A Poly(ethylene glycol) Supported Chiral Auxiliary for Asymmetric Michael Reactions

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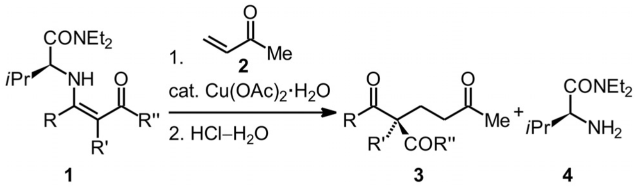
Abstract: The synthesis of a novel polymer-bound L-valine derived auxiliary **10** is reported. Its synthetic use is demonstrated in asymmetric copper(II)-catalyzed Michael reactions of cyclic β-oxo esters **12** with methyl vinyl ketone (**2**), yielding the corresponding addition products **3** with quaternary stereocenter in selectivities up to 99% ee. The immobilized auxiliary **10** can be recovered by simple precipitation from diethyl ether.

Key words: chiral auxiliary, Michael addition, immobilization, quaternary stereocenters, soluble polymer

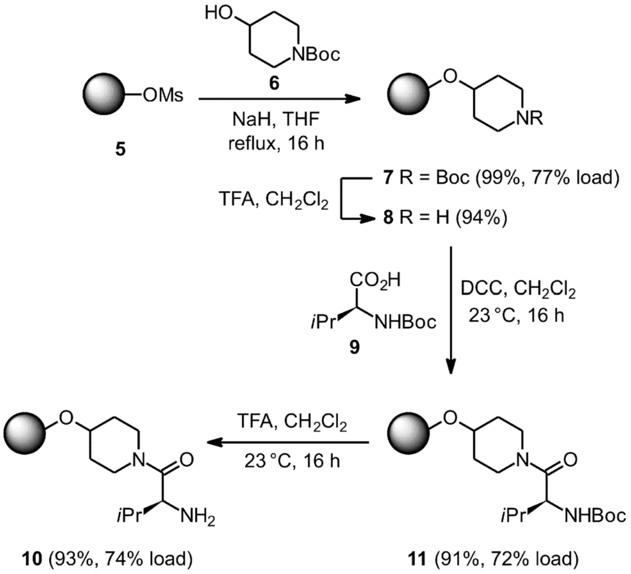
The asymmetric Michael reaction is one of the most powerful tools for stereoselective C–C bond formation.[1] Among the numerous chiral auxiliaries and catalysts reported in the literature some have proved their utility in the formation of quaternary stereocenters, however, a search for new, more effective ones remains a great challenge for synthetic organic chemistry.[2] There have been several reports on polymer-bound catalysts in this field,[3a–e] but only very few of them give Michael adducts with high stereoselectivity. One of the most successful systems was so far the polystyrene (Merrifield resin) supported cinchona alkaloid catalyst developed by d'Angelo and coworkers, allowing the generation of quaternary stereocenters with 87% ee.[3f] An auxiliary-mediated copper-catalyzed Michael reaction has been introduced by our group (Scheme 1).[4] Enamines **1** which are formed from β-dicarbonyl compounds, e.g., β-oxo esters or β-diketones, and the auxiliary L-valine diethylamide (**4**) react with methyl vinyl ketone (**2**) at ambient temperature to give the corresponding Michael products **3**. After completion of reaction, the auxiliary has to be re-isolated in a separate step. Therefore, in order to facilitate auxiliary separation and recovery and furthermore, to operate the reaction sequence continuously, we envisioned to develop a polymer-bound auxiliary.



Scheme 1 Auxiliary-mediated asymmetric Michael reaction.

In the past years soluble polymers have gained attraction due to practically homogeneous reaction conditions,[5] and a number of reviews have appeared on the use of soluble polymer-supported catalysts and reagents.[6] Also the application of soluble polymer catalysts for a continuously operated asymmetric reaction was reported.[7] The lack of polymer-bound systems for constructing quaternary stereocenters motivated us to prepare a soluble L-valine derived immobilized auxiliary. In this communication we wish to report its synthesis and application in the asymmetric Michael reaction.

Starting from commercially available poly(ethylene glycol) dimesylate (**5**) with an average molecular mass of 2000 Da, *N*-Boc-protected 4-hydroxypiperidine (**6**) was attached to the polymeric backbone by ether formation. The polymeric material was quantitatively recovered (99%), the conversion was 77% (determined by elemental analysis and ^{1}H NMR; Scheme 2). Deprotection of carbamate **7** with TFA gave the free amine **8**, which was converted to amide **11** in the reaction with *N*-Boc-L-valine (**9**) in the presence of DCC as activating agent. The two latter steps proceeded with quantitative conversion.



Scheme 2 Synthesis of the immobilized L-valine auxiliary, only one of the two polyglycol chain termini is given. Yields are referred to the mass of re-isolated polymer and load to the substitution level of the polymer.

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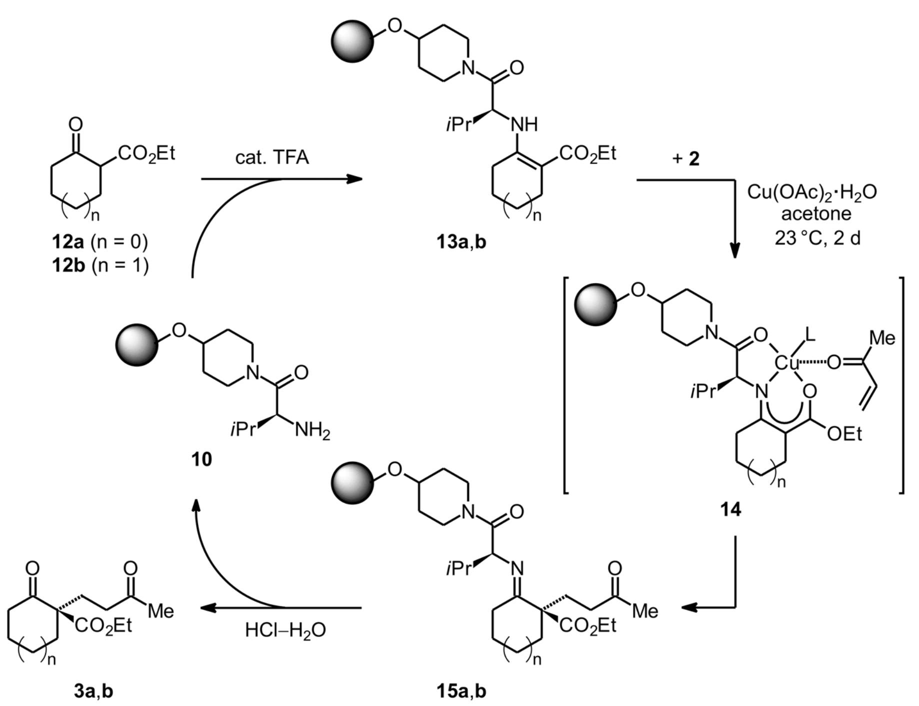
Symmetry of the amine **6** is crucial in order to avoid new stereogenic elements such as *E*/*Z* isomerism of the amide bond in **11** or a stereocenter at the former secondary alcohol carbon atom. Deprotection of **11** with TFA finally gave the immobilized auxiliary **10** as a novel chiral linker again with quantitative conversion. The final polymer load was 74%. Load values calculated from ^{1}H NMR spectra[8] and elemental analysis usually differed by no more than 5%.

Having linker **10** in hand, enamines **13a**,**b** were prepared from ethyl cyclopentanecarboxylate **12a** and ethyl cyclohexanecarboxylate **12b**, respectively, by condensation, with TFA as Brønsted acidic catalyst in practically quantitative yields.[9] Addition of a water-scavenging agent was not necessary (Scheme 3, Table 1).

The supported enamines **13** were converted with methyl vinyl ketone (**2**) in asymmetric, copper(II)-catalyzed Michael reactions via proposed intermediate complex **14** to give the immobilized imines **15**.[10] Subsequent hydrolysis with hydrochloric acid (c = 1 mol dm^{-3}) afforded the Michael products **3** in practically quantitative yields. In the case of **3b**, a purity of 97% was determined by ^{1}H NMR indicating only minor impurities.[11]

The enantiomeric excesses of Michael products **3a** and **3b** were determined by GLC on a chiral phase. Perfect enantioselectivities of 99% ee and 97% ee for the derivatives of cyclopentanone **3a** and cyclohexanone **3b**, respectively, have been obtained. To the best of our knowledge, these are the highest ee values achieved for the stereoselective generation of quaternary stereocenters by applying polymer supported ligands or auxiliaries.

The absolute configuration of product (+)-**3b** is known to be (*R*).[12,13] This result agrees with our suggested mechanism:[14] after deprotonation of the enamine by acetate, copper(II) coordinates to the azadionato moiety and to the amide oxygen forming chelate **14**. Methyl vinyl ketone (**2**) coordinates and alkylates the donor from the *Re* side, yielding an imine which is subsequently hydrolyzed to give the *R*-configured addition product **3**.



Scheme 3 Substrate attachment and asymmetric Michael reaction with supported auxiliary.

Table 1 Asymmetric Michael Reaction with Supported Auxiliary **10**[a]

Oxo ester		Auxiliary	Enamines **13**			Imines **15**			Products **3**	
12	n	**10**	**13**	Yield (%)[b]	Load (%)	**15**	Yield (%)[b]	Load (%)	**3**[c]	ee (%)
12a	0	44% Load	**13a**	96	42	**15a**	98	39	(*R*)-**3a**	99
12b	1	74% Load	**13b**	99	72	**15b**	99	69	(*R*)-**3b**	97

[a] The immobilized auxiliary **10** with 44% load resulted from an unoptimized batch.

[b] Given yields regarding the mass of re-isolated polymer.

[c] The absolute configuration was established by comparison (GLC on a chiral phase) with authentic material from our group.[12,13]

The immobilized auxiliary was recycled by precipitation from diethyl ether and reused for enamine formation with β-oxo ester **12b** and subsequent Michael reaction, giving product **3b** with a slightly lower though still very good selectivity of 90% ee.

In summary, the synthesis of a novel polymer supported L-valine derived auxiliary **10** was realized by a four-step reaction starting from commercially available poly(ethylene glycol) derivative **5** in high 79% overall yield. We are able to show the utilization of **10** in asymmetric Michael reactions. For the first time quaternary stereocenters were constructed with almost quantitative selectivity (99% ee) by using a chiral linker.

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(8) Load values were calculated by ^{1}H NMR integrals with the polymer signal at δ = 3.45–3.80 ppm as a standard. In the case of **13b** the signal at δ = 4.13 ppm (2 H) and for **15b** the signal at δ = 2.22 ppm (3 H) were used for integration.

(9) **Supported *N*-(2-Ethoxycarbonyl-1-cyclohexenyl)-L-valine(4-hydroxypiperidide) (13b).**
Immobilized auxiliary **10** (2.50 g, 1.54 mmol), **12b** (3.00 g, 17.6 mmol) and one drop of TFA in abs. toluene (8 mL) were heated at 55 °C for 16 h. Two fold precipitation from abs. Et_2O (80 mL) yielded **13b** (2.58 g, 99%) as a pale yellow polymer. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, ^3J = 6.9 Hz, 3 H, CH_3), 1.03 (d, ^3J = 6.9 Hz, 3 H, CH_3), 1.26 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.47–1.68 (m, 6 H), 1.77–1.92 (m, 2 H), 1.95–2.14 (m, 2 H), 2.21–2.32 (m, 3 H), 3.23–3.36 (m, 2 H), 3.50–3.74 (m, 140 H, PEG–H), 3.91–4.01 (m, 1 H), 4.13 (q, ^3J = 7.2 Hz, 2 H, OCH_2), 9.31 (d, br, ^3J = 8.8 Hz, 1 H, NH) ppm. All other signals are overlapped by resonances of the polymer backbone. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 14.65 (CH_3), 18.42 (CH_3), 19.90 (CH_2CH_3), 22.35 (CH_2), 22.57 (CH_2), 23.91 (CH_2), 26.75 (CH_2), 30.74 (CH_2, br, C-3′), 31.81 (CH_2, br, C-3′), 31.98 (CH, $CHCH_3$), 39.45 (CH_2, br, C-2′), 42.69 (CH_2, br, C-2′), 58.38 (CH, CHNH), 58.74 (CH_2, OCH_2), 74.36 (CH, OCH), 91.47 (C, C-2″), 157.51 (C, br, CNH), 170.48 (C, CON), 170.62 (C, COO) ppm. IR (ATR): 1/λ = 3483 (w, br), 2882 (s), 1645 (m), 1592 (m), 1466 (m), 1359 (m), 1341 (s), 1279 (m), 1233 (s), 1146 (m), 1103 (vs), 1063 (vs), 948 (s), 841 (s) cm^{-1}. Anal. Calcd for **13b** assuming 44 ethylene oxide units in a polymeric backbone of 2000 Da at 72% load: C, 56.77; H, 9.18; N, 1.62. Found: C, 56.42; H, 9.18; N, 1.57.

(10) **Supported (*R*)-*N*-[2-Ethoxycarbonyl-2-(3-oxobutyl)-1-cyclohexylidene-L-valine (4-hydroxypiperidide)] (15b).**
To a solution of polymer **13b** (0.40 g) in acetone (2 mL) was added $Cu(OAc)_2\cdot H_2O$ (4.0 mg, 0.02 mmol). The mixture was stirred for 1 h at 23 °C, then **2** (1.00 g, 14.3 mmol) was added. After stirring of the mixture for 2 d, the product polymer was precipitated from Et_2O (50 mL) to yield a brown polymer **15b** (0.39 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, ^3J = 6.2 Hz, 3 H, $CHCH_3$), 0.92–1.02 (m, 3 H, $CHCH_3$), 1.25 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.41–1.90 (m, 8 H), 2.09–2.16 (m, 7 H), 2.22 (s, 3 H, $COCH_3$), 2.31–2.70 (m, 2 H), 2.51 (t, ^3J = 6.2 Hz, 2 H), 2.72–3.38 (m, 2 H), 3.44–3.81 (m, 131 H, PEG–H), 3.98–4.23 (m, 2 H), 4.11–4.21 (m, 2 H, OCH_2) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 18.92 (CH_3), 25.19 (CH_2), 28.40 (CH_2), 29.96 (CH_2), 32.58 (CH_2), 38.87 (CH_2, NCH_2), 42.87 (CH_2, NCH_2) 60.82 (CH, CHN), 67.55 (CH, OCH), 141.78 (C, CN), 173.91 (C, COO), 208.46 (C, CO) ppm. Missing signals cannot be identified from background noise.

(11) **Ethyl (*R*)-2-Oxo-1-(3-oxobutyl)cyclohexanecarboxylate (3b).**[15]
Polymer **15b** (1.00 g, 0.52 mmol) was stirred in HCl (2 mL, c = 1 mol dm^{-3}) at 0 °C for 3 h. H_2O (20 mL) was added, and the mixture was then extracted with Et_2O (3 × 20 mL). The combined ether layers were washed with H_2O (50 mL), dried ($MgSO_4$) and evaporated to give **3b** (108 mg, 0.45 mmol, 87% reg. **15b**) as a colorless oil with 97% purity (determined by ^{1}H NMR spectroscopy). GC for determination of ee value: Bondex unβ[16] [20 m × 0.3 mm with hydrogen carrier gas (0.4 bar)], 120 °C isotherm; $t_R(R)$ = 29.75 min; $t_R(S)$ = 30.88 min, 97% ee.

Extraction of the water layers with CH_2Cl_2 (3 × 50 mL), subsequent washing of the combined CH_2Cl_2 layers with H_2O (50 mL), drying ($MgSO_4$) and removal of all volatile materials under high vacuum gave the re-isolated polymer **10** (867 mg).

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(16) Bondex-unβ-5.5-et-105 is a chiral poly(dimethylsiloxane) phase which is modified with 0.55 mol% permethyl β-cyclodextrin, covalently bonded by an undecamethylene spacer between one 2-O-function of the cyclodextrin and the polysiloxane backbone. The polysiloxane additionally has 5.25% $Si(C_2H_5)_2$ instead of $Si(CH_3)_2$ groups in the backbone. See: Karpf, M. *Dissertation*; Universität: Stuttgart, **1995**.