Direct aldol reactions catalyzed by intramolecularly folded prolinamide dendrons: dendrimer effects on stereoselectivity†

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Dendritic effects on both the enantioselectivity and diastereoselectivity of the direct aldol reaction were observed for pyridine-2,6-dicarboxamide dendrons terminated with L-prolinamides.

The topological resemblance of dendrimers to globular proteins has inspired intense interest in exploiting the three-dimensional nature of their structures to improve catalytic efficiency.[1] Although extensive research efforts toward this goal over the last decade have led to discoveries of a number of positive dendrimer effects[2] in periphery functionalized catalytic dendrimers, most other dendritic catalysts display properties similar to the monomeric counterparts most likely due to the lack of well-defined secondary structures as in natural enzymes. The positive dendritic effects reported in these systems stimulate rate enhancements[3] or alter regioselectivity[4] by increasing the congestion and local proximity of catalytic groups at the dendrimer periphery. Generation-dependent amplification of enantioselectivity has only been documented in a few cases and similarly accounted for by the proximity effect.[5] We report herein notable dendritic effects on the stereoselectivity of direct aldol reactions catalyzed by dynamically folded dendritic[6] organocatalysts.

Natural enzymes achieve nearly perfect selectivities and remarkable rate enhancements through the dynamically folded nature of their higher order structures. Recent evidence suggests that structural dynamics significantly influence the efficiency of biological[7] and non-biological[8] catalysts. Consequently, we became interested in probing the ability of our dynamically folded dendrimers[6,9] to enhance the stereoselectivity of an organocatalytic reaction.

We focused on the proline-catalyzed direct aldol reaction[10] because recent studies provide strong evidence for a single-proline enamine mechanism for this reaction.[11] This mechanistic information reduces the potential for a proximity effect that could lead to enhanced selectivity. Accordingly, previous investigations by others on proline-terminated flexible dendrimers as organocatalysts for the direct aldol reaction revealed enantioselectivities that were slightly diminished compared with L-proline.[12] In contrast, Portnoy and co-workers observed that polymer-supported dendritic proline catalysts afforded generation-dependent increases in enantioselectivity.[5b,c]

On the basis of these observations, we prepared folded dendritic organocatalysts based on the pyridine-2,6-dicarboxamide branching unit (Fig. 1). The L-prolinamide catalytic units were linked to the pyridine-2,6-dicarboxamide branch point *via* an *o*-phenylenediamide rather than an anthranilamide linkage typical of these dendrons.[6] To probe the impact of terminal group congestion on stereoselectivity, we compared the catalytic properties of two series of dendrons having either an L-prolinamide group at every (Gn-all) or alternating (Gn-alt.) terminal positions as a function of generation. Additionally, the role of dendron structure was explored by evaluating Type I G2 (**3** and **7**) and Type II G2 (**4** and **8**) dendrons.[6d,e]

We examined these dendritic prolinamides[13] as catalysts for the aldol reactions of a series of acyclic and cyclic aldol donors with 4-nitrobenzaldehyde (**10**). The aldol reactions were performed in DMF in the presence of excess ketone, catalytic acetic acid and water (1000 mol%). The addition of water was necessary to ensure a reasonable rate of the aldol reaction.[14] Previous studies indicate that the addition of water does not disrupt the folded conformations of this class of dendrimers.[6b] The catalyst loading for each reaction was adjusted to maintain a constant number of catalytic units per reaction for a given ketone.

In contrast to acetone, which exhibited only marginal changes in selectivity with generation (Table 1, entries 1–9), significant increases emerged at higher dendron generation for cyclic and substituted ketones. In fact, plots of % ee *vs.* generation

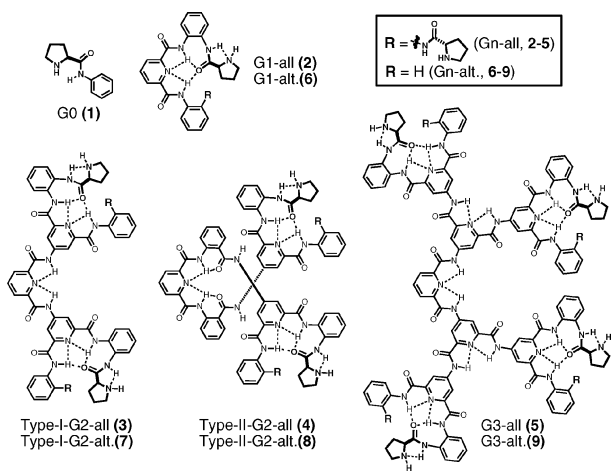

Fig. 1 Folded dendrons with prolinamides at each (Gn-all) or alternating (Gn-alt.) terminal positions.

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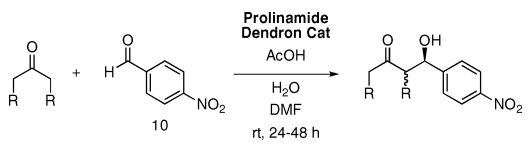
Table 1 Direct aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by prolinamide dendrons[a]



Entry		Catalyst	Mol%	Yield[b] (%)	dr[c] *anti–syn*	% ee[d] *anti–syn*
1		G0 (**1**)	20	75	—	49
2		G1-all (**2**)	10	59	—	36
3		I-G2-all (**3**)	5	50	—	59
4		II-G2-all (**4**)	5	55	—	45
5		G3-all (**5**)	2.5	38	—	55
6		G1-alt. (**6**)	20	70	—	58
7		I-G2-alt. (**7**)	10	42	—	56
8		II-G2-alt. (**8**)	10	44	—	58
9		G3-alt. (**9**)	5	64	—	66
10		G0 (**1**)	8	98	1 : 2.2	33/6
11		G1-all (**2**)	4	87	1 : 2.9	63/14
12		I-G2-all (**3**)	2	87	1.6 : 1	92/71
13		II-G2-all (**4**)	2	87	1.5 : 1	92/84
14		G3-all (**5**)	1	91	1.6 : 1	92/72
15		G1-alt. (**6**)	8	77	1 : 2.6	36/26
16		I-G2-alt. (**7**)	4	90	2.2 : 1	88/50
17		II-G2-alt. (**8**)	4	87	2.6 : 1	90/32
18		G3-alt. (**9**)	2	88	2.5 : 1	90/48
19		G0 (**1**)	20	99	5.3 : 1	64/28
20		G1-all (**2**)	10	90	4.4 : 1	59/48
21		I-G2-all (**3**)	5	73	15 : 1	96/26
22		II-G2-all (**4**)	5	69	6.5 : 1	84/3
23		G3-all (**5**)	2.5	99	21 : 1	97/10
24		G1-alt. (**6**)	20	92	4.6 : 1	78/79
25		I-G2-alt. (**7**)	10	87	24.5 : 1	93/44
26		II-G2-alt. (**8**)	10	87	14 : 1	93/29
27		G3-alt. (**9**)	5	92	32 : 1	96/28

[a] Reactions were performed at rt in DMF in the presence of ketone (27 eq.), acetic acid (1 eq. per prolinamide) and 1000 mol% H_2O for 48 h (entries 1–9) and 24 h (entries 10–27). [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] Determined by chiral HPLC.

revealed nearly identical selectivity trends for both the Gn-all and Gn-alt. systems (see ESI†). For example, the enantioselectivity of the *anti*-aldol product of the reaction of **10** with cyclopentanone increased from 33 to 92% ee for Gn-all and to 90% for Gn-alt., upon progressing from L-prolinanilide (G0, **1**) to G3 dendrons (Table 1, entries 10–18). Similarly, the enantioselectivity of the *syn*-aldol product increased from 6% for G0 (**1**) to 72% for G3-all (**5**) and to 48% for G3-alt. (**9**). The diastereomeric ratios reversed from *syn*-selective for G0 (**1**) and G1 (**2/6**) to *anti*-selective for both series of G2 and G3 dendrons. It is noteworthy that these selectivity trends were nearly independent of the prolinamide density at the periphery (Gn-all *versus* Gn-alt.) and that the Type I and Type II G2 dendrons afforded similar selectivities (Table 1, entries 12, 13 and 16, 17).

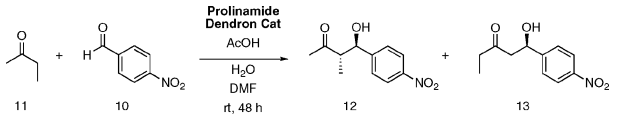
Comparable selectivity trends were observed in the reaction of **10** with cyclohexanone using the prolinamide-dendron catalysts (Table 1, entries 19–27). G0 (**1**) and G1 (**2/6**) catalysts afforded the *anti* and *syn*-aldol products with similar diastereoselectivities and enantioselectivities ranging from 59 to 78% for the *anti* product. The ee of the *anti*-aldol product improved from 64% for G0 (**1**) to 97% for G3-all (**5**) and to 96% for G3-alt. (**9**). In contrast to cyclopentanone, the % ee of the *syn*-aldol product progressively decreased with generation for both dendron series. Generation-dependent increases in the *anti–syn* ratio were also observed in each series ranging from 4.4 : 1 for G1-all (**2**) to 21 : 1 for G3-all (**5**) and from 4.6 : 1 for G1-alt. (**6**) to 32 : 1 for G3-alt. (**9**). In both series, the Type-II-G2 dendrons (**4** and **8**) provided lower *anti–syn* ratios than the corresponding higher generation Type I catalysts (Table 1, entries 22 and 26).

The fact that the reaction of cyclic ketones with **10** experienced much larger generational effects than acetone suggests that steric effects play a role in mediating the dendritic effects on selectivity. In order to explore the generality of this observation, the reaction of 2-butanone (**11**) with **10** was performed. A generation-dependent increase in % ee from 63 to 94% for Gn-all and from 88 to 92% for Gn-alt. series was observed for *anti*-aldol product **12** (Table 2). Similar to cyclohexanone, the *syn*-aldol product (not shown) experienced a decrease in % ee from 64 to 36% for Gn-all and from 78 to 50% for Gn-alt. In contrast to the *anti* product, the % ee of regioisomer **13** showed an increase from 58 to 78% for Type-I-Gn-all and from 26 to 78% for Type-I-Gn-alt. Similarly, the Type-II-G2 catalysts afforded lower % ee than the corresponding Type-I-G2 dendrons in both series (Table 2, entries 4 and 7).

X-Ray crystal structures of G1-alt. (**6**) and the *N*-benzyl derivative of G1-all (*N*-Bn) (SI-40) confirmed a *syn–syn* conformation of the pyridine-2,6-dicarboxamide moiety. All four N–H groups of both structures were involved in intramolecular hydrogen bonds that preorganize the structure (Fig. 2). In contrast to the flattened conformation of G1-alt., G1-all (*N*-Bn) adopts a *P*-helical bias in the solid state.

Circular dichroic spectra (CD) of the *N*-benzyl derivatives[15] of G1-all (SI-40) and G2-all (SI-41) revealed apparent excitonic couplets centered at *ca.* 290 nm, corresponding to $\pi \rightarrow \pi^*$ transitions of the *o*-diamidobenzene chromophore (Fig. 3). Time-dependent density functional theory (TD-DFT) calculations, performed at the B3LYP/TZVP[16] level of theory,

Table 2 Direct aldol reaction of 4-nitrobenzaldehyde with 2-butanone catalyzed by prolinamide dendrons[a]



Entry	Catalyst	Mol%	Yield[b] (%)	dr[c] (**12**) *anti–syn*	% ee[d] (**12**) *anti–syn*	% ee[b] (**13**)	**12** : **13**
1	G0 (**1**)	20	97	2.6 : 1	76/56	69	1 : 1.2
2	G1-all (**2**)	10	50	1.5 : 1	63/64	58	2.7 : 1
3	I-G2-all (**3**)	5	45	3.0 : 1	92/26	66	1.5 : 1
4	II-G2-all (**4**)	5	48	2.6 : 1	90/44	40	2.4 : 1
5	G3-all (**5**)	2.5	35	4.5 : 1	94/36	78	3.0 : 1
6	G1-alt (**6**)	20	58	2.6 : 1	88/78	26	1 : 1.4
7	I-G2-alt. (**7**)	10	52	7.8 : 1	92/54	58	2.2 : 1
8	II-G2-alt. (**8**)	10	49	4.5 : 1	92/60	36	1.8 : 1
9	G3-alt. (**9**)	5	48	7.7 : 1	92/50	78	2.4 : 1

[a] Reactions were performed at rt in DMF in the presence of ketone (27 eq.), acetic acid (1 eq. per prolinamide) and 1000 mol% H_2O for 48 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] Determined by chiral HPLC.

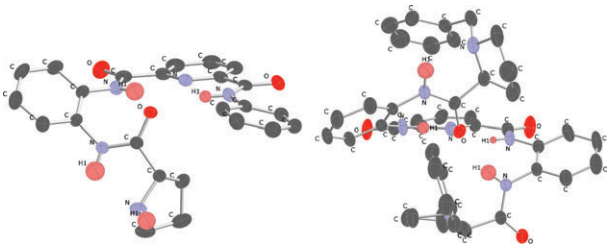


Fig. 2 X-Ray crystal structures of G1-alt. (**6**) (left) and the *N*-benzyl derivative of G1-All (SI-40) (right).

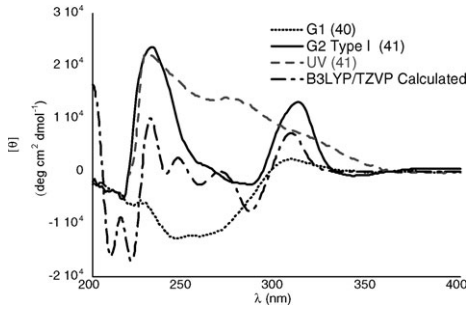


Fig. 3 Experimental (CH_3CN, 25 °C) and calcd. CD spectra.

on the *P*-helical crystallographic structure of G1-all (SI-40) match well with the experimental CD spectra, indicating a similar *P*-helical bias in solution. In contrast, the calculated CD spectra for the *M* structure did not match experimental spectra (see ESI†).

The increase in *P*-helical bias going from the G1 to G2 dendron correlates well with the corresponding improvements in selectivity. However, it is noteworthy that despite the flattened structure of G1-alt. in the solid state, the Gn-all and Gn-alt. series display nearly parallel selectivity trends. Although a potential source of chirality, the increase in *P*-helical bias at higher generation also indicates a concomitant increase in structural order.[6] Therefore, given the conformational differences between the two dendritic series, it is likely that the dendritic effects emerge from an increase in structural preorganization, rather than from the chiral influence of the helical bias or from a proximity effect.

In conclusion, dendritic effects that amplify the stereoselectivity of an organocatalytic process were observed. A few selectivity trends can be summarized as follows: (i) a significant enhancement in selectivity is generally achieved using low generation dendrons rather than much larger dendrimers, (ii) the % ee of the *anti*-aldol is enhanced for higher generation dendrons and similar among G2 and G3 dendrons, (iii) the Type I G2 dendron system in general affords similar or slightly higher selectivities than the corresponding Type II G2 catalyst, and (iv) the alterations of stereoselectivities are most pronounced with cyclic and substituted ketones.

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