**Multicomponent Asymmetric Catalysts**

# “Catalyst Analogue”: A Concept for Constructing Multicomponent Asymmetric Catalysts (MAC) by Using a Polymer Support**

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Highly organized multicomponent asymmetric catalysts (MACs; Figure 1) have recently been developed as the result of work by numerous chemists.[1–3] In MAC catalyzed enantioselective reactions, synergistic cooperation between each component plays an important role in realizing highly stereoselective reactions.

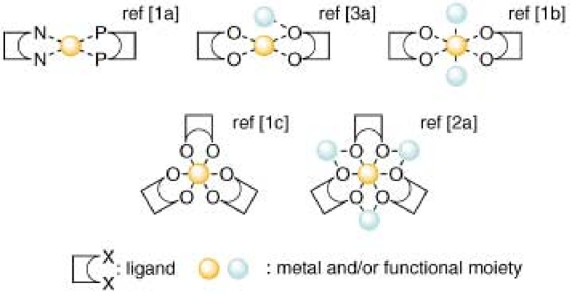

***Figure 1.*** Schematic representation of typical multicomponent catalysts.

If ligands are attached to a polymer backbone and the position of each ligand in a catalyst is controlled appropriately to form a MAC, the polymer support would enhance MAC formation and stabilize the resulting catalyst. To that end a study of the polymer-supported catalysts would provide a general method for the construction of further useful MACs. However, conventional methods for the preparation of polymer-supported catalysts which rely on the random introduction of ligands into a sterically irregular solid polymer backbone (e.g., polystyrene resin) produce undesirable results for MACs because of the highly disordered orientation of the ligands along the polymer chain. To further the development of polymer-supported MACs, herin we report a new method for constructing polymer-supported MACs based on the use of a “catalyst analogue”.

In the new procedure (Scheme 1), after the copolymerization of a catalyst analogue with a monomer in the presence

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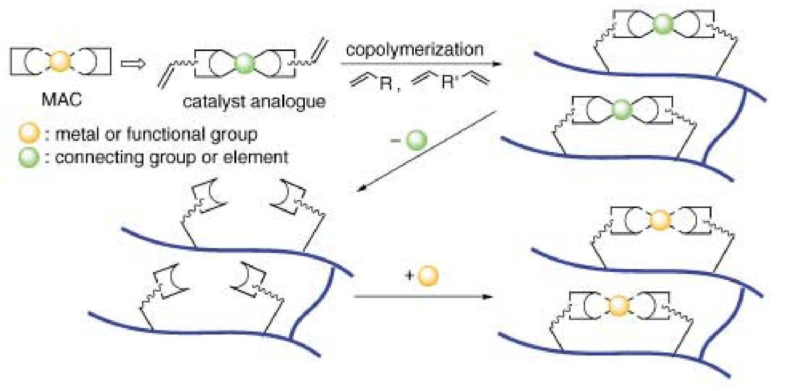


***Scheme 1.*** Proposed construction of a MAC by using a polymer support.

of a crosslinker, the resulting polymer is used to prepare an active catalyst by exchanging the connecting group or element with the catalytically active metal atom or functional group. In this way, the position and orientation of each ligand in the resulting polymers can be controlled. The proposed method outlined in Scheme 1 was applied to AlLi-bis(binaphthoxide) complex (ALB), a MAC that we developed.[3] The connecting group in the catalyst analogue is expected to exchange readily with aluminum in the polymer matrix assuming that the analogue is stable under the required polymerization conditions. A Si-tethered binaphthol was employed as the catalyst analogue for this synthesis because of its structural similarity to ALB (Figure 2).

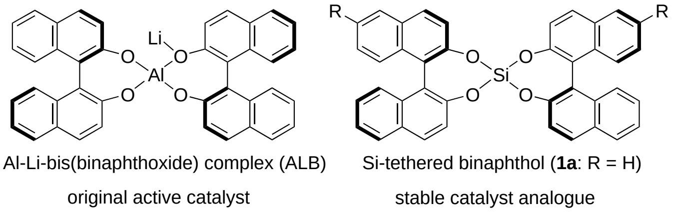
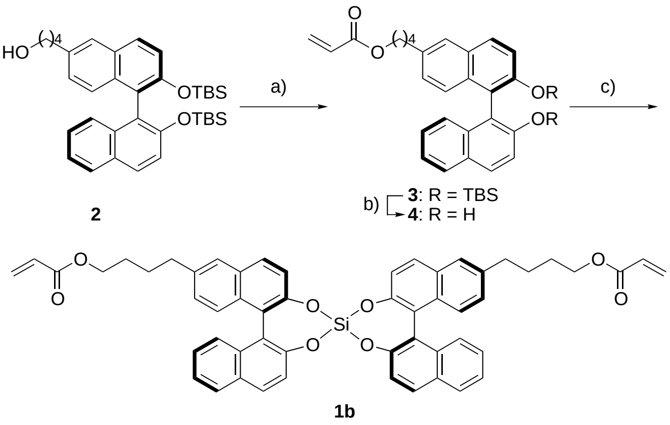


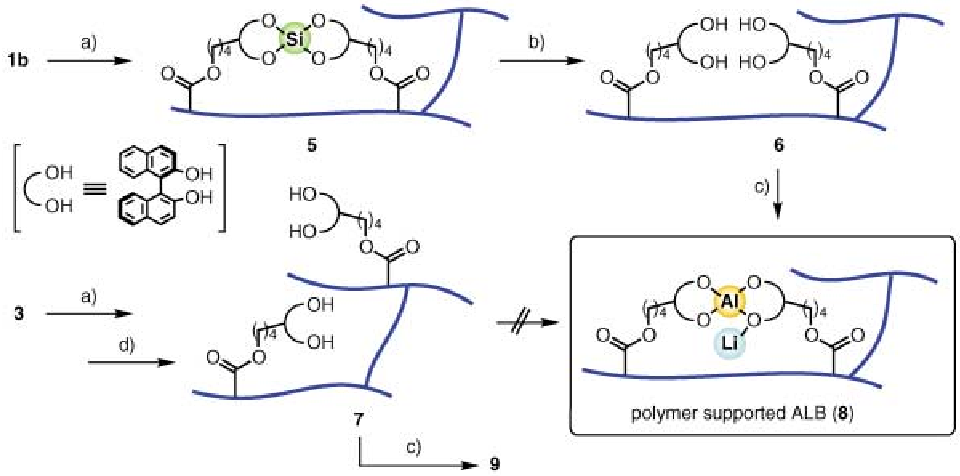
***Figure 2.*** Target MAC and preferred catalyst analogue.

The Si-tethered binaphthol **1a** was found to be adequately stable under the conditions typical of radical polymerization (azobisisobutyronitrile (AIBN), 70 °C). A 6-substituted binaphthol derivative was used as the starting point for the synthesis of the soluble monomer **1b** (Scheme 2).

The binaphthol derivative **2**[4] was coupled with acryloyl chloride to give the ester **3**. After removal of the TBS group of **3**, the catalyst analogue **1b** was almost quantitatively prepared by the reaction of **4** with $SiCl_4$ in THF, and used directly in subsequent experiments.[5] The copolymerization of **1b** with methyl methacrylate (MMA) at a ratio of 1:20 was initiated by using 5 mol% of AIBN[6] with 1 mol% of ethylene glycol dimethacrylate (EGDMA) as a crosslinker. After completion of copolymerization, the Si–O bond in polymer **5** was cleaved by treatment with $H_2O$ to give polymer-supported binaphthol **6A** (Scheme 3).



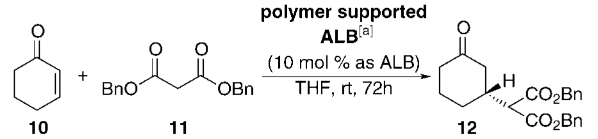
***Scheme 2.*** Synthesis of the catalyst analogue **1b** (TBS = *tert*-butyldimethylsilyl). a) Acryloyl chloride, $Et_3N$, THF, 0 °C; b) TBAF, RT, 30 min, obtained quantatively in two steps; c) $SiCl_4$, $Et_3N$, THF, 0 °C.



***Scheme 3.*** Preparation of polymer-supported ALB. a) MMA, crosslinker, AIBN, THF, reflux; b) $H_2O$; c) $AlMe_3$, *t*BuLi, THF, −78 °C; d) TBAF, THF.

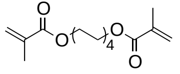
The resulting polymer **6A** was characterized by gel-permiation chromotography (GPC; $M_w = 17800$, PDI = 2.03). The copolymerization of **3**, which has no Si tether, with MMA (**3**:MMA = 1:10) and EGDMA was also examined to afford **7A** as a reference. The polymer-supported AlLi-bis(binaphthoxide) catalyst (**8A**), generated by the treatment of a solution of **6A** in THF with $AlMe_3$ and *t*BuLi, promoted the Michael reaction of 2-cyclohexen-1-one (**10**) with dibenzyl malonate (**11**) to give the Michael adduct **12** in 73% yield with 91% *ee* (Table 1, entry 1).

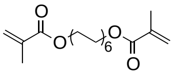
***Table 1:*** Asymmetric Michael reaction catalyzed by polymer-supported ALB.



| Entry | Polymer-supported binaphthol[b] | Catalyst | Yield of **12** [%] | *ee* of **12** [%] |
|---|---|---|---|---|
| 1 | **6A** (**1b** + EGDMA) | **8A** | 73 | 91 |
| 2 | **7A** (**3** + EGDMA) | **9A** | 77 | 21 |
| 3 | **6B** (**1b** + **13**) | **8B** | 84 | 80 |
| 4 | **7B** (**3** + **13**) | **9B** | 20 | 8 |
| 5 | **6C** (**1b** + **14**) | **8C** | 29 | 78 |
| 6 | **7C** (**3** + **14**) | **9C** | 42 | 34 |

[a] Polymers for entries 1, 3, and 5 were prepared in the ratio of **1b**:MMA = 1:20. Polymers for entries 2, 4, and 6 were prepared in the ratio of **3**:MMA = 1:10. [b] 1 mol% of crosslinkers was utilized in each polymerization.


C8DMA (**13**)


C12DMA (**14**)

As shown in entry 2 corresponding catalyst **9A**, which was constructed from polymer **7A**, gave **12** with only 21% *ee*, thus indicating that the use of a catalyst analogue is advantageous for constructing polymer-supported MACs.[7] The effect of the length of the crosslinker can also be seen in Table 1. The polymers **6B** and **6C** were also prepared by use of **13** and **14** as a crosslinker, respectively. The catalysts **8A, 8B**, and **8C**, prepared by using the catalyst analogue, exhibited better enantioselectivity for the formation of **12** than the corresponding catalysts **9A, 9B**, and **9C**.[8] In the case of the polymer-supported ALB experiments reported herein, an increase in the ratio of crosslinker in the polymer resulted in a reduction of the selectivity.[9] As an alternative approach towards the construction of polymer-supported MACs, the application of the method of molecular imprinting polymers (MIPs) might be fascinating.[10,11] In contrast to MIPs, our method using a "catalyst analogue" allowed chiral ligands to be arranged at suitable positions along the polymer chains even in the case of a flexible polymer.

In conclusion, a new and general approach for the efficient construction of polymer-supported MACs is proposed based on the use of a catalyst analogue. The polymer-supported MACs are readily obtained by a simple exchange of the connecting atoms in the polymer with catalytically active atoms.[12]

## *Experimental Section*

**3**: $NEt_3$ (0.77 mL, 5.5 mmol) and acryloyl chloride (0.38 mL, 4.6 mmol) were added to a solution of (*R*)-4-[2,2′-bis(*tert*-butyldimethylsilyloxy)-1,1′-binaphth-6-yl]butan-1-ol (**2**) (2.5 g, 4.26 mmol) in THF (30 mL) at 0°C. The reaction mixture was stirred for 30 min, then quenched with $H_2O$ (5 mL) at 0°C and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent under vacuum, the crude product was purified by flash column chromatography ($SiO_2$, AcOEt/hexane = 1:5) to give **3** (2.73 g, 4.26 mmol, quant.) as a pale-yellow oil. IR(neat): $\tilde{\nu}_{max} = 1070.4$, 1247.8, 1730.0 $cm^{-1}$; HR-MS (ESI) for $C_{39}H_{52}O_4Si_2Na^+$ $[M+Na]^+$: calcd: 663.3219, Found: 663.3236; $^1H$ NMR (270 MHz, $CDCl_3$): $\delta = 7.80$ (d, $J = 8.9$ Hz, 2H), 7.77 (d, $J = 8.9$ Hz, 1H), 7.72 (s, 1H), 7.14–7.58 (m, 6H), 7.05 (dd, $J = 1.6$, 8.6 Hz, 1H), 6.39 (dd, $J = 1.5$, 17 Hz, 1H), 6.11 (dd, $J = 10$, 17 Hz, 1H), 5.79 (dd, $J = 1.5$, 10 Hz, 1H), 4.18 (t, $J = 6.1$ Hz, 2H), 2.75 (d, $J = 6.8$ Hz, 2H), 1.72–1.77 (m, 4H), 0.47 (s, 18H), 0.01 (d, $J = 4.0$ Hz, 6H), −0.16 ppm (d, $J = 4.0$ Hz, 6H); $^{13}C$ NMR (67.7 MHz, $CDCl_3$): $\delta = 166.1$, 150.9, 150.4, 136.5, 134.4, 133.0, 130.3, 129.3, 129.1, 128.5, 128.0, 127.5, 127.1, 126.1, 125.9, 125.8, 125.7, 123.1, 122.1, 121.9, 120.4, 120.3, 64.5, 35.3, 28.2, 27.6, 25.1, 17.7, −4.2, −4.3, −4.4 ppm; $[\alpha]_D^{25} = +35.61$ ($c = 0.689$, $CHCl_3$).

**4**: TBAF in THF (1.0 M, 7.2 mL, 7.2 mmol) was added dropwise to a solution of **3** (1.9 g, 3.0 mmol) in THF (30 mL) at 0°C. The reaction mixture was stirred for 30 min, then quenched with $H_2O$ (20 mL) at 0°C and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent under vacuum, crude product was purified by flash column chromatography ($SiO_2$, AcOEt/hexane = 1:3) to give **4** (1.23 g, 3.0 mmol, quant.) as a pale yellow oil. IR(neat) $\tilde{\nu}_{max} = 1714.6$, 3408.0 $cm^{-1}$; HRMS (ESI) for $C_{27}H_{24}O_4Na^+$ $[M+Na]^+$: calcd: 435.1572, Found: 435.1564; $^1H$ NMR (270 MHz, $CDCl_3$): $\delta = 7.88$–7.99 (m, 3H), 7.67 (s, 1H), 7.28–7.40 (m, 6H), 7.06–7.17 (m, 3H), 6.38 (dd, $J = 1.4$, 17 Hz, 1H), 6.10 (dd, $J = 10$, 17 Hz, 1H), 5.80 (dd, $J = 1.4$, 10 Hz, 1H), 4.18 (t, $J = 6.1$ Hz, 2H), 2.77 (d, $J = 6.8$ Hz, 2H), 1.73–1.76 ppm (m, 4H); $^{13}C$ NMR (67.7 MHz, $CDCl_3$): $\delta = 166.1$, 152.5, 152.1, 137.5, 133.3, 131.8, 131.1, 130.7, 130.5, 129.4, 129.3, 128.6, 128.3, 128.2, 127.3, 126.9, 124.2, 124.1, 123.8, 117.7, 117.6, 111.0, 110.8, 64.4, 35.3, 28.3, 27.6 ppm; $[\alpha]_D^{25} = -22.66$ ($c = 2.14$, $CHCl_3$).

**1b**: $NEt_3$ (0.11 mL, 0.8 mmol) and tetrachlorosilane in $CH_2Cl_2$ (1.0 M, 0.2 mL, 0.2 mmol) were added to a solution of **4** (165 mg, 0.4 mmol) in THF (2.0 mL) at 0°C. The reaction mixture was stirred for 30 min and used for the next polymerization. Selected physical properties of **1b**: $^1H$ NMR (270 MHz, $CDCl_3$): $\delta = 7.84$–8.01 (m, 2H), 7.57–7.69 (m, 4H), 7.49 (s, 2H), 7.26–7.40 (m, 2H), 6.82–7.18 (m, 12H), 6.19 (m, 2H), 5.97 (m, 2H), 5.65 (m, 2H), 4.04 (t, $J = 6$ Hz, 4H), 2.59–2.71 (m, 4H), 1.60–1.70 ppm (m, 8H); $^{13}C$ NMR (67.7 MHz, THF): $\delta = 165.8$, 149.0, 148.5, 139.5, 134.0, 132.5, 132.1, 131.8, 131.6, 131.2, 130.2, 129.4, 128.9, 128.8, 128.5, 128.4, 128.0, 127.6, 127.2, 127.1, 126.6, 125.4, 123.2, 121.7, 121.1, 120.8, 119.3, 64.6, 35.9, 29.2, 28.4 ppm.

Polymer **6A** from **1b**: EGDMA (8 μL, 0.044 mmol) and MMA (430 μL, 4 mmol) were added to a cooled solution (0°C) of **1b** (0.2 mmol) and AIBN (36 mg, 0.22 mmol) in THF (3.7 mL). The reaction mixture was heated at 70°C for 10 h under Ar, then $H_2O$ was added to cleave the Si–O bonds. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the polymer was dissolved in about 2 mL THF, and this mixture was slowly added to stirring MeOH (30 mL). The precipitated polymer was collected by centrifugation at 3000 rpm for 10 min, and dried in vacuo to give light yellow polymer **6A**.

Typical procedure for the preparation of polymer supported ALB: Polymer **6A** (39.7 mg, 0.04 mmol as binol) was dried under reduced pressure at 45 °C for 2 h. A solution of AlMe$_3$ in hexane (0.98 M, 20.4 µL, 0.02 mmol) and *t*BuLi in pentane (1.48 M, 13.5 µL, 0.02 mmol) were added to a cooled ($-78$ °C) solution of **6A** in THF (0.4 mL). The reaction mixture was stirred at $-78$ °C for 10 min, then was warmed to room temperature. A clear gel was precipitated and used directly as a polymer-supported ALB **8A**.

Typical experimental procedure for polymer-supported ALB catalyzed asymmetric Michael reaction: 2-Cyclohexen-1-one (**10**; 25 µL, 0.22 mmol) and dibenzyl malonate (**11**; 50 µL, 0.2 mmol) were added to an insoluble polymer-supported ALB catalyst **8A** (10 mol %) in THF (0.5 M). The reaction mixture was stirred for 72 h, then quenched with HCl (1 N, 1 mL) at 0 °C and extracted with AcOEt. The combined organic extract was washed with saturated aqueous NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to give an oily residue. The mixture was dissolved in THF ($\approx$ 1 mL) and this solution was slowly added to stirring MeOH (30 mL). The precipitated polymer was collected by centrifugation at 3000 rpm for 10 min, and the supernatant was evaporated to give a crude product. Purification by flash chromatography (SiO$_2$, acetone/hexane = 1:10) gave **12** in 73 % yield with 91 % *ee*. The enantiomeric excess of **12** was determined by chiral HPLC analysis (DAICEL CHIRALPAK AS, *i*PrOH/hexane = 1:4, 1.0 mL min$^{-1}$, 254 nm).

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**Keywords:** · asymmetric catalysis · immobilization · polymerization · synthetic methods

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[5] The monomer **1b** was stable under neutral anhydrous conditions. The diasteroselectivity on **1b** was about 1:1.

[6] The amount of AIBN and the crosslinker is based on the total amount of **1b** and MMA.

[7] The polymer-supported ALB generated from the polymer prepared in the ratio of **1b**:MMA = 1:1 and **3**:MMA = 1:1 gave the Michael adduct **12** with 48 % *ee* and 2 % *ee*, respectively.

[8] The reusability of polymer **6A** was investigated by using another batch of polymer **6A** ($M_w = 26000$, PDI = 1.91). After the first and second run, **12** was obtained in 74 % yield with 89 % *ee*, and 76 % yield with 88 % *ee*, respectively. The polymer **6A** was recovered in 97 % after the second use ($M_w = 24000$, PDI = 1.81).

[9] The polymer-supported ALB prepared by use of 30 mol % and/or 90 mol % of crosslinker gave **12** in 32 % yield with 39 % *ee* and 32 % yield with 36 % *ee*, respectively.

[10] MIPs have been produced to order for the construction of chemo- and/or stereoselective receptors, sensors, columns, and/or artificial enzymes by using multisite recognition. In the application of MIPs to asymmetric metal catalysis, the molecular imprinting process is carried out using a chiral template of a transition state analogue, which is then removed for constructing a chiral cavity after the polymerization. Thus, the catalytic activities and selectivities are highly dependent on the efficiency of imprinting and the rigidity of the cavity. The requirement of a high loading of crosslinker for keeping the cavity rigid causes a serious decline in the activity of the catalyst.

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