Synthesis of Novel Functionalized Polymers for the Diastereoselective Protonation of Chiral Enolates

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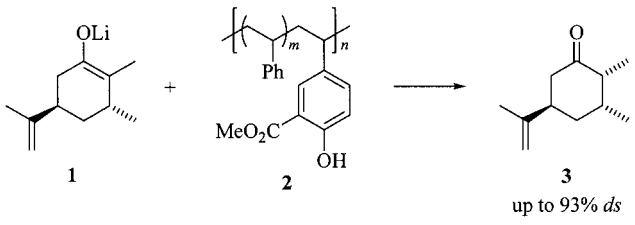
The polymeric, chelating proton donors **7** and **8** were synthesized by radical polymerization of the monomers **5/6** with different amounts of styrene. Protonation of chiral lithium enolates derived from silyl enol ethers **9** gave *cis*/*trans* ratios of up to 94:6 (**10a**) and 99:1 (**10b**), respectively. The polymers can be recycled and used repeatedly without appreciable loss of selectivity.

Introduction

The stereoselective formation of a C−H bond by protonation a prochiral or chiral enolate is an attractive method for the construction of a new stereogenic center in an organic molecule. For the diastereoselective protonation of endocyclic keto enolates, chelating proton donors with a salicylate structure are the reagents of choice since the formation of a rather rigid chelate complex between the enolate and the proton source ensures a highly *cis*-selective, reagent controlled proton transfer.[1,2] Several applications in target-oriented synthesis[2,3] emphasize the practicability of the method. Furthermore, in order to enable the repeated use of the proton donor and to facilitate its separation from the product, we have introduced the first polymeric, chelating protonating agents of type **2** which allowed the protonation of enolate **1** to be carried out with up to 93% diastereoselectivity (Scheme 1).[4]



Scheme 1. Diastereoselective protonation of chiral enolate **1** with polymeric, chelating proton donors **2**

In order to reach stereoselectivities of this magnitude, it has turned out to be essential that the salicylate units in the polymer are "diluted" by copolymerization with styrene; furthermore, the protonation has to be carried out in a solvent system which enables (at least partial) dissolution of the polymer (use of ethyl acetate or dichloromethane as a cosolvent).[4] Nevertheless, there is still room for improvement, and we now report two new types of polymeric chelating proton donors which provide diastereoselectivities of up to 99% in the protonation of chiral enolates.

Results and Discussion

The common precursor for both polymer types is 4-vinylbenzyl chloride (**4**) which was transformed into the salicylate derivative **5** by esterification with sodium salicylate in the presence of sodium iodide and a phase-transfer catalyst (53% yield).[5] Alternatively, the ether **6** was formed with 51% yield by treatment of **4** with ethyl 2,5-dihydroxybenzoate and potassium carbonate (Scheme 2).[6] The formation of the homopolymers **7a/8a**, as well as of statistical copolymers with 5, 9 or 15 equiv. of styrene, was carried out by heating the monomer **5** or **6** with the appropriate amount of styrene in the presence of AIBN (60−95% yield).[7,8] The average molecular weight of several of the polymers was determined by GPC and ranges from 7200 to 25600 g/mol.

The substrates for the diastereoselective protonation, the lithium enolates of type **1**, were formed by treatment of the thermodynamic silyl enol ethers **9a/b**[2,4] with 1 equiv. of methyllithium in THF solution (Scheme 3). Addition to a fivefold excess of the polymeric proton donor **7** or **8** in dichloromethane and quenching of the lithium salts with acetic acid as described earlier[1−3] was followed by gas chromatographic determination of the diastereomeric ratio (Table 1).

In the protonation of the chiral lithium enolate derived from silyl enol ether **9a**, *cis*/*trans* ratios around 90:10 were achieved with all polymeric proton sources examined. In

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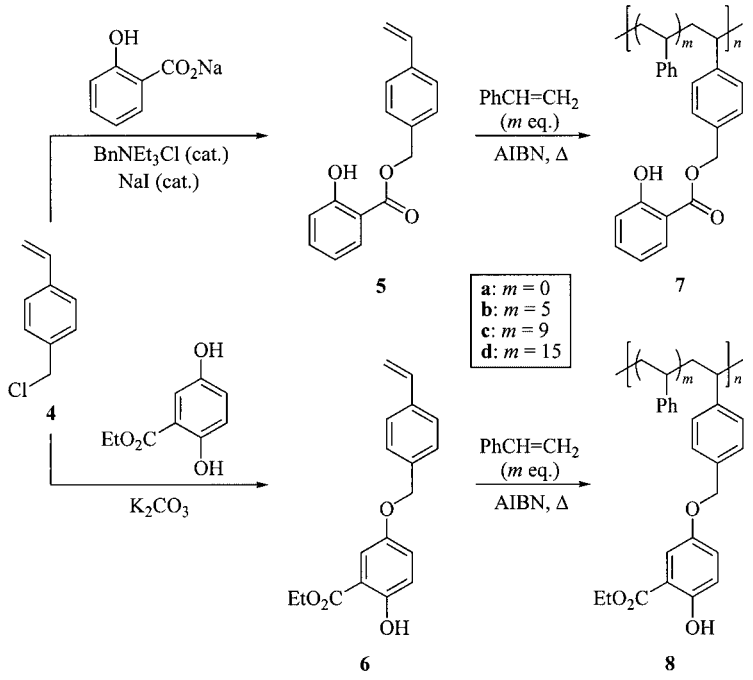
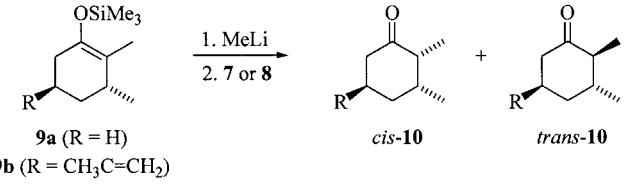


Scheme 2. Synthesis of polymeric proton donors **7** and **8**



Scheme 3. Diastereoselective protonation of chiral enolates derived from silyl enol ethers **9** with polymeric proton donors **7/8**

Table 1. Diastereoselectivity of the protonation of chiral enolates derived from silyl enol ethers **9** with 5 equiv. of polymeric proton donors **7/8**

Proton source	R = H *cis*-**10a**/*trans*-**10a**[a]	R = $H_3C-C=CH_2$ *cis*-**10b**/*trans*-**10b**[b] [c]
7a	87:13[d]	99:1
7b	86:14	98:2
7c	90:10	88:12[e]
7d	88:12	92:8
8a	83:17	78:22[f]
8b	92:8	85:15
8c	90:10	92:8
8d	89:11	93:7

[a] *cis*-**10a**/*trans*-**10a** = 92:8 with 5 equiv. of monomer **5**; *cis*-**10a**/*trans*-**10a** = 93:7 with 5 equiv. of monomer **6**. [b] *cis*-**10b**/*trans*-**10b** = 98:2 with 5 equiv. of monomer **5** or **6**. [c] *cis* and *trans* refer to the relative configuration of the two methyl groups of **10b**. [d] *cis*-**10a**/*trans*-**10a** = 94:6 with 10 equiv. of **7a**. [e] *cis*-**10b**/*trans*-**10b** = 96:4 with 10 equiv. of **7c**. [f] *cis*-**10b**/*trans*-**10b** = 86:14 with 10 equiv. of **8a**.

contrast to the earlier observation made for polymers **2**,[4] the "concentration" of salicylate units hardly affects the stereoselectivity of the protonation. However, the ratio of *cis*-**10a**:*trans*-**10a** = 87:13 observed for the protonation with 5 equiv. of homopolymer **7a** could be improved to 94:6 by using a larger excess (10 equiv.) of the protonating agent.[4] This value is very close to the ratio of 96:4 found when the protonation is carried out with ethyl salicylate.[1,2] In the case of the carvone-derived silyl enol ether **9b**, polymers **7** afforded higher selectivities than their counterparts **8**, in particular **7a** and **7b** which gave excellent *cis*/*trans* ratios of 99:1 and 98:2, respectively. In some cases, the diastereoselectivity could again be improved by employing a larger excess of the proton donor (see Table 1). The recovered polymeric proton sources can be used repeatedly without appreciably loss of stereoselectivity; for example, the selectivity of the protonation of the enolate formed from substrate **9a** with 5 equiv. of copolymer **7c** decreased only slightly from *cis*-**10a**:*trans*-**10a** = 90:10 (first cycle) to 87:13 in the fifth cycle.

Conclusion

The novel polymeric, chelating proton donors **7** and **8** were synthesized by radical polymerization of the monomers **5/6** with different amounts of styrene. Protonation of the chiral lithium enolates derived from silyl enol ether **9a** gave *cis*/*trans* ratios of up to 94:6, whereas the corresponding carvone-derived silyl enol ether **9b** furnished the product *cis*-**10b** with up to 99% diastereoselectivity. In both cases, the homopolymer **7a** afforded the highest selectivities, proving that a "dilution" of the salicylate units in the polymer chain is not necessary with polymeric proton donors of this type. The polymers can be recycled and used repeatedly without appreciable loss of stereoselectivity.

Experimental Section

General Remarks: The reactions were performed in oven-dried glassware under Ar. Diethyl ether and THF were distilled from sodium/benzophenone. Column chromatography was carried out with MERCK silica gel F 60 (70−230 mesh). For gel permeation chromatography, microgel set A22 was used with $CHCl_3$ as the solvent and polystyrene as the standard. GC analyses were carried out with a Carlo Erba GC 8000 gas chromatograph, equipped with a OV-1701 capillary column (carrier gas: helium). NMR spectra were obtained with a BRUKER DRX 400 spectrometer with $CDCl_3$ as solvent and internal standard (^{1}H NMR: δ = 7.26. ^{13}C NMR: δ = 77.0 ppm). IR spectra were measured with a BRUKER IFS 66 spectrometer. MS and HRMS: FINNIGAN MAT 8200 (EI, 70 eV).

4-Vinylbenzyl 2-Hydroxybenzoate (5): A suspension of sodium salicylate (24.0 g, 0.15 mol), 4-vinylbenzyl chloride (**3**; 15.3 g, 0.10 mol), benzyltriethylammonium chloride (2.28 g, 0.01 mol) and sodium iodide (1.50 g, 0.01 mol) in 300 mL of THF was heated to reflux for 16 h. After cooling to room temperature, 100 mL of brine was added, and the organic layer was separated. The aqueous layer was washed twice with ethyl acetate, the combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo. Crystallization of the crude product from cyclohexane furnished **5** (13.4 g, 53% yield) as slightly yellow crystals (m.p. 54 °C). ^{1}H NMR: δ = 10.80 (s, 1 H, OH), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.53−7.37 (m, 5 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 6.88 (t, *J* = 7.9 Hz, 1 H), 6.75 (dd, *J* = 10.8, 17.6 Hz, 1 H, C*H*=CH$_2$), 5.80 (dd, *J* = 0.8, 17.6 Hz, 1 H, CH=C*H*$_2$), 5.40 (s, 2 H, OCH$_2$), 5.35 (dd, *J* = 0.8, 10.8 Hz, 1 H, CH=C*H*$_2$) ppm. ^{13}C NMR: δ = 170.4 (×, C=O), 162.2 (×, C-OH), 138.3, 135.1 (2 ×), 136.6, 136.2, 130.4, 129.0, 126.9, 119.6, 118.0 (7 +), 115.0 (−, CH=*C*H$_2$), 112.8 (×), 67.1 (−, OCH$_2$) ppm. IR: ṽ = 3129, 1673, 1611, 1514, 1086 cm^{-1}. MS: *m*/*z* (%) = 254 (5) [M$^+$], 233 (45), 207 (5), 143 (33), 117 (100), 91 (15), 77 (6), 65 (13). HRMS: *m*/*z*: calcd. for $C_{16}H_{14}O_3$: 254.0943; found 254.0948.

Ethyl 5-(4-Vinylbenzyloxy)-2-hydroxybenzoate (6): A suspension of ethyl 2,5-hydroxybenzoate (7.90 g, 43.4 mmol), 4-vinylbenzyl chloride (**3**; 10.0 g, 65.5 mmol), and K_2CO_3 (16.0 g, 116 mmol) in 100 mL of acetone was heated to reflux for 22 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. Column chromatography of the crude product (cyclohexane/ethyl acetate, 20:1) afforded **6** (6.60 g, 51%) as colorless crystals (m.p. 78 °C). ^{1}H NMR: δ = 10.46 (s, 1 H, OH), 7.43−7.36 (m, 5 H), 7.12 (dd, *J* = 3.0, 9.0 Hz, 1 H), 6.89 (d, *J* = 9.0 Hz, 1 H), 6.71 (dd, *J* = 10.8, 17.6 Hz, 1 H, C*H*=CH$_2$), 5.75 (d, *J* = 17.6 Hz, 1 H, CH=C*H*$_2$), 5.25 (d, *J* = 10.8 Hz, 1 H, CH=C*H*$_2$), 4.99 (s, 2 H, CH$_2$Ar), 4.38 (q, *J* = 7.3 Hz, 2 H, C*H*$_2$CH$_3$), 1.40 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR: δ = 170.3 (×, C=O), 156.7, 151.4, 146.9, 137.8 (4 ×), 136.8, 128.2, 126.8, 124.9, 118.9, 114.2 (6 +), 114.6 (−, CH=*C*H$_2$), 112.6 (×), 71.1 (−, CH$_2$Ar), 61.9 (−, *C*H$_2$CH$_3$), 14.6 (+, CH$_2$*C*H$_3$) ppm. IR: ṽ = 3420, 3062, 2977, 2874, 1669, 1610, 1514, 1080 cm^{-1}. MS: *m*/*z* (%) = 298 (10) [M$^+$], 253 (5), 225 (4), 209 (4), 153 (5), 135 (8), 117 (100), 91 (18), 77 (3), 65 (7). HRMS: *m*/*z*: calcd. for $C_{18}H_{18}O_4$: 298.1205; found 298.1198.

General Procedure for the Polymerization of 5: A mixture of **5**, the appropriate amount of freshly distilled styrene, and AIBN was degassed by three freeze-pump-thaw cycles and then heated under argon to 80 °C for 16 h. After cooling to room temperature, the resulting solid was dissolved in 20 mL of CH_2Cl_2, and the product was precipitated by addition of 200 mL of pentane. After 2 h standing at room temperature, the supernatant liquid was removed, and the polymer was dried in vacuo. NMR spectroscopy revealed that the polymers were free of detectable amounts of monomer inclusions or solvent.

Homopolymer 7a: From **5** (6.50 g, 25.6 mmol) and AIBN (0.30 g, 1.83 mmol); yield: 3.91 g (60%) of **7a** as a colorless solid. Average molecular weight: 7822 g/mol, polydispersity: 3.23.

Copolymer 7b: From **5** (6.00 g, 23.6 mmol), styrene (12.3 g, 118 mmol), and AIBN (0.30 g, 1.83 mmol); yield: 13.2 g (72%) of **7b** as a colorless solid.

Copolymer 7c: From **5** (3.03 g, 11.9 mmol), styrene (11.0 g, 106 mmol), and AIBN (0.20 g, 1.22 mmol); yield: 13.3 g (95%) of **7c** as a colorless solid. Average molecular weight: 25625 g/mol, polydispersity: 2.05.

Copolymer 7d: From **5** (1.03 g, 4.05 mmol), styrene (6.30 g, 60.5 mmol), and AIBN (0.10 g, 0.61 mmol); yield: 5.60 g (76%) of **7d** as a colorless solid. Average molecular weight: 24934 g/mol, polydispersity: 1.76.

General Procedure for the Polymerization of 6: A solution of **6**, the appropriate amount of freshly distilled styrene, and AIBN in 100 mL of benzene was degassed by three freeze-pump-thaw cycles and then heated under argon to 50 °C for 16 h. The mixture was then cooled to room temperature and poured into 200 mL of pentane. After 2 h standing at room temperature, the polymer was isolated by removal of the supernatant liquid and dried in vacuo. NMR spectroscopy revealed that the polymers were free of detectable amounts of monomer inclusions or solvent.

Homopolymer 8a: From **6** (12.6 g, 42.2 mmol) and AIBN (0.20 g, 1.22 mmol); yield: 8.60 g (68%) of **8a** as a colorless solid.

Copolymer 8b: From **6** (2.97 g, 9.96 mmol), styrene (5.28 g, 50.7 mmol), and AIBN (0.23 g, 1.36 mmol); yield: 5.46 g (66%) of **8b** as a colorless solid. Average molecular weight: 7288 g/mol, polydispersity: 2.40.

Copolymer 8c: From **6** (3.00 g, 10.1 mmol), styrene (9.40 g, 90.3 mmol), and AIBN (0.20 g, 1.22 mmol); yield: 7.50 g (60%) of **8c** as a colorless solid. Average molecular weight: 9387 g/mol, polydispersity: 1.94.

Copolymer 8d: From **6** (6.00 g, 20.1 mmol), styrene (31.4 g, 301 mmol), and AIBN (0.30 g, 1.83 mmol); yield: 27.7 g (74%) of **8d** as a colorless solid.

General Procedure for the Protonation of Chiral Enolates: A solution of 1.0 mmol of the silyl enol ether in 10 mL of THF was treated at −50 °C with MeLi (0.63 mL, 1.0 mmol, 1.6 M solution in diethyl ether). The mixture was stirred for 1 h at −50 °C and then cooled to −80 °C. It was added via Teflon tubing in five aliquots to precooled solutions (−80 °C) of five different polymeric proton donors **7** or **8** (each containing 1.0 mmol of salicylate units) in 80 mL of CH_2Cl_2. After 5 min at −80 °C, the samples were warmed to room temperature, and each sample was treated with ca. (50 mg, 0.8 mmol) of acetic acid in a small amount of CH_2Cl_2. The sample was then concentrated in vacuo to a volume of ca. 30 mL, and 80 mL of pentane was added. The precipitate was allowed to settle, and the supernatant liquid was removed. After another concentration step, the diastereomeric ratio was determined by GC. The remaining polymer was dissolved in 20 mL of CH_2Cl_2, and the solution was washed with a satd. $NaHCO_3$ solution and water. After drying with $MgSO_4$, the polymer was isolated by addition of 80 mL of pentane, removal of the supernatant liquid, and

drying in vacuo. The quality of the recovered polymer was checked by NMR spectroscopy which showed it to be free of detectable amounts of solvent or water.

Acknowledgments

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