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A soluble polymer-bound Evans' chiral auxiliary: synthesis, characterization and use in cycloaddition reactions

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Abstract—The synthesis of novel soluble polymer-supported optically-active oxazolidinone (Evans' chiral auxiliary) with different chiral monomer/styrene ratios is described. The polymer was obtained in high yields and then functionalized with *trans*-crotonic anhydride to give a high loading polymer (2.42 mmol/g). The reactivity was tested in the 1,3-dipolar cycloaddition with diphenylnitrone under catalyzed and uncatalyzed conditions. The cycloadducts could be obtained in high purities and fair yields after reductive cleavage. The stereoselectivity is parallel to that obtained with the model substrate under classical solution conditions.

Crosslinked, insoluble polymer supports for organic synthesis have recently witnessed a resurgence of interest for applications in combinatorial chemistry.[1] Most recently, a variety of catalysts for enantioselective organic synthesis on insoluble supports have appeared in the literature.[2] Tuning of the reactivity of the supported organic compounds in the unavoidably heterogeneous-phase reactions, as well as the detection and analysis of the functionalized, supported products can, however, be extremely problematic. Several groups have recently explored the use of soluble linear polymeric,[3] dendritic[4] and precipiton[5] supports. The advantages of solid-phase synthesis are retained, since the macromolecular support is easily removed from the reaction mixture via precipitation from an appropriate solvent, but the synthetic pathway can be carried out under more convenient homogeneous solution conditions, with easier characterization of the covalently bound substrates.

Chiral 3-substituted 1,3-oxazolidin-2-ones, originally introduced by Evans,[6a] act as chiral auxiliaries in several C–C bond forming reactions as well as in metal-catalyzed cycloaddition reactions between a variety of 1,3-dipoles and dienes, with good control of diastereo- and enantioselectivity.[6] Typically, the catalytic processes involve the dissolution in organic solvents of the metal salts (added as a heterogeneous solid) as a result of coordination of the metal cation to the 1,3-dicarbonyl moiety in the chiral auxiliary. Grafting of this chiral auxiliary to Merrifield and Wang resins has already been achieved by us[7] and other groups,[8] but the metal-catalyzed reactions of these resin-supported auxiliaries have shown some differences in stereoselectivity in comparison to the solution-phase reactions.[7a] A carrier for the cation was found to be necessary in solid-phase chemistry to allow interaction of the Lewis acid with the grafted coordinating substrate and to simulate classical catalysis conditions in solution, with the Wang support showing higher sensitivity to salt concentrations than the Merrifield resin-supported auxiliary.[7b]

Herein, we communicate the synthesis, characterization, and functionalization of a novel, soluble polymer-supported optically-active oxazolidinone. Since the two most common support strategies developed for soluble macromolecular supports are polyethylene glycol and polystyrene-based,[3c] we chose the latter in order to avoid competitive interactions between the oxygen atoms of the polymer chains and the Lewis acidic metal cation. Furthermore, polystyrene supports are removed by precipitation in polar organic solvents in which all the excess reagents should remain soluble. Preliminary investigations on the reactivity of the soluble polymer-

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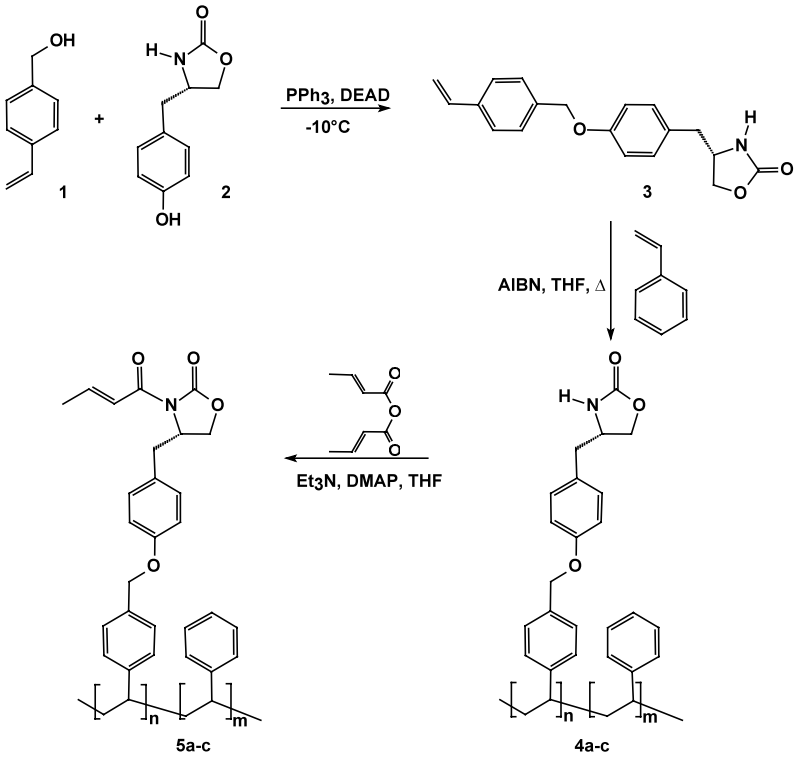
bound dipolarophile in the 1,3-dipolar cycloaddition reaction with diphenylnitrone, under catalyzed and uncatalyzed conditions, will be also presented.

Condensation of 4-vinylbenzyl alcohol **1**[9] and the tyrosine derived-oxazolidinone **2**[10] under Mitsunobu conditions gave the monomer **3** in good yield (Scheme 1).[11] Monomer **3** is insoluble in many organic solvents, but sparingly soluble in THF, and therefore it was copolymerized with styrene in such a solvent in variable copolymer ratios with AIBN as a radical initiator.[12]

Polymers **4a** and **4b**, incorporating respectively 30 and 50% of monomer **3**, could be obtained after purification in EtOH in good yields. Polymer **4c** was too polar to be precipitated in EtOH and therefore considered unsuitable as a support. GPC analysis (polystyrene standards) indicated somewhat low molecular weights (M_n<15,000) (Table 1), but the insolubility of monomer **3** in other solvents, more suitable for free radical polymerization, prevented us from exploring the behavior of higher molecular weight samples.

The ^{1}H NMR spectrum of **4b** (Fig. 1) was in accordance with the proposed structure and the analysis of the integral ratios confirmed a ratio styrene/**3** of 1:1.

Functionalization of the polymer-bound oxazolidinone **4b** was achieved as indicated in Scheme 1, and polymer **5b** was obtained in pure form after precipitation from EtOH.[13] GPC analysis confirmed the increase in molecular weight, and the comparison between the ^{1}H NMR spectra (Fig. 1) revealed complete functionalization, as evidenced nicely from the differences between the spectra of functionalized (top, Fig. 1) and unfunctionalized polymer samples (bottom, Fig. 1). Elemental analyses of samples of polymers **4b** and **5b** revealed a close correspondence between the observed and calculated (based on the feed) ratio of monomers in the copolymer composition.



Scheme 1.

Table 1. Characterization of polymers **4** and **5**

Polymer	Feed ratio[a]	Yield[b]	Loading[c]	M_n[d]	M_w[d]	PD[d]
4a	3/7	85	1.81	6,800	9,800	1.5
4b	5/5	80	2.42	5,800	7,000	1.2
4c	7/3	(e)	2.82	–[e]	–[e]	–[e]
5b	5/5	100	2.42	7,500	10,000	1.3

[a] Monomers ratio in the polymerization (% **3**/% styrene).
[b] After purification by precipitation in EtOH.
[c] Calculated loading (mmol/g) of chiral auxiliary on the basis of the monomer feed ratio.
[d] As determined by GPC relative to polystyrene standards.
[e] Not determined.

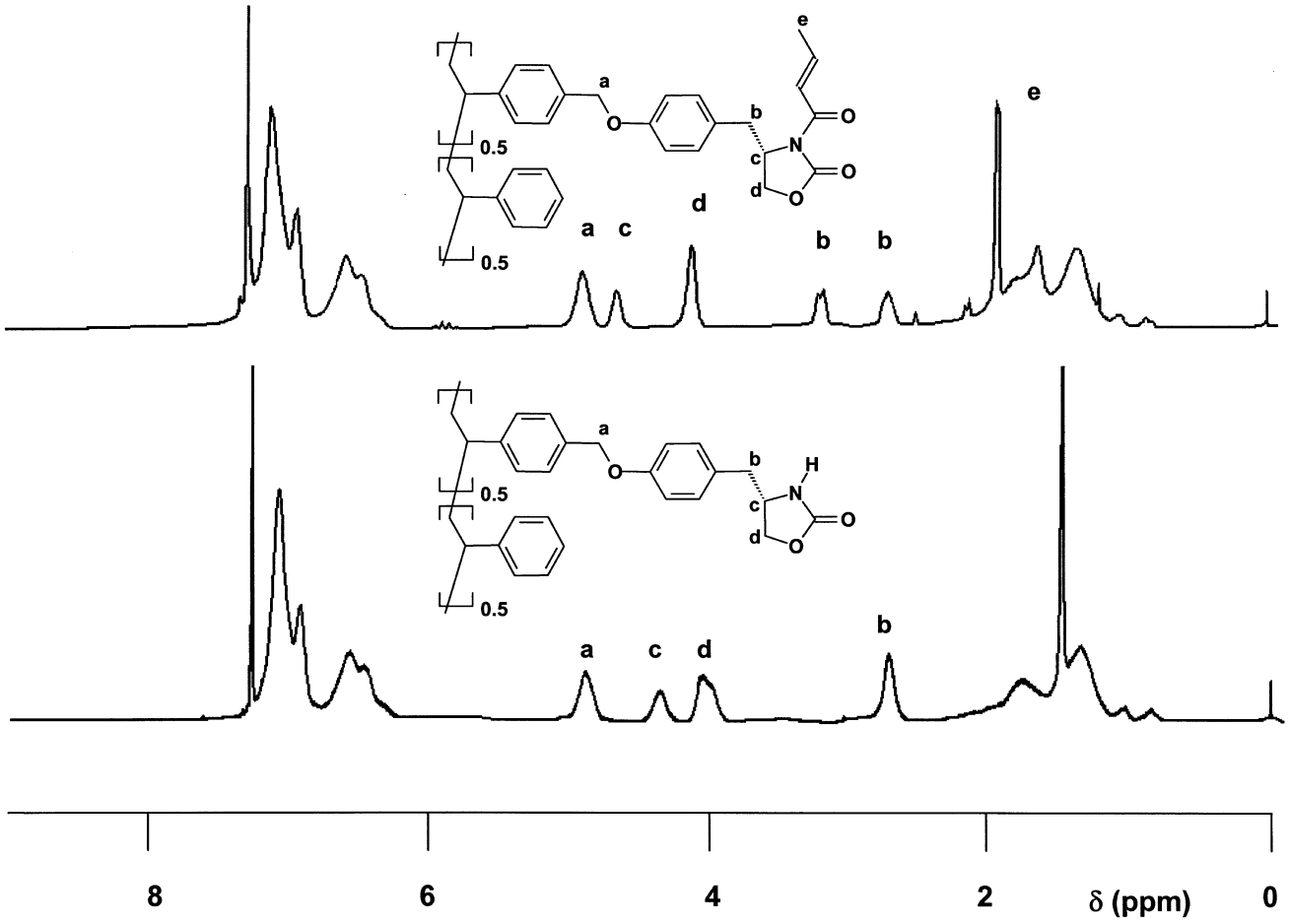
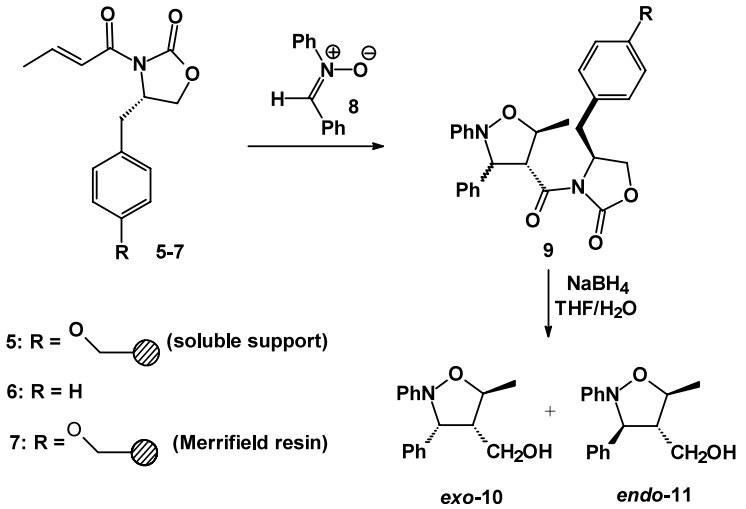


Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of polymer **4b** and its derivative **5b**.

The incorporation up to 50% of monomer **3** in copolymers **4b** and **5b** corresponds to an effective calculated loading for such polymers well above that of the commercially-available Merrifield resins currently used by us.[7] Furthermore, polymer **5b** showed good solubility in solvents such as CH_2Cl_2 and $CHCl_3$ and it was able to dissolve catalytic amounts of inorganic salts such as $Mg(ClO_4)_2$ (MgP) or $Sc(OTf)_3$ (ScT), directly added as solids, without any precipitation and without the need for competing polar solvents.

The polymer-bound oxazolidinone **5b** was then allowed to react with diphenylnitrone **8**,[14] according to a well known reaction scheme to afford compounds **9** (Scheme 2).[14,15]



Scheme 2.

Table 2. Comparison between solution and solid-phase reactivity of supported chiral auxiliaries in 1,3-dipolar cycloaddition reaction with nitrone **8**[a]

Entry	Substrate	Catalyst (equiv.)	Time/yield	*exo*-10:*endo*-11	% *ee exo*-**10**	% ee *endo*-**11**
1	**6**[b]	–	15 days[c]	83:17	83 (3*R*,4*S*,5*S*)	>99 (3*R*,4*R*,5*R*)
2		MgP (0.1)	2.5 days[c]	85:15	93 (3*S*,4*R*,5*R*)	>99 (3*S*,4*S*,5*S*)
3		ScT (0.1)	5 h[c]	24:76	83 (3*S*,4*R*,5*R*)	>99 (3*S*,4*S*,5*S*)
4	**5b**	–	40 days/28%[d]	68:32	89 (3*R*,4*S*,5*S*)	26 (3*R*,4*R*,5*R*)
5		MgP (0.1)	7 days/34%[d]	60:40	90 (3*S*,4*R*,5*R*)	92 (3*S*,4*S*,5*S*)
6		ScT (0.1)	7 days/32%[d]	30:70	56 (3*S*,4*R*,5*R*)	80 (3*S*,4*S*,5*S*)
7	**7**[e]	–	40 days/12%[d,e]	53:47	88 (3*R*,4*S*,5*S*)	22 (3*R*,4*R*,5*R*)
8		MgP (0.1)	7 days/20%[d,f]	58:42	90 (3*R*,4*S*,5*S*)	27 (3*R*,4*R*,5*R*)

[a] Reaction conditions: CH_2Cl_2, rt; the catalyst, when present, was added as a solid.
[b] Data taken from Ref. 15.
[c] Not applicable (see footnote d).
[d] Yields refer to the average of three synthetic steps: functionalization, cycloaddition reaction and cleavage.
[e] Data taken from Ref. 7a.
[f] Catalyst $Mg(ClO_4)_2$ added as a 1.0 M solution in MeCN, see Ref. 7b.

After purification by precipitation from EtOH to remove unreacted materials, the polymers, were then subjected to reductive cleavage[16] to afford diastereomeric isoxazolidine **10** and **11**.

The cycloadducts were obtained after aqueous workup and extraction in organic solvents, and the supported chiral auxiliary **4b** was removed by precipitation from EtOH and recovered by a simple filtration. Chiral HPLC analysis of the diastereomeric mixture evidenced the presence of only pure *endo* and *exo* cycloadducts with no need for any further purification.

The results obtained in the cycloadditions involving **5b** as dipolarophile, compared with those previously reported using either **6** (model compound for solution chemistry) or **7** (insoluble support), are reported in Table 2. The soluble polymer **5b** undergoes 1,3-dipolar cycloaddition reaction with **8** in higher overall yields with respect to the dipolarophile supported on Merrifield resin **7** (entries 4 and 5 versus 7 and 8). Furthermore, the observed stereoselectivities are more similar to those reported for the model substrate **6** under classical solution conditions. The use of MgP at a level of 10% reverses the preferred stereochemistry of both *endo* and *exo* cycloadducts in the case of **7** and **5b**, but not in the reaction involving the Merrifield supported dipolarophile **7** (entries 2 and 5 versus 8). The use of 10% of ScT shifts stereoselectivity towards the *endo* adduct formation (entries 3 and 6) and again both *endo* and *exo* adducts are formed with the opposite stereochemistry obtained under uncatalyzed conditions. The inversion of both *exo* and *endo* enantioselectivity can be rationalized by a mechanism involving the cation bicoordination to the 1,3-dicarbonyl moiety of the dipolarophile.[7b,15]

The use of soluble polymers instead of cross-linked ones (Merrifield resin) allows higher loading, easier characterization of the intermediates and easier interactions between metal cations and coordinating substrates, thus avoiding some of the intrinsic disadvantages of solid-phase chemistry. The soluble polymer **5b** gives results that are more similar to those obtained under solution than the Merrifield supported auxiliary **7**.

Several issues, such as the role of the polymer structure, polymer recyclability, as well as extension of the applications of these polymers to other stereoselective C–C bond forming reactions, will be addressed in the near future.

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11. *p*-Vinylbenzylalcohol **1** (0.67 g, 5 mmol), *(4S)*-(4-hydroxybenzyl)-1,3-oxazolydin-2-one **2** (0.95 g, 5 mmol) and Ph_3P were dissolved in dry THF (8 mL) and the stirred suspension was cooled at –10°C. A solution of DEAD (1.04 g, 6 mmol) in dry THF (3 mL) cooled at –10°C was added dropwise to the suspension at such a rate needed to maintain the solution colorless (about 10 min). The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo, the residue was treated with a small amount of MeOH (5 mL) and filtered to afford **3** as a white solid (1.1 g, 71%). Mp: 169–171°C; $[\alpha]_D = +51.9$ (c 0.73, $CHCl_3$). ^1H NMR ($CDCl_3$) $\delta = 7.49$ (d, 2H; $J = 8.4$ Hz, Ar′), 7.40 (d, 2H; $J = 8.4$ Hz, Ar′), 7.11 (d, 2H; $J = 8.8$ Hz, Ar), 6.96 (d, 2H; $J = 8.8$ Hz, Ar), 6.75 (dd, 1H; $J_{cis} = 10.9$ Hz, $J_{trans} = 17.6$ Hz, Ar-CH), 5.77 (dd, 1H; $J_{cis} = 10.9$ Hz, $J_{gem} = 1.0$ Hz, CH=CH_2), 5.29 (dd, 1H; $J_{trans} = 17.6$ $J_{gem} = 1.0$ Hz, CH=CH_2), 5.07 (s, 2H; CH_2-Ar′), 4.95 (bs, 1H; NH), 4.49 (t, 1H; $J_{5-4} = 8.6$ $J_{gem} = 8.6$ Hz, *H5*), 4.16 (dd, 1H; $J_{5-4} = 5.5$ $J_{gem} = 8.6$ Hz, *H5*), 4.05 (m, 1H; *H4*), 2.85 (dd, 1H; $J_{CH2-4} = 5.5$ $J_{gem} = 13.5$ one of CH_2Ar), 2.79 (dd, 1H; $J_{CH2-4} = 8.2$, $J_{gem} = 13.5$, CH_2Ar). ^{13}C NMR ($CDCl_3$) $\delta =$ 158.9, 157.8, 137.3, 136.3, 131.7, 130.0, 129.9, 127.6, 126.4, 115.3, 114.1, 69.7, 69.6, 53.8, 40.6. Alternatively, monomer **3** can be directly obtained by nucleophilic substitution on commercially-available 4-vinylbenzyl chloride under phase-transfer catalysis conditions, but the reaction yields and product purity were significantly lowered.
12. Freshly purified monomers were dissolved in THF in the ratios indicated in Table 1 (monomer **3** was at the same concentration, 0.15 M). AIBN (2 mol% with respect to total monomer) was added and the mixture was deoxygenated with three freeze–thaw cycles. The reaction mixture was heated at 70°C for 30 h. **4b**, reprecipitated into EtOH. Yield: 80%. IR (cm^{-1}): 3413, 1755. Anal. calcd for $C_{27}H_{27}NO_3$: C, 78.5; H, 6.5; N, 3.4. Found: C, 79.2; H, 6.7; N, 3.2%.
13. Polymer **4b** (200 mg) was dissolved in THF (2.5 mL). DMAP (0.18 g), Et_3N (0.22 mL) were added and the solution was cooled at 0°C. Crotonic anhydride (0.44 mL) was added dropwise and the solution was stirred at 70°C for 48 h. **5b**, reprecipitated into EtOH, was obtained in quantitative yield. IR (cm^{-1}): 1779. Anal. calcd for $C_{31}H_{31}NO_4$: C, 77.3; H, 6.4; N, 2.9. Found: C, 78.7; H, 6.7; N, 2.7%.
14. Polymer **5b** (80 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1 mL) and, when required, catalyst (0.1 equiv.) was directly added to the solution. The solution was stirred for 30 min until catalyst dissolution and then diphenylnitrone **8** (33 mg, 0.17 mmol) was directly added to the solution. After 7 days at room temperature, the reaction mixture was dropped in EtOH (50 mL) under vigorous stirring. The precipitated polymer was recovered by filtration and dissolved in THF (2 mL). $NaBH_4$ (20 mg) in EtOH (0.5 mL) was added and the reaction mixture was stirred overnight at room temperature. The solution was added to EtOH (50 mL), polymer **4b** was recovered by filtration, while the combined organic extract was evaporated under vacuum. The residue was treated with CH_2Cl_2 in order to recover the reaction products: the solution was washed with water, dried over Na_2SO_4, and the residue obtained was analyzed by HPLC. The characterization of these cycloadducts has been reported in a previous paper.[7b]
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