The enantioselective benzoin condensation promoted by chiral triazolium precatalysts: stereochemical control *via* hydrogen bonding†

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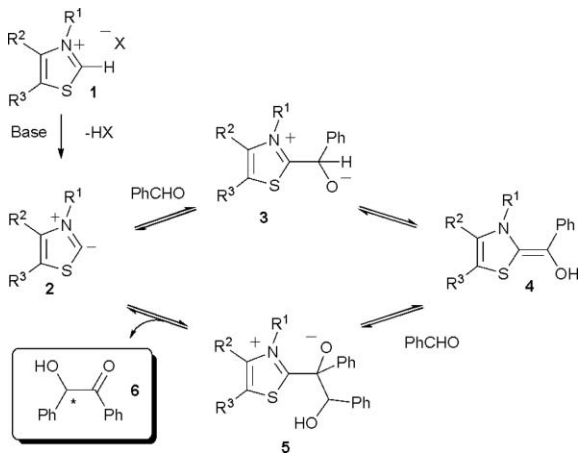
The design of a new class of triazolium ion precatalysts incorporating protic substituents is described. These materials promote the enantioselective benzoin condensation of a range of aromatic aldehydes (1–62% ee). Catalyst evaluation studies strongly support the involvement of hydrogen bond donation by the catalyst in the stereocentre-forming step of the catalytic cycle.

Introduction

In 1832, Wöhler and Liebig[1] discovered the cyanide-catalysed[2] carbon–carbon bond forming reaction between two benzaldehyde molecules, now commonly known as the benzoin condensation.[3] Over 70 years later Ukai and coworkers[4] demonstrated that the process could also be catalysed by thiazolium ions under basic conditions—which led to the later realisation that the catalytic activity of the cofactor thiamine (vitamin B_1) derives from the thiazolium ring component.[5] The mechanism of the thiazolium-catalysed benzoin condensation was elucidated by Breslow in 1958: initial deprotonation of salt **1** generates **2** (which could also be considered a carbene), which adds to benzaldehyde (for example), affording the key nucleophilic intermediate **4** *via* adduct **3**. Addition of **4** to a second benzaldehyde molecule furnishes **5**, leading to the formation of benzoin after elimination of **2**, which then re-enters the catalytic cycle (Scheme 1).[6]



Scheme 1 Mechanism of the thiazolium-derived carbene-catalysed benzoin condensation.

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The first chiral catalysts for the asymmetric variant of the benzoin condensation reaction were designed by Sheehan and Hunnemann in 1966.[7] The prototype catalyst promoted the reaction with low enantioselectivity. Later, a second generation thiazolium salt (**7**; Fig. 1) promoted more selective benzoin condensations; while the product could be isolated with an optimal enantiomeric excess of 52% ee, yields were low (6%).[8,9] Several groups later attempted to improve upon the performance of **7** through the design of mono-[10,11,12] and bicyclic thiazolium[13,14,15] ion variants—while yields could be improved (often at high catalyst loadings), product enantiomeric excess never rivalled that obtained by Sheehan.

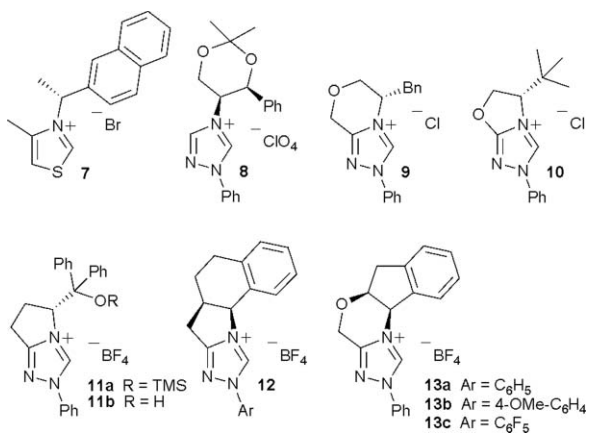


Fig. 1 Chiral precatalysts for the enantioselective benzoin condensation: selected examples.

In 1996, Enders and coworkers disclosed the design of the first chiral triazolium ion precatalyst. Salt **8** (Fig. 1) was capable of unprecedentedly selective catalysis in the presence of K_2CO_3, for example, benzaldehyde could be converted to benzoin in 66% yield and 75% ee, with other aldehyde substrates both product yield (22–72%) and enantioselectivity (20–88% ee) varied considerably. The same group later developed the improved conformationally restricted precatalyst variant **10** (building on earlier work by Leeper,[14] who developed precatalyst **9** in 1998), with this material benzoin could be prepared in 83% yield and 90% ee at ambient temperature, while as before both efficacy and selectivity were highly variable with substituted aldehyde substrates.[17]

Very recently the pyroglutamic acid-derived precatalyst **11a** has been developed—benzoin could be synthesised using this material in an outstanding 95% ee (66% yield); however, as has been the case with pre-catalysts **9–10**, substrates either more or less electron rich than benzaldehyde proved problematic.[18] Enders *et al.*[19] have also developed the tetracyclic triazolium precatalyst **12**—this material is similar in structure to the highly successful catalysts of general type **13** designed by the Rovis group[20,21] for enantioselective Stetter reactions and promoted highly selective intramolecular crossed-benzoin reactions.[22]

The rationale behind the design of **10–13** (for example[23]) is based on the use of the triazolium aryl- and rigid chiral substituent to selectively block three of the four quadrants dividing the space above and below the plane of the triazolium ion.[24] It is clear that **10–12** accomplish this particularly well, as high enantioselectivity with benzaldehyde as a substrate is possible; however, selectivity with activated aromatic aldehyde substrates and product yields using donor-substituted benzaldehydes are significantly lower. Since it is unlikely, therefore, that the design of a catalyst of increased steric requirement would offer any significant advantage over **10–13**, we were encouraged to consider a very different approach to precatalyst design—the development of a chiral triazolium ion devised to bring about stereocontrol through the donation of hydrogen bonds.

To the best of our knowledge, only two examples of hydrogen bond-donating carbene catalysts have been reported in the literature; Miller *et al.* found that the thiazolylalanine-derived catalyst **14** (Fig. 2) could promote enantioselective Stetter[25] and intermolecular aldehyde–imine couplings,[26] while very recently, Ye *et al.* disclosed the first protic triazolium systems (of which **11a** is representative) for the promotion of enantioselective aza-Morita–Baylis–Hillman[27] and ketene dimerisation[28] reactions. We were therefore encouraged to develop the first triazolium ion precatalyst system incorporating hydrogen bond-donating substituents for catalysis of the enantioselective benzoin condensation. In principle, such a catalyst would possess the potential to activate the aldehyde substrate towards nucleophilic attack by the carbene moiety *via* general acid catalysis, while simultaneously controlling the stereochemical outcome of the reaction.

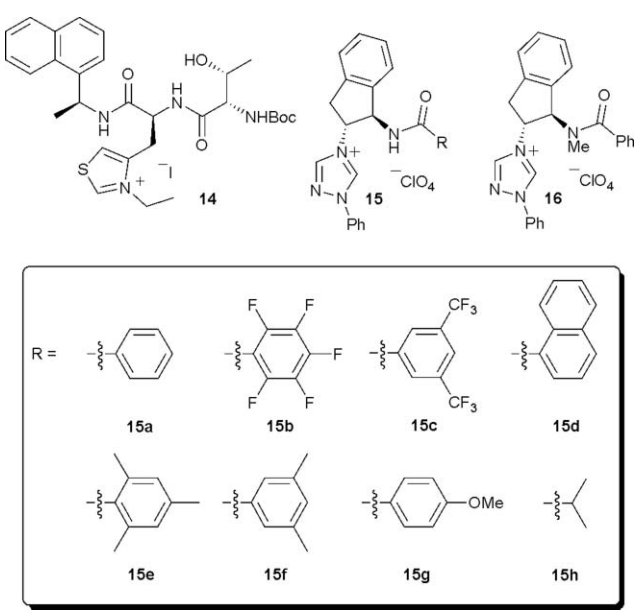


Fig. 2 Hydrogen bond-donating carbene precatalysts.

We designed catalysts of general structure **15** based on several criteria:

1. The pK_a of the hydrogen bond donating group should not be lower than that of the triazolium ion—thus, an amide functional group was chosen to serve as the catalyst's 'acidic' component.

2. The acidity of the hydrogen bond donor should be subject to a measure of control (*i.e.* catalysts **15a–c**,**f**, **g** and **h**) and its contribution to catalysis should be verifiable (*i.e. via* a comparison of the performance of catalysts **15a** and **16**).

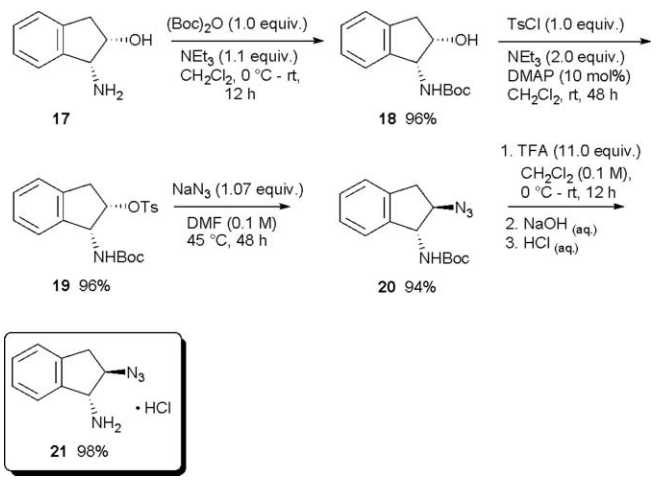
3. The steric requirement of the hydrogen bond donor should also be variable (catalysts **15a**,**d**,**e** and **h**)

4. At the proof of concept stage, the catalyst should be relatively rigid, but not necessarily conformationally locked, so as to allow for maximum scope for potential cooperation between the nucleophilic and hydrogen bond-donating components.

5. The catalyst should be easily accessible from a readily available, rigid chiral starting material.

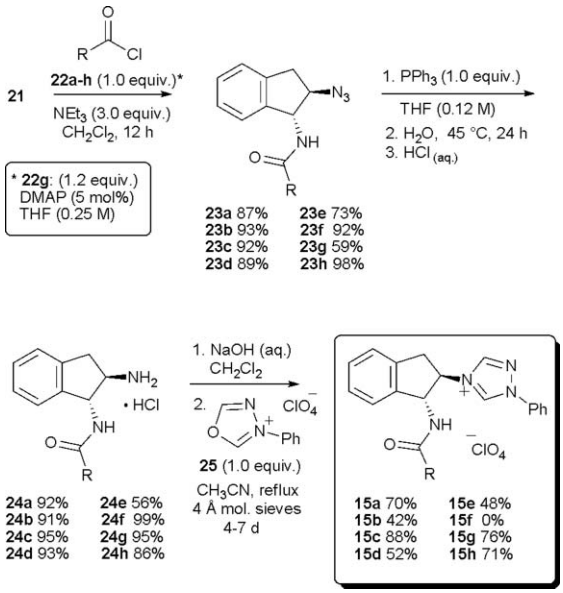
Catalyst synthesis

The preparation of catalysts **15a–h** and **16** was largely straightforward: Boc-protection of (1*R*,2*S*)-*cis*-1-amino-2-indanol (**17**) furnished alcohol **18**, which was tosylated and treated with NaN_3 to give azide **20** *via* **19**. Removal of the protecting group gave the corresponding primary amine—this serves as the common precursor to catalysts **15–16** and was isolated as its hydrochloride salt **21** in excellent overall yield (Scheme 2).



Scheme 2 Synthesis of common catalyst precursor **21**.

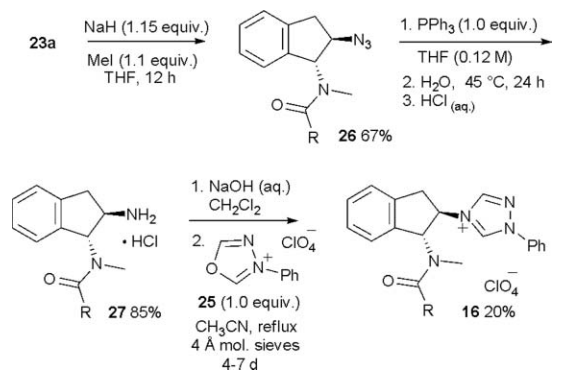
The acylation of **21** with acid chlorides **22a–h** proceeded smoothly in all cases, save that of the deactivated methoxy-substituted electrophile **22g**, which required the addition of catalytic DMAP and the use of THF solvent to obtain high product yield. Staudinger reduction of azides **23** gave the catalyst precursors **24** which could—after conversion to the corresponding free-base—then be reacted with freshly prepared oxadiazolium salt **25** in acetonitrile to afford catalysts **15**. While this route proved generally reliable (Scheme 3) and the catalysts could be purified by column chromatography, the almost complete insolubility of both



Scheme 3 Synthesis of precatalysts **15**.

24f and its corresponding free base in a range of organic solvents precluded the formation of triazolium ion **15f**.

The non-hydrogen bond-donating *N*-methyl catalyst **16** was prepared *via* the methylation of **23a** followed by an analogous sequence of reactions to that used to prepare **15a** from **23a** (Scheme 4).

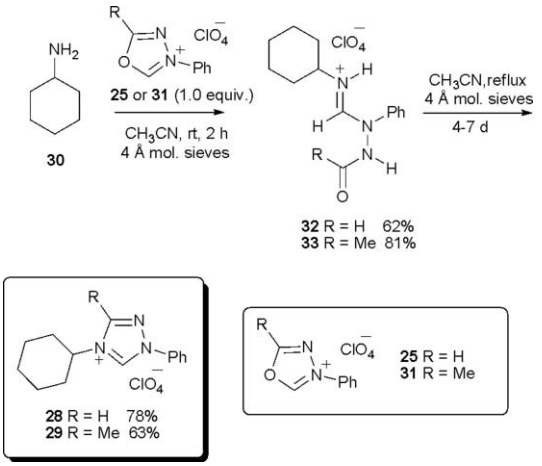


Scheme 4 Synthesis of precatalyst **16**.

Enders *et al.*[16] have reported that carbenes derived from triazolium ions devoid of substitution at C-3 are less stable catalysts than their C-3 substituted analogues. In order to probe this, we also synthesised the achiral catalysts **28** and **29** from cyclohexyl amine (**30**) and diazolium salts **25** and **31**(Scheme 5)—addition of the amine to the diazolium salts furnished isolable adducts **32** and **33**, which could then be slowly cyclised[29] in acetonitrile at reflux temperature to give the novel triazolium salts **28** and **29** in good yields.

Catalyst evaluation and optimisation of conditions

With **28** and **29** in hand, we wished both to ascertain if catalyst C-3 substitution is necessary for high activity and to determine the optimum conditions for catalysis of the benzoin condensation



Scheme 5 Synthesis of precatalysts **28** and **29**

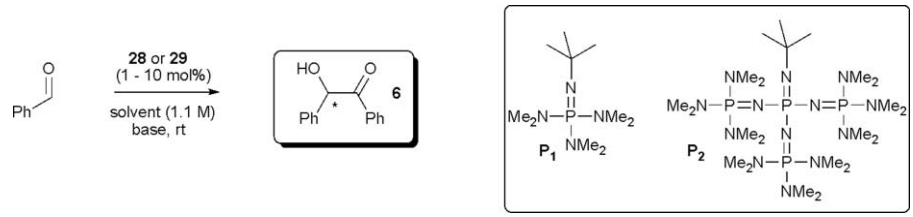
using salts of this general structure. A selection of results from this extensive screening programme is presented in Table 1.

We began by using caesium carbonate as the base (1 mol% loading of catalyst **28**) and identified THF as the only suitable solvent for use under these conditions (entries 1–9). The compatibility of other simple bases with the methodology was then evaluated: at 4 mol% catalyst loading (3.2 mol% base) Li_2CO_3, Na_2CO_3 and $NaHCO_3$ proved completely ineffective (entries 10–12), while $KHCO_3$ and K_2CO_3 furnished promising product yields of 32 and 42%, respectively, under identical conditions (entries 13 and 14). Optimisation of the loading of both catalyst and base using K_2CO_3 led to conditions under which **6** could be obtained in up to 58% yield (entries 14–20); however, this methodology was unsatisfactory due to a difficulty in arriving at a system of acceptable reproducibility (*i.e.* <5% discrepancy in yield between runs), despite considerable experimentation (>150 iterative runs) and the rigorous exclusion of air, moisture, *etc*. Likewise, the hygroscopic rubidium and caesium carbonate bases were capable of mediating product formation but were found to be very difficult to use reliably, despite extreme experimental care being exercised (entries 21–22).

Cadmium carbonate, potassium hydroxide, amine bases, KHMDS, sodium azide and phosphazene bases all failed to generate the carbene *in situ* (entries 23–30); however, somewhat surprisingly, a mixture of potassium carbonate and potassium hydroxide (1 : 1) was found to serve as a useful, and more importantly, a reproducible binary base system, which afforded **6** in 40% yield (entry 31). Optimisation of the ratio of bases and the base : catalyst ratio resulted in a pair of conditions under which the product could be reliably formed in *ca.* 50% yield (entries 32–35) over a series of repeated experiments using catalyst **28** at 4 mol% loading. At this point it is unclear why the combination of these two bases leads to a reproducible system—this phenomenon is currently under investigation.

Inspired by a recent study by Enders and Han disclosing the use of KHMDS in toluene solvent to generate carbene catalysts from triazolium salt precursors,[18] we decided to re-examine the use of KHMDS as a base. We subsequently discovered that despite the (reproducible) unsuitability of this base in THF solvent, its use in toluene results in good (>70%) yields of benzoin product if used at 10 mol% levels in conjunction with an equivalent amount

Table 1 Optimisation of conditions for the benzoin condensation involving achiral precatalysts **28** and **29**



Entry	Catalyst	Catalyst loading/mol%	Base	Base loading/mol%	Solvent	Time/h	Conversion (%)[a]	Yield (%)[b]
1	**28**	1.0	Cs_2CO_3	0.8	THF	66	41	31
2	**28**	1.0	Cs_2CO_3	0.8	CH_2Cl_2	48	7	7
3	**28**	1.0	Cs_2CO_3	0.8	$^iPr_2O$	48	0	0
4	**28**	1.0	Cs_2CO_3	0.8	MeCN	48	7	7
5	**28**	1.0	Cs_2CO_3	0.8	PhMe	48	1	1
6	**28**	1.0	Cs_2CO_3	0.8	1,4-dioxane	48	1	1
7	**28**	1.0	Cs_2CO_3	0.8	^{t}BuOH	48	2	2
8	**28**	1.0	Cs_2CO_3	0.8	Me_2CO	48	5	5
9	**28**	1.0	Cs_2CO_3	0.8	H_2O	48	0	0
10	**28**	4.0	Li_2CO_3	3.2	THF	48	0	0
11	**28**	4.0	Na_2CO_3	3.2	THF	48	0	0
12	**28**	4.0	$NaHCO_3$	3.2	THF	48	0	0
13	**28**	4.0	$KHCO_3$	3.2	THF	48	36	32
14	**28**	4.0	K_2CO_3	3.2	THF	48	47	42
15	**28**	1.0	K_2CO_3	0.8	THF	48	41	38
16	**28**	5.0	K_2CO_3	4.0	THF	48	28	25
17	**28**	10.0	K_2CO_3	8.0	THF	48	74	58
18	**28**	4.0	K_2CO_3	8.0	THF	48	21	22
19	**28**	4.0	K_2CO_3	1.8	THF	48	45	42
20	**28**	5.0	K_2CO_3	0.57	THF	48	56	39
21	**28**	4.0	Rb_2CO_3	3.2	THF	48	52	48
22	**28**	1.0	Cs_2CO_3	3.2	THF	66	23	24
23	**28**	4.0	$CdCO_3$	3.2	THF	48	0	0
24	**28**	4.0	KOH	3.2	THF	48	0	0
25	**28**	4.0	NEt_3	3.2	THF	60	0	0
26	**28**	4.0	DBU[c]	3.2	THF	33	18	17
27	**28**	4.0	KHMDS	3.2	THF	48	4	4
28	**28**	4.0	NaN_3	3.6	THF	48	0	0
29	**28**	4.0	P_1	3.6	THF	48	7	7
30	**28**	4.0	P_2	3.6	THF	48	0	0
31	**28**	4.0	K_2CO_3/KOH	1.6/1.6	THF	48	42	40
32	**28**	4.0	K_2CO_3/KOH	1.6/3.2	THF	48	12	11
33	**28**	4.0	K_2CO_3/KOH	2.4/1.6	THF	48	40	37
34	**28**	4.0	K_2CO_3/KOH	2.88/0.32	THF	66	46	41
35	**28**	4.0	K_2CO_3/KOH	2.88/0.64	THF	48	50	44
36	**28**	1.0	KHMDS	1.0	PhMe	48	3	3
37	**28**	4.0	KHMDS	4.0	PhMe	48	37	30
38	**28**	10.0	KHMDS	10.0	PhMe	48	98	79
39	**29**	10.0	KHMDS	10.0	PhMe	48	91	75
40	**29**	6.0	KHMDS	6.0	PhMe	48	56	36

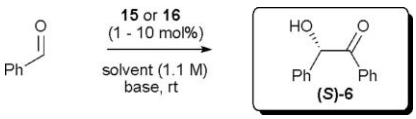
[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [c] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

of precatalyst **28** (entries 36–38). Interestingly, we also found that the C-3 methylated catalyst **29** exhibited an almost identical reactivity profile to **28** under these conditions, indicating that extensive catalyst decomposition *via* deprotonation of **28** at C-3 is not problematic in this system (entries 39–40).[16] Thus, at the conclusion of the study we had identified two sets of potentially useful reaction conditions under which we could evaluate the chiral catalysts **15** and **16**: one set using 4 mol% catalyst in THF in the presence of weak bases, and another employing a powerful base at higher catalyst and base loadings in a *less polar solvent* more potentially conducive to catalysis involving the donation of hydrogen bonds.

Asymmetric benzoin condensations

We next evaluated the performance of catalysts **15** and **16** in the asymmetric benzoin condensation reaction of benzaldehyde using the binary base system in THF (Table 2). Use of 4 mol% of the phenyl-substituted amide precatalyst **15a** resulted in a 25% yield of **(*S*)-6** in 54% ee (entry 1). Somewhat surprisingly, precatalysts **15b** and **15c**, which incorporate electron-withdrawing amide substituents (which we anticipated would facilitate hydrogen bond donation by the catalyst), furnished the benzoin product with lower yield and selectivity (entries 2 and 3, respectively). The 1-naphthyl-substituted amide (**15d**) exhibited a reactivity and

Table 2 The asymmetric benzoin reaction: catalyst evaluation studies



Entry	Cat.	Cond.[a]	Catalyst Loading/ mol%	Base Loading/ mol%	Yield (%)[b]	Ee(%)[c]
1	**15a**	A	4	2.88/0.64	25	54
2	**15b**	A	4	2.88/0.64	16	24
3	**15c**	A	4	2.88/0.64	11	16
4	**15d**	A	4	2.88/0.64	27	40
5	**15e**	A	4	2.88/0.64	27	31
6	**15g**	A	4	2.88/0.64	16	46
7	**15h**	A	4	2.88/0.64	28	47
8	**16**	A	4	2.88/0.64	23	13
9[d]	**15a**	A	4	2.88/0.64	0	—
10[e]	**15a**	A	4	2.88/0.64	1	—
11[f]	**15a**	A	4	2.88/0.64	16	60
12[g]	**15a**	A	4	2.88/0.64	4	37
13[h]	**15a**	B	10	10	19	47
14[i]	**15a**	B	10	10	60	31
15[j]	**15a**	B	10	9.8	63	9
16[k]	**15a**	B	5.0	5.0	11	19
17[l]	**15a**	B	10	9.0	21	45[m]
18[l]	**15a**	B	10	9.0	8	54[n]
19[l]	**15a**	B	10	10	12	62[n]

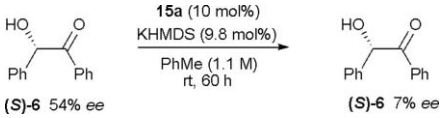
[a] Refers to conditions. Condition set **A**: THF (1.1 M), rt, K_2CO_3/KOH, 48 h. Condition set **B**: toluene (1.1 M), rt, KHMDS. [b] After chromatography. [c] Determined by chiral HPLC using a Chiralpak AD column (4.6 × 250 mm). [d] At 0 °C. [e] 0.1 M in THF. [f] 0.5 M in THF. [g] 2.0 M in THF. [h] Addition of KHMDS to the other components, rt, 48 h. [i] Addition of KHMDS to the other components, −78–0 °C, 66 h. [j] Addition of KHMDS to the other components, rt, 66 h. [k] Addition of KHMDS to the other components, rt, 69 [l] Addition of benzaldehyde to the other components. [m] 88 h reaction time. [n] 18 h reaction time

selectivity profile similar to that observed using **15a**, while catalysis with the hindered mesityl-substituted precatalyst **15e** resulted in reduced product enantioselectivity (entry 5). Precatalyst **15g**, with a relatively electron rich amide substituent furnished relatively good levels of enantioselectivity, albeit at the expense of product yield (entry 6). The aliphatic amide **15h** also proved a useful member of this suite of catalysts: the product yield was higher but the enantioselectivity was lower than that associated with the use of **15a**(entry 7). Thus, on balance it can be seen that while the use of electron deficient amide substituents is not well tolerated by the catalyst, no clear advantages with respect to *both* product yield and enantioselectivity associated with the incorporation of analogous electron-rich or bulky groups could be identified.

Most importantly, a comparison of the performance of **15a** with its *N*-methylated analogue (*i.e.* **16**), which is not capable of the donation of hydrogen bonds but is otherwise similar structurally to **15a**, is instructive: the use of **16** afforded the product in a similar yield to that obtained using **15a** but with considerably lower enantioselectivity (54% *vs.* 13% ee, entries 1 and 8 respectively). *This strongly indicates that the donation of hydrogen bonds by* ***15a*** *is a key control element in these processes.*[30] To the best of our knowledge, this represents the first example of the use of hydrogen bonding to control the stereochemical outcome of a benzoin condensation reaction.

With the superiority of **15a** identified, attention now turned to the question of optimisation of the conditions. At 0 °C no reaction was observed. While at a low concentration of 0.1 M only traces of product were obtained, at 0.5 M concentration product enantiomeric excess improved to 60% (with a concomitant reduction in yield), and at 2.0 M both product yield and selectivity were compromised (entries 9–12).

We also evaluated the efficiency and selectivity of the reaction under conditions involving the use of KHMDS as the base (entries 36–40, Table 1 and entries 13–19, Table 2). The results of these experiments were interesting—an inverse correlation between reaction yield and enantioselectivity was observed (entries 13–16), strongly indicative of product racemisation *in situ*. To confirm this, the catalytic process outlined in Table 2, entry 15 was repeated with enantioenriched (*S*)-benzoin (54% ee) replacing benzaldehyde as the starting material. After stirring for 60 h, the benzoin was recovered in greatly reduced enantiomeric excess (Scheme 6). To the best of our knowledge, such racemisation has not been reported previously.[18]



Scheme 6 Racemisation of **6** under the reaction conditions.

In an attempt to circumvent this problem, the asymmetric benzoin condensation was repeated under 'reverse addition' conditions (*i.e.* addition of benzaldehyde to a stirred mixture of the base and triazolium salt). With all the KHMDS consumed prior to the formation of **6**, racemisation was minimised, leading to the isolation of **6** with a maximum ee of 62% (entries 17–19). While these reactions were satisfactory from a selectivity standpoint, the isolated yield of the benzoin products diminished considerably.

With the optimum catalysts (*i.e.* **15a** and **15d**) and reaction conditions in hand, attention now turned to substrate scope (Table 3). We were struck by the dearth of material concerning the use of *ortho*-substituted aromatic substrates in catalytic asymmetric benzoin condensations in the literature and thus included them in this study. The reaction of 2-naphthaldehyde (**34**) in the presence of trizolium salt **15a** and KHMDS produced the aryloin product in 36% yield and 35% ee (entry 1). The hindered *o*-tolualdehyde (**35**) furnished no product, while use of the *para*-isomer **36** resulted in low product yield but improved product enantiomeric excess (entries 2 and 3). *o*-Anisaldehyde (**37**) is a relatively useful substrate, which gives the corresponding aryloin in 29% yield and 54% ee (entry 4). The analogous *para*-isomer **38** was not of sufficient activity to afford product under these conditions (entry 5). Concerning the chlorobenzaldehydes **39–41**—in line with previous studies in this reaction—the deactivated *meta*- and *para*-isomers **40** and **41** gave aryloins in relatively good yield but poor enantiomeric excess; however, somewhat surprisingly, the trend is reversed in the case of the *o*-chloroisomer **39**, the use of which leads to the isolation of **48** in poor yield but comparatively good ee (entries 6–8). Furfuraldehyde (**42**) is a substrate that allows the efficient formation of **51**; however, the enantiomeric excess was again poor (entry 9).

Finally, selected aldehydes (one electron neutral, one deactivated and one activated) were treated with the triazolium precatalyst **15d** in THF in the presence of the binary base system. Identical trends with respect to catalyst efficacy and product

Table 3 Evaluation of substrate scope

34 Ar = 2-naphthyl
35 Ar = 2-Me-C_6H_4
36 Ar = 4-Me-C_6H_4
37 Ar = 2-OMe-C_6H_4
38 Ar = 4-OMe-C_6H_4
39 Ar = 2-Cl-C_6H_4
40 Ar = 3-Cl-C_6H_4
41 Ar = 4-Cl-C_6H_4
42 Ar = 2-furyl

43 Ar = 2-naphthyl
44 Ar = 2-Me-C_6H_4
45 Ar = 4-Me-C_6H_4
46 Ar = 2-OMe-C_6H_4
47 Ar = 4-OMe-C_6H_4
48 Ar = 2-Cl-C_6H_4
49 Ar = 3-Cl-C_6H_4
50 Ar = 4-Cl-C_6H_4
51 Ar = 2-furyl

Entry	Cat.	Substrate	Cond.[a]	Yield (%)[b]	Ee (%)[c]	Abs. Config.[d]
1	**15a**	**34**	C	36	35	*S*
2[e]	**15a**	**35**	C	0	0	—
3[e]	**15a**	**36**	C	10	45	*S*
4[f]	**15a**	**37**	C	29	54	*S*
5[f]	**15a**	**38**	C	0	0	—
6	**15a**	**39**	C	8	28	*S*
7	**15a**	**40**	C	47	1	*S*
8	**15a**	**41**	C	32	6	*S*
9[e]	**15a**	**42**	C	49	1	*S*
10[g]	**15a**	**34**	A	26	38	*S*
11[g]	**15a**	**37**	A	7	52	*S*
12[g]	**15a**	**41**	A	66	5	*S*

[a] Refers to conditions. Condition set **C**: toluene (1.1 M), rt, KHMDS (10 mol%), 10 mol% catalyst, 16 h, addition of the aldehyde to the other components. Condition set **A**: THF (1.1 M), rt, K_2CO_3/KOH (2.88/0.64 mol%), 65 h, 4 mol% catalyst. [b] After chromatography. [c] Determined by chiral HPLC using either a Chiralpak AD, OD-H or OJ-H column (4.6 × 250 mm). [d] Refers to absolute configuration of the product. [e] 18 h reaction time. [f] 24 h reaction time. [g] 65 h reaction time.

enantioselectivity to those seen with the use of KHMDS as the base were observed (entries 10–12), thereby confirming that the disparate performances of substrates **34–42** in these reactions is due to the steric and electronic characteristics of the aldehydes themselves rather than the base or solvent used.

Conclusions

To summarise, we have designed a new class of chiral triazolium ion precatalysts, which incorporate protic substituents. These materials catalysed enantioselective benzoin condensations at loadings of 4–10 mol% under two sets of convenient conditions. The maximum product enantiomeric excess obtained was 62% and it was unambiguously demonstrated for the first time in this reaction class that the donation of hydrogen bonds by the catalyst is a key control element governing the stereochemical outcome of this bimolecular reaction. This offers an alternative to strategies based on the construction of the highly rigid fused systems, which dominate current thinking in this field. Although the bifunctional precatalysts are not yet of sufficient activity and selectivity to be of use on a process scale, the confirmation that hydrogen bond donation can be exploited to bring about augmented stereocontrol in this reaction should open new vistas in triazolium precatalyst design.

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Experimental

General

Proton nuclear magnetic resonance spectra were recorded on 400 and 600 MHz spectrometers in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), and DMSO-d_6 referenced relative to residual DMSO (H) (δ = 2.51 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz and 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a diamond Perkin Elmer Spectrum 100 FT-IR spectrometer using a universal ATR sampling accessory. Flash chromatography was carried out using silica gel, particle size 0.04–0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by either UV irradiation or $KMnO_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Toluene, ether and THF were distilled from sodium. Methylene chloride and triethylamine were distilled from calcium hydride. Analytical CSP-HPLC was performed using Daicel CHIRALCEL AD, CHIRALCEL OD-H and CHIRALCEL OJ-H (4.6 mm × 25 cm) columns. Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. Unless otherwise specified, all reactions were carried out in oven-dried glassware with magnetic stirrers under an atmosphere of argon.

Synthesis of oxadiazolium salts 25 and 31

***N*,*N*′-Diformyl-*N*-phenylhydrazine.** To a 25 cm^3 round bottomed flask equipped with a magnetic stirring bar was charged phenyl hydrazine (2.0 cm^3, 20.330 mmol). The reaction was cooled to 0 °C and treated with formic acid (2.2 cm^3, 57.320 mmol) turning the solution a crimson colour. The reaction was fitted with a reflux condenser and heated under reflux at 80 °C for 8 h and left to solidify overnight. The resulting mixture was triturated with ether and filtered to give a cream solid. Recrystallisation from hot ethanol gave the product (1.998 g, 59%) as an off-white crystalline solid, mp 125–126 °C, lit.,[31] 125–126 °C. The ^{1}H and ^{13}C NMR spectra of this compound indicate the presence of 4 rotameric species at rt in DMSO-d_6—the ratio of these was found to be 0.05 : 0.10 : 0.35 : 0.50; δ_H (600 MHz, DMSO-d_6) 7.22–7.52 (5H, m), 8.13 (0.10H, d, *J* 8.3), 8.28 (0.50H, s), 8.29 (0.35H, s), 8.37–8.39 (0.4H, m), 8.53 (0.05H, s), 8.80 (0.50H, s), 8.93 (0.10H, s), 10.27 (0.10H, d, *J* 8.3), 10.69–10.76 (0.55H, m), 11.07 (0.35H, s); δ_C (150 MHz, DMSO-d_6) 119.6, 120.1, 121.0, 121.4, 125.9, 126.0, 126.1, 126.3, 128.9, 129.1, 129.5, 129.6, 139.3, 139.4, 140.2, 140.5, 159.5, 159.9, 161.4, 161.6, 163.8, 164.1, 167.1, 167.2; ν_{max} (neat)/cm^{-1} 3161, 2929, 1658, 1590, 1346, 753, 691; *m*/*z* (ES) 187.0485 (M^+ + Na. $C_8H_8N_2O_2Na$ requires 187.0483).

3-Phenyl-[*1,3,4*]oxadiazol-3-ium perchlorate (25). To an oven-dried 25 cm^3 round bottomed flask equipped with a magnetic stirring bar was charged *N*,*N*′-diformyl-*N*-phenyl-hydrazine (2.180 g, 13.290 mmol). The reaction was cooled to 0 °C under an atmosphere of Ar and acetic anhydride (10.90 cm^3) was added *via* syringe. Perchloric acid (70%, 1.09 cm^3, 7.575 mmol) was added slowly over 15 min. The reaction changed from a cream suspension to a peach colour with precipitation of an off-white

solid. The reaction was triturated with ether and the solid was vacuum filtered under a stream of Ar to give **25** (2.755 g, 84%) as a white solid, mp 135–136 °C (dec), lit.,[26] 135 °C (dec.). Note **25** was too unstable to be characterised fully using NMR spectroscopy; product reverted back to starting material *via* hydrolysis caused by water present in DMSO solvent; ν_{max} (neat)/cm^{-1} 3066, 1691, 1328, 1058, 767, 684.

Acetic acid *N*-phenylhydrazide. A 100 cm^3 reaction vessel equipped with a magnetic stirring bar was charged with phenylhydrazine (3.0 cm^3, 30.493 mmol) and placed under an atmosphere of Ar. 20 cm^3 CH_2Cl_2 was added and the reaction cooled to 0 °C. Triethylamine (2.60 cm^3, 18.293 mmol) was added *via* syringe. After 15 min the reaction was equipped with an oven-dried 100 cm^3 pressure equalising dropping funnel and the reaction returned to an atmosphere of Ar. A solution of acetic anhydride (1.5 cm^3, 16.159 mmol) in 35 cm^3 CH_2Cl_2 was charged to the dropping funnel. The solution was added to the reaction dropwise at 0 °C over 8 h and left to come to ambient temperature overnight. NaOH (2.0 M, 25 cm^3) was added until the pH of the aqueous layer was 12. The organic layer was separated and the aqueous phase was extracted further with CH_2Cl_2 (4 × 25 cm^3). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (1 : 1 EtOAc–hexane, R_f 0.2) gave the desired product (2.360 g, 97%) as an off-white solid, mp 121–122 °C. The ^{1}H and ^{13}C NMR spectra of this compound indicate the presence of 2 rotameric species at rt in DMSO-d_6—the ratio of these was found to be 0.12 : 0.88; δ_H (600 MHz, DMSO-d_6) 1.86 (0.36H, s), 1.90 (2.64H, s), 6.70–6.71 (2.64H, m), 6.74–6.77 (0.36H, app. t), 7.12–7.15 (1.76H, app. t), 7.18–7.21 (0.24H, app. t), 7.63 (0.88H, d, *J* 2.3), 7.95 (0.12H, s), 8.91 (0.12H, s), 9.59 (0.88H, d, *J* 2.3); δ_C (150 MHz, DMSO-d_6) 19.2, 20.7, 111.7, 112.1, 118.3, 118.8, 128.7, 129.0, 148.8, 149.3, 168.9, 175.1; ν_{max} (neat)/cm^{-1} 3281, 3029, 1640, 1594, 1372, 754, 691; *m*/*z* (ES) 173.0697 (M^+ + Na. $C_8H_{10}N_2ONa$ requires 173.0691).

***N*′-Acetyl-*N*-formyl-*N*-phenylhydrazine.** Prepared as per the synthesis of *N*,*N*′-diformyl-*N*-phenylhydrazine using acetic acid *N*-phenylhydrazide (2.299 g, 15.320 mmol) and formic acid (1.63 cm^3, 43.203 mmol). The reaction was heated at 50 °C for 15 h and precipitation from ether gave the product (2.327 g, 85%) as a white solid, mp 83–85 °C, lit.,[31] 86 °C. The ^{1}H and ^{13}C NMR spectra of this compound indicate the presence of 2 rotameric species at rt in DMSO-d_6—the ratio of these was found to be 0.40 : 0.60; δ_H (600 MHz, DMSO-d_6) 2.00 (1.80H, s), 2.04 (1.20H, s), 7.20–7.50 (5H, m), 8.27 (0.40H, s), 8.80 (0.60H, s), 10.52 (0.60H, s), 10.95 (0.40H, s); δ_C (150 MHz, DMSO-d_6) 20.36, 20.41, 119.3, 120.7, 125.5, 125.6, 128.7, 129.3, 139.7, 140.9, 159.6, 164.1, 168.3, 169.8; ν_{max} (neat)/cm^{-1} 3474, 3374, 3172, 2968, 1692, 1660, 1590, 763, 683; *m*/*z* (ES) 201.0641 (M^+ + Na. $C_9H_{10}N_2O_2Na$ requires 201.0640).

5-Methyl-3-phenyl-[*1,3,4*]oxadiazol-3-ium perchlorate (31). Prepared as per the synthesis of **25** using *N*′-acetyl-*N*-formyl-*N*-phenylhydrazine (0.930 g, 5.220 mmol), acetic anhydride (4.3 cm^3) and perchloric acid (70%, 0.43 cm^3, 2.975 mmol). Filtration under a stream of Ar gave **31** (1.202 g, 88%) as a white solid, mp 215–216 °C (dec), lit.,[26] 215–216 °C (dec). Note **31** was too unstable to be characterised fully using NMR spectroscopy, product reverted back to starting material *via* hydrolysis due to water present in DMSO solvent; ν_{max} (neat)/cm^{-1} 3075, 2946, 1624, 1068, 768, 686.

Synthesis of precatalysts 28 and 29

Cyclohexyl-(*N*-formyl-*N*-phenyl-hydrazinomethylene)-ammonium perchlorate (32). To an oven-dried 10 cm^3 round bottomed flask equipped with a small magnetic stirring bar and oven-dried molecular sieves (4Å, 0.60 g) was charged **25** (0.498 g, 2.020 mmol) and the reaction quickly put under an atmosphere of Ar. A solution of cyclohexylamine (0.23 cm^3, 2.020 mmol) in CH_3CN (4.8 cm^3) was added *via* syringe. (Note: exothermic reaction.) The resulting pale yellow solution formed a white precipitate after several minutes. The reaction was stirred at ambient temperature for 2 h. Ether was added to the reaction to encourage further formation of the precipitate. Filtration of the precipitate under a stream of Ar gave **32** (0.433 g, 62%) as a white solid, mp 187–188 °C (dec.); δ_H (400 MHz, DMSO-d_6) 1.09–1.15 (1H, m), 1.22–1.31 (2H, m), 1.40–1.49 (2H, m), 1.61–1.65 (1H, app. d), 1.78–1.81 (2H, app. d), 1.90–1.93 (2H, app. d), 3.63–3.70 (1H, m), 7.39 (1H, t, *J* 6.8), 7.51–7.56 (4H, m), 8.34 (1H, s), 9.09 (1H, d, *J* 13.6), 10.32 (1H, dd, *J* 13.6, 7.8), 11.59 (1H, s); δ_C (100 MHz, DMSO-d_6) 24.5 (2C), 32.2, 57.7, 119.6, 127.7, 129.7, 140.1, 153.6, 159.9. 10C signals should be noted, 2C coalescing at 24.5 ppm; ν_{max} (neat)/cm^{-1} 3237, 2937, 2905, 1723, 1683, 1375, 761, 693; *m*/*z* (ES) 246.1597 ($M^+ - ClO_4$. $C_{14}H_{20}N_3O$ requires 246.1606).

4-Cyclohexyl-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium perchlorate (28). A 25 cm^3 round bottomed flask equipped with a magnetic stirring bar and oven-dried molecular sieves (4Å, 0.60 g) was charged with **32** (0.433 g, 1.252 mmol) and 10 cm^3 CH_3CN was added *via* syringe. The flask was fitted with a reflux condenser and heated under reflux at 90 °C for 4 d under an atmosphere of Ar. The crude reaction was filtered under a stream of Ar to remove the molecular sieves. Removal of the filtrate solvent *in vacuo* yielded a yellow solid. Recrystallisation from hot CH_3CN gave **28** (0.320 g, 78%) as white crystals, mp 248–250 °C; δ_H (400 MHz, DMSO-d_6) 1.09–1.19 (1H, m), 1.30–1.40 (2H, m), 1.60–1.82 (5H, m), 2.15–2.18 (2H, app. d), 4.32–4.39 (1H, m), 7.53 (1H, t, *J* 7.1), 7.61–7.65 (2H, m), 7.85 (2H, d, *J* 8.0), 9.47 (1H, s), 10.79 (1H, s); δ_C (100 MHz, DMSO-d_6) 24.2, 24.4, 32.0, 58.4, 120.7, 130.1, 130.5, 135.1, 140.5, 143.9; ν_{max} (neat)/cm^{-1} 3125, 2940, 2860, 1486, 1092, 1064, 761, 685; *m*/*z* (ES) 228.1510 ($M^+ - ClO_4$. $C_{14}H_{18}N_3$ requires 228.1501).

(*N*-Acetyl-*N*-phenyl-hydrazinomethylene)-cyclohexyl-ammonium perchlorate (33). Prepared as per the synthesis of **32** using molecular sieves (4Å, 3.00 g), **31** (1.202 g, 4.616 mmol), cyclohexylamine (0.50 cm^3, 4.396 mmol) and CH_3CN (11 cm^3). Purification of the resulting product *via* filtration under a stream of Ar gave **33** (1.273 g, 81%) as a white solid, mp 230–231 °C; δ_H (400 MHz, DMSO-d_6) 1.06–1.16 (1H, m), 1.23–1.32 (2H, m), 1.41–1.51 (2H, m), 1.63–1.66 (1H, app. d), 1.80–1.83 (2H, app. d), 1.90–1.94 (2H, m), 2.08 (3H, s), 3.63–3.69 (1H, m), 7.38 (1H, t, *J* 7.0), 7.47–7.55 (4H, m), 9.05 (1H, d, *J* 13.4), 10.24 (1H, dd, *J* 13.4, 8.1), 11.43 (1H, s); δ_C (100 MHz, DMSO-d_6) 21.5, 25.0 (2C), 32.7, 58.2, 120.0, 128.1, 130.1, 140.8, 154.3, 168.6. 11C signals should be noted, 2C coalescing at 25.0 ppm; ν_{max} (neat)/cm^{-1} 3235, 2931, 2857, 1725, 1686, 1372, 762, 693; *m*/*z* (ES) 260.1764 ($M^+ - ClO_4$. $C_{15}H_{22}N_3O$ requires 260.1763).

4-Cyclohexyl-3-methyl-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium perchlorate (29). Prepared as per the synthesis of **28** using molecular sieves (4Å, 6.30 g), **33** (2.270 g, 6.308 mmol) and CH_3CN (63 cm^3). H_2SO_4 (2.40 cm^3, 44.158 mmol) was added to the reaction *via* syringe prior to heating under reflux at 90 °C. The reaction was filtered after 7 d and removal of the filtrate solvent gave a yellow oily residue. Recrystallisation from hot CH_3CN gave **29** (1.356 g, 63%) as white crystals, mp 198–199 °C; δ_H (400 MHz, DMSO-d_6) 1.18–1.29 (1H, m), 1.44–1.54 (2H, m), 1.72–1.82 (3H, m), 1.89–1.92 (2H, app. d), 2.19–2.22 (2H, app. d), 2.73 (3H, s), 4.36–4.44 (1H, m), 7.61 (1H, t, *J* 7.4), 7.68 (2H, m), 7.94 (2H, d, *J* 8.2), 10.79 (1H, s); δ_C (100 MHz, DMSO-d_6) 10.6, 24.95, 25.0, 32.7, 57.5, 120.9, 130.5, 130.7, 135.5, 140.7, 153.7; ν_{max} (neat)/cm^{-1} 3132, 3101, 2949, 2928, 1584, 1470, 1074, 766, 680; *m/z* (ES) 242.1653 ($M^+ - ClO_4$. $C_{15}H_{20}N_3$ requires 242.1657).

Synthesis of common catalyst percursor 21

(1*R*,2*S*)-*cis*-(2-Hydroxy-indan-1-yl)-carbamic acid *tert*-butyl ester (18). An oven-dried 500 cm^3 reaction vessel containing a magnetic stirring bar and **17** (7.00 g, 46.920 mmol) was fitted with a septum seal and placed under an atmosphere of Ar. To this was added CH_2Cl_2 (140 cm^3) *via* syringe and the resulting solution cooled to 0 °C. Triethylamine (7.18 cm^3, 51.612 mmol) was added *via* syringe and the reaction stirred for 20 min. A 250 cm^3 pressure equalising dropping funnel was attached to the flask and the reaction returned to an Ar atmosphere. A solution of di-*tert*-butyl dicarbonate (97%, 10.56 g, 46.920 mmol) in CH_2Cl_2 (153 cm^3) was charged to the dropping funnel *via* syringe. The solution was added dropwise into the reaction at 0 °C over 8 h and the resulting clear colourless solution was left to stir overnight. CH_2Cl_2 (250 cm^3) and deionised water (300 cm^3) were then added. The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4 × 200 cm^3). The organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give **18** (11.230 g, 96%) as an off-white solid, not purified further, mp 76–77 °C, $[\alpha]_D^{20} = -13.6$ (*c* 3.00 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s), 2.30 (1H, s), 2.92 (1H, dd, *J* 16.6, 2.0), 3.11 (1H, dd, *J* 16.6, 5.0), 4.59–4.61 (1H, m), 5.07–5.22 (2H, m), 7.26–7.31 (4H, m); δ_C (100 MHz, $CDCl_3$) 28.0, 38.9, 58.4, 73.2, 79.4, 124.0, 124.9, 126.7, 127.7, 139.4, 140.4, 155.9; ν_{max} (neat)/cm^{-1} 3429, 3350, 2983, 2933, 1688, 1522, 1389, 1167, 735; *m/z* (ES) 272.1251 (M^+ + Na. $C_{14}H_{19}NO_3Na$ requires 272.1263).

(1*R*,2*S*)-*cis*-Toluene-4-sulfonic acid-1-*tert*-butoxycarbonylamino-indan-2-yl ester (19). To a 250 cm^3 round bottomed flask equipped with a stirring bar was added **18** (11.692 g, 46.920 mmol). A rubber septum seal was fitted and the reaction placed under an atmosphere of Ar and charged with CH_2Cl_2 (164 cm^3). The solution was cooled to 0 °C and triethylamine (13.06 cm^3, 93.840 mmol), tosyl chloride (8.940 g, 46.920 mmol) and dimethylaminopyridine (0.573 g, 4.692 mmol) were added sequentially. The mixture was warmed to ambient temperature and stirred for 48 h. The resulting pale yellow solution was diluted with CH_2Cl_2 (250 cm^3) and washed consecutively with 5% (v/v) HCl (164 cm^3), 5% (w/v) $NaHCO_3$ (164 cm^3) and brine (164 cm^3). The organic extract was then dried over $MgSO_4$ and concentrated *in vacuo* to give **19** as an off-white solid (18.223 g, 96%), no further purification, mp 162–163 °C; $[\alpha]_D^{20} = -108.8$ (*c* 0.53 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s), 2.48 (3H, s), 3.11 (2H, d, *J* 2.5), 5.03 (1H, d, *J* 9.5), 5.24 (1H, t of d, *J* 5.0, 2.5), 5.30 (1H, dd, *J* 9.5, 5.0), 7.20–7.27 (4H, m), 7.36 (2H, d, *J* 8.0), 7.80 (2H, d, *J* 8.0); δ_C (100 MHz, $CDCl_3$) 21.3, 27.9, 37.0, 57.1, 79.5, 83.2, 123.2, 124.6, 127.0, 127.4, 127.9, 129.5, 133.2, 137.7, 139.4, 144.4, 155.1; ν_{max} (neat)/cm^{-1} 3362, 2981, 2934, 1683, 1520, 1349, 1178, 1161, 818, 753; *m/z* (ES) 426.1369 (M^+ + Na. $C_{21}H_{25}NO_5NaS$ requires 426.1351).

(1*R*,2*R*)-*trans*-(2-Azido-indan-1-yl)-carbamic acid *tert*-butyl ester (20). An oven-dried 500 cm^3 reaction vessel equipped with a magnetic stirring bar was charged with a solution of **19** (18.240 g, 45.206 mmol) in DMF (452 cm^3). Sodium azide (3.150 g, 48.370 mmol) was added and the reaction placed under an atmosphere of Ar. The solution was heated at 45 °C for 48 h. The resulting clear yellow solution was cooled to room temperature and EtOAc (904 cm^3) added. The reaction was washed with ice cold deionised water (4 × 904 cm^3). The organic solvent was dried ($MgSO_4$) and solvent removed *in vacuo* to give **20** (11.630 g, 94%) as a cream solid, no further purification, mp 145–146 °C; $[\alpha]_D^{20} = -2.4$ (*c* 2.00 in $CHCl_3$). The ^1H NMR spectrum of this compound indicates the presence of 2 rotameric species at rt in $CDCl_3$—the ratio of these was found to be 0.10 : 0.90. The ^{13}C spectrum indicates the major rotamer only. δ_H (600 MHz, $CDCl_3$) 1.53 (8.10H, s), 1.59 (0.90H, s), 2.87 (1H, dd, *J* 15.8, 7.2), 3.26 (1H, dd, *J* 15.8, 7.4), 4.05–4.09 (1H, m), 4.55 (0.10H, s), 4.81 (0.90H, s (broad)), 5.04 (0.10H, s), 5.15 (0.90H, s (broad)), 7.23 (1H, d, *J* 6.8), 7.29–7.30 (3H, m); δ_C (150 MHz, $CDCl_3$) 28.3, 35.7, 61.1, 68.4, 80.0, 123.9, 124.8, 127.4, 128.6, 138.9, 140.0, 155.2; ν_{max} (neat)/cm^{-1} 3337, 2983, 2913, 2096, 1690, 1519, 1368, 1169, 747; *m/z* (ES) 297.1321 (M^+ + Na. $C_{14}H_{18}N_4O_2Na$ requires 297.1327).

(1*R*,2*R*)-*trans*-2-Azido-indan-1-yl-ammonium chloride (21). A 250 cm^3 round bottomed flask equipped with a magnetic stirring bar was charged with **20** (9.128 g, 33.276 mmol) and 130 cm^3 CH_2Cl_2. The reaction was cooled to 0 °C and TFA (28.2 cm^3, 366.037 mmol) was added dropwise over 30 min. The resulting solution was warmed to ambient temperature and left to sir overnight. NaOH (2.0 M, 75 cm^3) was added to raise the pH to 10. The organic layer was removed and the remaining aqueous layer washed with CH_2Cl_2 (4 × 50 cm^3). The organic extracts were combined, dried over $MgSO_4$ and solvent removed under reduced pressure to yield a brown liquid. The crude amine was dissolved in HCl (4.0 M, 100 cm^3) and solvent removed *in vacuo* to yield **21** (6.870 g, 98%) as a pale yellow solid, mp 194–195 °C; $[\alpha]_D^{20} = -78.0$ (*c* 0.90 in MeOH); δ_H (600 MHz, DMSO-d_6) 2.96 (1H, dd, *J* 16.3, 5.5), 3.52 (1H, dd, *J* 16.3, 7.3), 4.47–4.49 (1H, m), 4.60–4.61 (1H, m), 7.33–7.39 (3H, m), 7.63 (1H, d, *J* 7.3), 8.83 (3H, s (broad)); δ_C (150 MHz, DMSO-d_6) 36.2, 59.3, 64.4, 125.0, 125.2, 127.3, 129.6, 136.4, 140.4; ν_{max} (neat)/cm^{-1} 2837, 2715, 2118, 1608, 1521, 1459, 748; *m/z* (ES) 175.0992 ($M^+ - Cl$. $C_9H_{11}N_4$ requires 175.0984).

Synthesis of catalyst 15a

(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-benzamide (23a). A 50 cm^3 reaction vessel equipped with a magnetic stirring bar and **21** (2.000 g, 9.494 mmol) was placed under an atmosphere of Ar and 10 cm^3 CH_2Cl_2 added *via* syringe. The reaction was cooled to 0 °C and triethylamine (3.96 cm^3, 28.482 mmol) was charged. The reaction was stirred vigorously for 20 min and a solution of

22a (1.32 cm^3, 11.393 mmol) in CH_2Cl_2 (11 cm^3) was then added *via* syringe. The reaction was stirred at 0 °C for 30 min and left to stir at ambient temperature overnight. NaOH (2.0 M) was added to increase the pH to 12. The organic layer was removed and the aqueous phase extracted further with CH_2Cl_2 (4 × 20 cm^3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (7 : 3 CH_2Cl_2–hexane, R_f 0.2) yielded **23a** (2.296 g, 87%) as a white solid, mp 170–171 °C; $[\alpha]_D^{20} = -28.8$ (*c* 0.94 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.97 (1H, dd, *J* 16.1, 6.5), 3.35 (1H, dd, *J* 16.1, 7.3), 4.22–4.27 (1H, m), 5.63 (1H, dd, *J* 8.0, 6.0), 6.43 (1H, d, *J* 8.0), 7.28–7.36 (4H, m, (under $CHCl_3$ resonance), 7.45–7.49 (2H, app. t), 7.54 (1H, t, *J* 7.4), 7.83 (2H, d *J* 7.4); δ_C (100 MHz, $CDCl_3$) 36.3, 60.3, 68.1 124.3, 125.1, 127.1, 127.8, 128.7, 129.0, 131.9, 133.9, 139.7, 139.8, 167.5; ν_{max} (neat)/cm^{-1} 3262, 3070, 2911, 2099, 1638, 1526, 1342, 743; *m/z* (ES) 301.1071 (M^+ + Na. $C_{16}H_{14}N_4ONa$ requires 301.1065.

(1*R*,2*R*)-*trans*-1-Benzoylamino-indan-2-yl-ammonium chloride (24a). A 50 cm^3 round bottomed flask equipped with a stirring bar was charged with **23a** (1.066 g, 3.832 mmol) and triphenylphosphine (1.005 g, 3.832 mmol), and the reaction put under an atmosphere of Ar. THF (32 cm^3) was added *via* syringe and the resulting clear colourless solution was stirred at 45 °C for 14.5 h. Deionised water (8.0 cm^3) was added and the reaction was stirred at 45 °C for an additional 24 h. Solvent was removed under reduced pressure to give a yellow oil. This was dissolved in CH_2Cl_2 (40 cm^3) and HCl (3.0 M, 160 cm^3) was added, forming a white solid which dissolved slowly into the aqueous layer. The aqueous layer was separated and washed with CH_2Cl_2 (4 × 25 cm^3). The aqueous layer was concentrated *in vacuo* to give a white solid. Recrystallisation from hot methanol gave the hydrochloride salt **24a** (1.020 g, 92%) as a white solid, mp 285–287 °C; $[\alpha]_D^{20} = -19.8$ (*c* 0.88 in MeOH); δ_H (400 MHz, DMSO-d_6) 3.00 (1H, dd, *J* 15.6, 9.0), 3.34–3.40 (1H, m (under H_2O resonance)), 3.96–4.02 (1H, app. q), 5.70–5.74 (1H, app. t), 7.18 (1H, d, *J* 7.0), 7.20–7.33 (3H, m), 7.50 (2H, app. t), 7.56 (1H, t, *J* 7.0), 7.97 (2H, d, *J* 7.8), 8.63, (3H, s (broad)), 9.04 (1H, d, *J* 8.5); δ_C (100 MHz, DMSO-d_6) 34.6, 56.4, 57.6, 123.7, 124.8, 127.4, 127.6, 128.2, 128.3, 131.5, 134.0, 138.4, 141.0, 166.9; ν_{max} (neat)/cm^{-1} 3323, 2860, 2768, 1636, 1526, 1492, 748, 731, 694; *m/z* (ES) 253.1345 (M^+ – Cl. $C_{16}H_{17}N_2O$ requires 253.1341).

(1*R*,2*R*)-*trans*-4-(1-Benzoylamino-indan-2-yl)-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium perchlorate (15a). To an oven-dried 25 cm^3 round bottomed flask equipped with a magnetic stirring bar and oven-dried molecular sieves (4 Å, 2.26 g) was charged **25** (0.571 g, 2.316 mmol) and the reaction quickly put under an atmosphere of Ar. Hydrochloride salt **24a** (0.701 g, 2.427 mmol) was converted to the corresponding free base by dissolving the salt in NaOH (2.0 M, 5 cm^3) and washing with CH_2Cl_2 (4 × 10 cm^3). The organic extracts were combined, dried ($MgSO_4$) and solvent removed *in vacuo* to give the free-based amine of **24a** as a translucent solid. A solution of the amine (0.556 g, 2.206 mmol) in CH_3CN (10.3 cm^3) was added *via* syringe. The resulting pale orange solution was stirred overnight at ambient temperature. Removal of the solvent left a pale brown solid, crude intermediate, which was not isolated as per the procedure for synthesis of **28**. Oven-dried molecular sieves (4Å, 2.40 g) and CH_3CN (9 cm^3) were added to the crude reaction. The flask was fitted with a reflux condenser and heated under reflux at 90 °C for 5 d under an atmosphere of Ar. The crude reaction was filtered under a stream of Ar to remove the molecular sieves. Removal of the solvent of the filtrate *in vacuo* yielded a pale brown solid. Recrystallisation from cold $CHCl_3$ and diisopropyl ether gave **15a** (0.979 g, 92%) as an off-white solid, mp 121–123 °C; $[\alpha]_D^{20} = -70.6$ (*c* 1.42 in MeOH); δ_H (600 MHz, DMSO-d_6) 3.61 (1H, dd, *J* 15.8, 9.4), 3.73 (1H, dd, *J* 15.8, 8.7), 5.34 (1H, ddd, *J* 9.4, 8.7, 7.9), 6.13 (1H, dd, *J* 8.3, 7.9), 7.34 (1H, d, *J* 7.2), 7.37–7.45 (3H, m), 7.49–7.51 (2H, app. t), 7.57 (1H, t, *J* 7.3), 7.66 (1H, t, *J* 7.5), 7.73–7.76 (2H, app. t), 7.92 (2H, d, *J* 7.5), 7.96 (2H, d, *J* 7.9), 9.24 (1H, d, *J* 8.3), 9.75 (1H, s), 11.22 (1H, s); δ_C (150 MHz, DMSO-d_6) 36.4, 60.1, 65.4, 120.6, 123.9, 124.7, 127.6, 127.7, 128.3, 128.6, 130.3, 130.6, 131.7, 133.5, 134.9, 137.7, 139.2, 141.4, 144.7, 167.4; ν_{max} (neat)/cm^{-1} 3350, 3125, 3074, 2925, 1646, 1601, 1570, 1522, 1486, 1305, 1075, 757, 687; *m/z* (ES) 381.1722 (M^+ – ClO_4. $C_{24}H_{21}N_4O$ requires 381.1715)

Benzoin condensation: condition set A: K_2CO_3/KOH as base

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar were added K_2CO_3 (99.995%, anhydrous, 8.76 mg, 0.0634 mmol) and KOH (0.79 mg, 0.0141 mmol) that had both been finely ground using a mortar and pestle. The reaction vessel was rigorously dried (heat) under vacuum. When cooled to ambient temperature, the appropriate catalyst (0.088 mmol) and (*E*)-stilbene (49.57 mg, 0.275 mmol) were added. The flask was fitted with a septum seal and placed under an atmosphere of Ar. THF (1.78 cm^3) and the aldehyde (purified by a preliminary base wash with aq. $NaHCO_3$ followed by distillation) were then added *via* syringe and the reaction was stirred at room temperature for 48 h. CH_2Cl_2 (3.0 cm^3) and deionised H_2O (3.0 cm^3) were added. The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4 × 3.0 cm^3). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was purified using column chromatography. For full characterisation and CSP-HPLC conditions please see the ESI.†

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