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Figure 2. 1cREMPI/TOF spectra of diasteromeric  $P_{R}B_{R}$  at  $\lambda = 266.68$  nm (a) and  $P_{R}B_{S}$  clusters at  $\lambda = 266.77$  nm (b) at a total stagnation pressure of  $2 \times 10^{5}$  Pa. The structures of the ground state  $P_{R}B_{R}$  and  $P_{R}B_{S}$  clusters, calculated with modified molecular mechanics (MMX), are given in (a) and (b), respectively.

ences in the photoionization fragmentation pattern of the diastereomeric clusters obtained from complexation of the chiral molecule with suitable chiral partners, and on the different bathochromic shifts of their electronic band origin relative to that of the pure chromophore. The latter indicates that attractive interactions within the clusters are more pronounced in the excited than in the ground state. Under consideration of the order of stability in the ground state,  $P_R B_R > P_R B_S$ , a greater stabilization of the  $P_R B_S$  cluster in the  $S_1$  state relative to that of  $P_R B_R$  tends to cancel the stability order in the excited state. Differences in the absorption frequencies of gaseous jet-cooled species were recently used for isotope-enrichment procedures.<sup>[16]</sup> This study demonstrates that the same approach can be applied to jet-cooled diastereomeric clusters to enantiomerically enrich a racemate.

#### **Experimental Section**

The experimental setup for the generation of van der Waals clusters and their REMPI/TOF analysis was previously described [7,11,17]. Diastereomeric pairs  $P_{R}B_{R}$  and  $P_{R}B_{S}$  were obtained by in a supersonic beam by adiabatic expansion of a carrier gas (Ar) seeded with the corresponding alcohols (Aldrich) through a pulsed 400-µm nozzle kept at 85 °C. The molecular beam was allowed to pass through a 1-mm skimmer into a second chamber equipped with a TOF spectrometer. The laser system consisted of a frequency-doubled Nd: YAG laser ( $\lambda = 532$  nm), which pumps two dye lasers. The dye frequencies were doubled and, when necessary, mixed with residual 1064-nm radiation. The ions formed by REMPI ionization in

the TOF source were mass discriminated and detected by a channeltron after a 50-cm flight path.

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- A. Findlay, A. N. Campbell, *The Phase Rule and Its Applications*, Dover, New York, **1945**, pp. 136,256.
- [2] Y. Kubo, S. Maeda, S. Tokita, M. Kubo, Nature 1996, 382, 522.
- [3] See for instance E. M. Arnett, S. P. Zingg, J. Am. Chem. Soc. 1981, 103, 1221.
  [4] M. Sawada, Y. Takai, H. Yamada, S. Hirayama, T. Kaneda, T. Tanaka, K. Kamada, T. Mizooku, S. Takeuchi, K. Ueno, K. Hirose, Y. Tobe, K. Naemura, J. Am. Chem. Soc. 1995, 117, 7726, and references therein.
- [5] A. R. Al-Rabaa, E. Bréhéret, F. Lahmani, A. Zehnacker, Chem. Phys. Lett. 1995, 237, 480.
- [6] B. Brutschy, Chem. Rev. 1992, 92, 1567.
- [7] S. Piccirillo, M. Coreno, A. Giardini-Guidoni, G. Pizzella, M. Snels, R. Teghil, J. Mol. Struct. 1993, 293, 197.
- [8] S. Piccirillo, D. Consalvo, M. Coreno, A. Giardini-Guidoni, S. Duin, P. Parneix, P. Brechignac, Chem. Phys. 1994, 187, 97.
- [9] R. E. Ballard, J. Jones, E. Sutherland, D. Read, A. Inchley, Chem. Phys. Lett. 1986, 126, 311.
- [10] S. Piccirillo, A. Giardini-Guidoni, unpublished results.
- [11] D. Consalvo, A. van der Avoird, S. Piccirillo, M. Coreno, A. Giardini-Guidoni, A. Mele, M. Snels, J. Chem. Phys. 1993, 99, 8398.
- [12] Careful adjustment of the expansion parameters allowed us to maximize the concentration of two-body  $P_R B_R$  and  $P_R B_S$  clusters relative to that of larger adducts.
- [13] M. D. Brookes, D. J. Hughes, B. J. Howard, J. Chem. Phys. 1996, 104, 5391.
- [14] Molecular mechanics calculations were performed by using "automatic and systematic quasi-flexible docking processing" (S. Alcaro, F. Gasparrini, O. Incani, M. Pierini, C. Villani, J. Comput. Chem., submitted) and applying MMX force field, as implemented in the PC-model software (PC Model Molecular Modeling Software, Serena Software, P. O. Box 3076, Bloomington, IN 17102-3076 (USA)).
- [15] The energy absorbed by  $P_R B_R$  exceeds that absorbed by  $P_R B_S$  by n13 cm<sup>-1</sup>, where *n* is the number of absorbed photons, and 13 cm<sup>-1</sup> the red shift between the two clusters.
- [16] A. Giardini-Guidoni, E. Borsella, R. Fantoni, Europhys. News 1985, 16, 2.
- [17] M. Coreno, S. Piccirillo, A. Giardini-Guidoni, A. Mele, A. Palleschi, P. Brechignac, P. Parneix, *Chem. Phys. Lett.* **1995**, 236, 580.

## Multipolymer-Supported Substrate and Ligand Approach to the Sharpless Asymmetric Dihydroxylation\*\*

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Since the initial solid-phase synthesis of oligopeptides by Merrifield<sup>[1]</sup> the use of polymers as supports, reagents or even catalysts for various reactions has increased.<sup>[2]</sup> Recently a high level of activity has been devoted to this field due to the application of combinatorial chemistry to drug discovery.<sup>[3]</sup> Although a resurgence of interest in polymers for organic synthesis has been seen, little effort has been paid to defining the structural

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parameters of the supports. This is most evident for automated organic synthesis.

We demonstrated how a chiral ligand can be integrated onto a soluble polymeric species so that ligand-accelerated catalysis (LAC) can operate in an unhindered manner.<sup>[4]</sup> However, the converse case in which a small organic moiety is attached to a polymeric matrix has yet to be investigated. The implication of the combination of these two scenarios—immobilization of the ligand and the substrate—is that a multipolymer LAC reaction may be a feasible. We studied the influence of the structure of solid- and liquid-phase polymers on the Sharpless asymmetric dihydroxylation (AD) reaction. The outgrowth of these findings allowed us to successfully run a multipolymer Sharpless AD reaction.

A variety of supports have been used in organic synthesis.<sup>[5]</sup> Typically, they may be grouped into three categories: 1) minimal cross-linked supports that form well-solvated gels,<sup>[6]</sup> 2) porous but rigid supports with a high degree of crosslinking,<sup>[7]</sup> and 3) linear, soluble polymers that are also known as liquid-phase supports.<sup>[8]</sup> Three supports belonging to the first category, two low divinylbenzene-cross-linked polystyrene beads (Merrifield and Wang resin) and the graft copolymer polystyrene polyethylene glycol (Tentagel), were utilized. The choice of these resins was based on their fundamental differences. Merrifield and Wang resins are relatively hydrophobic matrices, whereas Tentagel is considered to be a hydrophilic tentacle polymer with more "solution-like" characteristics.[8b] The support used from the third category was polyethylene glycol (PEG). This homopolymer was enlisted because it fulfills the criteria for a third-group polymer, and its chemical reactivity differences contrasted that of Tentagel.

*trans*-Cinnamic acid was immobilized on the four polymeric supports (Figure 1). This ensured that the olefin was tethered as



Figure 1. Polymer-bound *trans*-cinnamate esters 1-4 used in the Sharpless AD reaction as well as non-polymer counterpart 5.

an ester on all supports, and that the overall reactivity was determined only by composition of the polymer. Because the AD reactivity of ethyl *trans*-cinnamate (5) using the ligand 1,4-phthalazinediyl diether hydroquinidine  $[(DHQD)_2PHAL, 7]$  has been documented,<sup>[9]</sup> a direct correlation could be made between the solution and polymeric reactions [Eq. (1)].



Table 1 shows the results of the AD reaction of the four polymer-bound *trans*-cinnamate esters 1-4 using ligands 7 and 8.



The amount of metal/ligand used, reaction time required for product conversion, and enantiomeric excess observed vary greatly depending on the support. The non-cross-linked liquidphase resin 4 (Table 1, entries 6 and 10) provides the best overall results when considering reaction time and metal/ligand ratio. These results compare favorably with those from the reaction of the simple ethyl ester 5 (entry 11).

Table 1. AD reactions conducted with trans-cinnamate esters using ligands 7 and 8.

Entry	Olefin	<i>t</i> [h]	OsO4 [a]	Method [b]	Conversion [%]	[c] <i>ee</i> [%] [d]
1	1	72	0.01	A	_	_
2	2	72	0.01	А	-	
3	3	24	0.01	А	3	99
4	3	24	0.02	А	63	98
5	3	24	0.10	А	96	99
6	4	0.5	0.10	А	100	99
7	1	24	0.01	В	100	88
8	2	24	0.01	В	100	90
9	3	24	0.01	В	100	87
10	4	24	0.008	А	80	97
11	5	24	0.008	А	100	97
12 [e]	3	24	0.02	А	60	98
13 [e]	3	24	0.10	А	98	98

[a] Equivalents of OsO<sub>4</sub> based on olefin. [ligand]/[OsO<sub>4</sub>] = 2.5. [b] Method A:  $K_3$ [Fe(CN)<sub>6</sub>] and *t*-BuOH/water (1/1) at room temperature. Method B: NMO and acetone/water (10/1) at 4 °C. [c] Determined from the ratio of the signals of diol protons to that of the remaining olefin in the <sup>1</sup>H NMR spectrum. Absolute yields (entries 4–13) were between 25–85%. [d] Determined by NMR analysis of the derived bis(Mosher) ester of the diol. [e] Polymer-bound ligand **8** was used as the catalyst source (**18**]/[OsO<sub>4</sub>] = 2.5).

Among the three insoluble supports Tentagel (3) outperformed the Wang (2) and Merrifield resins (1) with  $K_3[Fe(CN)_6]$ as oxidant (entries 1–5). However, the cross-linked polystyrene supports 2 and 3 can provide a suitable environment for LAC when *N*-methylmorpholine *N*-oxide (NMO) is applied as the oxidant and acetone/water as the solvent (entries 7 and 8). It may be that supports 1 and 2 show an overall inability to support the AD reaction with  $K_3[Fe(CN)_6]$  due to poor swelling properties in *t*-BuOH/water as solvent.<sup>[61</sup> The consequences of poor swelling include limited chain mobility, which could compromise the location and distribution of catalyst and olefin within these matrices.

Somewhat unexpected was the large amount of metal and ligand that was required for the Tentagel resin (3) to provide a reasonable reaction time, degree of conversion, and enantioselectivity (compare entries 3-5). Interestingly, there appears to be a threshold of catalyst amount that is required for any conversion into diol to be seen (compare entries 3 and 4). We investigated this aspect further. In reaction 4 (Table 1), fresh, unbound olefin 5 (0.125 mmol) was added after 24 h along with  $OsO_4$  (0.02 equiv based on olefin),  $K_2CO_3$  (3.0 equiv), and  $K_3[Fe(CN)_6]$  (3.0 equiv). There was only 10 % conversion of 5 into 6c after a further 10 h. If unbound olefin 5 was used throughout the entire reaction, recharging the mixture with more 5 provided complete conversion into 6c within 2.5 h. These results suggest that the catalyst becomes entangled in the insoluble support, thereby limiting its availability. Although resin 3 is more hydrophilic than 1 and 2, it still must be considered as a "quasi-homgeneous" matrix that is subject to some of the same limitations as insoluble resins.

In evaluating these results we recognized that a correct combination of soluble and insoluble polymers (that is, a multipolymeric reaction) could, in principle, be suitable for AD reactions. The use of more than a single polymeric reagent and catalyst either simultaneously or consecutively was accomplished, but its exploitation has been limited to date.<sup>[10]</sup> The combination of Tentagel resin (**3**) and MeO-PEG-[(DHQD)<sub>2</sub>PHAL] (**8**)<sup>[4, 11]</sup> was investigated as the multipolymer components. Entries 12 and 13 in Table 1 show that this combination of polymers can successfully support LAC. Although these two polymers are physically quite different, the outgrowth of this methodology translates into facile product separation and ligand reisolation. The significance of such technology should have direct applications to the automation of synthetic processes.<sup>[3, 12]</sup>

### **Experimental Section**

Dichloromethane and methanol were dried over CaH<sub>2</sub> and powdered magnesium, respectively. Polyethylene glycol monomethyl ether (Aldrich, MeO-PEG,  $M_r = 5000$ ) was dried over P<sub>2</sub>O<sub>5</sub> under vacuum before use; Merrifield, Wang, and Tentagel resins were bought from Novabiochem. All other solvents and chemicals were obtained from commercial sources, and used without further purification unless stated otherwise. NMR spectra were measured on a Bruker AM-300 spectrometer.

1-4: trans-Cinnamic acid was coupled to each resin with the aid of coupling agents 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)/N,N-dimethyl 4-pyridinamine (DMAP) in CH<sub>2</sub>Cl<sub>2</sub>. For the soluble polymer MeO-PEG, a dicyclohexylcarbodiimide (DCC)/DMAP combination was used for preparing 4. Upon completion of reaction the urea formed was removed by filtration. Diethyl ether was added to the filtrate, and 4 separated as a white solid from the mixture. The degree of loading for each polymer was greater than 98%, determined by measuring the release of cinnamic acid and its methyl ester from the polymers with trifluoroacetic acid (TFA)/CH2Cl2 (v/v 95/5) and NaOMe in MeOH, respectively. Asymmetric dihydroxylation: method A: A small aliquot of OsO4 in t-BuOH (2.5% solution (wt %), see Table 1 for the amount used in each reaction) was added to a mixture of the ligand (see Table 1), K<sub>3</sub>[Fe(CN)<sub>6</sub>] (0.250 g, 6 equiv based on olefin), K<sub>2</sub>CO<sub>3</sub> (0.052 g, 3 equiv), and methanesulfonamide (0.012 g, 1 equiv) in t-BuOH/ water (4 mL, v/v 1/1) at room temperature. After the reaction mixture was stirred for 10 min, the polymer-bound olefin (0.125 mmol, 1 equiv) was added in one portion, and the mixture further stirred for 24 h. Solid Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> was added(0.400 g), and the mixture stirred for an additional 5 min, filtered, and successively washed with acctone and CH2Cl2. The resin was dried over Na2SO4 under vacuum. The results of the reaction were determined by two methods: 1) The resin was suspended in TFA/CH<sub>2</sub>Cl<sub>2</sub> (v/v 95/5) for 30 min. The resin was removed by filtration, and then solvent removed from the filtrate. The degree of conversion of the olefin into the dihydroxylated product was determined by NMR spectroscopy. 2) The resin was suspended in a solution of NaOMe in MeOH. The mixture was stirred for 2 h at room temperature, and the solvent removed under vacuum. The desired diolmethylester was isolated by column chromatography (silica gel; ethyl acetate/hexane 1/1). The enantiomeric excess of this product was determined by NMR analysis of the derived bis(Mosher) ester. Method B: A similar procedure to Method A was followed except acetone/water as solvent and NMO were used. The reaction mixture contained a small amount of OsO<sub>4</sub> in *t*-BuOH (2.5% solution, 13  $\mu$ L, 0.01 equiv based on olefin), the ligand (0.0025 g, 0.025 equiv), NMO (0.022 g, 1.5 equiv), and tetraethylammonium acetate tetrahydrate (0.033 g, 1.0 equiv) in acetone/water (4 mL, 10/1 v/v) at 4 °C.

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- [2] a) J. L. Crowley, H. Rappoport, Acc. Chem. Res. 1976, 9, 135-144; b) C. C. Leznoff, Acc. Chem. Res. 1978, 11, 327-333; c) G. Manceke, W. Storek, Angew. Chem. 1978, 90, 691-704; Angew. Chem. Int. Ed. Engl. 1978, 17, 657-670; d) J. M. J. Frechet Tetrahedron 1981, 37, 663-688; e) P. Hodge in Synthesis and Seperations Using Functional Polymers (Eds.: D. C. Sherrington, P. Hodge), Wiley, New York, 1988, p. 43.
- [3] a) Molecular Diversity and Combinatorial Chemistry (Eds.: I. M. Chaiken, K. D. Janda) American Chemical Society, Washington, D. C., USA, 1996;
  (b) J. S. Fruchtel, G. Jung, Angew. Chem. 1996, 108, 19-46; Angew. Chem. Int. Ed. Engl. 1996, 35, 17-42; c) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *ibid.* 1996, 108, 2436-2487 and 1996, 35, 2288-2337;
  (c) K. D. Janda, Proc. Natl. Acad. Sci. USA 1994, 91, 10779-10785.
- [4] H. Han, K. D. Janda, J. Am. Chem. Soc. 1996, 118, 7632-7633.
- [5] a) N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki. J. Steel, *Tetrahedron* 1995, 51, 8135-8173; b) L. A. Thompson, J. A. Ellman, *Chem. Rev.* 1996, 555-600; c) P. H. H. Hermkens, H. C. J. Ottenheijm, D. Rees. *Tetrahedron* 1996, 52, 4527-4554.
- [6] R. B. Merrifield, Angew. Chem. 1985, 97, 801-812; Angew. Chem. Int. Ed. Engl. 1985, 24, 799-810.
- [7] A. Gugot, M. Bartholin, Prog. Polym. Sci. 1982, 8, 277-332.
- [8] a) K. E. Geckeler, Adv. Polym. Sci. 1995, 121, 31-79; b) E. Bayer, Angew Chem. 1991, 103, 117-133; Angew. Chem. Int. Ed. Engl. 1991, 30, 113-129;
  c) D. E. Bergbreiter in Proc. 6th Annu. IUCCP Symp. Functional Polymers (Eds.: D. E. Bergbreiter, C. R. Martin), Plenum Press, New York, 1989, p. 143.
- [9] K. B. Sharpless, W. Amberg, Y. L. Bennan, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M Wang, D. Xu, X.-L Zhang, J. Org. Chem. 1992, 57, 2768-2771.
- [10] Examples of peptide syntheses: a) G. Heusel, G. Bovermann, W. Göhring, G. Jung, Angew. Chem. 1977, 89, 681-682; Angew. Chem. Int. Ed. Engl. 1977, 16, 642-643; b) H. Frank, H. Hagenmaier, Experentia 1975, 31, 131-133; examples other than peptides: c) B. J. Cohen, M. A. Kraus, A. Patchornik, J. Am. Chem. Soc. 1977, 99, 4165-4167; d) C. V. Pittman, L. R. Smith, *ibid.* 1975, 97, 1749-1754; e) J. P. Collman, K. M. Kosydar, M. Bressan, W. Lamanna, T. Garrett, *ibid.* 1984, 106, 2569-2579; f) D. E. Bergbreiter, R. Chandran, *ibid.* 1987, 109, 174-179; g) *ibid.* 1985, 107, 4792-4793; h) J. J. Parlow, *Tetrahedron Lett.* 1995, 36, 1395-1396; i) F. Svec, J. M. J. Frechet, Science 1996, 273, 205-211; detection of highly reactive intermediates with two polymeric reagents ("three-phase test"): J. Rebek, *Tetrahedron* 1979, 35, 723-731, and references therein.
- [11] H. Han, K. D. Janda, Tetrahedron Lett. 1997, 38, 977-980.
- [12] a) A. R. Frisbee, M. H. Nantz, G. W. Kramer, P. L. Fuchs, J. Am. Chem. Soc.
   1984, 106, 7143-7145; b) S. H. Dewitt, A. W. Czarnik, Curr. Biol., 1995, 6, 640-645; c) G. W. Kramer, P. L. Fuchs, Chemtech 1989, 19, 682-688; d) S. Hobbs Dewitt, A. W. Czarnik, Acc. Chem. Res. 1996, 29, 114-122.

<sup>[1]</sup> R. B. Merrifield, J. Am. Chem. Soc. 1963, 85, 2149-2154.