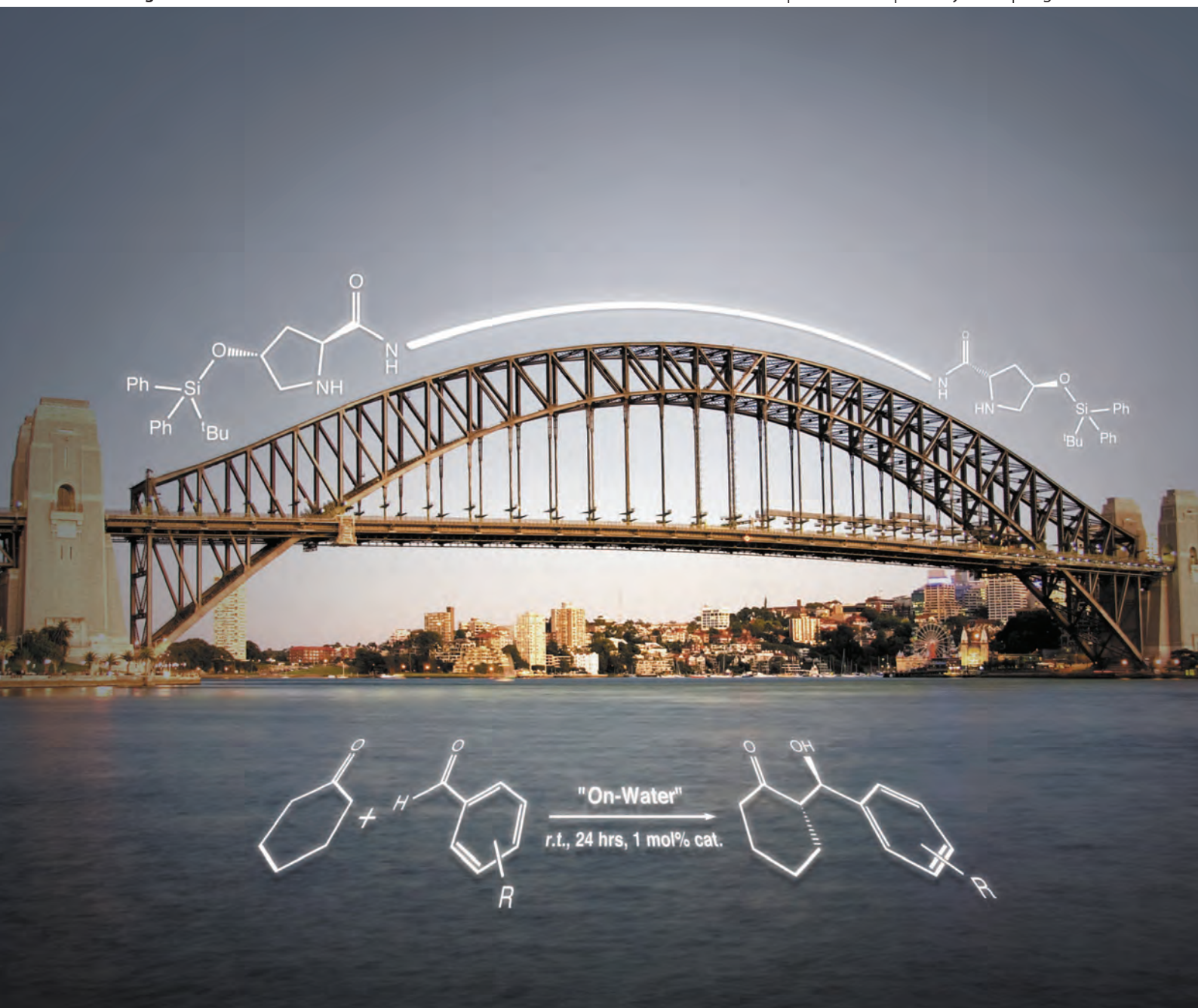


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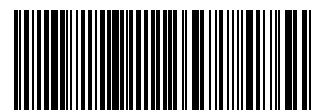
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PAPER

Luke C. Henderson *et al.*

Synergistic effects within a C₂-symmetric organocatalyst: the potential formation of a chiral catalytic pocket



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Synergistic effects within a C_2 -symmetric organocatalyst: the potential formation of a chiral catalytic pocket†

Joshua P. Delaney,^a Hannah L. Brozinski^a and Luke C. Henderson^{*a,b}

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This study describes the synthesis of five novel C_2 -symmetric organocatalysts that facilitate the on-water asymmetric aldol reaction at low catalyst loading (1 mol%) without the use of additives. Each catalyst is composed of two diprolineamide units joined by a symmetric alkyl bridging group allowing for systematic modulation of catalytic site proximity. Typically, catalysts in this manuscript which bear the catalytic units in close proximity gave the best reaction outcomes in terms of conversion (up to >99%), diastereomeric ratio (4/96, *syn/anti*) and enantiomeric excess (up to 97%). This effect has been attributed to the assembly of a chiral pocket, facilitated by hydrogen bonding at the oil-in-water interface.

Introduction

Since the seminal work of List and Barbas, organocatalysis has experienced a dramatic increase in the intensity of investigation.¹ Proline-derived organocatalysts have been the most explored scaffold having been applied to a vast range of chiral bond forming reactions in a broad selection of solvents and conditions. In order to improve the activity, versatility and chiral induction of proline based catalysts; the proline motif has been subjected to substantial modification and elaboration.²

Rigorous modification of L-proline throughout the past decade has seen a myriad innovations to the catalyst structure. Fundamental elaborations such as functionalization at the 4 position, as demonstrated by Hayashi *et al.*,³ have resulted in vastly improved activity and chiral induction of proline catalysts. Similarly, elaboration *via* the carboxyl group of proline have seen great success.⁴ To this end, there has been an increasingly broad range of organic transformations carried out by highly derivatised, novel proline-based organocatalysts such as small peptides, proline-thioamides and ionic liquid tagged prolines are but a few.⁵ Despite the progress made towards catalyst generality, organocatalysed asymmetric transformations in water at low catalyst loadings remain a topic of great interest in the synthetic chemistry community.

Aside from the prominent use of steric influences, properties such as catalytic site proximity and catalyst pre-organisation are largely overlooked, thus spurring our interest in C_2 -symmetric organocatalysts. The use of C_2 -symmetric ligands is commonplace among transition metal catalysis but has been applied to organocatalysis only a few times.⁶ Embracing C_2 -symmetric architectures provides a means to control spatial properties within an oligomeric catalyst, an aspect that has yet to be embraced as a significant aspect of organocatalyst design.

Recently, we reported the synthesis and evaluation of a novel C_2 -symmetric organocatalyst which demonstrated high catalytic activity for the asymmetric aldol reaction in an 'on-water' reaction system (Fig. 1).⁷

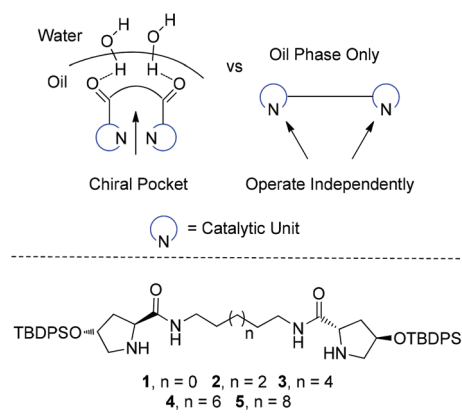


Fig. 1 Proposed catalytic conformation adopted by C_2 -symmetric organocatalysts, on-water (left) and organic (right) reaction medium. Diprolineamide schematic is below.

^aStrategic Research Centre, Faculty of Science and Technology, Deakin University, Geelong, Victoria 3216, Australia. E-mail: luke.henderson@deakin.edu.au; Fax: (+613) 52271045; Tel: (+613) 52272767

^bInstitute for Frontier Materials, Deakin University, Geelong, Victoria 3216, Australia
†Electronic supplementary information (ESI) available: ¹H and ¹³C NMR of all novel compounds and chiral HPLC traces and their corresponding racemates is provided. See DOI: 10.1039/c3ob27250h



Based on this previous work, our hypothesis for this study was that the intramolecular distance of the prolinamide units within the organocatalyst influences their cooperation and therefore may lead to highly stereoselective aldol reactions. To test this hypothesis several organocatalysts were synthesised with sequentially increasing distance between the prolinamide units. The rationale being that the shorter spacer lengths, such as that present in catalysts **1** (4 methylene units) would encourage prolinamide cooperation, while the larger intramolecular distances present in catalysts **4** and **5** (10 and 12 methylene units, respectively) would minimize the catalytic site interaction and thus diminishing the cooperative potential of each diproline. Herein we present the comparison of organocatalysts **1–5** using the asymmetric aldol reaction on-water. Based on this experimental evidence we propose the formation of a chiral catalytic pocket by this class of catalyst.

Results and discussion

The described organocatalysts are easily accessed *via* a four step synthesis utilizing affordable starting materials (Scheme 1). Incorporation of a *tert*-butyldiphenylsilyl moiety onto *trans*-4-hydroxyproline **6** was achieved in excellent yield (96%) following a protocol reported by McQuade *et al.*⁸ and the crude product was directly *N*-protected using a *tert*-butoxycarbamate (Boc) group furnishing **7** in a high yield (82%) over two steps. The protected proline unit was then tethered to each end of a series of linear diamines *via* an EDCI mediated peptide coupling to afford bis-prolinamides **8–12**. Removal of the *N*-Boc protecting groups was obtained in moderate to excellent yield using a TFA-CH₂Cl₂ (10% v/v) protocol furnishing the desired organocatalysts **1–5**.

By utilizing the well understood aldol reaction as a model system, variations in reaction outcome can be attributed to catalyst structure with greater confidence. The clearer insight into potential transition states of each C₂-symmetric diproline can be achieved. Additionally the aldol reaction is one of the most important C–C bond forming reaction in organic

Table 1 Preliminary comparison of catalysts **1–5**

Entry	Catalyst	Conversion ^a (%)	dr ^a (<i>syn/anti</i>)	ee ^b (%)
1	1	68	10/90	86
2 ^c	2	45	8/92	66
3	3	70	16/84	55
4	4	87	20/80	70
5	5	32	15/85	68

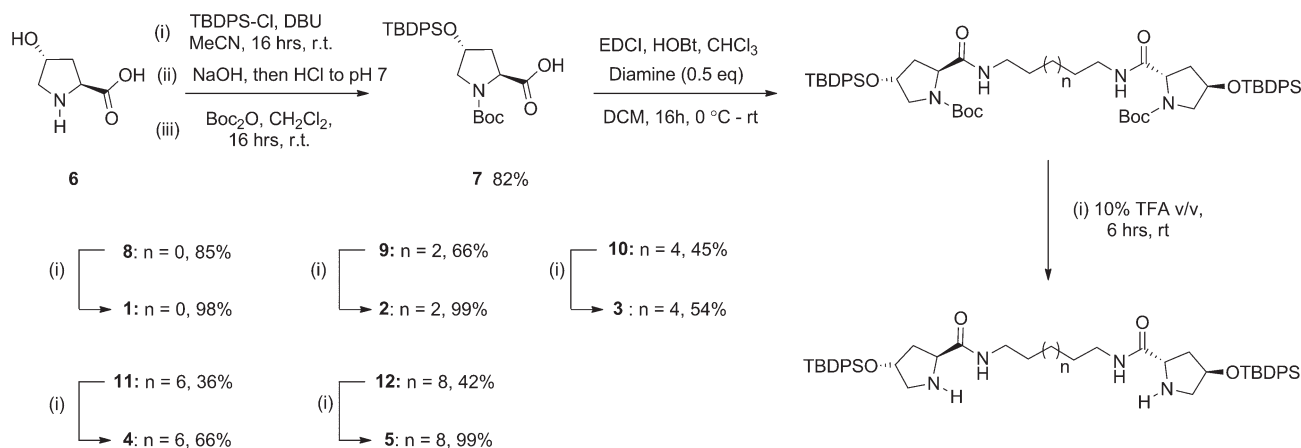
^a Determined by integration of key signals in the ¹H NMR spectrum. ^b Determined by Chiral HPLC, Chiralpak AD-H, 1 mL min⁻¹, 2-propanol-*n*-hexane, 1:9. ^c Results obtained from a previous study but provided here for clarity.^{7a}

chemistry.⁹ The on-water aldol reaction between cyclohexanone **13** and benzaldehyde **14** (Scheme 1) was chosen as the model reaction.

Employing diproline **1** (Table 1, entry 1) at a catalyst loading of 1 mol%, we were pleased to see that the aldol product **15a** was obtained in good yield and high stereopurity, dr of 10/90 (*syn/anti*) and ee of 86%. Continuing the comparison with the remaining catalysts (Table 1, entries 2–5) afforded inferior ee's in all cases compared to **1**, and similar sacrifices were observed regarding dr. The general decline in stereochemical purity of the aldol products as prolinamide tether length increases supports our original hypothesis of potential catalytic site cooperation.

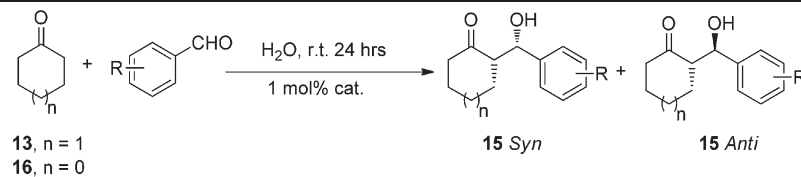
Encouraged by these preliminary results our attention turned to investigating each catalyst in combination with other commonly employed benzaldehydes and a second ketone (cyclopentanone) to see if catalyst **1** outperforming catalysts **2–5** was indeed a general trend.

Employing cyclopentanone **16** as the donor ketone (Table 2, entries 1–5) demonstrated the same general trend with respect



Scheme 1



Table 2 Reaction scope of organocatalysts 1–5

Entry	n	R	15	1			2 ^c			3			4			5		
				Con. ^a (%)	dr (syn/anti) ^a	ee ^b (%)	Con. ^a (%)	dr ^a (syn/anti)	ee ^b (%)	Con. ^a (%)	dr ^a (syn/anti)	ee ^b (%)	Con. ^a (%)	dr ^a (syn/anti)	ee ^b (%)	Con. ^a (%)	dr ^a (syn/anti)	ee ^b (%)
1	0	H	15b	92	25/72	74	90	64/36	50	99	61/39	64	92	60/40	68	56	60/40	70
2	0	4-Br	15c	96	50/50	72	99	59/41	52	98	47/53	68	99	43/57	54	99	61/39	56
3	0	4-F	15d	97	27/73	80	85	64/36	42	99	43/57	65	99	42/58	68	99	62/38	66
4	0	4-NO ₂	15e	97	39/61	8	61	24/76	14	99	73/27	8	72	49/51	14	40	66/34	12
5	0	3-NO ₂	15f	55	88/12	96	99	54/46	52	99	52/48	56	98	53/47	46	99	51/49	50
6	0	2-NO ₂	15g	74	91/9	99	37	34/66	78	99	40/60	82	92	30/70	66	36	35/65	69
5	0	4-Ph	15h	78	38/62	80	70	59/41	46	78	58/42	50	76	63/37	40	38	57/43	44
6	1	4-Br	15i	99	9/91	88	97	14/86	86	96	14/86	80	37	19/81	56	77	16/84	82
7	1	4-F	15j	71	6/94	86	88	9/91	92	86	21/79	82	99	19/81	84	76	17/83	86
8	1	4-NO ₂	15k	99	4/96	97	91	4/96	99	62	23/77	80	50	25/75	52	65	20/80	64
9	1	3-NO ₂	15l	85	7/93	99	57	16/84	88	73	19/81	86	36	17/83	84	61	17/83	86
10	1	2-NO ₂	15m	73	3/97	92	71	15/85	72	65	16/84	74	92	16/84	64	61	13/87	46
11	1	4-Ph	15n	67	12/88	94	37	15/85	80	44	18/82	80	44	21/79	89	19	15/85	80

^a Determined by integration of key signals in the ¹H NMR spectrum, Chromatography was restricted to reaction mixtures showing conversions <20%, similar to such protocols employed by groups such as Penhoat,^{11a} Giacalone^{11b} and Guellena^{11c} in order to accurately quantify catalyst activity. ^b Determined by Chiral HPLC, Chiralpak AD-H, 1 mL min⁻¹, IPA-Hexane, 1 : 9.

^c Results obtained from a previous study but provided here for clarity of comparison. ^{7a} Results in bold were determined to be the best of the series by the authors.



to catalyst **1** as was observed in Table 1 whereby the smallest prolinamide linker furnishes the superior reaction outcomes.

In all cases the catalyst bearing the smallest intramolecular distance between proline moieties exhibited the best optical purity of aldol products obtained. In general, the reaction conversions were good to excellent, though no discernible trend was obvious when comparing conversion values to catalyst structure. When comparing the diastereomeric ratio of the products obtained from each of the catalysts examined, the predominant diastereomer is *syn*, a stark contrast to those in Table 1. Cyclopentanone has been reported to exhibit moderate diastereoisomeric ratio in the aldol reaction and indeed this was the case with catalysts **1–5**.¹⁰ However, catalyst **1** displays behaviour which is countermand whereby in most cases the *anti* diastereoisomer is preferred, while the aldol products furnished by **2–5** were primarily composed of the *syn* diastereomer. This aberration in results suggests that there is an important role being played by the intramolecular distance between these prolinamide units that contributes to the diastereomeric purity of the generated aldol products. We were further pleased as examination of the ees furnished by catalyst **1** were superior to those in all cases to those shown by catalysts **2–5**.

Although, compound **15e** (Table 2, entry 4) was deemed an outlier due to a consistently poor compatibility among the catalysts series. In this instance we considered the superior conversion demonstrated by catalyst **1** to be the optimal outcome.

Repeating this series with cyclohexanone (Table 2, entries 6–9) gave a similar trend where the smallest organocatalyst **1** gave the best reaction outcomes. In this series of reaction employing cyclohexanone **13**, albeit the superiority of catalyst **1** to catalysts **2–5** was not as pronounced as it was when employing cyclopentanone. It should be noted that in two instances the results obtained for catalyst **1** and **2** were comparable in both conversion and stereochemical aspects. When using 4-fluorobenzaldehyde as the reaction partner (Table 2, entry 7) catalyst **2** was deemed superior to catalyst **1**, though only by a marginal amount (17% higher yield and 6% improved ee).

These catalysts were also employed to catalyse the aldol reaction using various ketones and electron rich aldehydes. Unfortunately, under these conditions the catalysts proved ineffective at facilitating high levels of conversion or optical purity. These data are presented in the ESI.†

A prominent trend becomes apparent when considering the dr of each aldol product, with diastereochemical control becoming markedly reduced among the larger catalysts **3–5**. This may be a result of a more flexible, and thus less stereochemically defined, transition state allowing for multiple approaches of the incoming aldehyde.

Based on the experimental evidence, it is apparent that the transition state which is formed is significantly influenced by catalytic site proximity. It was reasoned that each diprolinamide must adopt a transition state that allows for potential catalytic site cooperation, be that *via* hydrogen bonding effects or purely in a steric fashion *i.e.* the second prolinamide serving

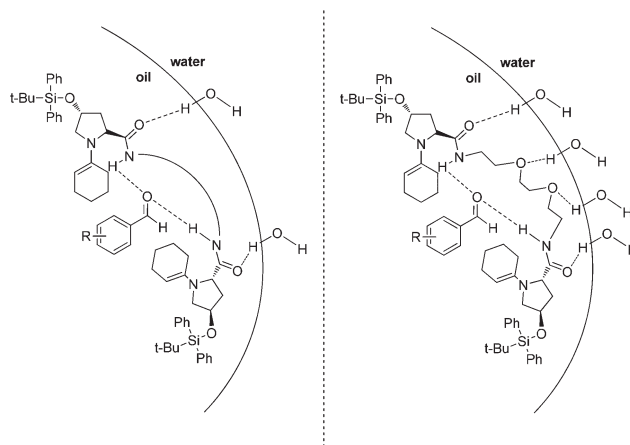


Fig. 2 Proposed conformation taken by catalysts **1–5** (left) and a proposed catalyst **16** which is H-bond stabilized (right).

as a directing group for the first, and its degree of cooperation that results in the observed discrepancies in catalytic ability. To address the trends observed within each reaction outcome across the catalysts **1–5**, the formation of a chiral pocket has been proposed (Fig. 2).

It has been noted that on-water organocatalysis allows for particular advantages derived from abundant H-bonding interactions at the oil–water interphase.^{9,12} This participation of water has led to proposed transition states such as that by Pedrosa *et al.*¹³ who describe an on water organocatalysed aldol reaction by a prolinamide bearing multiple amide groups. This transition state presents each amide as both a H-bond acceptor, leading to organization at the oil–water interface, and H-bond donors which facilitate a controlled means of aldehyde approach. Additionally, the concept of multiple hydrogen bonding donors to facilitate the asymmetric aldol reaction with high stereochemical outcome has been used previously by Gong *et al.*¹⁴ and Singh *et al.*¹⁵ who employed a prolinamide based amino alcohol to assist in direct the approach of the incoming aldehyde.

Through hydrogen bonding involving the amide groups at the oil–water interphase, each diprolinamide could potentially align along the surface of the oil droplet, a confirmation supported by lipophilic TBDSO groups pointing into the oil phase. The impact of this potential formation has dramatic implications regarding both the catalytic activity and chiral induction furnished by each catalyst.

Due to the symmetric nature of the proposed transition state, each catalytic unit is situated equidistant to the approaching aldehyde, and so the activity would be bolstered due to a high relative concentration of the activated chiral enamine. From a chiral standpoint, this symmetry ensures that each enamine reacts with the appropriate *Re* or *Si* face of the incoming aldehyde, furnishing the observed enantio-enriched aldol product. This proximal advantage would diminish as each catalytic unit is moved apart, reducing the likelihood of cooperation between diprolinamide units and



resulting in the poor stereochemical outcomes which were observed for the larger diprolinamides.

This alignment at the interface also presents an opportunity for the linking group to act as a sterically directing moiety, restricting the approach of the aldehyde through the formation of a chiral catalytic pocket – a stereochemically defined environment. This further restricts the configuration by which the reacting aldehyde may approach, significantly improving the optical purity of the obtained products.

Considering the proposed catalytic pocket in Fig. 2 (left), the alignment of the hydrocarbon linker along the oil–water interface was considered to be an unfavourable interaction. This effect would be minimal for catalysts bearing the smaller hydrocarbon chains (such as catalysts **1** and **2**). Though for the larger catalysts, such as **3–5**, this unfavourable interaction may be responsible for the observed reductions in catalyst performance for catalysts bearing the larger, and thus more hydrophobic, alkyl chains.

To address this unfavourable interaction, an oxygen rich catalyst **16** (analogous in size to catalyst **3**) was synthesised and evaluated in the on-water asymmetric aldol system. It was reasoned that the oxygenated linker between prolinamide units would reinforce the chiral assembly, as proposed in Fig. 2 (right), *via* H-bonding at the oil–water interface while retaining the hydrophobic nature of the TBDPS groups on the prolinamide units.

It is important to note that the intramolecular distance between prolinamide units in catalyst **16** is approximately the same as that of catalyst **3**. Thus a comparison could be drawn between each catalysts and the effect of this ethereal linker.

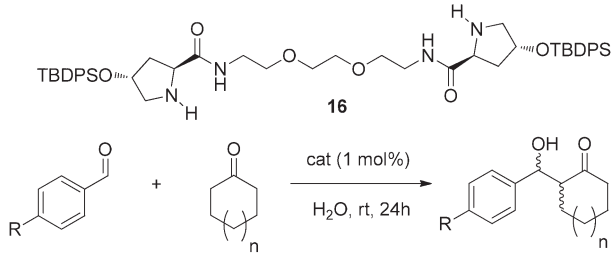
To probe how the absence of H-bonding may impact the activity of the oxygenated dimer, catalyst **16** was initially evaluated in the absence of water by conducting the reaction in neat cyclohexanone **13**.

These experiments (Table 3, entries 1 and 2) show the similarly sized catalysts **3** and **16** affect near identical reaction outcomes, suggesting that without the presence of water, the oxygenated linking chain has no bearing on catalytic ability.

Significant improvements to reaction outcome were observed when water was added to the reaction vessel. With respect to the cyclohexanone containing examples (Table 3, entries 3–5), **16** shows a marked improvement in both conversion, dr and ee compared to the purely alkyl bridged organocatalyst **3**. Thus suggesting that there is some effect elicited by the combination of oxygenated linker group and water at the emulsion interface. In a similar trend observed throughout this study, the use of cyclopentanone as the donor ketone resulted in decreased enantiomeric excesses and only moderate control over diastereomeric ratio.

Although not definitive, the experimental results presented in this manuscript can be rationalised by the formation of a chiral assembly at the oil-in-water interface. We believe that full elucidation of this catalytic mechanism is beyond the scope of this comparative study. Never-the-less the data presented herein will assist in the design of organocatalysts bearing multiple proline groups.

Table 3 Examination of organocatalyst **6** in the asymmetric aldol reaction



Entry	<i>n</i>	Catalyst	R	Solvent	Conv. ^a (%)	dr ^a (<i>syn/anti</i>)	ee ^b
1	1	3	H	Neat	88	13/87	64
2	1	16	H	Neat	90	25/75	66
3	1	16	H	H ₂ O	98	15/85	76
4	1	16	NO ₂	H ₂ O	92	14/86	87
5	1	16	F	H ₂ O	96	11/88	76
6	0	16	H	H ₂ O	99	61/39	62
7	0	16	NO ₂	H ₂ O	56	63/37	20
8	0	16	F	H ₂ O	99	61/39	70

^a Determined by integration of key signals in the ¹H NMR spectrum.
^b Determined by Chiral HPLC, Chiralpak AD-H, 1 mL min⁻¹, IPA-*n*-Hexane, 1 : 9.

Conclusions

In conclusion, this manuscript describes the synthesis of a range of C₂-symmetric organocatalysts **1–5** and **16** consisting of multiple *trans*-TBDPS-prolinamides bearing systematically increasing linker lengths. Each of these organocatalysts were evaluated for their ability to facilitate the asymmetric aldol reaction on-water at a low catalyst loading of 1 mol% without the use of additives or co-solvents. It was observed that as the distance between the prolinamide units increased, both the conversion to the desired product and the optical purity (dr and ee) decreased among each aldol reactions. Also described is a new intramolecular organocatalytic interaction between prolinamide moieties that allows for a cooperative catalytic process. This effect was attributed to the formation of a hypothesized chiral ‘catalytic pocket’ providing conformational influences giving rise to aldol products of high optical purity at low loadings.

The results obtained from this study will aid the rational design of organocatalysts and introduces the concept of catalytic site proximity within an oligomeric prolinamide system as being a key property that contributes to the activity and chiral induction of future novel catalysts.

Experimental section

General procedure for organocatalysed aldol reactions

Water (1.6 mL) was added to a round-bottom flask charge with organocatalyst (0.002 g, 0.01 eq.) dissolved in ketone (0.127 mL, 1.22 mmol, 5 eq.). Benzaldehyde (0.244 mmol, 37 mg, 1 equiv.) was introduced to the emulsion and the



reaction mixture was then stirred vigorously at room temperature for 24 h. The emulsion was then extracted with CHCl_3 (2×10 mL) and the combined organic phase was washed with 10% citric acid (10 mL). The organic phase was then dried over MgSO_4 and the solvent was removed under vacuum to give the crude product as a yellow solid. Analysis by ^1H NMR spectroscopy was used to determine the desired product, reaction conversion and the diastereomeric ratio. In cases where conversion was determined to be $<20\%$, the crude product was purified by silica gel column chromatography (1/3 EtOAc : Pet. Spirits). The pure products were analysed by chiral HPLC (Chiral Pak AD-H, hexane : 2-propanol, 90 : 10, 1 mL min^{-1}) to determine the enantiomeric excess. All reactions were performed a minimum of three times and the data presented was considered representative of these results.

trans-4-tert-Butyldiphenylsiloxy-N-Boc-L-proline-carboxylic acid 7. *trans-4-Hydroxy-L-proline* (1.0 g, 0.763 mmol) was added to acetonitrile (20 mL) and stirred. TBDPS-Cl (6.94 mL, 0.026 mol) was added to the stirring solution and the reaction was cooled to 0°C . DBU (4.22 mL, 0.028 mol) was subsequently added to the stirring solution and the mixture was allowed to reach room temperature and stirred for 24 h. The resulting reaction mixture was then quenched with hexane and the product was extracted into hexane (3×30 mL). The combined hexane layers were combined and the solvent was removed *in vacuo*. The resulting oil was redissolved in a methanol (32 mL), THF (18 mL), water (16 mL) and 2 M NaOH (24 mL) mixture and allowed to stir for 90 min at room temperature. The solution was then titrated to a pH of 6 with 2 M HCl before removing the organic solvents under reduced pressure. To the resulting water layer a 1 : 1 ratio of Et_2O was added and the biphasic mixture was allowed to stand for 24 h, resulting in crystals forming in the organic phase. The solid was filtered and washed with cold Et_2O to give the silylated intermediate as white crystals (2.71 g, 0.733 mol, 96%). ^1H NMR (400 MHz, CD_3OD) δ 7.67–7.64 (m, 4H), 7.45–7.42 (m, 6H), 4.59 (s, $J = 0.27$, 1H), 4.23 (1H, m), 3.30 (dd, $J = 10.8$, 5.4 Hz, 1H), 3.29 (dt, $J = 13.5$, 2.7 Hz, 1H), 2.31 (ddt, $J = 13.5$, 7.56, 1.88 Hz, 1H), 1.93 (ddd, $J = 13.5$, 9.99, 4.05 Hz, 1H), 1.08 (s, 9H). Compound was identified by ^1H NMR and was consistent with literature values.⁸ Without further purification, TBDPSO-proline (2.71 g, 0.734 mmol) was dissolved in a 1 : 1 ratio of THF– H_2O (20 mL : 20 mL). To this mixture was added NaOH (0.733 g, 0.018 mol) along with Boc_2O (2.08 g, 0.953 mmol) and the solution was stirred for 16 h at room temperature. The resulting solution was then acidified with 2 M HCl and extracted into diethyl ether (3×20 mL). The combined organic phase was dried over MgSO_4 and the solvent was removed *in vacuo* to afford clear viscous oil. The crude mixture was purified *via* flash chromatography (1/4 EtOAc : Pet spirits) to give the pure *N*-Boc protected monomer as a colourless oil (2.82 g, 0.6 mol, 86%). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.64 (m, 4H), 7.39 (m, 6H), 4.56 (t, $J = 8$ Hz, 1H), 4.43 (m, 1H), 3.59–3.29 (m, 2H), 2.28–2.04 (m, 2H), 1.47 (m, 9H), 1.07 (m, 9H). Compound was identified by ^1H NMR and was consistent with literature values.⁸

1,4-Di(trans-N-Boc-4-tert-butyldiphenylsiloxy-L-prolinamide) butane 8. *trans-N-Boc-4-tert-butyldiphenylsiloxy-L-proline* 7 (0.295 g, 0.623 mmol) was dissolved in DCM (20 mL) and cooled to 0°C . HOBt (0.02 g, 0.015 mmol) was added to the solution and the mixture was stirred for 5 min. EDCI (0.142 g, 0.074 mmol) was added to the mixture followed by 3 min additional stirring followed by the introduction of 1,4-diaminobutane (0.03 mL, 0.297 mmol). The mixture was allowed to reach room temperature and stirred for 16 h. The final reaction mixture was diluted with additional DCM (30 mL) and washed with 10% citric acid (3×30 mL), saturated NaHCO_3 (3×30 mL) and brine (1×30 mL). The resulting organic phase was dried over MgSO_4 and the solvent was removed *in vacuo* to give the crude boc protected diprolinamide **8** as a colourless oil. The crude mixture was purified *via* flash chromatography (1/3 EtOAc : Pet spirits \rightarrow 1/1 EtOAc : Pet spirits) to give the pure dimer as a viscous colourless oil (0.292 g, 0.254 mmol, 85%). $R_f = 8/33$ (1 : 1 EtOAc : Pet. Spirits); ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.62 (m, 8H), 7.40 (m, 12H), 4.40 (br, 4H), 3.72 (br, 1H), 3.43 (br, 1H), 3.23 (br, 4H), 2.22 (br, 2H), 1.88–1.76 (br, m, 2H), 1.43 (br, 18H), 1.25 (br, 4H), 1.03 (br, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 172.0, 155.9, 135.7, 133.6, 129.9, 127.9, 71.0, 60.5, 59.1, 55.2, 40.2, 38.9, 37.7, 28., 26.9, 19.2; $[\alpha]_D^{22.2} = -30.8^\circ$ (0.00089, CHCl_3); $\text{IR}_{\text{max}} \lambda = 2930$ (m), 1660 (s), 1105 (s), 700 (s); HRMS calculated for $[\text{C}_{56}\text{H}_{79}\text{N}_4\text{O}_8\text{Si}_2]^+$ $M = 991.5431$, found 991.5401.

1,4-Di(trans-4-tert-butyldiphenylsiloxy-L-prolinamide) butane 1. *N*-Boc protected diprolinamide **8** (0.394 g, 0.398 mmol) was solvated in DCM (18 mL) and stirred. To the stirring solution was added TFA (2 mL) to bring the solution to a 10 vol% concentration of acid/DCM. The solution was stirred for 6 h under an inert atmosphere at room temperature. The final mixture was basified with saturated NaHCO_3 (50 mL) and extracted into DCM (3×30 mL). The combined organic phase was then washed with additional NaHCO_3 (3×30 mL) and the organic phase was dried over MgSO_4 . The solvent was removed *in vacuo* to give an opaque oil. Residual solvent was azeotroped with Et_2O to give the final organocatalyst **1** as an amorphous pale brown solid (0.309 g, 0.39 mmol, 98%). $R_f = 4/33$ (1 : 9 MeOH : EtOAc); $\text{Mp} = 205.5\text{--}207^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.61 (m, 8H), 7.36 (m, 12H), 4.35 (br m, 2H), 4.00 (t, $J = 8.4$ Hz, 2H), 3.14 (m, 4H), 2.90 (d, $J = 12.1$, 2H), 2.58 (d, $J = 2.94$, 12.1, 2H), 2.26 (m, 2H), 1.70 (m, 2H), 1.45 (br, 4H), 1.04 (br, 18H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 173.7, 135.8, 133.2, 129.9, 127.9, 71.8, 65.9, 59.4, 51.9, 38.9, 26.7, 19, 15.4; $[\alpha]_D^{23.3} = -37.6^\circ$ ($c = 0.0025$, CHCl_3); $\text{IR} \nu_{\text{max}} = 2925$ (m), 1624 (s) 698 (s); HRMS calculated for $[\text{C}_{46}\text{H}_{63}\text{N}_4\text{O}_4\text{Si}_2]^+$ $M = 791.4382$, found 791.4395.

1,6-Di(trans-N-Boc-4-tert-butyldiphenylsiloxy-L-prolinamide) hexane 9. *trans-N-Boc-4-tert-butyldiphenylsiloxy-L-proline* 7 (0.714 g, 1.52 mmol) was dissolved in DCM (20 mL) and cooled to 0°C . HOBt (0.042 g, 0.36 mmol) was added to the solution and the mixture was stirred for 5 min. EDCI (0.271 g, 1.41 mmol) was added to the mixture followed by 3 min additional stirring followed by the introduction of 1,6-diaminohexane (0.084 g, 0.72 mmol) was introduced. The mixture



was allowed to reach room temperature and stirred for 16 h. The final reaction mixture was diluted with additional DCM (30 mL) and washed with 10% citric acid (3 × 30 mL), saturated NaHCO₃ (3 × 30 mL) and brine (1 × 30 mL). The resulting organic phase was dried over MgSO₄ and the solvent was removed *in vacuo* to give the crude boc protected diprolinamide **8**. The crude mixture was purified *via* flash chromatography (1/3 EtOAc:Pet spirits) to give the pure dimer as a white amorphous solid (0.484 g, 0.475 mmol, 66%). ¹H NMR (270 MHz, CDCl₃) δ (ppm) = 7.59–7.25 (m, 20H), 4.39 (m, 4H), 3.69–3.42 (m, 4H), 3.17 (br s, 4 H), 2.39–1.97 (br m, 4H), 1.43 (s, 18H), 1.40 (br, 4H), 1.24 (br, 4H), 1.02 (s, 18H). The compound was confirmed by correlation to published spectra.⁷

1-6-Di(*trans*-4-*tert*-butyldiphenylsiloxy-L-prolinamide) hexane

2. *N*-Boc protected diprolinamide **9** (0.318 g, 0.312 mmol) was solvated in DCM (18 mL) and stirred. To the stirring solution was added TFA (2 mL) to bring the solution to a 10 vol% concentration of acid/DCM. The solution was stirred for 6 h under an inert atmosphere at room temperature. The final mixture was basified with saturated NaHCO₃ (50 mL) and extracted into DCM (3 × 30 mL). The combined organic phase was then washed with additional NaHCO₃ (3 × 30 mL) and the organic phase was dried over MgSO₄. The solvent was removed *in vacuo* to give an opaque oil. Residual solvent was azeotroped with Et₂O to give the final organocatalyst **1** as an amorphous pale brown solid (0.252 g, 0.31 mmol, 99%). 7.608 (br m, 8H), 7.38 (br m, 12H), 4.35 (br, 2H), 3.99 (t, *J* = 8.4 Hz, 1H), 3.14 (sept, 4H), 2.89 (d, *J* = 12.1 Hz, 2H), 2.56 (dd, *J* = 4.45, 7.7 Hz, 2H), 2.24 (m, 2H), 1.7 (m, 2H), 1.41 (m, 4H), 1.27 (m, 4H), 1.03 (br s, 18H). Product was confirmed by ¹H NMR spectroscopy.⁷

1,8-Di(*trans*-*N*-Boc-4-*tert*-butyldiphenylsiloxy-L-prolinamide) octane **10.** *trans*-*N*-Boc-4-*tert*-butyldiphenylsiloxy-L-proline **7** (0.565 g, 1.20 mmol) was dissolved in DCM (15 mL) and cooled to 0 °C. HOBt (0.030 g, 0.022 mmol) was added to the solution and the mixture was stirred for 5 min. EDCI (0.241 g, 1.25 mmol) was added to the mixture followed by 3 min additional stirring followed by the introduction of 1,8-diaminooctane (0.082 g, 0.57 mmol). The mixture was allowed to reach room temperature and stirred for 16 h. The final reaction mixture was diluted with additional DCM (30 mL) and washed with 2 M HCl (2 × 30 mL), saturated NaHCO₃ (2 × 30 mL) and brine (2 × 30 mL). The resulting organic phase was dried over MgSO₄ and the solvent removed *in vacuo* to give the crude boc protected diprolinamide as a colourless oil. The crude mixture was purified *via* flash chromatography (1/9 EtOAc:Pet spirits) to give the pure dimer **10** as a viscous colourless oil (0.507 g, 0.544 mmol, 45%). *R*_f = 11/31 (1/3 EtOAc:Pet. Spirits); ¹H NMR (270 MHz, CDCl₃) δ (ppm) = 7.69–7.36 (m, 20H), 4.52–4.36 (m, 4H), 3.67–3.65 (m, 4H), 3.52–3.37 (m, 4H), 2.29–1.79 (m, 4H), 1.57 (s, 4H), 1.43 (s, 18H), 1.24 (s, 8H), 1.03 (s, 18H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 173.7, 153.9, 135.7, 133.6, 123.0, 127.7, 71.6, 70.8, 58.3, 57.8, 54.9, 54.6, 52.2, 52.0, 39.7, 38.9, 28.5, 28.4, 26.9, 19.4. [α]_D^{21.2} = –89.2° (*c* = 0.001, CHCl₃); IR ν_{\max} = 2928 (s), 1664 (s), 1162 (s), 702 (s); HRMS calculated for [C₆₀H₈₇N₄O₈Si₂]⁺ *M* = 1047.6057, found 1047.6075.

1,8-Di(*trans*-4-*tert*-butyldiphenylsiloxy-L-prolinamide) octane **3.** *N*-Boc protected diprolinamide **10** (568 mg) was solvated in DCM (18 mL) and stirred. To the stirring solution TFA (2 mL) was added to bring the solution to a 10 vol% concentration of acid/DCM. The solution was stirred for 7 h under an inert atmosphere at room temperature. The final mixture was basified with saturated NaHCO₃ (50 mL) and extracted into DCM (3 × 30 mL). The combined organic phase was then washed with additional NaHCO₃ (3 × 30 mL) and the organic phase was dried over MgSO₄. The solvent was removed *in vacuo* to give an opaque oil. Residual solvent was azeotroped with Et₂O to give the final organocatalyst **3** as pale brown solid (0.248 g, 0.29 mmol, 54%). *R*_f = 20/33 (1:9 MeOH–EtOAc); M.p. = 88.9–90 °C; ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.6 (m, 8H), 7.38 (m, 12H), 4.36 (br, 2H), 4.08 (t, *J* = 8 Hz, 2H), 3.15 (q, *J* = 4 Hz, 4H), 2.95–2.91 (dt, *J* = 12, 1.6 Hz, 2H), 2.62 (dd, *J* = 12, 3.2 Hz, 2H), 2.29 (m, 2H), 1.74 (ddd, *J* = 13.2, 8.4, 4.4 Hz, 2H), 1.42 (m, 8H), 1.23 (m, 4H), 1.04 (m, 18H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 174.37, 135.74, 135.69, 134.03, 133.73, 129.90, 129.86, 127.84, 127.82, 77.49, 77.17, 76.86, 74.81, 59.93, 55.62, 40.03, 38.86, 29.61, 29.15, 27.00, 26.82, 19.17; [α]_D^{22.5} = –16.0° (*c* = 0.001, CHCl₃); IR ν_{\max} = 2929 (s), 1657 (s), 702 (s); HRMS calculated for [C₅₀H₇₁N₂O₄Si₂]⁺ *M* = 847.5008, found 847.5016.

1,10-Di(*trans*-*N*-Boc-4-*tert*-butyldiphenylsiloxy-L-prolinamide) decane

11. *trans*-*N*-Boc-4-*tert*-butyldiphenylsiloxy-L-proline **7** (0.296 g, 0.63 mmol) was dissolved in DCM (15 mL) and cooled to 0 °C. HOBt (0.016 g, 0.012 mmol) was added to the solution and the mixture was stirred for 5 min. EDCI (0.127 g, 0.66 mmol) was added to the mixture followed by 3 min additional stirring followed by the introduction of 1,10-diaminodecane (0.051 g, 0.30 mmol). The mixture was allowed to reach room temperature and stirred for 16 h. The final reaction mixture was diluted with additional DCM (30 mL) and washed with 2 M HCl (2 × 30 mL), saturated NaHCO₃ (2 × 30 mL) and brine (2 × 30 mL). The resulting organic phase was dried over MgSO₄ and the solvent removed *in vacuo* to give the crude Boc protected diprolinamide as a colourless oil. The crude mixture was purified *via* flash chromatography (1/4 EtOAc:Pet spirits) to give the pure dimer **11** as a viscous colourless oil (0.246 g, 0.23 mmol, 36%). *R*_f = 18/31 (1/3 EtOAc:Pet. Spirits); ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.59 (m, 8H), 7.37 (m, 12H), 4.39 (s, 4H), 3.64–3.44 (m, 4H), 3.17 (br, 4H), 2.60 (dd, *J* = 12, 4 Hz, 2H), 2.28 (m, 2H), 1.73 (m, 2H), 1.43 (m, 4H), 1.28–1.90 (m, 4H), 1.44 (br, 18H), 1.4 (br, 4H), 1.2 (br, 12H), 1.02 (s, 18H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 173.66, 153.91, 135.69, 133.62, 129.99, 127.87, 70.85, 58.28, 57.78, 54.90, 54.56, 52.21, 52.01, 39.66, 38.88, 28.48, 28.35, 26.90, 19.14; [α]_D^{23.6} = –29.4° (*c* = 0.001, CHCl₃); IR ν_{\max} = 2929 (s), 1700 (s), 1162 (s), 702 (s); HRMS calculated for [C₆₂H₉₁N₄O₈Si₂]⁺ *M*⁺ = 1075.6370, found 1075.6345.

1,10-Di(*trans*-4-*tert*-butyldiphenylsiloxy-L-prolinamide) decane

4. *N*-Boc protected diprolinamide **11** (253 mg) was solvated in DCM (18 mL) and stirred. To the stirring solution TFA (2 mL) was added to bring the solution to a 10 vol% concentration of acid/DCM. The solution was stirred for 6 h under an inert atmosphere at room temperature. The final mixture was



basified with saturated NaHCO_3 (50 mL) and extracted into DCM (3×30 mL). The combined organic phase was then washed with additional NaHCO_3 (3×30 mL) and the organic phase was dried over MgSO_4 . The solvent was removed *in vacuo* to give an opaque oil. Residual solvent was azeotroped with Et_2O to give the final organocatalyst **4** as pale brown oil (0.136 g, 0.15 mmol, 66%). $R_f = 21/33$ (1 : 9 MeOH–EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) = 7.62 (m, 8H), 2.38 (m, 12H), 4.36 (s, 2H), 4.03 (t, $J = 8.4$ Hz, 2H), 3.15 (m, 4H), 2.92 (d, $J = 12$ Hz, 2H), 2.60 (dd, $J = 12$, 3.2 Hz, 2H), 2.32–2.26 (m, 2H), 1.73 (ddd, $J = 12.8$, 8, 4.4 Hz, 2H), 4.13 (br m, 4H), 1.22 (br s, 12H), 1.04 (s, 18H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ (ppm) = 174.3, 135.7, 134.0, 133.6, 129.8, 121.8, 59.9, 55.5, 47.9, 40.0, 38.8, 29.6, 29.4, 29.2, 26.9, 26.85, 19.0; $[\alpha]_{\text{D}}^{24.1} = -49.4^\circ$ ($c = 0.001$, CHCl_3); IR $\nu_{\text{max}} = 2928$ (s), 1662 (s), 702 (s); HRMS calculated for $[\text{C}_{52}\text{H}_{75}\text{N}_4\text{O}_4\text{Si}_2^+]$ $M = 875.5321$, found 875.5337.

1,12-Di(trans-N-Boc-4-tert-butylidiphenylsiloxy-L-prolinamide) dodecane 12. *trans-N-Boc-4-tert-butylidiphenylsiloxy-L-proline 7* (0.3 g, 0.64 mmol) was dissolved in DCM (25 mL) and cooled to 0°C . HOBt (0.021 g, 0.015 mmol) was added to the solution and the mixture was stirred for 5 min. EDCI (0.129 g, 0.67 mmol) was added to the mixture followed by 3 min additional stirring followed by the introduction of 1,12-diaminododecane (0.061 g, 0.305 mmol) was introduced. The mixture was allowed to reach room temperature and stirred for 16 h. The final reaction mixture was diluted with additional DCM (30 mL) and washed with 10% citric acid (3×30 mL), saturated NaHCO_3 (3×30 mL) and brine (1×30 mL). The resulting organic phase was dried over MgSO_4 and the solvent was removed *in vacuo* to give crude boc protected diprolinamide as colourless oil. The crude compound was purified *via* flash chromatography (1/3 EtOAc : Pet spirits) to give the pure dimer **12** as a viscous colourless oil (0.14 g, 0.127 mmol, 42%). $R_f = 1/3$ (1 : 1 EtOAc : Pet. Spirits); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) = 7.62 (m, 8H), 7.38 (m, 12H), 4.41–4.32 (br m, 4H), 3.71 (br, 2H), 3.44 (br, 2H), 3.16 (m, 4H), 2.31 (br, 2H), 2.06–1.94 (br m, 2H), 1.42 (br, 18H), 1.25 (br, 20H), 1.04 (br, 18H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm) = 171.4, 156.5, 135.7, 133.6, 129.9, 127.9, 71.0, 60.6, 58.9, 55.2, 40.2, 39.4, 36.9, 32.0, 29.8, 29.6, 29.34, 28.4, 26.9, 19.2; $[\alpha]_{\text{D}}^{24.6} = -46.7^\circ$ (0.00033, CHCl_3); IR $\nu_{\text{max}} = 2927$ (s), 11 656 (s), 700 (s); HRMS calculated for $[\text{C}_{64}\text{H}_{95}\text{N}_4\text{O}_8\text{Si}_2^+]$ $M = 1103.6683$, found 1103.6698.

1,12-Di(trans-4-tert-butylidiphenylsiloxy-L-prolinamide) dodecane 5. *N-Boc protected diprolinamide 12* (0.16 g, 0.0145 mmol) was dissolved in (18 mL) and stirred. To the stirring solution was added TFA (2 mL) to bring the solution to a 10 vol% concentration of acid/DCM. The solution was stirred for 6 h under an inert atmosphere at room temperature. The final mixture was basified with saturated NaHCO_3 (50 mL) and extracted into DCM (3×30 mL). The combined organic phase was then washed with additional NaHCO_3 (3×30 mL) and the organic phase was dried over MgSO_4 . The solvent was removed *in vacuo* to give a pale yellow oil. Residual solvent was azeotroped with Et_2O to give the final organocatalyst **5** as a viscous pale yellow oil (0.13 g, 0.144 mmol, 99%). $R_f = 20/33$ (1 : 9

MeOH : EtOAc); $^1\text{H NMR}$ (270 MHz, CDCl_3) δ (ppm) = 7.59 (br m, 8H), 7.38 (m, 12H), 4.36 (br, 1H), 4.09 (t, $J = 8.4$ Hz, 1H), 3.14 (m, 4H), 2.94 (d, $J = 11.9$ Hz, 2H), 2.65 (dd, $J = 11.9$, 3.32 Hz, 2H), 2.27 (m, 2H), 1.76 (m, 2H), 1.41 (br, 4H), 1.21 (br, 16H), 1.03 (br, 18H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm) = 173.9, 135.7, 133.9, 133.6, 129.1, 127.8, 74.6, 65.9, 59.8, 55.5, 39.7, 39.03, 29.78, 29.62, 29.52, 29.24, 26.7, 19.1, 15.4; $[\alpha]_{\text{D}}^{24.3} = -12.8^\circ$ (0.00113, CHCl_3); IR $\nu_{\text{max}} = 2927$ (s), 1658 (s), 1105 (s), 700 (s); HRMS calculated for $[\text{C}_{54}\text{H}_{79}\text{N}_4\text{O}_4\text{Si}_2^+]$ $M = 903.5634$, found 903.56196.

Di-tert-butyl 5,5'-(5,8-dioxa-2,11-diazadodecane-1,12-diyl)-bis(3-((tert-butylidiphenylsilyloxy)pyrrolidine-1-carboxylate). trans-4-tert-Butylidiphenylsiloxy-N-Boc-L-proline (7) (0.250 g, 0.533 mmol) was dissolved in DCM (15 mL) and cooled to 0°C . HOBt (0.014 g, 0.101 mmol) was added to the solution and the mixture was stirred for 5 min. EDCI (0.107 g, 0.558 mmol) was added to the mixture followed by 3 min additional stirring followed by the introduction of 1,8-diamino-3,6-dioxaoctane (0.037 mL, 0.253 mmol). The mixture was allowed to reach room temperature and stirred for 16 h. The final reaction mixture was diluted with additional DCM (30 mL) and washed with 2 M HCl (2×30 mL), saturated NaHCO_3 (2×30 mL) and brine (2×30 mL). The resulting organic phase was dried over MgSO_4 and the solvent removed *in vacuo* to give the crude boc protected diprolinamide as a colourless oil. The crude mixture was purified *via* flash chromatography (99/1 EtOAc : EtOH) to give the pure dimer as a viscous colourless oil (0.165 g, 0.157 mmol, 29%). $R_f = 20/37$ (99/1 EtOAc : EtOH); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) = 7.62–7.36 (m, 20H), 4.39 (m, 4H), 3.66 (m, 4H), 3.51 (m, 6H), 3.36 (m, 6H), 2.29–1.90 (m, 4H), 1.47 (s, 18H), 1.08 (s, 18H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm) = 135.73, 135.66, 133.56, 129.95, 127.86, 70.29, 55.23, 53.73, 28.42, 26.89, 19.15; $[\alpha]_{\text{D}}^{21.1} = -1.70^\circ$ ($c = 0.002$, CHCl_3); IR $\nu_{\text{max}} = 2930$ (s), 1701 (s), 1162 (s), 703 (s); HRMS calculated for $[\text{C}_{58}\text{H}_{83}\text{N}_4\text{O}_{10}\text{Si}_2^+]$ $M = 1051.5642$, found 1051.5623.

N,N'-((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(4-((tert-butylidiphenylsilyloxy) pyrrolidine-2-carboxamide) 16. *N-Boc protected oxygenated diprolinamide* (0.166 g, 0.158 mmol) was solvated in DCM (18 mL) and stirred. To the stirring solution TFA (2 mL) was added to bring the solution to a 10 vol% concentration of acid/DCM. The solution was stirred for 7 h under an inert atmosphere at room temperature. The final mixture was basified with saturated NaHCO_3 (50 mL) and extracted into DCM (3×30 mL). The combined organic phase was then washed with additional NaHCO_3 (3×30 mL) and the organic phase was dried over MgSO_4 . The solvent was removed *in vacuo* to give a yellow oil. Residual solvent was azeotroped with Et_2O to give the final organocatalyst as an orange solid (0.097 g, 0.114 mmol, 72%). $R_f = 21/32$ (1 : 9 MeOH–EtOAc); M.p. = 61–62.5 $^\circ\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) = 7.6 (m, 8H), 7.37 (m, 12H), 4.38 (br s, 2H), 4.14 (t, $J = 8$ Hz, 2H), 3.47 (m, 12H), 2.97 (d, $J = 12$ Hz), 2.71 (dd, $J = 12$, 4 Hz), 2.26 (m, 2H), 1.79 (m, 2H), 1.02 (m, 18H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm) = 135.75, 135.73, 135.72, 135.69, 133.84, 133.61, 129.93, 129.91, 127.88, 127.86, 127.84, 127.83, 74.38, 70.27, 69.94,



65.94, 59.83, 55.34, 39.80, 38.88, 26.96, 19.15, 19.14, 19.13, 19.08, 15.36; $[\alpha]_{\text{D}}^{22.5} = -0.17^\circ$ ($c = 0.01$, CHCl_3); IR $\nu_{\text{max}} = 2929$ (s), 1662 (s), 1111 (s), 703 (s); HRMS calculated for $[\text{C}_{48}\text{H}_{67}\text{N}_4\text{O}_4\text{Si}_2^+]$ $M = 851.4594$, found 851.4569.

Representative syntheses for aldol product racemates (benzaldehyde)

Procedure A: A stirred solution of water (15 mL) was charged with 10 M NaOH (1 mL). Ketone (0.28 mL, 2.7 mol, 5 equiv.) was added and the solution was stirred for 1 min. To the mixture was added aryl aldehyde (0.6 mL, 0.54 mmol, 1 equiv.) and the solution was stirred for 3 h. The mixture was extracted into CHCl_3 (3×20 mL) and the combined organic phase was dried with MgSO_4 . The racemic mixture was isolated *via* flash chromatography (1/3 EtOAc/Petroleum spirits).

Procedure B: Pyrrolidine (0.44 mL, 0.53 mmol, 1 equiv.) was added to a stirred solution of CHCl_3 . To the stirred mixture was added ketone (0.223 mL, 2.65 mmol, 5 equiv.) and aldehyde (80 mg, 0.53 mmol, 1 equiv.). Benzoic acid (20 mg, 0.16 mmol, 0.3 equiv.) was added to the mixture and the reaction was stirred at room temperature for 16 h. The reaction mixture was taken up in additional CHCl_3 and washed with 2 M HCl (2×20 mL). The organic phase was dried with MgSO_4 . The racemic mixture was analysed by chiral HPLC without purification.

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