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Elucidation of Architectural Requirements from a Spacer in Supported Proline-Based Catalysts of Enantioselective Aldol Reaction

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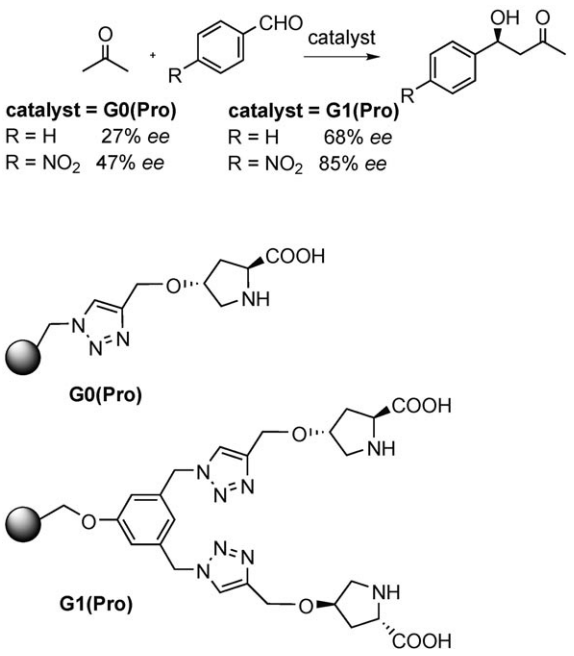
Abstract: In order to delineate the properties of the spacer architecture responsible for the strong positive dendritic effect exhibited by polymer-supported proline-based catalysts, we prepared two series of polystyrene-bound model catalysts. The first series was based on a linear and partially dendritic spacers (of reduced branching and valency) imitating the length of the second generation spacer, while the second series was based on the first generation dendron spacer with one functional (proline-terminated) and one non-functional arm. Comparative studies of the model and original (fully dendritic) catalysts in the asymmetric aldol reaction of aromatic aldehydes with acetone disclose the features characteristic to the dendritic architecture, such as proximity between the terminal catalytic units and enhanced branching, as crucial for inducing higher yield and enantioselectivity in catalysis.

Keywords: aldol reaction; asymmetric organocatalysis; dendrimers; solid-phase synthesis; supported catalysts

Over the past years a growing number of studies in the field of asymmetric catalysis were devoted to organic catalysts, metal-free small molecules, capable of promoting chemical transformation with high efficiency and enantioselectivity.[1] Although heterogenized catalysts benefit from a number of economic, environmental and technical advantages as compared to their homogeneous analogues, reports of successful immobilization of enantioselective organocatalysts on solid supports remain relatively scarce.[2] L-Proline provides an excellent model for organocatalyst immobilization studies due to its simplicity and the ready availability of various derivates,[3] in spite of a question mark on the economic profitability of developing a successful immobilized proline catalyst because of the low price of this amino acid and the possibility of its easy recovery from homogeneous reaction mixtures. Moreover, immobilization frequently provides catalysts with an altered reactivity profile and can indirectly afford valuable mechanistic information. In earlier studies, unfortunately, the immobilization of proline led to reduced selectivity,[4] and only recently have a limited number of covalently heterogenized proline-based catalysts, exhibiting enantioselectivity approaching that of their soluble analogues, been reported.[5] While these catalysts demonstrated excellent results in the aldol reactions with cyclic ketones, only a few supported proline-containing peptides could match the performance of proline in the reaction with acetone.[5a–c]

Recently, we observed that the introduction of a short dendritic spacer between the polymer core and the 4-hydroxyproline-derived catalytic units immobilized *via* azide-alkyne "click" chemistry provides a more active and remarkably more enantioselective catalyst, as compared to the spacer-less non-dendritic analogue. (Scheme 1).[6]

Although this was an extraordinary manifestation of a positive dendritic effect, the first of its kind in supported organocatalysis,[7] the question of the possible origin of the effect remains unresolved. Positive dendritic effects were observed in the past in supported organometallic catalysis, but their possible explanations were based (in those cases discussed) on the proximity and cooperativity of the ligating sites in the metal *coordination* events, but not on cooperative interaction of two ligands or complexes with the substrates.[8] In the case of organocatalysts such as proline, however, it is tempting to suggest cooperative action of two proximal proline units on the substrates, in order to explain the aforementioned effect.

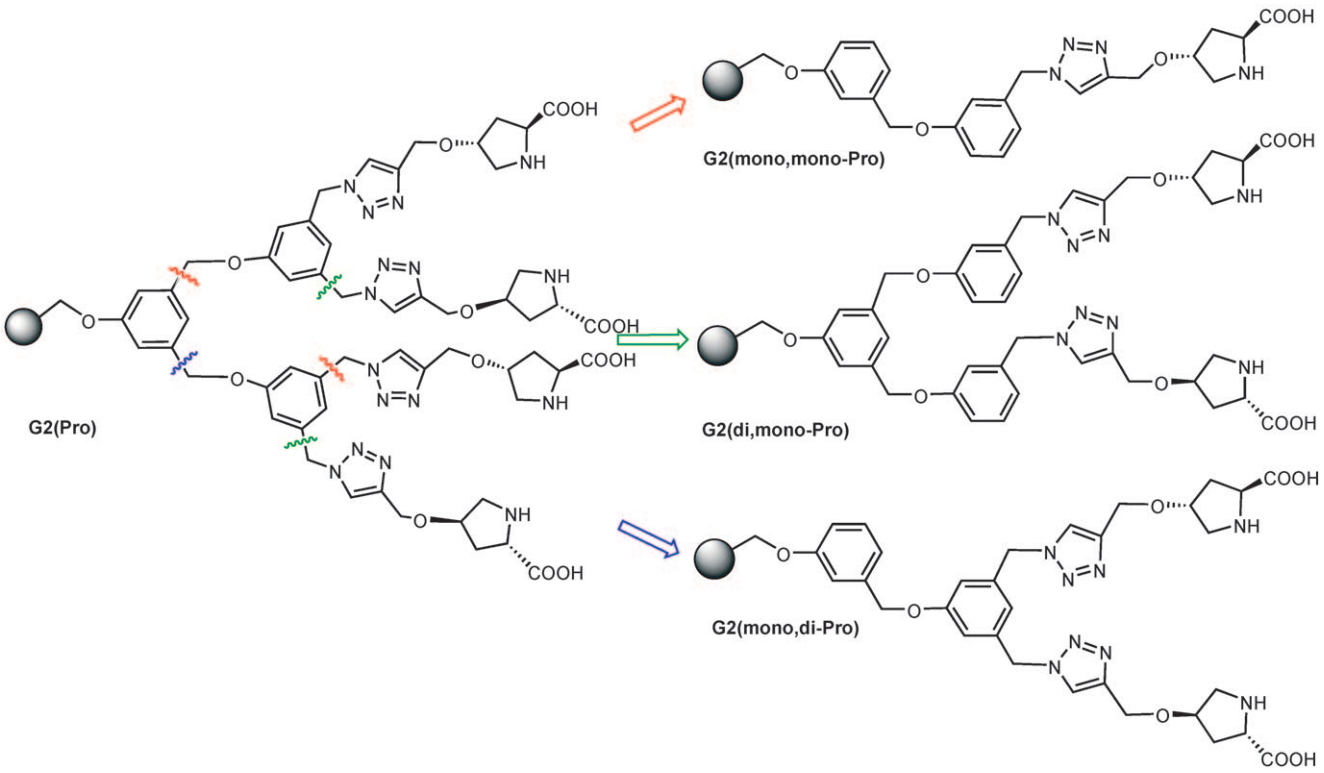


Scheme 1. Asymmetric aldol reaction with immobilized hydroxyproline-derived catalysts.[6]

On the other hand, over the years unequivocal experimental evidence was disclosed, supported by theoretical study, for a unimolecular mechanism of the proline catalysis of the aldol reaction.[9,10] It was demonstrated, particularly by List and Houk and Barbas, that in solution only one proline molecule is associated with the substrates, intermediates and product along the catalytic cycle.[9] Moreover, it was recently demonstrated that all earlier reports claiming nonlinear effects in this reaction, originate from the nonhomogeneity of the reaction mixture with the proline catalyst being in equilibrium between the solution and solid phases.[11]

In the light of these reports, we wondered whether the dendritic effect, which we had observed, was due to the alternative bimolecular catalytic mechanism, operative in supported catalysis only and benefiting from the bi- or multi-valency of the dendritic spacers, or whether it was a result of the other properties of the dendritic architecture of the spacer and the mechanism of the catalysis is solely unimolecular. In this manuscript we describe the synthesis of model proline-based supported catalysts incorporating linear, dendritic and partially dendritic spacers and the comparative catalytic study of these systems with the previously reported dendritic analogues, which may shed light on the question presented above.

While in the previous communication we reported the synthesis of a linear analogue of the G1 catalyst, herein we focus on analogues of the G2 catalytic dendron. Possible modes of dendritic arm truncation are depicted in Scheme 2. Truncation of one of the lower branches (shown in green) leads to the structure



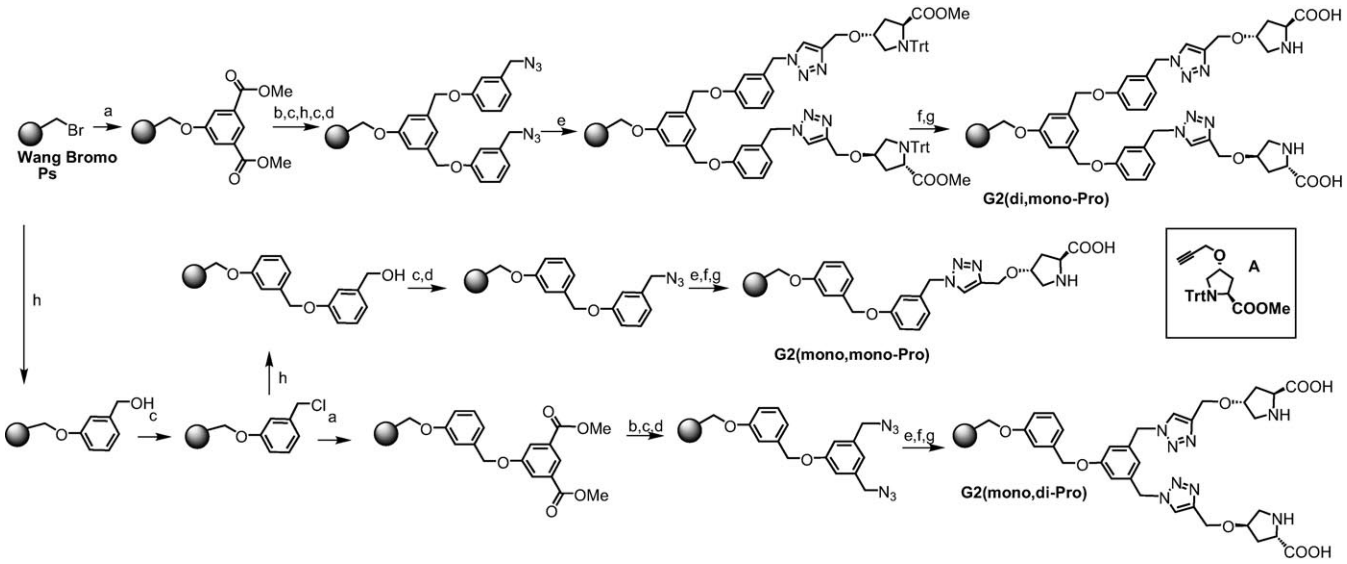
Scheme 2. Truncated spacer models of the G2 catalyst.

G2(mono,di-Pro), which preserves the mutual positions of the proline units (particularly the through-bonds distance), but reduces the branching in the dendritic spacer (the branched/linear unit ratio). Truncation of two upper branches (shown in red) leads to the structure **G2(di,mono-Pro)**, which preserves a certain proximity between the two remaining proline units, but is likely to increase the average distance between them, while reducing again the branching of the spacer. Truncation of all branches but one (shown in blue) leads to a linear-spacer catalyst **G2(mono, mono-Pro)**.

The synthesis of the three truncated spacers is depicted in Scheme 3. As in the case of the perfect dendritic structures, the branching units of the spacers were derived from dimethyl-5-hydroxyisophthalate building block, which is immobilized *via* nucleophilic substitution and activated by a reduction-chlorodehydroxylation sequence.[12] The linear units were derived from 3-hydroxybenzyl alcohol, which was immobilized *via* nucleophilic substitution and activated by a chlorodehydroxylation reaction. The preparation of the azide-terminated spacers and the propargyl-carrying protected hydroxyproline as well as the cycloaddition and deprotection reactions, leading to the active supported catalytic systems, were carried out by procedures used for the perfect dendrons without substantial changes.[6]

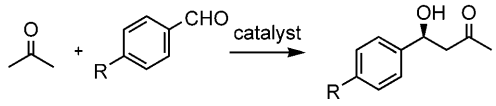
The three new supported catalytic systems were tested in the aldol addition reaction of acetone to benzaldehyde or 4-nitrobenzaldehyde and compared to the previously obtained catalysts (Table 1). The trend in the G2 series (entries 3–6 and 9–12) very clearly points out that proximity between two proline moieties is critical for achieving higher yield and enantioselectivity. The *ee* sharply decreases as we proceed from the bivalent structures [**G2(mono,di-Pro)**, **G2(di,mono-Pro)**] to the monovalent catalyst **G2(mono,mono-Pro)**. For the bivalent structures a shorter average distance between the proline units is clearly preferred [**G2(mono,di-Pro)** *vs.* **G2(di,mono-Pro)**]. While it would be difficult to estimate this distance due to the many degrees of freedom in the structures, it is clear that the through-bonds distance between the proline units will be the major contributing factor to the distance parameter. Thus, in **G2(mono,di-Pro)** (as well as in all fully dendritic structures) there are 16 covalent bonds connecting the two proline units. This must lead to a much shorter through-space separation of the units than in the case of **G2(di,mono-Pro)** with 26 covalent bonds separating the two proline units. Formally, even **G2(mono,mono-Pro)**, **G1(mono-Pro)** and **G0(Pro)** can be considered "multivalent" catalysts, since proline units in these polymers are covalently connected to the common polystyrene matrix. However, in these resins the amount of the bonds separating the prolines is much higher even in the optimal case: 56, 46 and 36 bonds, respectively, and only if the linkers are attached to the neighboring repeating units of the polystyrene chain. On average the "separating bond count" for these catalysts will be significantly higher, and thus, their multivalency is purely fictional.

One can erroneously conclude that the tetravalent **G2(Pro)** is preferred over the bivalent catalyst. However, the comparison with the **G1** series points out



Scheme 3. Synthesis of the G2 catalyst models. *Reagents and conditions:* a) dimethyl 5-hydroxyisophthalate, LiH, TBAI, DMF, 60 °C, overnight; b) $LiBH_4$, $B(OMe)_3$, THF, 60 °C, overnight; c) PPh_3, C_2Cl_6, THF, room temperature, overnight; d) NaN_3, TBAI, DMF, 60 °C, 24 h; e) **A**, sodium ascorbate, $CuSO_4$, DMF, 50 °C, overnight; f) 0.2% TFA in DCM, room temperature, 5 min; g) LiOH, THF/H_2O, 40 °C, 4 h; h) 3-hydroxybenzyl alcohol, LiH, TBAI, DMF, 60 °C, overnight.

Table 1. Aldol reaction with G1 and G2 catalysts incorporating dendritic, partially dendritic and linear spacers.[a]



Entry	Catalyst	R	Conversion [%]	Yield [%][b]	*ee* [%][c]
1	**G1(Pro)**	**H**	**73**	**52**	**68**
2	G1(mono-Pro)	H	61	36	28
3	**G2(Pro)**	**H**	**100**	**58**	**68**
4	G2(mono,di-Pro)	H	100	44	56
5	G2(di,mono-Pro)	H	100	43	45
6	G2(mono,mono-Pro)	H	69	35	24
7	**G1(Pro)**	**NO_2**	**100**	**95**	**85**
8	G1(mono-Pro)	NO_2	91	79	23
9	**G2(Pro)**	**NO_2**	**100**	**94**	**84**
10	G2(mono,di-Pro)	NO_2	100	95	61
11	G2(di,mono-Pro)	NO_2	100	94	51
12	G2(mono,mono-Pro)	NO_2	71	71	25

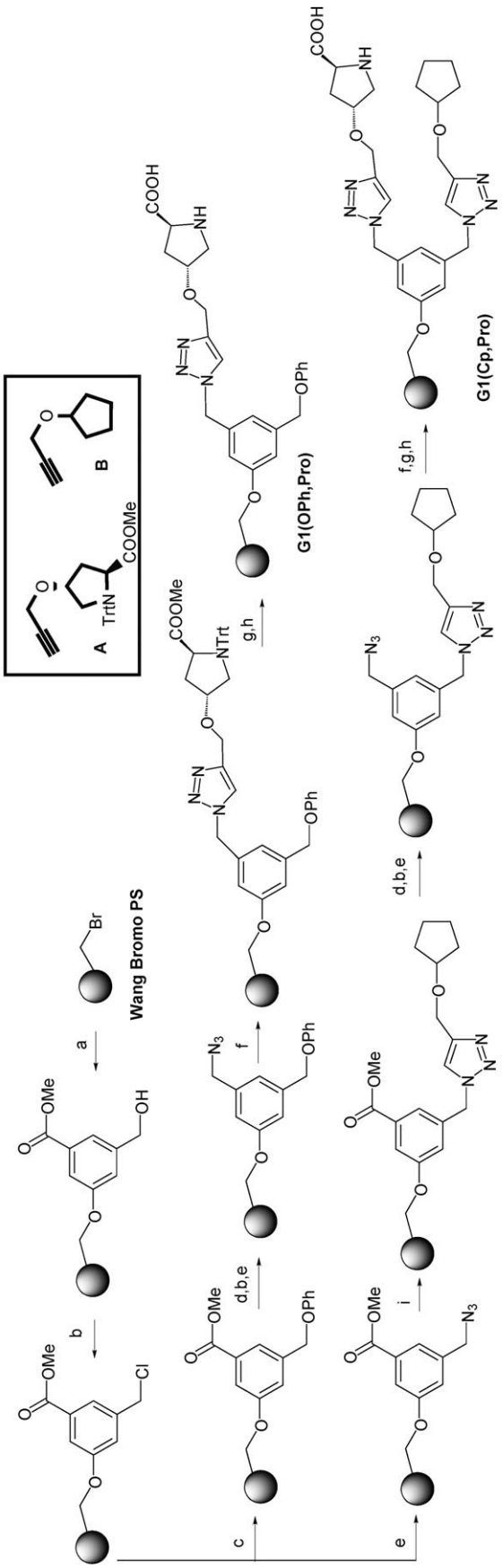
[a] *Reaction conditions:* 1 equiv. of benzaldehyde/4-nitrobenzaldehyde, 27 equiv. of acetone and 0.3 equiv. of catalyst in DMSO for 4 days at room temperature.
[b] NMR yield.
[c] The *ee* was determined by HPLC, using Chiralpak AD (R = H) or Chiralcel OJ ($R = NO_2$) columns.

that the differences between **G2(Pro)** and **G2(mono,di-Pro)** are due to the reduced branching/increased flexibility of the spacer, since **G1(Pro)**, which is bivalent, is almost as good as **G2(Pro)**. The deterioration in the performance upon reduction of the "branching per length unit" parameter of the spacer is further evidenced by comparison of **G2(mono, mono-Pro)** to **G1(mono-Pro)** in the benzaldehyde reaction (entries 2 and 6).

Having established these trends, we decided to prepare two additional **G1**-analogues, which preserve the branching nature of the spacer, but contain only one proline-functionalized arm, while the other arm lacks the proline unit or any other nucleophilic or acidic site (Scheme 4). Both structures were based on the methyl 3-hydroxy-5-hydroxymethylbenzoate heterofunctional branching unit that was immobilized on Wang Bromo polystyrene *via* nucleophilic substitution (similar to the other phenolic modules used in the synthesis of perfect or truncated dendrons, *vide supra*). Then the non-functional arm was assembled first *via* chlorodehydroxylation-phenoxydechlorination or chlorodehydroxylation-azidodechlorination "click" cycloaddition chemistry. Once the non-functional arm was in place, the ester was reduced, thus again forming the hydroxymethyl group for the functional arm assembly *via* the five-step sequence as in the preceding synthetic schemes.

The new model catalyst **G1(OPh,Pro)** was only marginally better than **G1(mono-Pro)** (Table 2, entry 3 *vs.* 2). The model **G1(Cp,Pro)** was a somewhat more active and enantioselective catalyst (46% *ee*) in this reaction, but this improvement was achieved at the expense of the catalyst chemoselectivity as a large amount of by-products was formed (Table 2, entry 4). Although the difference between **G1(OPh,Pro)** and **G1(Cp,Pro)** can be explained by the lower steric bulk of the non-functional arm of the former, the influence of the triazole cannot be ruled out.[5f]

From the comparison of these results with those previously obtained it seems that the branching nature of the spacers contributes to the improved selectivity of the dendritic catalysts, but the major contribution comes from the multi- or bivalency of the dendritic catalyst and relative proximity of the proline units. This proximity can potentially be translated into interaction of the units with each other and/or the substrates, possibly through hydrogen bonding. Although at the moment we lack direct proof, indirect support for such interactions can also be provided by a substantial decrease in the dendritic effect in the reaction of benzaldehyde with acetone upon substitution of 15% of DMSO by MeOH, a polar protic solvent, which usually disrupts hydrogen bonding. In this solvent mixture, under conditions otherwise equal to the abovementioned, the dendritic catalysts exhibited lower chemoselectivity (in spite of high aldehyde consumption) as compared to the non-dendritic analogue [yields of 14, 8 and 4% for **G0(Pro)**, **G1(Pro)** and **G2(Pro)** respectively]. Moreover, the improvement in the enantioselectivity due to dendronization was minimal (*ee* of 33, 46, and 34% for 0^{th}- to 2^{nd}-generation catalysts, respectively). Although the change in the reaction media can influence the aldol reaction in many different ways,[13] these findings fall in line with the model studies described above.



Scheme 4. *Reagents and conditions:* a) methyl 3-hydroxy-5-(hydroxymethyl)benzoate, LiH, TBAI, DMF, 60 °C, overnight; b) PPh_3, C_2Cl_6, THF, room temperature, overnight; c) phenol, LiH, TBAI, DMF, 60 °C, overnight; d) $LiBH_4$, $B(OMe)_3$, THF, 60 °C, overnight; e) NaN_3, TBAI, DMF, 60 °C, 24 h; f) **A**, sodium ascorbate, $CuSO_4$, DMF, 50 °C, overnight; g) 0.2% TFA in DCM, room temperature, 5 min; h) LiOH, THF/H_2O, 40 °C, 4 h; i) **B**, sodium ascorbate, $CuSO_4$, DMF, 50 °C, overnight.

In recent years a number of homogeneous catalysts with two proline-derived units in the catalyst molecule were prepared and studied in the asymmetric aldol reaction.[14] Of particular interest could be their comparison with the mono-proline analogues. However, such an analogue with a truly non-functional moiety replacing the second proline unit was only once reported by Benaglia.[14a] PEG with two O-tethered hydroxyproline units was examined alongside with MeO-PEG functionalized with one such unit. Interestingly, when compared under similar conditions (DMSO, 20–24 h) and equal loading of proline moieties, the performance of the bis-proline catalyst was notably better than that of the mono-proline analogue (67 *vs.* 36% yield and 74 *vs.* 60% *ee*). Although the two proline units in this PEG-based catalyst are separated by a significantly longer spacer than in our systems, such coincidence with our findings may imply a general phenomenon of enhanced activity/enantioselectivity in bivalent proline-based systems and will be a subject for our further investigation.

In conclusion, we have demonstrated using simple models of supported dendritic catalysts, based on linear or more sophisticated partially dendritic spacers, that the proximity of the two proline units is crucial and responsible for achieving higher yield and enantioselectivity in the aldol reaction. High branching of the spacer probably provides a benefit of a smaller magnitude, while an incremental positive contribution of the triazole connecting unit is also a possibility.

Whether these findings imply that in the general case of bivalent or polyvalent proline-decorated catalysts the mechanism of the reaction deviates from the monomolecular pathway, established in the literature, remains to be investigated.

Experimental Section

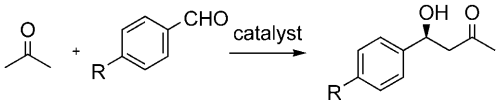
General Procedure for 1,3-Dipolar Cycloaddition

Propargylated derivative (5 equiv. per azidobenzyl unit), sodium ascorbate (1 equiv. per azidobenzyl unit, 1 M in DMF) and copper(II) sulfate pentahydrate (0.25 equiv. per azidobenzyl unit) were added to a suspension of polystyrene azidobenzyl-terminated resin (1 equiv.) in DMF (10 mL per 1 g resin). 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.

General Procedure for Deprotection of Proline

Cleavage of trityl protecting group: The protected proline resin (1 equiv.) was washed 3 times for 5 min with a solution of 0.1% TFA and 1% H_2O in DCM (10 mL per g resin).

Table 2. Aldol reaction with G1 catalysts with two and one functional arms.[a]



Entry	Catalyst	R	Conversion [%]	Yield [%][b]	*ee* [%][c]
1	**G1(Pro)**	**H**	**73**	**52**	**68**
2	G1(mono-Pro)	H	61	36	28
3	G1(OPh,Pro)	H	70	36	31
4	G1(Cp,Pro)	H	100	21	46
5	**G1(Pro)**	**NO_2**	**100**	**95**	**85**
6	G1(mono-Pro)	NO_2	91	79	23
7	G1(OPh,Pro)	NO_2	92	78	24

[a] *Reaction conditions:* 1 equiv. of benzaldehyde/4-nitrobenzaldehyde, 27 equiv. of acetone and 0.3 equiv. of catalyst in DMSO for 4 days at room temperature.
[b] NMR yield.
[c] The *ee* was determined by HPLC, using Chiralpak AD (R = H) or Chiralcel OJ (R = NO_2) columns.

Hydrolysis of methyl ester: Lithium hydroxide (5 equiv. per methyl ester unit) was dissolved in THF/H_2O (10:1) (10 mL per 1 g resin) and then added to a suspension of the proline methyl ester-terminated resin (1 equiv.) in THF (10 mL per 1 g resin). 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.

General Procedure for the Aldol Reaction

The catalytic resin (0.3 mmol of proline units, 0.3 equiv.) was added to a mixture of DMSO:acetone 4:1 (8 mL:2 mL). The suspension was stirred for 5 min at room temperature and then the aldehyde (1 mmol, 1 equiv.) was added. The suspension was mixed at room temperature for 4 days. The resin was separated from the solution by filtration and washed with ethyl acetate. Water (10 mL) and saturated aqueous NH_4Cl solution (10 mL) were added to the combined filtrate. The mixture was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried on $MgSO_4$. The solvent was evaporated, and the crude material was analyzed to determine conversion and yield, and then chromatographed on a silica gel column (1:9 EtOAc:hexanes up to 3:7 EtOAc:hexanes) to yield the pure product as a yellow oil. The product *ee* was determined by HPLC, using Chiralpak AD (benzaldehyde product) or Chiralcel OJ (4-nitrobenzaldehyde product) columns.

Acknowledgements

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