Going soft (or hard) in asymmetric catalysis?

Simon Woodward

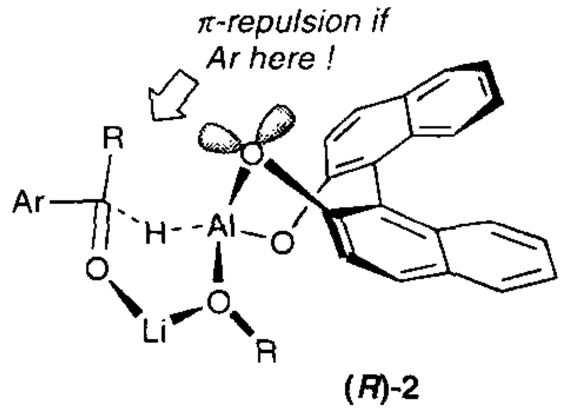
Department of Chemistry, University of Hull, Kingston-upon-Hull HU6 7RX, United Kingdom

The quest for highly efficient routes to enantiopure chemicals for use in the pharmaceutical, fine chemical and agrochemical sectors has accelerated greatly in the last decade due to legislative and environmental pressures. Organometallic chemistry offers attractive approaches to the generation of asymmetric catalysts of superlative activity and selectivity. This article summarizes the activities of the author's group in applying the Hard–Soft-Lewis-Acid–Base (HSAB) concept to this area and compares these to other approaches in the current literature.

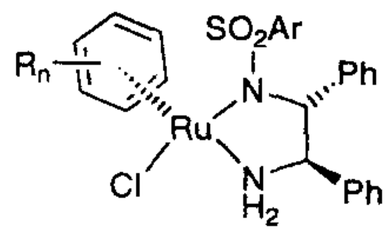
Introduction

Given the innate chirality of living systems, differential interaction with stereogenic biologically active compounds is expected. Well-known examples are the flavour properties of limonene[1] [the (*R*) isomer in orange oil, (*S*) in lemons] and the scent of carvone[2] [the (*R*) enantiomer smells of spearmint, the (*S*) isomer of caraway]. Of greater notoriety are the analgesic/mutagenic properties of the enantiomers of Thalidomide[3]. Enormous legislative and environmental pressures have developed in the 80s and 90s for the production of single enantiomer products in pharmaceutical and fine chemical markets. The current global market for single enantiomer compounds is dominated by classical resolution of racemic mixtures. However, organometallic catalysis has, and will continue to, make significant contributions in this area. For example, enantiopure *sec*-alcohols are produced on industrial scales using a 'CBS' oxazaborolidene catalyst, introduced by Corey[4], in the presence of BH_3 sources (Figure 1)[5]. It is relevant to this article to realize that the transition state **1** that gives rise to this remarkably selective reaction is held together by Lewis acid–base interactions. The most sterically accessible lone pair of the precursor ketone is bound to the Lewis acidic boron. Simultaneously the BH_3 reducing agent is activated by coordination to the nitrogen lone pair. Recently we were able to make a contribution to this area by introducing $LiH/BF_3.OEt_2$ as a low cost borane source[6].

A second driver in commercialized asymmetric chemistry is the purely economic need to reduce the amount of organometallic reagent required for a given transformation. For example, the discovery in 1984 by Noyori that a BINAL reagent could reduce aryl/alkyl ketones in ~ 100% e.e. via the electronically controlled transition state **2** was a landmark result[7]. However, three equivalents of BINAL reagent were required per mole of ketone reduced. Perhaps the most impressive 'downsizing' in this area is the introduction of the catalyst **3** which will carry out transformations equivalent to BINAL but at catalyst loadings of less than 0.5 mol% (ref. 8).



(*R*)-2



(*R,R*)-3

Soft catalysts hard reagents

We considered if Pearson's Hard–Soft-Acid–Base (HSAB) concept[9] might be used as a method for engendering highly efficient and selective catalytic systems if all the components of the catalytic system were carefully matched. Despite considerable advances in theoretical descriptions of HSAB one very useful approach is to consider equilibria such as eq. (1)[9], where H indicates hard components and S soft species.

$$(H_1S_1 + H_2S_2) = H_1H_2 + S_1S_2 \qquad (1)$$

The HSAB concept tells us that such systems will relax towards their 'matched pairs'. The driving force for such

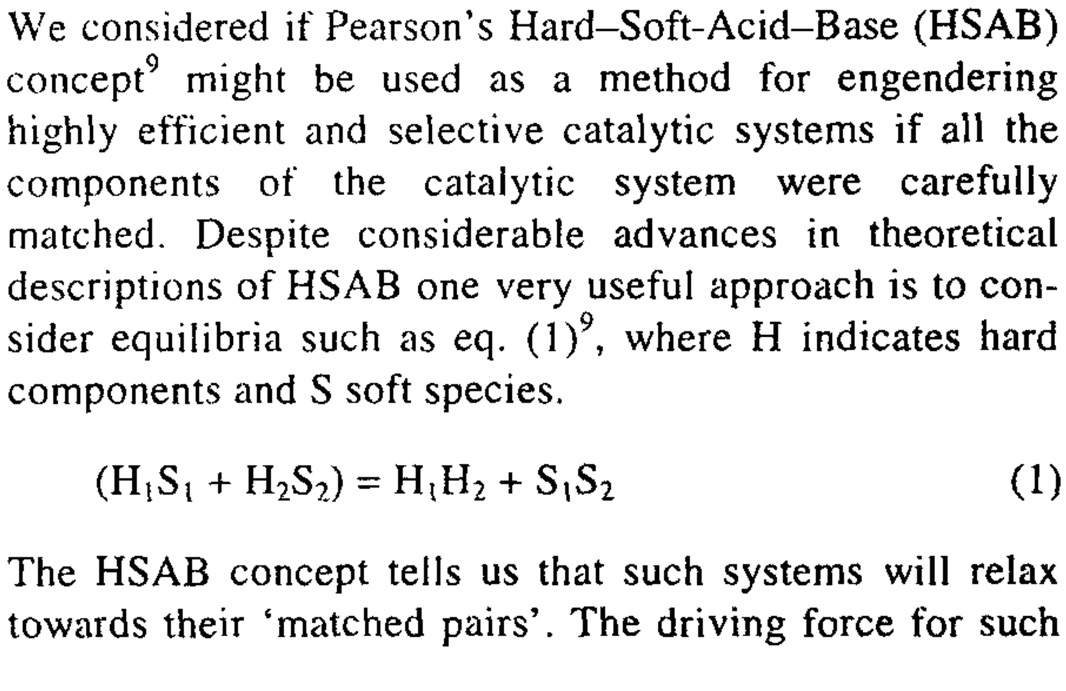


Figure 1. Chiral *sec*-alcohols produced industrially using **'CBS'** catalysis.

e-mail: S.C.Woodward@chem.hull.ac.uk

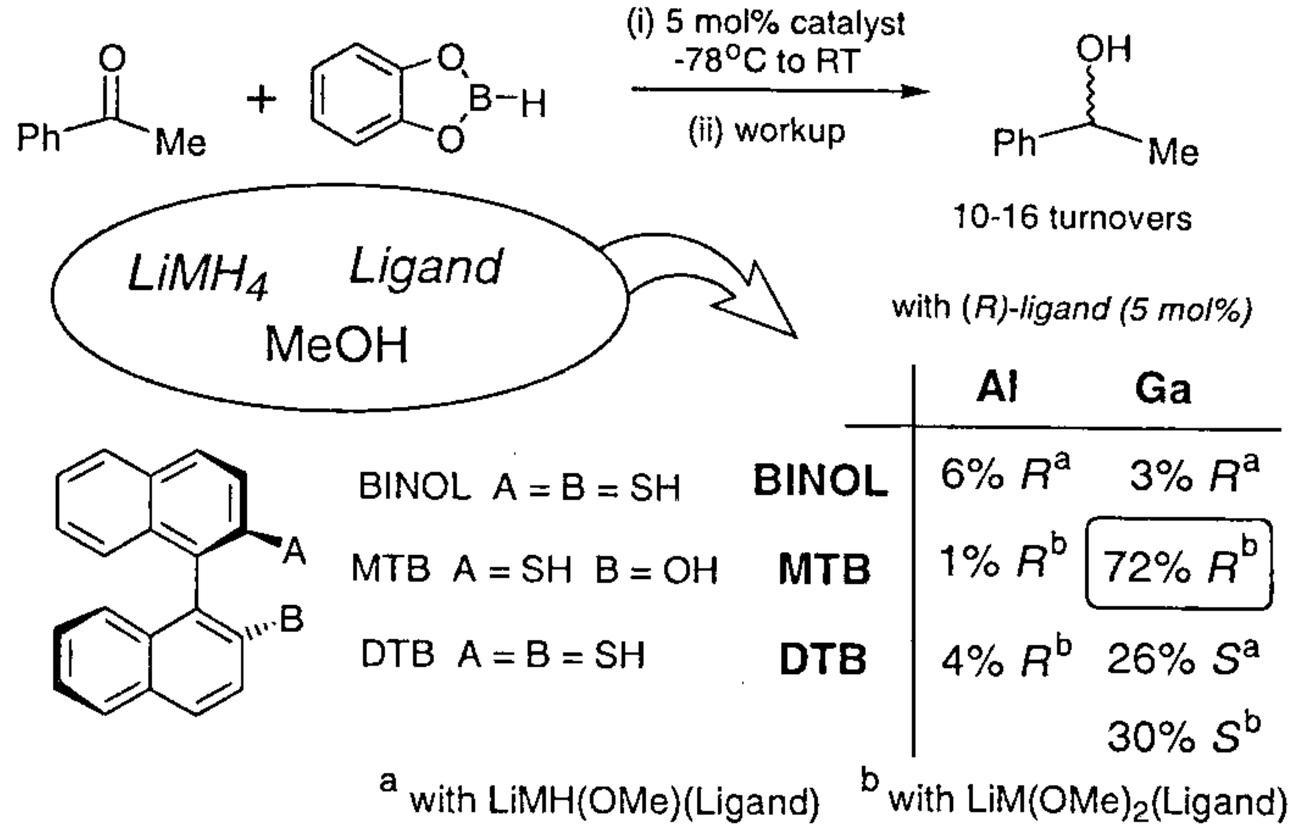


Figure 2. Testing the HSAB matching theory; e.e. values vs metal and ligand.

Table 1. Typical bond energies (in kcal mol^{-1}) for Group 13 M–X species (X = O, S)

Metal	B	Al	Ga
Bond energy M–O	192	107	70
Bond energy M–S	119	82	~ 70
Δ (Bond energy)	73	25	~ 0
HSAB type	hard	hard	soft

Table 2. Enantioselective reduction of ketones by Li[Ga(**MTB**)$_2$] (2.5 mol%) and catecholborane

Ketone ArC(=O)R			
Ar	R	Yield /%	e.e. /%
Ph	Me	95	91
Ph	Et	96	93
Ph	Bu″	80	92
Ph	Bu′	65	92
4-BrPh	Me	80	87
4MePh	Me	95	87

reactions can be predicted from simple thermodynamic data. Using bond energy data allows not only the 'hardness' of a component to be judged but also the overall reaction thermodynamic viability to be accessed. Consider now that H_1 and H_2 constitute a *substrate* and *reagent* pair, that H_1H_2 is the desired organic *product* and that S_1/S_2 is a *catalytic metal* and its *chiral ligand.* Thus, $(H_1S_1 + H_2S_2)$ constitutes the key 'mismatched' intermediate in the catalytic cycle which, if it can be prepared, will decompose quickly to the product. To test these ideas we determined to design a *catalytic* version of Noyori's BINAL reagent **2**. Acetophenone and catecholborane were selected as the hard substrate/reagent pair. Acetophenone is 'hard' by benefit of the ketonic oxygen. To select a soft catalytic metal/ligand pair it is instructive to consider typical bond energy data for M–X (X = O, S) for the Group 13 metals (Table 1). These data suggest that gallium complexes in the presence of thiolate donors will be appropriate catalysts.

A series of trial reactions were carried out using $LiMH_4$ (M = Al, Ga) and the ligands **BINOL, MTB**, and **DTB** (Figure 2). It is helpful to know that the Noyori transition state **2** predicts that the (*R*) ligand leads to the (*R*) *sec*-alcohol product and that in the original formulations methanol was added in the reagent preparation. The initial screen matrix soon revealed the validity of the HSAB matching approach as high chemical yields were realized with significant enantioselectivity for the gallium-**MTB** complex. Additionally the reversed enantioselectivity shown by the gallium-**DTB** species provided the key insight that although the soft–soft interactions of the catalytic metal/ligand must be accommodated, matching of the hard lithium cation is also important.

The key to improving the enantioselection in this system was the realization that added alkoxides lead to appreciable achiral catalysis via the formation of borohydride complexes ($[C_6H_4O_2BH(OR)]^-$ as in the original work of Lindsley and DiMare[10]). This could be eliminated by the simple expedient of not adding methanol. Further modification of the system spectator ligands to softer donors, especially a second **MTB** donor, led to a synthetically interesting Li[Ga(**MTB**)$_2$] catalyst which gave high yields and enantioselectivities (Table 2)[11].

We have also applied our HSAB matching ideas to asymmetric conjugate addition chemistry. In particular it was envisaged that a 'hard' enone and an appropriately 'hard' oxophilic RM reagent would be mismatched to a soft copper catalyst with the soft **MTB** ligand under the general approach of equilibrium eq. (1). Test reactions of Bu″Li or Bu″MgCl with cyclohexenone showed that dramatic rate enhancement was realized (Figure 3, especially for Grignard reagents)[12–14]. High chemical yields (c.y.) were realized with many typical enone test substrates. In

fact the Cu/**MTB** system is one of the few that can divert Bu^nLi from its usual reactivity as a base[12].

Unfortunately, it appears that the copper complexes that arise from the interaction of $[Cu(MeCN)_4]BF_4$ and **MTB** do not have appropriate geometries for the induction of high enantioselectivities in the addition of organometallic reagents to either cyclic or linear enones. At best 20–36% e.e. values have been realized[12–14].

Hard catalysts soft reagents

Our failure to realize significant levels of enantioselection in asymmetric conjugate addition using our **MTB** ligand caused us to rethink our strategy by using a hard catalyst soft reagent approach. This is shown schematically in Figure 4 where D_s is a soft donor capable of delivering a Gilman-like cuprate, CuR_2^-, to π-bond of the enone. In this particular case, however, less dramatic rate enhancements are to be expected as dissociation of the hard–hard Al–O interaction in the product enolate is likely to be rate limiting. Routine screening revealed that the thiourethane **4** in association with organoaluminium reagents led to a catalyst for the addition of alkyl functions (especially methyl groups) linear enones[15]. The highest e.e. values (~51%) are realized for $AlMe_3^-$ derived Lewis acids while the use of Grignard reagents leads only to high yields of racemic products. While the enantioselectivities shown by this system are not yet synthetically useful, they are significant given that enantioselective conjugate additions to aliphatic enones are particularly difficult to attain. While the exact nature of the active catalyst is not known the presence of the naphthoic OH and thioketone groups are vital to the catalysis. For example, ligands identical to **4** but with a simple carbonyl function do not lead to any significant levels of asymmetric induction and only poor product yields are realized (Table 3). Additionally, in accordance with the prediction of Figure 4 alkylation of the naphthoic OH in ligand **4** also leads to poor catalyst.

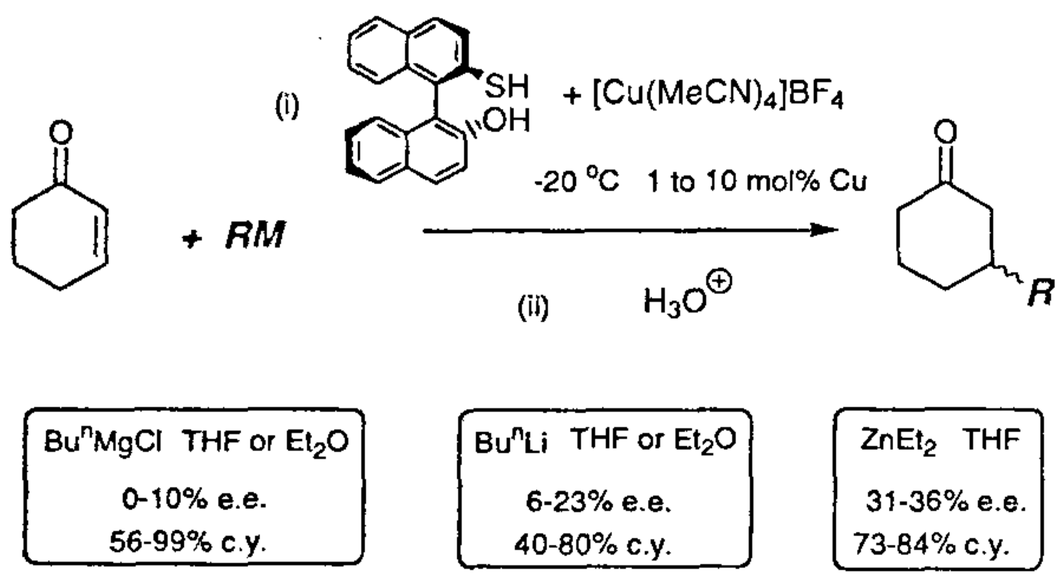


Figure 3. Asymmetric conjugate addition of organometallic reagents (RM) to cyclohexenone using copper(I)/**MTB** catalysts.

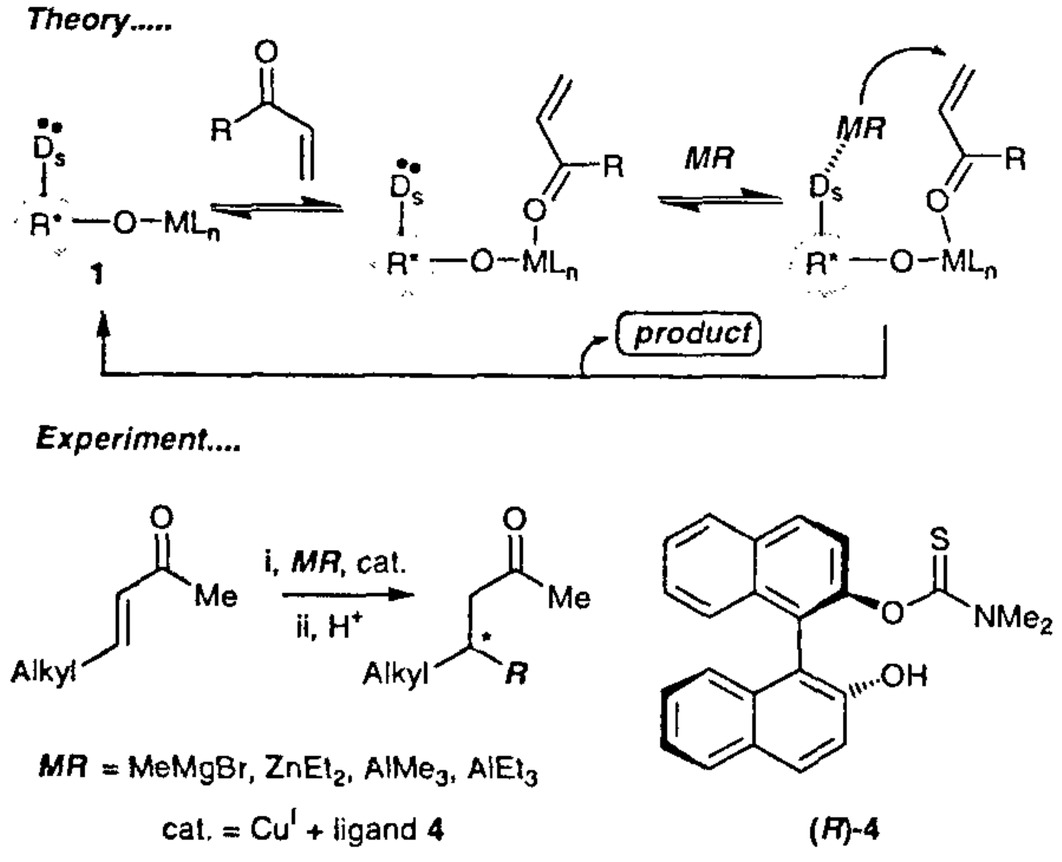


Figure 4. Alternative hard–soft strategy for asymmetric conjugate addition reactions.

Overview and conclusions

Aside from the processes outlined above one may assign the matched HSAB concept to many literature reactions.

Table 3. Asymmetric conjugate additions of RM reagent to alkyl C(H)=CH(COMe) in the presence of $[Cu(MeCN)_4]BF_4$ and ligand **4**

RM	Alkyl in enone	Yield/%	e.e./%
MeMgBr	$C_5H_{11}^n$	81	0
$ZnEt_2$	$C_5H_{11}^n$	66	35
$AlMe_3$	$C_5H_{11}^n$	80	51
$AlEt_3$	$C_5H_{11}^n$	40	32
$AlMe_3$	Pr^n	51	46
$AlEt_3$	Pr^n	42	26
$AlMe_3$	Pr^i	43	43
$AlEt_3$	Pr^i	36	10

Table 4. Recent examples from literature reactions showing excellent HSAB matching

Transformation	Catalyst	Substrate/reagent	Ref.
Ketone hydrosilylation	(Diphosphine)Rh	Ketone/Ph_2SiH_2	16
Conjugate addition	$(Phosphine)_2Cu$	Cyclohexeneone/$ZnEt_2$	17, 18
Conjugate addition	(RS)Cu	Benzylidene acetone/MeMgI	19
Conjugate addition	(BINOL)LaNa	Enone/RSH	20
Hydrophosphonylation	(BINOL)LaLi	RCHO/$HP(=O)(OMe)_2$	21
Hydrophoshonylation	(BINOL)LaK	Imine/$HP(=O)(OMe)_2$	22
Henry reaction	(BINOL)LaLi	RCHO/RCH_2NO_2	22

If one assumes a carbonyl oxygen to be a universal 'hard' donor then it is possible to think of many catalytic transformations of aldehydes, ketones, enones, etc. in the way outlined above. Because the HSAB concept is easily understood it possible to see these simple ideas in numerous transformations. To make this point a few examples from the recent literature are shown in Table 4. However, in order to attain the most from HSAB matching it is necessary to realize that the requirements of *every* component in the catalytic reaction mixture must be accommodated.

1. Williams, K. R. and Pierce, *J. Chem. Educ.*, 1998, **75**, 223; Blanch, G. P. and Nicholson, G. J., *J. Chromatogr. Sci.*, 1998, **36**, 37.
2. Bouwmeester, H. J., Davies, J. A. R. and Toxopeus, H., *J. Agric. Food Chem.*, 1995, **43**, 3057; Bounoshita, M., Hibi, K. and Nakamura, H., *Anal. Sci.*, 1993, **9**, 425.
3. Wnendt, S. and Zwingenberger, K., *Nature*, 1997, **385**, 303; Ashby, J., *Nature*, 1997, **389**, 118; Brower, V., *Nat. Biotechnol.*, 1997, **15**, 1238; Ashby, J. and Tinwell, *Nature*, 1995, **375**, 453.
4. Corey, E. J. and Helal, C. J., *Angew. Chem. Int. Ed. Engl.*, 1998, **37**, 2092; Corey, E. J., Bakshi, R. K., Shibata, S., Chen, C.-P. and Singh, V. K., *J. Am. Chem. Soc.*, 1987, **109**, 7925.
5. Figure 1 shows *sec*-alcohols currently produced on a 100–1000 + litre scale in 92–98% e.e. by Merck, Pfizer, and Sipsy using 'CBS' systems. I thank Dr John Blacker at Zeneca Fine Chemicals Ltd. (Huddersfield) for this information.
6. Ford, A. and Woodward, S., *Synth. Commun.*, 1999, **29**, 189.
7. Noyori, R., Tomino, I., Tanimoto, Y. and Nishizawa, *J. Am. Chem. Soc.*, 1984, **106**, 6709.
8. Noyori, R. and Hashiguchi, S., *Acc. Chem. Res.*, 1997, **30**, 97.
9. Pearson, R. G., *Coord. Chem. Rev.*, 1990, **100**, 403.
10. Lindsley, C. W. and DiMare, M., *Tetrahedron Lett.*, 1994, **35**, 5141.
11. Ford, A. and Woodward, S., *Angew. Chem. Int. Ed. Engl.*, 1999, **38**, 336.
12. Green, J. and Woodward, S., *Synlett*, 1995, 155.
13. Azad, S. M., Bennett, S. M. W., Brown, S. M., Green, J., Sinn, E., Topping, C. M. and Woodward, S., *J. Chem. Soc., Perkin Trans. 1*, 1997, 687.
14. Bennett, S. M. W, Topping, C. M. and Woodward, *J. Chem. Soc., Perkin Trans. 1*, under preparation.
15. Bennett, S. M. W., Brown, S. M., Muxworthy, J. P. and Woodward, *Tetrahedron Lett.*, 1999, **40**, 1769.
16. Waldman, T. E., Schaefer, G. and Riley, D. P., *Am. Chem. Soc. Symp. Ser.*, 1993, **517**, 58.
17. de Vries, A. H. M., Meetsma, A. and Feringa, B. L., *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 2374.
18. Feringa, B. L., Pineschi, M., Arnold, L. A., Imbos, R. and de Vries, A. H. M., *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2620.
19. van Klaveren, M., Lambert, F., Eijkelkamp, D. J. F. M., Grove, D. M. and van Koten, G., *Tetrahedron Lett.*, 1994, **35**, 6135.
20. Emori, E., Arai, T., Sasai, H. and Shibasaki, M., *J. Am. Chem. Soc.*, 1998, **120**, 4043.
21. Sasai, H., Bougauchi, M., Arai, T. and Shibasaki, M., *Tetrahedron Lett.*, 1997, **38**, 2717.
22. Shibasaki, M., Sasai, H. and Arai, T., *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 1237.

MEETINGS/SYMPOSIA/SEMINARS

II National Conference on Spectrophysics (NCONS 2000)

Date: 9–11 August 2000
Place: Chennai, India

Topics include: Raman spectroscopy; Infrared spectroscopy; Vibrational analysis and molecular structure; Band shapes and band intensities; Macromolecules and biological systems; Surface and interfacial phenomenon; Inorganic materials, matrices; Semiconductors and semiconductor micro structures; Superconductors; Phase transitions, effects of temperature and pressure; Industrial and medical applications; Pollution analysis; Characterization of crystalline and ceramic compounds; Nuclear spectroscopy; Hyperfine structure studies; Laser and laser-based spectroscopy.

Contact: Dr. S. Gunasekaran
Convenor
II National Conference on Spectrophysics
P.G. and Research Department of Physics
Pachaiyappa's College
Chennai 600 030, India

International Conference on 'Global Sustainable Biotech Congress 2000 AD'

Date: 27 Nov. to 1 Dec. 2000
Place: Nagpur, India

Contact: Dr. Sudhir U. Meshram
Chairman Organising Committee
Biotech-Congress 2000 AD
P.G. Department of Microbiology
L.I.T. Premises
Nagpur University
Nagpur 440 010, India
Tel: (Off) 91-(0712)-536226/560620
(Res) 91-(0712)-222040/222080