9.801(2)], $c = 34.797(4)$ [17.1896(10); 12.071(3)] Å, $\alpha = 90$ [90; 82.20(2)], $\beta = 95.085(10)$ [94.768(6); 79.19(2)], $\gamma = 90$ [90; 67.21(2)]°, $V = 7981(2)$ [3221.0(3); 954.8(3)] Å^3, $Z = 4$ [4; 1], $\rho_{calcd} = 2.059$ [2.295; 2.450] g cm^{-3}, $T = 293(2)$ K, θ-range: 1.74–24.12 [2.20–25.93; 2.74–28.00]°, measured reflections: 46406 [45294; 16443], independent reflections: 12255 [5991; 4217] ($R_{int} = 0.0636$ [0.0694; 0.0620]), R values: final R values ($I > 2\sigma(I)$): $R1 = 0.0308$ [0.0247; 0.0353], $wR2 = 0.0685$ [0.0568; 0.0935], all data: $R1 = 0.0415$ [0.0303; 0.0420], $wR2 = 0.0738$ [0.0585; 0.0984]. Diffractometer: Stoe IPDS. Structure solution: direct methods [direct methods; Patterson]. Program used for solving the structure: SIR92 (Giacovazzo et al., 1993) [SHELXTL; SHELXS 86 (Sheldrick, 1990)]. Structure refinement: full-matrix least-squares methods against F^2. Program used for refining the structure: Siemens SHELXTL [SHELXTL; Siemens SHELXL 93 (Sheldrick, 1993)]. Data/parameters: 12248/904 [5991/381; 4217/232]. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100785. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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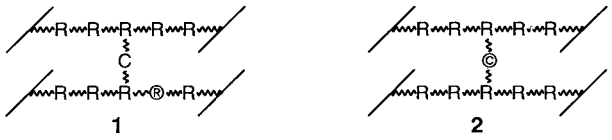
Functionalized Cross-Linked Copolymers: A "C_2-Symmetric" Solid-Phase Catalyst for Enantioselective Reactions**

Chris Halm and Mark J. Kurth*

Building on the pioneering work of Merrifield,[1] solid-phase synthesis,[2] polymer-supported reagents,[3] and polymer-bound catalysts[4] have revolutionized many aspects of synthetic chemistry. Most of these exploits were accomplished with styrene/divinylbenzene (PS/DVB) copolymers,[5] but there are notable exceptions.[6] Polymer-bound catalysts are typically prepared by covalent attachment of the catalytic moiety to the PS/DVB copolymer through the chloromethylated functionality (Merrifield's resin). While excellent enantioselectivities have been achieved with these heterogeneous catalysts,[7] this route to supported catalysts has been limited to placing the catalyst at a position pendant to the polymer backbone (**1**, Figure 1). What has been largely overlooked[8] is



1 **2**

Figure 1. Functionalized resins. R: chain monomer; C: cross-linked monomer; ®: pendant functionalization; ©: cross-link functionalization.

a supported-catalyst strategy in which the catalytic moiety is located at the resin cross-link (**2**, Figure 1). We report here the rapid and convenient synthesis of this type of cross-link-functionalized resin by suspension copolymerization to yield a solid-phase "C_2-symmetric" catalyst (although the two polymer chains are not identical, the local environment is C_2-symmetric) for application in enantioselective transformations. We believe this unique cross-link functionalization provides the least disturbance to the symmetry of the catalytic center, because the two cross-linked polymer chains can be considered as symmetrically equivalent. Possible applications therefore benefit from a decrease in the number of competing diastereomeric transition states inherent in C_2-symmetric systems.[9] In most pendant catalysts, one arm of the auxiliary is attached to the polymer backbone while the other terminates with a small organic fragment, causing inherent dissymmetry between the auxiliaries. We believe cross-link-functionalized chiral resins may afford important processing advantages over pendant versions. For example, cross-link functionalization should minimize interactions between active sites which may positively influence reaction parameters such as catalytic turnover. In addition, resin-supported catalytic reagents can ease product purification as well as catalyst recovery and reuse.

To obtain a cross-linked functionality, it was necessary to synthesize a monomeric chiral auxiliary (X) containing two polymerizeable units (i.e., $CH_2{=}CH{-}X{-}CH{=}CH_2$), which could then undergo suspension copolymerization with styrene. We reasoned that the resulting cross-link-functionalized polystyrene beads might provide an ideal opportunity for asymmetric catalysis, and selected enantioselective reductive alkylation of aldehydes as our target transformation.

Ohno and co-workers[10] reported that the chiral ligand **3** (1 mol%) together with titanium(IV) isopropoxide catalyzes the reductive alkylation of aldehydes (Scheme 1). We envisioned replacing the trifluoromethyl groups of **3** with styrenesulfonyl groups to give a cross-linking monomer (**4**) which, after copolymerization with styrene (**4** → **5**), could be evaluated for efficacy in the reaction of aromatic aldehydes and diethylzinc to form (*S*)-1-aryl-1-propanol. This auxiliary-mediated alkylation reaction was selected for our preliminary evaluation of cross-link efficacy in an enantioselective transformation because it competes with ligand-unassisted con-

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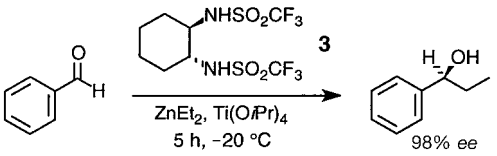
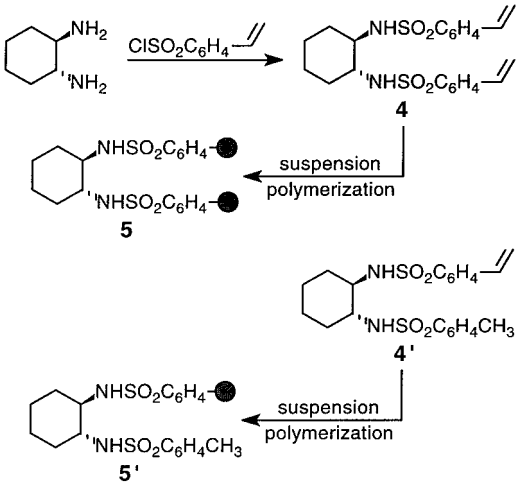


Scheme 1. Example for the enantioselective alkylation of aldehydes in toluene with disulfonamide **3** (1 mol%) as auxiliary.

version (i.e., formation of racemic product). Therefore, the objectives of this study were to place a chiral disulfonamide ligand at the cross-link of a polystyrene resin and to demonstrate that this ligand can successfully mediate enantioselective reductive alkylation of aldehydes in competition with ligand-unassisted conversion.

Disulfonamide **4** was readily prepared in 71% yield by the reaction of (*R*,*R*)-1,2-cyclohexanediamine[11] with styrenesulfonyl chloride[12] (CH_2Cl_2, 2 h, 0 °C). Subsequent copolymerization[13] of **4** with styrene afforded resin **5**, which is capable



of swelling, as beads, which were sorted with a series of macroporous filters of differing mesh size. Of course, the cross-link density of resin **5** can be manipulated by varying the ratio of monomers employed in the suspension copolymerization. For these studies we prepared **5** with cross-link densities from 0.25 to 2.5 mol% (this required a ratio of disulfonamide monomer to styrene of 1 to 10 wt%). Elemental analysis (C, H, N, S) was used to calculate the resin loading after copolymerization, which allowed us to submit the required amount of disulfonamide auxiliary (1–2 mol%) to the reaction.

In a control experiment, we first investigated the enantioselectivity of monomer **4** in the reaction of aromatic aldehydes and diethylzinc to form (*S*)-1-aryl-1-propanol. We were pleased to find that this auxiliary was as effective as triflate **3** (Table 1, compare entries 1–3 with 4–6). A significant difference between **3** and **4** is that the latter requires longer reaction times (5 h with **3** versus 24 h with **4**). This is probably due to the decreased Lewis acidity of the active Ti species derived from **4** compared to that derived from **3**.

With these results in hand, we turned to studying resin **5** as auxiliary for the same reaction. We were initially concerned that reagent transport to the polymeric active site, a requirement for resin-based disulfonamide, would fail to successfully compete with a ligand-unassisted reaction[11] of ArCHO with $ZnEt_2$/Ti(O*i*Pr)$_4$ and lead to products with low *ee* values. This problem was addressed by choosing a solvent which would swell the polymer sufficiently for reaction to take place. The measured swelling of **5** in toluene was more than four times the nonswollen volume. We later found that the use of nonswelling solvents such as hexane under identical reaction conditions gave products in low yields. It is precisely this swelling capacity in toluene that allowed for resin-bound reactions to occur at reasonable catalyzed rates. As presented in Table 1, resin **5** delivers (*S*)-1-aryl-1-propanol with *ee* values which nearly match those of solution reagents **3** or **4**. An advantage of resin-bound **5** is the ease of removal by simple filtration. This also allows for catalyst recycling; however, with 1–2 mol% catalyst, yields diminish from 82% with fresh catalyst down to about 60% with recycled catalyst.

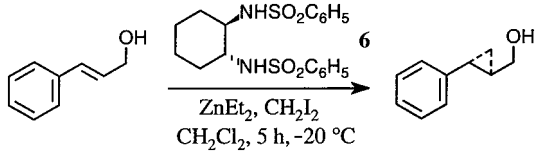
Table 1. Results of reactions with aldehydes RCHO according to Scheme 1.

Entry	R	Auxiliary[a]	Yield [%]	*ee* [%][b]
1	C_6H_5	**3**	98	98[c]
2	$C_6H_5CH{=}CH$	**3**	98	85–99[c, d]
3	*p*-ClC_6H_4	**3**	95	98
4	C_6H_5	**4**	96	98
5	$C_6H_5CH{=}CH$	**4**	98	70
6	*p*-ClC_6H_4	**4**	92	85
7	C_6H_5	**5**	82	98
8	$C_6H_5CH{=}CH$	**5**	80	63
9	*p*-ClC_6H_4	**5**	85	83
10	*p*-$MeOC_6H_4$	**5**	75	70
11	*o*-ClC_6H_4	**5**	85	56
12	*p*-MeC_6H_4	**5**	71	56
13	C_6H_5	**5′**	73	93

[a] 1–2 mol%. [b] Determined by ^{19}F NMR spectroscopy of Mosher's ester. [c] Ref. [10]. [d] With more than 1.2 equiv of diethylzinc, the *ee* values increased significantly.

In light of our results with **4** and **5**, we were not surprised that pendant ligand **5′** (prepared by suspension copolymerization of **4′**) also effectively mediates the reaction of aromatic aldehydes with diethylzinc to form (*S*)-1-phenyl-1-propanol. A comparison of cross-linked ligand **5** (Table 1, entry 7) and pendant ligand **5′** (entry 13) estabishes that the accessibility to cross-linked sites in this transformation is not compromised for **5**.

Solid-phase **5** also has applications in other enantioselective chemical transformations; for example, the cyclopropanation of allyl alcohols. Kobayashi et al.[14] reported that disulfonamide **6** catalyzes the cyclopropanation of cinnamyl alcohol with 65% *ee* (Scheme 2). The enantioselec-



Scheme 2. Example for enantioselective cyclopropanation with **6** (10 mol%) as catalyst.

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tivity obtained with **5** parallels solution-phase results (Table 2, compare entry 3 with entries 1 and 2).[15] Again, the enantioselectivity of this transformation is compromised by effective

Table 2. Results of the cyclopropanation according to Scheme 2.

Entry	Disulfonamide[a]	Yield [%]	*ee* [%][b]
1	**4**	70	65
2	**5**	68	65
3	**6**	75	68[c]

[a] 10 mol%. [b] Determined by ^{19}F NMR spectroscopy of Mosher's ester. [c] Ref. [16].

competition of the ligand-unassisted reaction. As with other cyclopropanation studies,[16] lower temperatures do not increase the enantioselectivities (at $-78\,^{\circ}C$ the *ee* was still 65%). When a larger molar amount of resin catalyst was used (20 mol%), the yield improved to 90%, and enantioselectivities increased to 70% *ee*.

In conclusion, suspension copolymerization of the bis-styryl monomer **4** and styrene delivers cross-link-functionalized resin **5**, whose loadings are controlled by reagent stoichiometry. The solid-phase catalyst **5** effectively mediates the reductive alkylation of aryl aldehydes and the cyclopropanation of cinnamyl alcohol.

Experimental Section

Copolymerization: Water (100 mL) and gum arabic (6.0 g) were placed in a 200-mL Morton flask and stirred rapidly under N_2 at $75\,^{\circ}C$ for 30 min using a metal rotor to afford a homogenous mixture. Chlorobenzene (10 g), styrene (9 g), **4** (1 g), and benzoyl peroxide (0.15 g) were added, and the mixture was stirred such that very small suspended organic droplets formed ($600\ U\,min^{-1}$). After 30 min a stabilizer (Al_2O_3, 0.1 g) was added to avoid bead aggregation. After an additional 2 h the stirring rate was reduced dramatically ($130\ U\,min^{-1}$) to avoid bead sheering, and stirring was continued at $75\,^{\circ}C$ for another 16 h. The polymerization was halted by adding 1M HCl, the mixture washed with THF, and the polymer recovered by filtration. Approximately 75% of the material was collected by filtration; 25% was unrecoverable. However, 85% of the remaining beads had a diameter between 70 and 250 μm, which is suitable for solid supports (when compared with commercially available resins). With this method, the bead size could be reduced further by increasing the ratio of aqueous to organic phase and increasing the stirring rate with minimal effect on yield and bead shape. This is an attractive advantage considering reaction rates are often dependent on the diffusion of the reagents (the rate increased with smaller bead size).

Typical procedure for the reductive alkylation of aldehydes: To disulfonamide **5**, swollen in toluene, was added $Ti(O\mathit{i}Pr)_4$ (1.2 equiv). The mixture was heated at reflux for 30 min and cooled to $-70\,^{\circ}C$, and $ZnEt_2$ (1M in hexanes, 1.2 equiv) added slowly. At this point, an orange (not a yellow) color indicated catalyst activation. Without this color change, yields were often poor. Benzaldehyde was added, and the mixture stirred at -70 °C for an additional 5–24 h. The reaction was quenched with 1M HCl, the polymer removed by filtration, and the alcohol isolated by flash chromatography (silica gel, EtOAc/hexanes 1/3) after extraction with an organic solvent.

Cyclopropanation of cinnamyl alcohol: To disulfonamide **5**, swollen in CH_2Cl_2, was added $ZnEt_2$ (1M in hexanes, 2 equiv) and CH_2I_2 (3 equiv) at $-70\,^{\circ}C$, and the mixture was stirred for 1 h. Cinnamyl alcohol was added, and the reaction allowed to slowly warm to room temperature over 24 h. The reaction was quenched with 1M NaOH, the polymer collected by filtration, and the alcohol isolated by flash chromatography (silica gel, EtOAc/hexanes 1/4) after extraction with an organic solvent.

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