Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1537–1541

TETRAHEDRON: *ASYMMETRY*

Asymmetric dihydroxylation using heterogenized cinchona alkaloid ligands on mesoporous silica

Hong Myung Lee,[a] Sang-Wook Kim,[b] Taeghwan Hyeon[b,*] and B. Moon Kim[a,*]

[a]*Center for Molecular Catalysis, School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, South Korea*

[b]*School of Chemical Engineering and Institute of Chemical Processes, Seoul National University, Seoul 151-742, South Korea*

Received 23 May 2001; accepted 13 June 2001

Abstract—Cinchona alkaloids have been successfully grafted on mesoporous silica. Asymmetric dihydroxylation using the heterogenized chiral ligands proceeded with varying degrees of enantioselection depending upon the nature of the chiral ligands. High asymmetric induction (up to >99.5% enantiomeric excess) almost equal to that obtained from the homogeneous catalyst system could be achieved using a dimeric alkaloid ligand with a six-carbon link between the ligand and the support (**L3**), while inferior results were obtained when a monomeric alkaloid ligand system was used. Reduced enantioselectivities were observed upon repeated recycling of the immobilized ligand system.

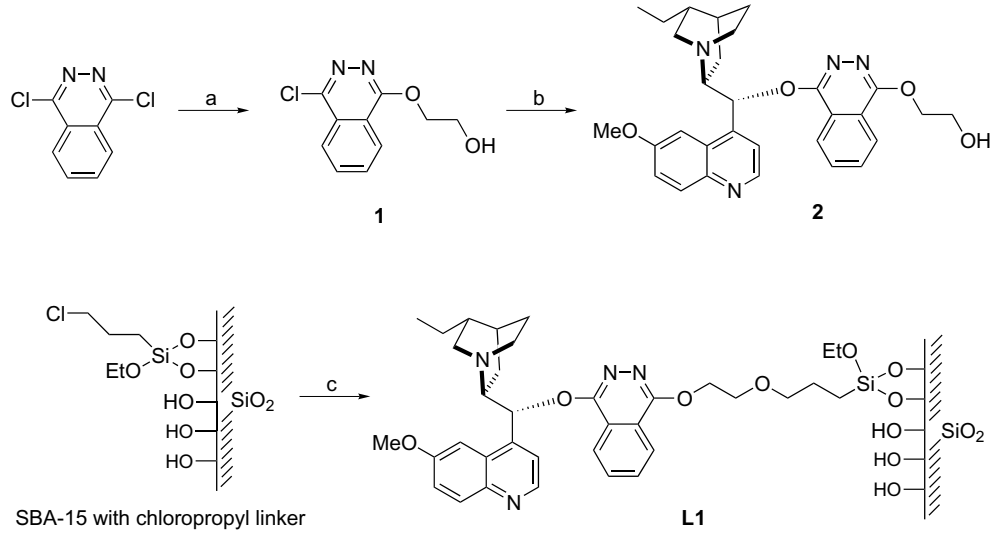
Asymmetric dihydroxylation (AD), developed by Sharpless et al. is one of the most efficient asymmetric reactions.[1] However, due to the high cost of the cinchona alkaloid ligand and osmium tetroxide, immobilization of the ligand on soluble or insoluble polymer supports and subsequent recycling have been the subject of intense investigation.[2] Toward this goal, several heterogenized AD methods were reported, which utilized organic polymer support,[3] polyethylene glycol (PEG) tethering system[4] or functionalized silica gel.[5] Although immobilization of homogenous catalysts onto a heterogeneous support material offers advantages in catalyst recovery and product purification, often diminished enantioselectivities are observed, a phenomenon which has been reported in some of the heterogenized AD reactions as well.[2] Recently, mesoporous silicas with various pore sizes[6] have been fabricated from the sol-gel polymerization of silica precursors in the presence of templates including self assemblies of surfactants and block copolymers. These mesoporous materials were successfully applied as the support for a variety of homogeneous chiral catalysts.[7,8] Mesoporous silica has the advantages of very high surface area and large pore sizes (>2 nm) over organic polymer supports, allowing for favorable reaction kinetics. Herein, we report on the successful heterogeneous AD of various olefins using chiral ligands grafted on the mesoporous SBA-15 silica support[6] with uniform pore size of 7 nm.

* Corresponding author. Tel.: 822-880-6644; fax: 822-872-7505; e-mail: kimbm@snu.ac.kr

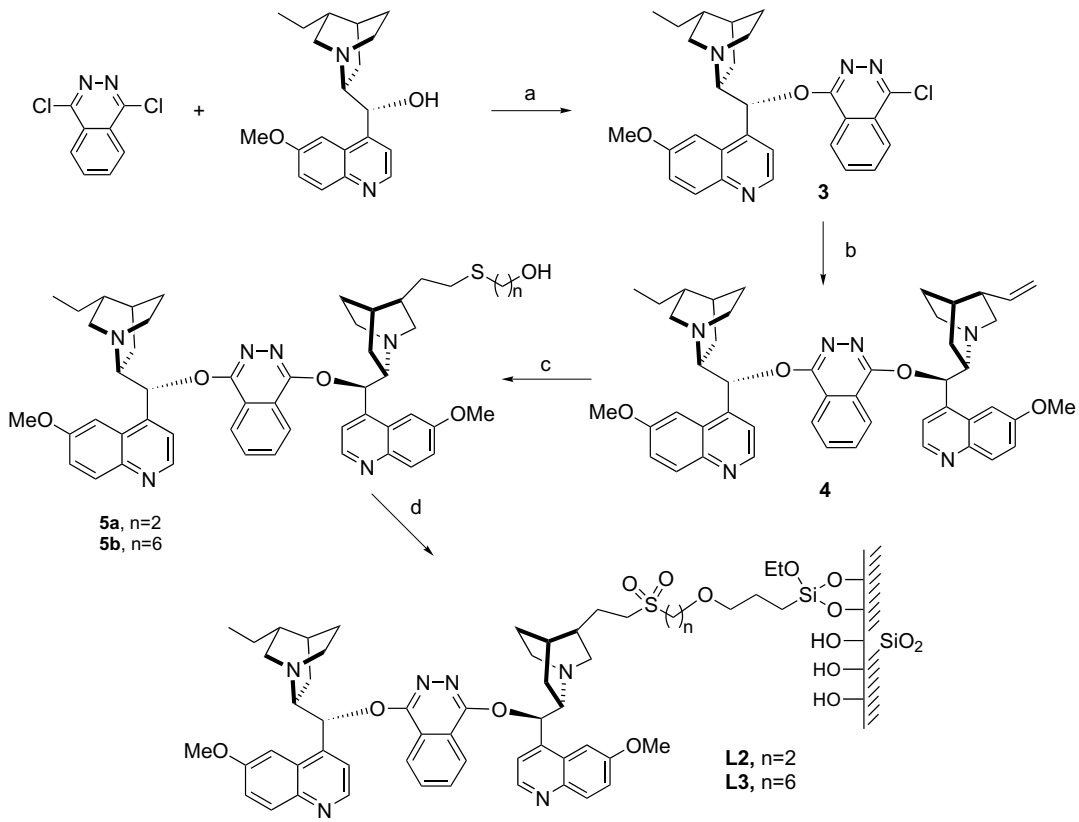
The ligands utilized in the preparation of chiral mesoporous silica catalysts were based on the known cinchona alkaloid–phthalazine system.[1a] Several different chiral silica-based catalysts have been prepared as shown in Schemes 1 and 2. Preparation of monomeric 1-(9-*O*-dihydroquininyl)-4-(2-hydroxyethyloxy)phthalazine (DHQ-PHAL-O-$(CH_2)_2$-OH) **1** and its immobilization onto SBA-15 are shown in Scheme 1. Treatment of 1,4-dichlorophthalazine with 1 equiv. of ethylene glycol followed by 1 equiv. of DHQ in the presence of K_2CO_3 and KOH in dry toluene with azeotropic removal of water provided **2** in 70% yield.[9] Anchoring of the modified ligand **2** onto the mesoporous silica was accomplished by heating the mixture of **2** and chloropropyl-grafted SBA-15 in xylene.

Since it has been well established that a dimeric arrangement of the cinchona alkaloid on the aromatic spacer is required for the best enantioselectivity in the AD reaction,[1a] the dimeric alkaloid ligand on silica was prepared as shown in Scheme 2. Also, in order to examine the effect of the linker length on the enantioselectivity of the AD reaction, we prepared $(DHQ)_2$-PHAL systems with two different lengths of linker, i.e. 2-mercaptoethanol and 6-mercapto-1-hexanol as shown in Scheme 2. Thus, starting from the monomeric 4-chloro-1-(9-*O*-dihydroquininyl)-phthalazine **3** prepared from 1,4-dichlorophthalazine, the dimeric ligand 1-(9-*O*-quininyl)-4-(9-*O*-dihydroquininyl)phthalazine **4** was synthesized in 70% yield. Refluxing **4** in benzene with a

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00284-1



Scheme 1. (a) NaH, rt, ethylene glycol, 15 h, 90%; (b) DHQ, K_2CO_3, KOH, reflux, toluene, 18 h, 70%; (c) **2**, reflux, xylene. For the synthesis of SBA-15 with a chloropropyl linker, see Ref. 6.



Scheme 2. (a) K_2CO_3, KOH, reflux, toluene, 18 h, 70%; (b) QN, K_2CO_3, KOH, reflux, toluene, 18 h, 70%; (c) AIBN, HS-$(CH_2)_n$-OH, 70°C, benzene, 48 h, 75%; (d) (i) SBA-15 with a chloropropyl linker, reflux, xylene, (ii) OsO_4, NMO, rt, acetone–H_2O (1:1), 24 h.

catalytic amount of AIBN and excess mercapto alcohol for 12 h then provided **5a** or **5b** in 75% yields.[10,11] The ligands **5a** and **5b** were immobilized on SBA-15 in the same way as used for the preparation of **L1**. Finally the sulfide in the linker was oxidized under OsO_4–NMO conditions for 1 day at room temperature to produce the two dimeric catalyst systems **L2** and **L3**.[3a,12] Some physical properties including the pore characteristics of the chiral catalyst systems are summarized in Table 1. As shown in the transmission electron micrographs (Fig. 1) and X-ray diffraction patterns (see Fig. 2), regular arrangement of uniform 7 nm sized mesopores

Table 1. Physical properties of catalysts for AD

	Surface area (m^2/g)[a]	Pore diameter (nm)[a]	Grafted amount[13] (mmol/g)[b]
L1	570	7.39	0.10
L2	476	7.43	0.08
L3	426	7.25	0.17

[a] N_2 adsorption and desorption isotherms were collected at STP on a Micromeritics ASAP2010 gas adsorption analyzer after the materials were degassed at 150°C at 30 μTorr for 5 h. The surface areas were calculated by BET method and the pore size distributions were calculated from the adsorption branch of the nitrogen isotherm by the BJH method.
[b] Determined from the elemental analysis of the grafted silicas.

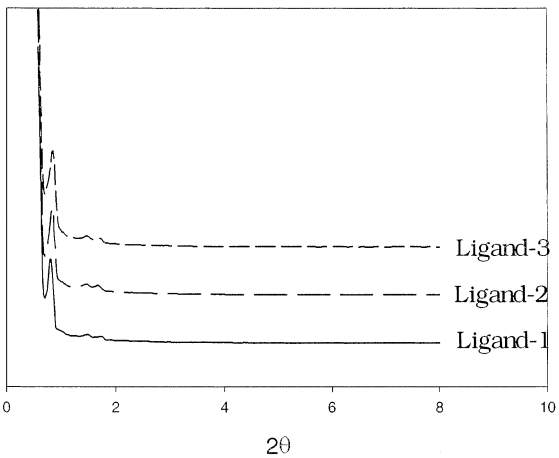


Figure 1. X-Ray diffraction patterns of cinchona alkaloid-grafted mesoporous SBA-15 silica materials.

were preserved even after the grafting of cinchona alkaloid ligands.

AD studies using the chiral silica catalyst systems **L1**–**L3** were carried out using a standard protocol utilizing 0.5 mol% of OsO_4, 1.0 mol% of the ligand and 300 mol% of $K_3Fe(CN)_6$–K_2CO_3 in H_2O–*tert*-butanol (1:1 v/v)[1a] and the results are summarized in Table 2. First of all, the AD reactions using all the silica catalysts proceeded almost at the same rate as the corresponding homogeneous reactions at 0°C. The enantioselectivities observed in the reactions utilizing the ligand **L1** were lower than those obtained from the reactions using free $(DHQ)_2$–PHAL. This may be due to the lack of the 'dimeric effect',[1a] which stabilizes the transition state through aromatic stacking with the substrate and the methoxyquinoline moiety of the ligand. The enantioselectivities of the AD reactions using **L2** generally improved, although the enantiomeric excesses (e.e.s) of the product diols from some olefins (entries 3–6) were still slightly lower than those from the solution phase reactions. The e.e. of the diol obtained from the reaction of ethyl cinnamate (entry 7) exceeded the solution phase selectivity, presumably due to the fact that our reactions were run at 0°C over a longer reaction period, while the solution phase reactions were completed at room temperature. The best selectivities were observed with the reactions using **L3** and e.e.s comparable to those from the solution phase were observed with almost all olefins examined. The results clearly indicate

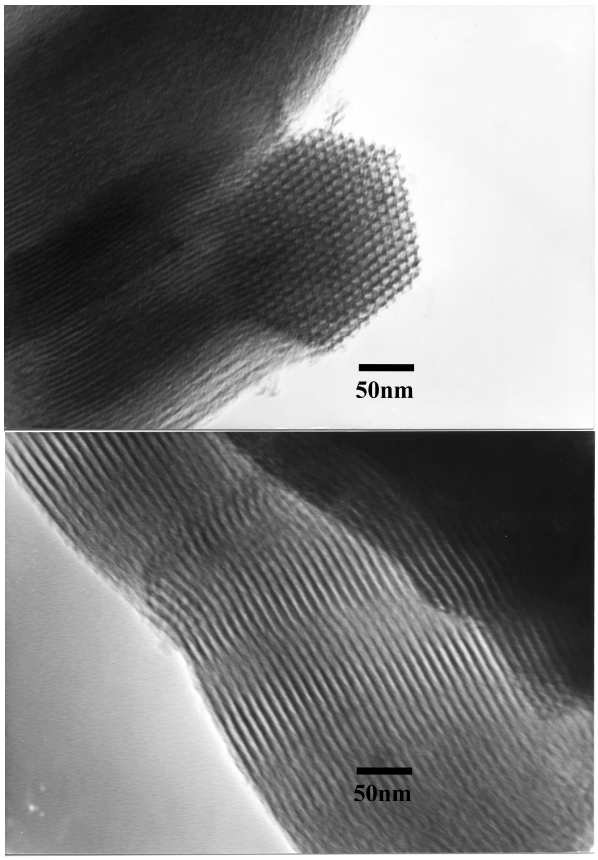
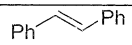
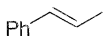
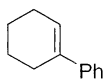
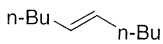
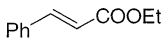


Figure 2. Transmission electron micrographs of cinchona alkaloid **L3**-grafted mesoporous SBA-15 silica materials.

the importance of the linker length for optimal geometry in the transition state of the dihydroxylation. It is presumed that the longer linker of **L3** may provide a larger degree of freedom to the methoxyquinoline in the channel of SBA-15, leading to a more favorable transition state.

To examine the recyclablility of SBA-15 based cinchona alkaloid ligand, **L2** and **L3** were filtered after reactions and re-used for the AD of *trans*-stilbene. The silica supported catalysts were easily recovered just by filtering and washing with water followed by ethyl acetate several times without noticeable mass change and were re-used for AD using a new batch of $K_3Fe(CN)_6$ and K_2CO_3. When the second AD was carried out using the recycled ligand system, product was obtained with sim-

Table 2. Results of the asymmetric dihydroxylation of various olefins with mesoporous silica supported ligands[a]

entry	Olefin	E.e. (%)[b]				
		L1	DHQD-CLB[c]	**L2**	**L3**	DHQ_2PHAL[d]
1		97	99	99	>99.5	>99.5
2		90	-	95	98	97
3		72	74	87	96	97
4		57	91	82	94	97
5		57	62	75	90	93
6		-	-	75	87	93
7		-	-	98	98	95[e]

[a] All reactions were carried out with a molar ratio of olefin/OsO_4/mesoporous silica ligand = 1/0.005/0.01 at 0°C for 24 h for entries 1–6 with quantitative yields and for 72 h for entry 7 with 72% conversion measured using GC.
[b] E.e.s were determined by HPLC analysis using a Chiralcel OJ column for entries 1, 4 and 5, a Chiralpak AD column for entry 7, and a Chiralcel OD-H column for entries 2, 3 and 6. The bisbenzoate of the product diol from entry 6 was made before HPLC analysis.
[c] Ref. 14.
[d] Ref. 1a.
[e] The reaction was carried out at room temperature.

Table 3. Asymmetric dihydroxylation of *trans*-stilbene with recycled mesoporous silica supported ligands

Ligand	E.e. (%) with consecutive use of recycled ligand					
	1st	2nd	3rd	4th	5th	6th
L2	99	96	96	85	93	88
L3	>99.5	94	96	94	92	92

ilar enantioselectivity. However, the reaction proceeded very slowly, indicating the loss of a major portion of the OsO_4 during the washing procedure. Addition of 0.25 mol% of OsO_4 before restarting an AD ensured a reasonable reaction rate. The recycling experiments were repeated five times according to this protocol and e.e.s of the diols obtained from the recycling experiments are shown in Table 3. As can be seen from Table 3, as the reactions were repeated, a slight decrease in the e.e.s observed from the product diol was observed. Even in the repeated experiment the catalyst system **L3** having longer linker performed better than **L2**, giving consistently higher e.e. values.

In summary, various cinchona alkaloid ligands anchored on SBA-15 were prepared and the reactions employing these catalyst systems provided comparably high enantioselectivity to that from the solution phase reaction in AD. This ligand was easily recovered and re-used five times without significant loss of enantioselectivity and reactivity.

References

1. For reviews, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (b) Johnson, R. A. In *Catalytic Asymmetric Synthesis*; Ojima, I.; Sharpless, K. B., Eds. Catalytic asymmetric dihydroxylation-discovery and development. VCH: New York, 2000; pp. 357–398; (c) Markó, I. E.; Svendsen, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Dihydroxylation of carbon–carbon double bonds. Springer: New York, 1999; pp. 714–787.
2. For reviews, see: (a) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21; (b) Bolm, C.; Hildebrand, J. P.; Muñiz, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. Recent advances in asymmetric dihydroxylation and aminohydroxylation. VCH: New York, 2000; pp. 399–428.
3. (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3003; (b) Pini, D.; Petri, A.; Nardi, A.; Rosini, C.; Salvadori, P. *Tetrahedron Lett.* **1991**, *32*, 5175; (c) Lohray, B. B.; Thomas, A.; Chittari, P.; Ahuja, J. R.; Dhal, P. K. *Tetrahedron Lett.* **1992**, *33*, 5453; (d) Song, C. E.; Roh, E. J.; Lee, S. G.; Kim, I. O. *Tetrahedron: Asymmetry* **1995**, *6*, 2687; (e) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2351; (f) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron* **1994**, *50*, 11321; (g) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Lett.* **1994**, *35*, 6559; (h) Petri, A.; Pini, D.; Salvadori, P. *Tetrahedron Lett.* **1995**, *36*, 1549; (i) Salvadori, P.; Pini, D.; Petri, A. *J. Am. Chem. Soc.* **1997**, *119*, 6929; (j) Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S. G. *Tetrahedron: Asymmetry* **1996**, *7*, 645; (k) Nandanan, E.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.*

1997, *38*, 2577; (l) Petri, A.; Pini, D.; Rapaccinni, S.; Salvadori, P. *Chirality* **1999**, *11*, 745.

4. (a) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632; (b) Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527; (c) Bolm, C.; Gerlach, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 741.
5. (a) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron: Asymmetry* **1996**, *7*, 2805; (b) Song, C. E.; Yang, J. W.; Ha, H. J. *Tetrahedron: Asymmetry* **1997**, *8*, 841; (c) Bolm, C.; Maischak, A.; Gerlach, A. *Chem. Commun.* **1997**, 2353.
6. (a) Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710; (b) Zhao, D.; Feng, J.; Huo, Q.; Melosh, N.; Fredrickson, G. H.; Chmelka, B. F.; Stucky, G. D. *Science* **1998**, *279*, 548; (c) Ying, J. Y.; Mehnert, C. P.; Wong, M. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 57.
7. For results from this laboratory, see: (a) Bae, S. J.; Kim, S.-W.; Hyeon, T.; Kim, B. M. *Chem. Commun.* **2000**, 31; (b) Kim, S.-W.; Bae, S. J.; Hyeon, T.; Kim, B. M. *Micropor. Mesopor. Mater.* **2001**, *44–45*, 523.
8. (a) Johnson, B. F. G.; Raynor, S. A.; Shephard, D. S.; Mashmeyer, T.; Thomas, J. M.; Sankar, G.; Bromley, S.; Oldroyd, R.; Gladden, L.; Mantle, M. D. *Chem. Commun.* **1999**, 1167; (b) Kim, G.-J.; Shin, J.-H. *Tetrahedron Lett.* **1999**, *40*, 6827; (c) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Li, S.-G.; Li, L.-S.; Che, C.-M. *Chem. Commun.* **1999**, 1789; (d) Piaggio, P.; McMorn, P.; Langham, C.; Bethell, D.; Bulman-Page, P. C.; Hancock, F. E.; Hutchings, G. J. *New J. Chem.* **1998**, 1167; (e) Bellocq, N.; Abrmason, M.; Lasperas, M.; Brunel, D.; Moreau, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3229.
9. Compound **2**: $[\alpha]_D^{30}=+29.1$ (*c* 1.0, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, $J=7.2$ Hz, 3H), 1.32–2.00 (m, 9H), 2.46–2.70 (m, 3H), 3.10–3.59 (m, 3H), 3.71–3.97 (m, 5H), 4.56 (q, $J=5.1$ Hz, 2H), 7.20 (d, $J=5.3$ Hz, 1H), 7.32 (dd, $J=10$ Hz and 3.0 Hz, 1H), 7.46 (d, $J=4.6$ Hz, 1H), 7.64 (d, $J=2.7$ Hz, 1H), 7.90–7.99 (m, 2H), 8.18 (d, $J=1.5$ Hz, 1H), 8.35 (d, $J=7.2$ Hz, 1H), 8.65 (d, $J=4.5$ Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.68, 156.44, 147.42, 144.83, 144.78, 132.28, 131.59, 127.29, 122.84, 122.53, 122.47, 121.86, 121.74, 118.46, 102.06, 60.07, 58.52, 55.72, 46.21, 42.85, 37.54, 28.65, 27.75, 25.58, 25.45, 23.58, 11.29. HRMS (FAB$^+$) calcd for $[C_{30}H_{34}N_4O_4+H^+]$: 515.2658. Found: 515.2642.
10. Inagaki, M.; Hiratake, J.; Yamamoto, Y.; Oda, J. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121.
11. Compound **5a**: $[\alpha]_D^{24}=+109.9$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, $J=8.0$ Hz, 3H), 1.25–2.63 (m, 25H), 2.68 (t, $J=6.7$ Hz, 2H), 2.96–3.50 (m, 6H), 3.69 (t, $J=6.7$ Hz, 2H), 3.91 (s, 3H), 3.94 (s, 3H), 7.04 (d, $J=5.3$ Hz, 2H), 7.32–7.43 (m, 4H), 7.90–8.02 (m, 4H), 8.31–8.34 (m, 2H), 8.64 (t, $J=4.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.83, 156.41, 147.36, 147.29, 146.93, 144.77, 144.54, 133.52, 132.40, 132.02, 131.57, 130.88, 129.52, 128.81, 127.26, 127.17, 122.88, 122.50, 122.14, 121.96, 118.43, 118.25, 102.04, 101.97, 75.94, 60.34, 60.02, 59.90, 59.22, 58.32, 58.02, 55.82, 42.87, 42.67, 38.74, 37.29, 35.38, 34.82, 34.77, 29.77, 28.93, 28.31, 27.66, 25.69, 25.41, 23.76, 22.99, 12.04. HRMS (FAB$^+$) calcd for $[C_{50}H_{58}N_6O_5S+H^+]$: 855.4268. Found: 855.4246.
Compound **5b**: $[\alpha]_D^{30}=+114.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, $J=8.0$ Hz, 3H), 1.25–2.71 (m, 35H), 2.95–3.56 (m, 6H), 3.64 (t, $J=7.3$ Hz, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 7.02 (d, $J=5.8$ Hz, 2H), 7.36 (dd, $J=10$ Hz and 3.0 Hz, 2H), 7.42 (d, $J=5.1$ Hz, 2H), 7.60 (m, 2H), 7.91–8.04 (m, 4H), 8.30–8.34 (m, 2H), 8.64 (dd, $J=5.0$ Hz and 2.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.79, 156.44, 147.40, 144.81, 144.76, 132.33, 131.61, 128.82, 127.29, 122.88, 122.84, 122.54, 121.92, 118.43, 118.25, 102.11, 102.10, 77.22, 62.84, 60.11, 58.48, 58.18, 55.78, 42.87, 42.73, 39.49, 39.07, 37.53, 34.90, 32.62, 32.24, 30.21, 29.71, 29.56, 28.63, 27.73, 25.72, 25.49, 25.38, 25.16, 12.10. HRMS (FAB$^+$) calcd for $[C_{54}H_{66}N_6O_5S+H^+]$: 911.4894. Found: 911.4919.
12. Kaldor, S. W.; Hammond, M. *Tetrahedron Lett.* **1991**, *32*, 5043.
13. The difference in the grafting amount is presumed to result from the different chain lengths of the ligands. Both **L1** and **L2**, which have shorter linkers than **L3**, exhibit lower degrees of grafting than **L3**.
14. (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585; (b) Norrby, P.-O.; Rasmussen, T.; Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 10186.