Polymer-supported proline-decorated dendrons: dendritic effect in asymmetric aldol reaction†

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The yield and enantioselectivity of an asymmetric aldol reaction, catalyzed by a proline derivative immobilized on polystyrene *via* dipolar cycloaddition, are remarkably improved by the dendronization of the support.

Among heterogeneous dendritic catalytic systems reported over the past few years, most were assembled on dendritic templates, prepared stepwise *via* solid-phase synthesis on insoluble organic or inorganic supports.[1] As we earlier demonstrated, some of these systems exhibit positive dendritic effects on activity and chemoselectivity.[2] Reduced cross linking upon coordination of the ligands to a metal center and differences in population of metal species on the dendronized support were postulated as major reasons for the effects. Since all known supported dendritic catalytic systems involve an active organometallic catalyst or reagent, the question must be asked, whether in the absence of factors related to metal coordination, the dendritic interface affects the polymer-supported catalysis. To address this subject, we decided to study a supported dendritic asymmetric organocatalytic system. Such systems have never been prepared or explored.[3] Moreover, a positive dendritic effect on the enantioselectivity has, thus far, been observed in heterogeneous catalysis only for the addition of diethylzinc to benzaldehyde.[4]

L-proline, a natural amino acid, is one of the most prominent organocatalysts. This catalyst rendered high yields and enantioselectivities in Michael addition, Robinson annulation and a variety of α-substitutions of aldehydes and ketones, particularly the aldol reaction.[5] Although the chemistry of L-proline in solution is being intensively investigated, only a limited number of heterogeneous proline-based catalysts have thus far been reported.[6] Mostly, these are proline-containing peptides catalyzing the aldol reaction of acetone and aromatic aldehydes,[6a–c] which are dependent on an acidic OH bond of the nearby amino acid or Lewis acid additive in order to ensure high enantioselectivity. Only a moderate ee was reported for the aldol reaction of aliphatic aldehydes with acetone catalyzed by proline directly tethered to a support through the carboxylate.[6e] Hydroxyproline is an attractive building block for proline-like catalysts, as its immobilization *via* the hydroxy group leaves the amine and carboxylate functions available for catalysis. Such an approach recently led to the preparation of a homogeneous dendritic organocatalyst.[7] Surprisingly, a single publication in 1985 describing a moderate-yield and low-selectivity catalyst for the Hajos–Parrish reaction remained the only example of such a mode of immobilization until very recently,[8a] when a few examples of immobilized hydroxyproline-derived catalysts were communicated.[8b–d]

Herein we report the preparation of non-peptidic hydroxyproline-based catalysts on dendronized supports and their exploration in an asymmetric aldol reaction. Polystyrene-bound poly(aryl benzyl ether) dendrons were exploited in this study (*e.g.* second generation dendron in Fig. 1).[9]

To our disappointment, all attempts to immobilize the unprotected or protected (2*S*,4*R*)-4-hydroxyproline *via* the hydroxy function on benzyl halide-terminated supports failed or led to low yield/purity products. Consequently, we adopted the Sharpless procedure of the Huisgen azide–alkyne dipolar cycloaddition as the strategy for immobilization of the catalytic units.[10] For this purpose, the methyl ester of the hydroxyproline (**1**) was protected with trityl and reacted with propargyl bromide, forming the methyl ester of (2*S*,4*R*)-*O*-propargyl-*N*-trityl-4-hydroxyproline (**3**, Scheme 1).[11] The polymer-bound benzylic halides (Wang Bromo polystyrene and chloromethyl-terminated first to third generation resins, **Gn(Cl)**) were converted to benzyl azide resins **Gn(N$_3$)** (n = 0–3, Scheme 2), and thereafter cleanly reacted with **3** to form the cycloaddition product **Gn(Tr-Pro-OMe)**.[12] A quantitative two-step conversion was achieved for all resins and the products were characterized by gel-phase ^{13}C NMR on the resin and by ^{1}H, ^{13}C NMR and MS in solution, following acidolytic cleavage.‡ The deprotection of the proline units was carried out with a 0.2% TFA solution in DCM (trityl deprotection) and LiOH

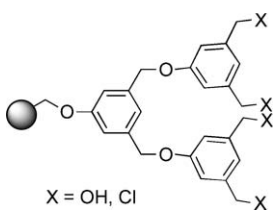
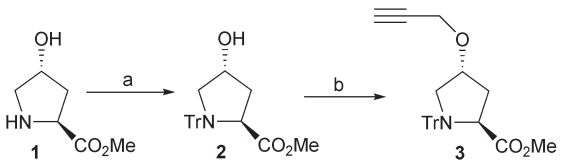


Fig. 1 Supported second generation polyether dendron (G2(X)).



Scheme 1 *Reagents and conditions*: (a) TrBr, Et$_3$N, DCM, rt, 2 h; (b) NaH, propargyl bromide, THF, 60 °C, 4 h.

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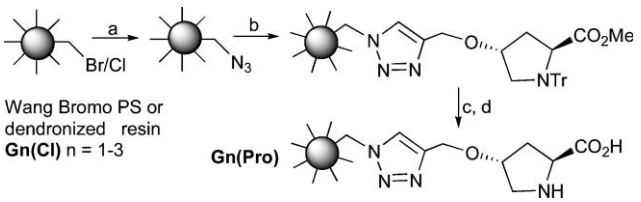
† Electronic supplementary information (ESI) available: General experimental conditions, synthesis of **3** and a typical catalytic procedure. See DOI: 10.1039/b703016a

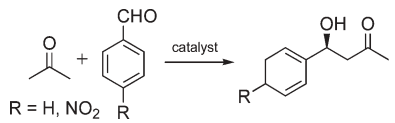


Scheme 2 *Reagents and conditions*: (a) NaN_3, TBAI, DMF, 60 °C, 24 h; (b) **3**, sodium ascorbate, $CuSO_4$, DMF, 50 °C, on; (c) 0.2% TFA in DCM, rt, 5 min; d) LiOH, THF–H_2O, 40 °C, 4 h.

in THF–H_2O (methyl ester hydrolysis), releasing the amine and carboxylate functions and forming the catalytic resins **Gn(Pro)**.§ Importantly, the ^{13}C NMR demonstrated that the proline units are diastereomerically pure, thus negating the possibility of the α-carbon epimerization during the deprotection steps.

The asymmetric transformation chosen to evaluate the dendritic catalysts is the aldol reaction, particularly the reactions of benzaldehyde and 4-nitrobenzaldehyde with acetone, investigated previously with proline catalysts in solution. When carried out in DMSO at room temperature, these reactions revealed a remarkable influence of the dendronization on the conversion, yield and enantioselectivity (Scheme 3, Table 1). For benzaldehyde, quantitative conversion and satisfying yield (58%) are achieved in 4 days with the 2nd generation catalyst as compared with the low yield and conversion (34% and 42% respectively) of the non-dendritic analogue. Moreover, the enantiomeric excess, induced by the non-dendritic **G0(Pro)**, is only 27% while, for the dendritic catalyst, it reaches 68%. For 4-nitrobenzaldehyde, the dendronization also positively affects the reaction outcome with a remarkable increase in ee (85% *vs.* 47%). Notably the enantioselectivity with **G1(Pro)** and **G2(Pro)** is higher than that achieved in solution with L-proline.[13]

For the second series of experiments, we broadened the set of catalysts under investigation, to include the third generation catalyst **G3(Pro)** and the mono-proline linear-spacer analogues of the first and second generation catalysts, **G1(mono-Pro)** and **G2(mono-Pro)** (Scheme 4). The experiments focused on benzaldehyde, a more challenging substrate for the aldol reaction, and examined also the efficiency of the catalyst recycling, while the single run time was increased to 9 days (Table 2). From this series of experiments, it is evident that the activity, upon recycling of the catalyst, is negatively affected by the dendronization. While **G0(Pro)** can be recycled several times, the conversion and yield upon recycling of **G1(Pro)**, **G2(Pro)** and **G3(Pro)** decrease significantly. Remarkably, the enantioselectivity is practically unaffected by the recycling. These findings point to decomposition of the catalyst as a cause of reduced activity upon recycling. A similar effect (though to a lesser extent) was observed in other



Scheme 3 The model reaction.

Table 1 The model aldol reaction with polymer-bound proline[a]

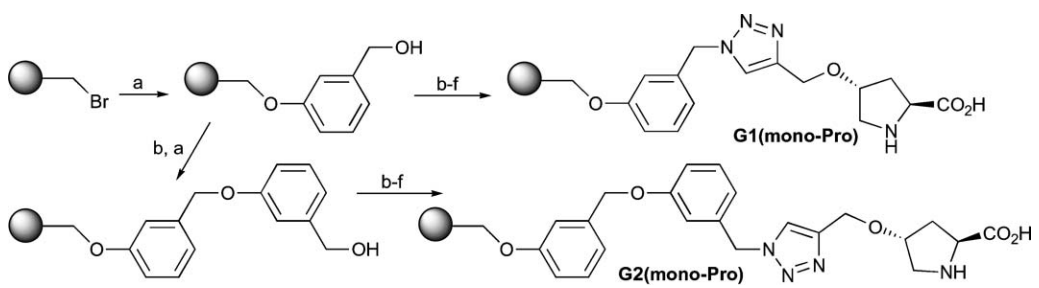
Catalyst	R	Conversion[b] (%)	Yield[b] (%)	ee[c] (%)
G0(Pro)	H	42	34	27
G1(Pro)	H	73	52(49)	68
G2(Pro)	H	100	58	68
G0(Pro)	NO_2	88	87	47
G1(Pro)	NO_2	100	95	85
G2(Pro)	NO_2	100	90	84

[a] *Reaction conditions*: 1 equiv. of aldehyde, 27 equiv. of acetone in DMSO (4 mL of DMSO per 1 mL of acetone), 0.3 equiv. of polymer-bound proline, 4 d, rt. [b] Conversions and yields determined by NMR, isolated yield in parentheses. [c] ee determined by HPLC.

Table 2 The catalytic experiments with an expanded set of catalysts[a]

Catalyst	Cycle	Conversion[b] (%)	Yield[b] (%)	ee[c] (%)
G0(Pro)	1	46	34	29
G0(Pro)	2	44	31	32
G0(Pro)	3	45	32	32
G1(Pro)	1	96	50	68
G1(Pro)	2	71	49	72
G1(Pro)	3	47	38	72
G2(Pro)	1	100	58(55)	67
G2(Pro)	2	38	25	64
G2(Pro)	3	37	15	66
G3(Pro)	1	100	35(32)	71
G3(Pro)	2	38	25	72
G3(Pro)	3	12	6	nd[d]
G1(mono-Pro)	1	61	36(34)	27
G1(mono-Pro)	2	46	32	32
G1(mono-Pro)	3	42	34	31
G2(mono-Pro)	1	69	35	24

[a] *Reaction conditions*: 1 equiv. of aldehyde, 27 equiv. of acetone in DMSO (4 mL of DMSO per 1 mL of acetone), 0.3 equiv. of polymer-bound proline, 9 d, rt. [b] Conversions and yields determined by NMR, isolated yields in parentheses. [c] ee determined by HPLC. [d] nd = not determined.



Scheme 4 *Reagents and conditions*: (a) 3-hydroxybenzyl alcohol, LiH, TBAI, DMF, 60 °C, on; (b) PPh_3, C_2Cl_6, THF, rt, on; (c) NaN_3, TBAI, DMF, 60 °C, 24 h; (d) **3**, sodium ascorbate, $CuSO_4$, DMF, 50 °C, on; (e) 0.2% TFA in DCM, rt, 5 min; (f) LiOH, THF–H_2O, 40 °C, 4 h.

studies with catalysts derived from proline immobilized on solid and soluble polymers.[6a,14] It seems that although the catalytic activity of proline units is boosted by the dendronization, so are the rates of unwanted reactions leading to their decomposition. It is likely that for higher generation catalysts (**G3**, or even **G2**) the deactivation/decomposition of the proline units already takes its toll on the aldol reaction outcome during the first run. Thus the optimal performance of the catalyst is observed for the first- or second-generation constructs. Elaborating the dendritic structure to the third generation is counter-productive as, in addition to the increased difficulty of preparation, the performance deteriorates.

To better understand the factors behind the dendritic effects, we designed **G1(mono-Pro)** and **G2(mono-Pro)**, with linear spacer imitations of the dendritic first- and second-generation spacers (Scheme 4). These catalysts provided only moderate conversion, low yield and low enantioselectivity (similar to the performance of **G0(Pro)**). These results demonstrate that the effects are not the reflection of the lengthening of the tether between the proline and the polymer, but are caused by the dendritic branched architecture of the spacer itself. The lack of further improvement in ee beyond **G1(Pro)** hints at the proximity of two proline moieties in the terminal units as the source of the effect, though additional influences of the dendritic architecture of the spacer on the enantioselectivity can not be ruled out.

In conclusion, we applied a new mode of immobilization of proline-based catalysts to the regular and dendronized polymeric supports. We demonstrated the remarkable positive influence of the dendritic spacers on the aldol reaction with these catalysts, where first and second generation catalysts exhibited yields and enantioselectivities comparable to or even exceeding those obtained with proline in solution. Using the model catalysts with the linear spacers, we proved that not the length of the spacer, but its dendritic/branched nature is important for the increase in the activity and selectivity of the systems. Additional experiments, aimed at the understanding of the mechanism of the dendritic effect and the improvement of the recyclability of the catalyst, are underway.

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Notes and references

‡ Typical procedure for preparation of **Gn(Tr-Pro-OMe)**: *Synthesis of **G1(Tr-Pro-OMe)***. 0.5 M solution of sodium azide (0.86 g, 13.2 mmol, 20 equiv., 0.5 M in DMF) and TBAI (1.43 g, 4.0 mmol, 6 equiv.) were added to a suspension of the resin **G1(Cl)** (1.0 g, 0.66 mmol, 0.66 mmol/g) in DMF (10 mL). The suspension was heated to 60 °C for 24 h. The resin was washed with water, DMF–water, DMF, THF–water, THF, DCM, dried under vacuum and suspended in DMF (10 mL). Then **3** (2.76 g, 6.5 mmol, 10 equiv.), sodium ascorbate (0.25 g, 1.3 mmol, 2 equiv., 1 M in DMF) and copper(II) sulfate pentahydrate (84 mg, 0.32 mmol, 0.5 equiv.) were added to the suspension. The suspension was heated to 50 °C overnight. The resin was washed with DMF–water, DMF, THF–water, THF, DCM and then dried under vacuum. Yield > 99%, loading 0.42 mmol/g. Partial gel-phase ^{13}C NMR (100 MHz, C_6D_6): δ 175.5, 145.0, 143.7, 129.3, 126.1, 122.2, 114.7, 77.4, 69.4, 63.1, 60.9, 53.5, 52.6, 50.8, 36.4. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$–TFA 1 : 1): δ 9.06 (br s, 1H); 8.28 (t, J = 7.5 Hz, 6H); 8.23 (s, 2H); 7.89 (t, J = 7.6 Hz, 12H); 7.69 (d, J = 7.2 Hz, 12H); 7.06 (s, 1H); 7.00 (s, 2H); 5.64 (s, 4H); 4.81 (m, 6H); 4.58 (m, 2H); 3.87 (m, 8H); 3.63 (m, 2H); 2.77 (m, 2H); 2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$–TFA 1 : 1): δ 211.3 (Tr^+), 169.6, 156.7, 143.7 (Tr^+), 142.4 (Tr^+), 140.1, 139.8 (Tr^+), 133.6, 130.7 (Tr^+), 126.0, 121.7, 117.8, 78.5, 59.2, 58.7, 56.7, 54.3, 52.0, 33.9; MS (FAB): Calcd. for $C_{26}H_{35}N_8O_7$ ((M − 2Tr + 3H)$^+$) 571.2, found 571.2.

§ Typical procedure for deprotection: *Synthesis of **G1(Pro)***. The resin **G1(Tr-Pro-OMe)** (1.0 g, 0.42 mmol, 0.42 mmol/g) was washed 3 times for 5 minutes with 10 mL of a solution of 0.2% TFA, 1% H_2O and 1% triisopropylsilane in DCM and then dried under vacuum. Lithium hydroxide (0.12 g, 5.0 mmol, 10 equiv.) was dissolved in 10 ml THF–H_2O (10 : 1) and added to a suspension of the resin in THF (10 mL). The suspension was heated to 40 °C for 4 h. The resin was washed with THF–H_2O, THF, DCM and then dried under vacuum. Conversion > 99%, yield 65%, loading 0.32 mmol/g. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$–TFA 1 : 1): δ 9.24 (br s, 1H); 8.28 (s, 2H); 7.72 (s, 2H); 7.08 (s, 1H); 7.02 (s, 2H); 5.67 (s, 4H); 4.86 (m, 6H); 4.66 (m, 2H); 3.91 (m, 2H); 3.67 (m, 2H); 2.88 (m, 2H); 2.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$–TFA 1 : 1): δ 172.2, 156.7, 140.4, 133.6, 126.0, 121.8, 117.8, 78.5, 59.3, 58.5, 56.7, 52.0, 34.0; MS (FAB): Calcd. for $C_{24}H_{30}N_8O_7Li$ (MLi^+) 549.2, found 549.2.

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