the dimethyl derivative **1b**. This result is clearly in keeping with the conclusions of Houk and Goldfuss, concerning the need of substituents on the C(O). The highest e.e. and a shorter reaction time were achieved with the diphenyl-substituted ligand (*S*)-**1d**. However, the presence of the bulkier *tert*-butyl groups in **1e** (run 7) led to a significant reduction in product e.e. and a longer reaction time. This result can be interpreted considering that the presence of the *tert*-butyl groups prevents efficient coordination of the second $ZnEt_2$ molecule and/or the aldehyde to the alkoxide (A) (Scheme 1), thus reducing the influence of the catalyst on the overall process.

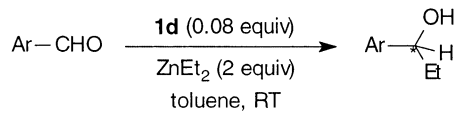
Table 1. Enantioselective addition of $ZnEt_2$ to benzaldehyde mediated by ligands **1b**–**1h**

Run	Ligand[a]	Time (h)	Temp. (°C)	Yield (%)[b]	E.e. (%)[c] (ac)[d]
1	(*S*)-**1b**	14	20	97[e]	64 (*S*)
2	(*S*)-**1c**	5	20	99	81 (*S*)
3	(*S*)-**1c**	16	0	99	78 (*S*)
4	(*S*)-**1c**[f]	16	20	99	75 (*S*)
5	(*S*)-**1d**	0.5	20	99	87 (*S*)
6	(*S*)-**1d**[g]	2	20	99	86 (*S*)
7	(*S*)-**1e**	14	20	99	64 (*S*)
8	(*S*,*R*)-**1f**	20	20	90[h]	38 (*R*)
9	(*S*,*S*)-**1g**	12	20	99	79 (*S*)
10	(*S*,*S*)-**1h**	3	20	99	84 (*S*)

[a] 8 mol% of ligand was used.
[b] Chromatographic (GLC) yield. No traces of benzyl alcohol were detected.
[c] Determined by HPLC on Chiralcel OD.
[d] Determined by elution order on Chiralcel OD.[7d]
[e] About 1 mol% of benzyl alcohol was detected.
[f] 3 mol% of ligand was used.
[g] Lithium salt of the ligand was used.
[h] 10 mol% of benzyl alcohol present.

It is interesting to note that by simply changing the nature of the R groups, without changing the chiral backbone of the molecule, we were able to markedly increase the enantioselectivity from the 49% e.e. of Noyori's ligand (*S*)-**1a**, to 64% with (*S*)-**1b**, 81% by the use of (*S*)-**1c** and 87% with (*S*)-**1d**. We then showed that making suitable structural modifications to these catalysts, which have only atropisomeric chirality and do not possess any stereogenic carbon atom, high enantioselectivities can be obtained. Previous experimental[7] and theoretical[8,9] investigations showed that the absolute configuration of C(O) primarily determines the stereochemical outcome of the β-aminoalcohol catalyzed reaction. In the present case no stereogenic center is present on the carbon bearing the hydroxy group, but the chiral environment created by the 1,1′-binaphthyl nucleus is transmitted through the molecule and affects events occurring at the N–Zn–O moiety. The possibility of this long range control of chirality depends on the nature of the substituents at the C(O) atom: it is low for R = H, higher for R = Me, and reaches a maximum value for R = Ph. In the latter case the presence of the diphenylhydroxymethyl group allows the maximum enantioselectivity, thus confirming the efficiency of this achiral moiety in asymmetric catalysis.[11]

The introduction of a stereogenic center on the C(O) in the monosubstituted ligands (*aS*,*R*)-**1f**, (*aS*,*S*)-**1g** and (*aS*,*S*)-**1h** led to some interesting observations. In all cases the enantioselectivities were lower with respect to the simply atropisomeric counterparts **1a**–**1e** (in Table 1 compare run 5 with runs 8 and 9). The ligand (*aS*,*R*)-**1f** induced the formation of the alcohol with opposite (*R*)-configuration and with low 38% e.e. while its epimer, (*aS*,*S*)-**1g**, led to the expected (*S*)-configured alcohol in 79% e.e. Clearly, in the former the stereogenic elements constitute a mismatched pair, while in the second reaction a matched pair effect is seen. These experiments also indicate that the stereochemical outcome of the reaction is mainly determined by the absolute configuration of the carbon atom bearing the OH.



Scheme 3.

Interestingly, (*aS*,*R*)-**1f** induced predominant formation of product with (*R*)-configuration, although we have shown above that the (*S*)-configuration of the binaphthyl moiety induces an (*S*)-configured alcohol (runs 1–7 in Table 1). This result is in keeping with Noyori's finding[6d] that (*R*)-1-phenyl-2-*N*,*N*-dimethylaminoethanol (structurally comparable with the aliphatic moiety of (*aS*,*R*)-**1f**) induced the formation of (*R*)-1-phenyl-1-propanol in 59% e.e. in the $ZnEt_2$ addition to benzaldehyde.

In order to better investigate the reactivity of such ligands the most efficient, (*S*)-**1d**, was used in the enantioselective addition of $ZnEt_2$ to different aryl aldehydes (Scheme 3) under standard conditions and the results are summarized in Table 2.

The reactivity of the substrates was clearly related to the electrophilic character[12] of the carbonyl group. Benzaldehyde (run 1) was fully reacted after 30 minutes. With electron donating ring substituents the reaction rate was lowered whilst electron withdrawing groups served to enhance the rate of reaction. Thus, the slowest reaction (90 minutes) was observed with 4-methoxybenzaldehyde (run 2), while a very rapid reaction of less than 10 minutes was observed with 4-cyanobenzaldehyde (run 3).

In contrast, the e.e. of the product was found to be little dependent on the nature of the substrate. This result is in agreement with many investigations[7] reporting that enantioselectivity is mainly determined by steric factors, but is in contrast with a recent report[5c] where enantioselectivity was observed to increase with substrate reactivity. The e.e.s obtained in the case of *para*-substituted benzaldehydes ranged from 80% for 4-methoxybenzaldehyde to 90% for 4-(trifluoro-

Table 2. Addition of $ZnEt_2$ to aryl aldehydes mediated by ligand (*S*)-**1d**[a]

Run	Ar	Time	Temp. (°C)	Yield (%)[b]	E.e. (%)[c] (ac)[d]
1	C_6H_5	30 min	20	99	87 (*S*)
2	4-$CH_3OC_6H_4$	90 min	20	99	80 (*S*)
3	4-CNC_6H_4	10 min	20	99	84[e] (*S*)[f]
4	4-$CF_3C_6H_4$	25 min	20	99	90[e] (*S*)[f]
5	2-Naphtyl	75 min	20	98	86[e] (*S*)[f]
6	1-Naphtyl	2 h	20	99	87 (*S*)
7	9-Anthryl	16 h	20	92	77 (*S*)[g]
8	C_6H_5-CH=CH	45 min	20	91	68 (*S*)

[a] 8% of aminoalcohol was used.
[b] Chromatographic (GLC) yield. No traces of benzyl alcohol were detected.
[c] Determined by HPLC on Chiralcel OD.
[d] Determined by elution order on Chiralcel OD.[7d]
[e] Determined by HPLC on Chiralcel OJ.
[f] Determined by comparison of $[\alpha]_D$ with literature values.[13]
[g] Tentatively assigned by comparison of $[\alpha]_D$ sign with literature value for (*S*)-1-(9-anthryl)-1-ethanol.[14]

methyl)benzaldehyde. In the case of 2-naphthaldeyde, an e.e. of 86%, similar to that of the sterically comparable benzaldehyde, was obtained. The more hindered 1-naphthaldehyde was also alkylated with a similar e.e. of 87% (run 6). These results seem to indicate that (*S*)-**1d** allows alkylation of aromatic aldehydes with little dependence on the steric effects in the substrate. Also a very rigid substrate such as 9-anthraldehyde (run 7) afforded a good 77% e.e., while lower 68% e.e. was obtained with *trans*-cinnamaldehyde (run 8) where the aromatic ring is far from the reaction center.

3. Conclusions

We have clearly demonstrated that enantiopure atropisomeric aminoalcohols having the structure of **1b**–**1h** can act as efficient promoters of the enantioselective addition of $ZnEt_2$ to aryl aldehydes. This result is important from a practical point of view, because a new class of efficient ligands has been made available, but also from a wider view, because in the most efficient ligands of this type, compounds **1b**–**1e**, their chirality results only from the atropisomerism of the binaphthyl nucleus and they do not have any stereogenic carbon atom.

It is interesting to note that this investigation fully confirms the theoretical analysis of Goldfuss and Houk[8] about the need of substituents at C(O) in order to achieve higher enantioselectivity. We are convinced that the present experimental results may stimulate further theoretical and experimental investigation aimed at clarifying the correlation between structure and catalytic activity of these aminoalcohol ligands. Work is now in progress to also study the efficiency of compounds **1b**–**1h** in other asymmetric reactions.

4. Experimental

4.1. General procedures

All the 1-aryl-1-propanols obtained by the diethylzinc addition to aryl aldehydes showed NMR spectra fully in agreement with literature data. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker Aspect 300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. E.e.s of the optically active 1-aryl-1-propanols were determined by HPLC analysis performed on a JASCO PU-1580 pump with a Varian 2550 UV detector and Daicel Chiralcel OD or OJ columns. Toluene was freshly distilled from sodium benzophenone ketyl under nitrogen atmosphere prior to use. Diethylzinc was used as a 1.0 M solution in hexane (Aldrich) and was used as purchased. Commercially available (Aldrich) benzaldehyde, 4-anisaldehyde, 4-trifluoromethylbenzaldehyde, 1-naphthaldehyde and *trans*-cinnamaldehyde were distilled prior their use and stored under nitrogen atmosphere. Commercially available (Aldrich) 4-cyanobenzaldehyde, 2-naphthaldehyde and 9-anthraldehyde were used as purchased. Analytical TLC was performed on 0.2 mm silica gel plates (Merck 60 F-254). Mixture composition was determined by GLC-MS on a Hewlett Packard 6890 chromatograph equipped with an HP-5973 mass detector.

4.2. Typical procedure for the diethylzinc addition to aldehydes

4.2.1. (*S*)-(−)-1-(9-Anthryl)-1-propanol. To a solution of (*S*)-**1d** (24.5 mg, 0.05 mmol) in dry toluene (3 mL), under a nitrogen atmosphere at rt, was added a solution of $ZnEt_2$ in hexane (1.0 M, 1.25 mL, 1.25 mmol). The mixture was stirred for 30 min. A solution of 9-anthraldehyde (129 mg, 0.625 mmol) in dry toluene (1.3 mL) was added. The reaction was monitored by GC–MS and when no more traces of the aldehyde were detected (16 h) the reaction was quenched by addition of 10% aqueous HCl. The mixture was extracted with Et_2O and the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent the solid residue was directly analyzed by GC–MS and HPLC. GC–MS yield 92%; e.e. 77% by HPLC on Chiralcel OD (hexane/propan-2-ol 9:1, flow 0.5 mL/min, t_{r1} 18.7 min, t_{r2} 34.9 min). The crude product was purified by column chromatography (silica gel, $CHCl_3$) to afford pure (−)-1-(9-anthryl)-1-propanol (128 mg, 87%). The sample was assigned (*S*)-configuration by comparison of the $[\alpha]_D$ sign with the literature value[14] for (*S*)-(−)-1-(9-anthryl)-1-ethanol. $[\alpha]_D^{20} = -19.2$ (*c* 0.53, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (t, 3H, $J = 7.4$ Hz); 2.1–2.3 (m, 1H); 2.32 (br s, 1H); 2.3–2.5 (m, 1H); 6.13 (t, 1H, $J = 7.3$ Hz); 7.4–7.5 (m, 4H); 8.0 (m, 2H); 8.36 (s, 1H); 8.5–8.8 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.0; 131.7; 129.4; 129.3; 127.9; 125.4; 125.0; 124.7; 72.6; 30.8; 11.3.

Acknowledgements

Financial support from MURST (COFIN2000) and Università della Basilicata (Potenza) is gratefully acknowledged.

References

1. Wynberg, H. *Topics Stereochem.* **1986**, *16*, 87.
2. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (b) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.
3. (a) Bolm, C.; Muniz-Fernandez, K.; Seger, A.; Raabe, G. *Synlett* **1997**, 1051; (b) Bolm, C.; Muniz-Fernandez, K.; Seger, A.; Raabe, G.; Gunther, K. *J. Org. Chem.* **1998**, *63*, 7860; (c) Bolm, C.; Muniz, K. *Chem. Commun.* **1999**, 1295; (d) Patti, A.; Nicolosi, G.; Howell, J. A. S.; Humphries, K. *Tetrahedron: Asymmetry* **1998**, *9*, 4381; (e) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444; (f) Watanabe, M. *Synlett* **1995**, 1050.
4. (a) Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* **1993**, *58*, 1238; (b) Jones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 261;

(c) Jones, G. B.; Huber, R. S.; Chapman, B. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1797.
5. (a) Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1998**, *9*, 667; (b) Vyskocil, S.; Jaracz, S.; Smrcina, M.; Sticha, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727; (c) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002.
6. (a) Mazaleyrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585; (b) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820; (c) Kanth, J. V. B.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1145; (d) Noyori, R.; Suga, S.; Okada, S.; Kawai, K.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Masuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19; (e) Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1994**, *59*, 649; (f) Kubota, H.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 6689; (g) Wimmer, P.; Widhalm, M. *Tetrahedron: Asymmetry* **1995**, *6*, 657; (h) Kubota, H.; Koga, K. *Heterocycles* **1996**, *42*, 543; (i) Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2971; (j) Aggarwal, V. K.; Wang, M. F. *Chem. Commun.* **1996**, 191; (k) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194; (l) Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073; (m) Arroyo, N.; Haslinger, U.; Mereiter, K.; Widhalm, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4207.
7. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *103*, 34; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833; (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757; (d) Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315 and references cited therein.
8. Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998.
9. For other recent computational studies on asymmetric diethylzinc addition to aldehydes, see: (a) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128; (b) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77 ; (c) Vazquez, J.; Pericas, M. A.; Maseras, F.; Lledos, A. *J. Org. Chem.* **2000**, *65*, 7303; (d) Goldfuss, B.; Steigelmann, M.; Rominger, F. *Eur. J. Org. Chem.* **2000**, 1785.
10. Mecca, T.; Superchi, S.; Giorgio, E.; Rosini, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1225.
11. Braun, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 519.
12. Corey, E. J.; Yuen, P.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1996**, *55*, 784.
13. Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523.
14. Reiners, I.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 27.