Tetrahedron 67 (2011) 10164–10170

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly enantioselective aldol reactions using a *tropos* dibenz[*c*,*e*]azepine organocatalyst

Barry Lygo [a,*], Christopher Davison [a], Timothy Evans [a], James A.R. Gilks [a], John Leonard [b], Claude-Eric Roy [a]

[a] School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK
[b] AstraZeneca, Silk Business Park, Macclesfield, Cheshire SK10 2NA, UK

ARTICLE INFO

Article history:
Received 1 July 2011
Received in revised form 19 September 2011
Accepted 21 September 2011
Available online 4 October 2011

Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday

Keywords:
Asymmetric catalysis
Aldol
Organocatalysis
Diamine
Stereoselective

ABSTRACT

The four-step synthesis of a chiral primary tertiary diamine salt, possessing a *tropos* dibenz[*c*,*e*]azepine ring is described. It is shown that 3.5–5 mol % of this salt is capable of promoting highly enantioselective crossed-aldol reactions between cyclohexanone and a series of aromatic aldehydes. In all cases, the aldol reactions proceed with high diastereoselectivity for the *anti*-aldol product. The outcome of crossed-aldol reactions involving other cyclic ketones and acyclic ketones are also described. All examples involving cyclic ketones result in selectivity for the *anti*-aldol products, whereas acyclic ketones were found to favour the *syn*-aldol products. A discussion on the role of the chiral primary tertiary diamine salt in the catalysis of the aldol reactions is also presented.

1. Introduction

For a number of years our research group has been investigating the potential of asymmetric organocatalysts based on *tropos* dibenz[*c*,*e*]azepines derived from simple chiral amines. This has led to the development of a range of chiral dibenz[*c*,*e*]azepinium salts that have proved highly effective in asymmetric phase-transfer alkylation reactions.[1] During the course of these studies we have acquired increasing evidence to suggest that a stereogenic centre external to the dibenz[*c*,*e*]azepine ring is capable of generating a catalyst that behaves as if it were a single atropisomer. For example, the *tropos* dibenz[*c*,*e*]azepinium salt **1**, derived from (*R*)-α-methylbenzylamine, gives high enantioselectivity in the PTC alkylation of glycine imines.[1a] The magnitude and sense of enantioselectivity obtained in these reactions is consistent with the active catalyst adopting an (*aS*)-conformation about the aryl–aryl bond during PTC alkylation reactions (Fig. 1).

These observations led us to wonder if a similar phenomenon might be possible using tertiary ammonium salts derived from *tropos* dibenz[*c*,*e*]azepines. With this in mind we were attracted to a recent publication identifying amine salt **2** as a highly effective bifunctional organocatalyst for asymmetric aldol reactions.[2] In this study it was shown that *atropos* dibenz[*c*,*e*]azepinium salt (*R*,*R*,*aR*)-**2** was capable of generating the *anti*-aldol product from cyclohexanone and 4-nitrobenzaldehyde in 98% ee and >98:2 dr. In contrast, the corresponding (*S*,*S*,*aR*)-diastereoisomer of the catalyst was reported to give the *anti*-aldol product 85% ee and 79:21 dr. These observations suggest that the axial chiral element in catalyst **2** is having a significant influence on the stereochemical outcome of the reaction. This led us to ask the question, what would happen if the binaphthyl group was replaced by a conformationally-labile biaryl group? To probe this we investigated the potential of dibenz[*c*,*e*]azepinium salt **3** (Fig. 2) as a catalyst for asymmetric aldol reactions.

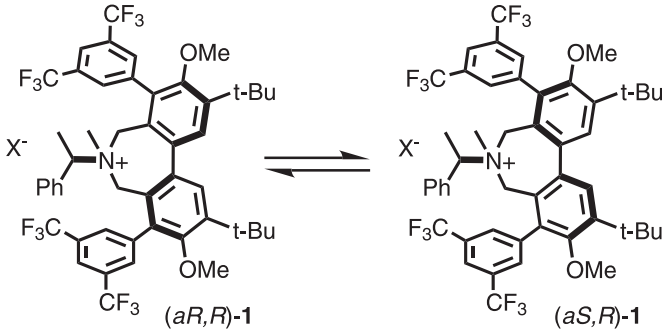


Fig. 1. *Tropos* dibenz[*c*,*e*]azepinium salt **1**.

* Corresponding author. E-mail address: b.lygo@nottingham.ac.uk (B. Lygo).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.101

In this paper we describe our preliminary findings, along with a discussion as to the possible role of the biaryl group in influencing the stereochemical outcome of aldol reactions involving catalyst **3**.

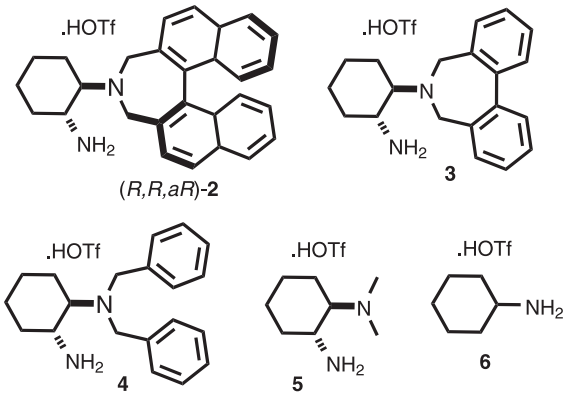
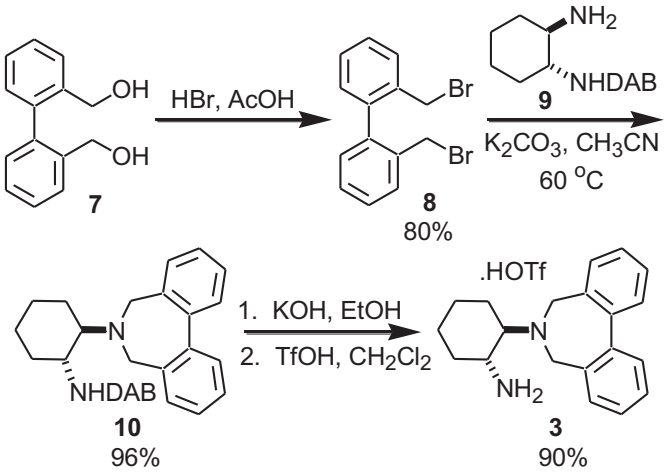


Fig. 2. Ammonium salts **2**–**6**.

2. Results and discussion

Diamine salt **3** was prepared as outlined in Scheme 1. Commercially-available diol **7** was converted into dibromide **8**, and then reacted with the known cyclohexane diamine derivative **9**.[3] Removal of the DAB-group followed by treatment with triflic acid then gave the desired salt **3** in 69% overall yield.



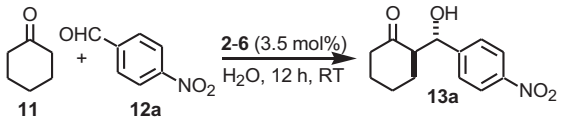
Scheme 1. Synthesis of ammonium salt **3**.

A slight modification of this route was also employed for the preparation of salts **4** and **5**. These additional diamine derivatives were prepared in order to aid evaluation of the role of the aryl–aryl bond in structure **3**.

Amine salts **3**–**5** were then tested as catalysts for the aldol reaction between cyclohexanone **11** and 4-nitrobenzaldehyde **12a**.[4] Cyclohexylamine salt **6** was also included in an effort to probe the influence of the tertiary amino group on the diastereoselectivity of these aldol processes. The reaction conditions initially employed were identical to those previously reported using catalyst **2**.[2] The results obtained are shown in Table 1.

It was found that the *tropos*-diamine salt **3** generated the *anti*-aldol product **13a** with high stereoselectivity.[5] The rate of reaction, diastereoselectivity and enantioselectivity observed were all almost identical to those reported for the *atropos*-diamine salt **2**. In contrast,

Table 1
Comparison of catalysts **2**–**6**



Catalyst	Conversion (%)	dr[a]	ee[b] (%)
2	100	98:2[2]	98[2]
3	100	98:2	98 (47)[c]
4	14	90:10	97
5	18	90:10	95
6[d]	≤2	36:64	—

[a] Determined by ^{1}H NMR spectroscopy.
[b] ee of *anti*-diastereoisomer.
[c] ee in parentheses is for *syn*-aldol product.
[d] A 1:1 mixture of cyclohexylamine and salt **6**.

N,*N*-dibenzyl analogue **4** generated the same aldol product, but with significantly reduced rate and diastereoselectivity. The lower diastereoselectivity obtained with this catalyst is in line with that reported for other primary-tertiary *trans*-1,2-diaminocyclohexane salts possessing alkyl substituents on the tertiary amine group.[6] It was also found that the *N*,*N*-dimethyl analogue **5** was a poor catalyst for this process, a result, that is, also in agreement with previous observations.[2,6] Under the conditions employed, cyclohexylamine salt **6** did not catalyze the reaction at all. However, a 1:1 mixture of cyclohexylamine and salt **6** did lead to ca. 2% conversion after 12 h, and gave a slight preference for the *syn*-aldol product.

These initial findings show that catalyst **3** is as effective as catalyst **2** for this aldol process, and suggest that the biphenyl group may play an important role in maximizing the diastereoselectivity. Moreover, as the (*S*,*S*,*aR*) diastereoisomer of **2** has been shown to be substantially less stereoselective, it suggests that catalyst **3** might preferentially adopt an *aR*-axis during the C–C bond forming step of the aldol process. If this were the case, it would represent another example of the power of induced atropisomerism in asymmetric catalysis.[8]

To probe this further, we investigated the effect of the reaction medium on the outcome of the aldol process. Cyclohexanone **11** and 4-nitrobenzaldehyde **12a** have low water solubility. As a consequence, the reaction conditions employed in Table 1 are heterogeneous. Switching from water to dichloromethane resulted in similar levels of stereoselectivity, but appeared to slow the reaction. As the reaction mixture in dichloromethane is homogeneous we sought to optimize the conditions before investigating a wider range of solvents. Using 5 mol % catalyst, it was found that varying ketone concentration between 0.5 M and 4 M had a dramatic effect on the rate of reaction (Fig. 3). At concentrations below 0.5 M the aldol took ca. 58 h to reach completion, whereas concentrations of 4 M and above gave complete conversion within 3 h. In neat cyclohexanone (9.7 M ketone) the reaction was complete within 2 h. This latter observation is interesting because the aldol reaction performed in the presence of water also has cyclohexanone in excess. In all cases the *anti*-aldol product **13a** was obtained with ≥97:3 dr and 97±1% ee.

As 5 mol % catalyst and a ketone concentration of 4.6 M resulted in complete conversion within 3 h at 20 °C, we employed these conditions to investigate the effect of varying the solvent (Table 2).

The results in Table 2 show that the process is tolerant of a wide range of solvents. In all cases the *anti*-aldol product **13a** was obtained as the major product. Diastereoisomeric ratios typically ranged from 95:5–98:2 and ees for the *anti*-aldol **13a** were typically 96–99%. Intriguingly, the stereoselectivity observed in dimethyl carbonate (94:6 dr, 93% ee) was significantly lower than in all the other solvents investigated. Sampling the reaction mixtures over time indicated that the stereoselectivity is maintained throughout the course of the reaction. This suggests that a well-

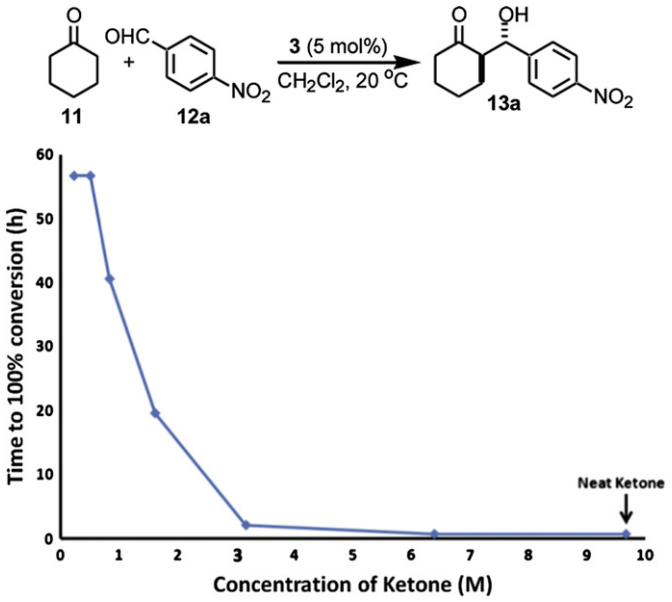
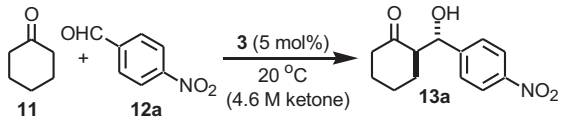


Fig. 3. Effect of ketone concentration on rate of reaction.

Table 2
Effect of solvent on stereoselectivity



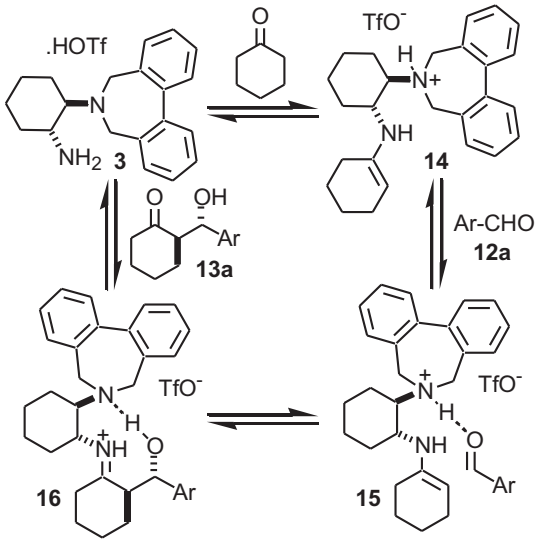
Solvent	ε	Time (h)[c]	dr[d]	ee[e] (%)
PhMe	2.4	3	96:4	96
$(MeO)_2CO$	3.1	3	94:6	93
t-BuOMe	4.5	3	97:3	97
EtOAc	6.0	3	97:3	96
2-MeTHF	7.0	3	97:3	96
THF	7.6	3	97:3	96
CH_2Cl_2	8.9	3	96:4	96
Cyclohexanone[a]	16.1	3	98:2	99
i-PrOH	19.9	3	97:3	98
EtOH	24.6	8	96:4	96
MeOH	32.7	15	95:5	98
CH_3CN	35.9	8	95:5	97
DMF	36.7	15	98:2	98
H_2O[b]	78.3	8	97:3	98

[a] Ketone (9.7 M).
[b] Heterogeneous reaction mixture.
[c] Time required for ≥97% conversion.
[d] Determined by ^1H NMR spectroscopy.
[e] ee of *anti*-diastereoisomer.

defined transition state is involved in the C–C bond forming step, and that solvent has a small but significant impact on both diastereoselectivity and enantioselectivity. Interestingly there also appears to be a significant reduction in the overall rate of reaction with more polar solvents (ε>20). It is possible that these solvents better stabilize polar reaction intermediates, and in this way retard the catalytic cycle (see below).

It is generally thought that primary tertiary 1,2-diamine salts of this type act as bifunctional catalysts in aldol reactions.[2,6,7] A possible catalytic cycle for diamine **3** is shown in Scheme 2. The results shown in Table 2 and Fig. 3 are entirely consistent with this, and the observation that (*R*,*R*)-**3** delivers similar stereoselectivity to (*R*,*R*,*aR*)-**2** suggests that the reaction may proceed preferentially with the *tropos*-biaryl element in **3** in the (*aR*)-conformation.

To probe this further we examined potential transition states for the transformation **15** to **16** using DFT calculations. These suggested



Scheme 2. Possible catalytic cycle for aldol reaction involving *tropos*-ammonium salt **3**.

that **TS-1** and **TS-2** (Fig. 4) were the two most viable transition states that could lead to the *anti*-aldol precursor **16**. Both of these have an antiperiplanar conformation about the enamine C–N bond, which is consistent with the high enantioselectivity observed in this reaction. Both transition states also have the aldehyde in the same orientation. The only difference between the two is the conformation of the azepinium ring, **TS-1** having an (*aS*)-conformation about the biaryl axis, and **TS-2** having an (*aR*)-conformation. In the gas phase, these two transition states were predicted to be almost identical in energy (**TS-1** being favoured by 0.1 kcal/mol).

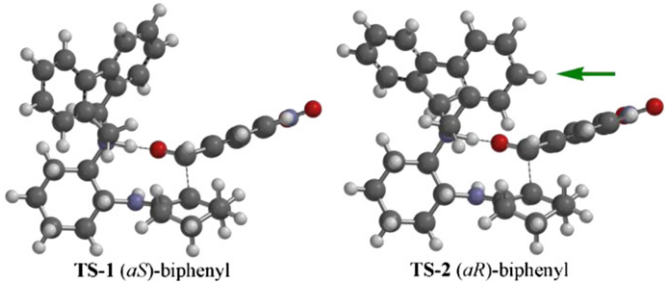


Fig. 4. Predicted transition state structures (B3LYP/6-31G**) for the conversion of **15** to **16**.

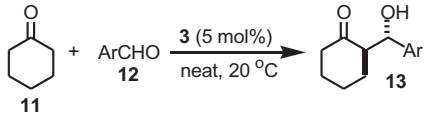
Inspection of the two transition state structures reveals that in **TS-2**, one of the aryl rings in the dibenz[*c*,*e*]azepinium fragment projects over the cyclohexene ring (indicated by an arrow in Fig. 4). This hinders alternative orientations of the aldehyde, and so is consistent with high *anti*-diastereoselectivity observed. In **TS-1**, this aryl ring is twisted away from the region above the cyclohexene ring and this may allow the aldehyde to approach in orientations that would lead to the minor *syn*-aldol product.

The two transition state structures shown are consistent with the proposal that the high diastereo- and enantioselectivities reported in Table 2 are a consequence of the dibenz[*c*,*e*]azepinium salt **3** acting as a bifunctional catalyst. They are also consistent with earlier observations that the corresponding (*R*,*R*,*aR*)-*atropos* dibenz[*c*,*e*]azepinium salt **2** also delivers high diastereo- and enantioselectivity, whereas its (*S*,*S*,*aR*)-diastereoisomer (which would lead to a transition state analogous to **TS-1**) results in significantly lower diastereoselectivity.[2] However, as **TS-1** and **TS-2** are predicted to be close in energy,[9] it may be that the high diastereoselectivity obtained using catalyst **3** is not a consequence of induced atropisomerism. Instead it may simply be the dynamic nature of the *tropos*

dibenz[*c*,*e*]azepinium ring that results in an effective steric barrier to orientations of the aldehyde that would lead to the minor *syn*-aldol product.

In order to probe this process further, we examined the effect of varying the nature of the aldehyde (Table 3). As this study included relatively unreactive aldehydes, all reactions were performed in neat cyclohexanone as this was found to give the shortest reaction times (see Fig. 3).

Table 3
Effect of aryl aldehyde structure



Entry	Ar	Time (h)	Yield (%)[a]	dr[b]	ee[c] (%)
a	4-$NO_2C_6H_4$	3	92	98:2	99
b	3-$NO_2C_6H_4$	3	88	97:3	96
c	2-$NO_2C_6H_4$	3	89	98:2	96
d	4-ClC_6H_4	4	84	98:2	98
e	4-BrC_6H_4	3	90	96:4	98
f	3-BrC_6H_4	3	92	95:5	98
g	2-BrC_6H_4	3	87	94:6	96
h	4-NCC_6H_4	3	91	98:2	97
i	Ph	6	61 (75)[d]	95:5	95
j	2-Naphthyl	5	63 (86)[d]	98:2	98
k	3-Furyl	15	65 (73)[d]	96:4	98
l	4-$MeOC_6H_4$	30	25 (93)[d]	87:13	95

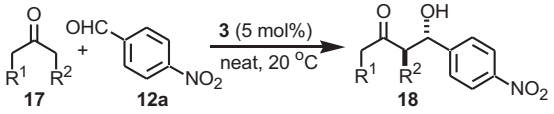
[a] Isolated yield after purification.
[b] Determined by ^{1}H NMR spectroscopy.
[c] ee of *anti*-diastereoisomer.
[d] Yield in parenthesis is based on consumed aldehyde.

Using 5 mol % catalyst, reactions involving electron-deficient aromatic aldehydes (**12a**–**h**) were complete within 4 h at room temperature. For these substrates the *anti*-aldol products **13** were obtained as the major product and diastereoisomer ratios ranged from 94:6 to 98:2. The ee of the *anti*-aldol products **13** were also high in all cases (95–99% ee). Although some variation in dr and ee was observed, this does not appear to correlate to the substitution pattern in the aromatic ring. This latter observation is consistent with the transition state structures depicted in Fig. 4, as both **TS-1** and **TS-2** can accommodate aldehydes substituted in the *o*-, *m*-, or *p*-positions.

For electron-neutral and electron-rich aromatic aldehydes (**12i**–**l**) the outcome is more complicated. All give the *anti*-aldol product **13** as the major isomer, and in all cases the ee of **13** is high (95–98% ee). However, with these substrates the aldol process is slower, and generally does not proceed to completion. The reaction times quoted in Table 3 refer to the point at which the ratio of starting material (aldehyde) to product remains constant. After this point, the proportion of product does not increase, but the dr starts to diminish. This is most pronounced for the electron-rich aromatic aldehyde **12l**, which after 6 h gives the *anti*-aldol product **13l** in 93:7 dr, but after 30 h at 20 °C this has fallen to 87:13. As the catalyst and starting materials do not appear to degrade under the reaction conditions, this is most likely a consequence of equilibration via retro-aldol reaction. It is known that diamine salts can promote retro-aldol process and that aldol products derived from electron-rich aldehydes react far faster that those derived from electron-poor aldehydes.[10] Low yields are often reported for amine-catalysed aldol reactions involving electron-rich aldehydes,[4] so this may be a common facet of this chemistry.

To further probe the utility of catalyst **3** the aldol reaction between 4-nitrobenzaldehyde and a number of other ketones (**17a**–**e**) was investigated (Table 4). We started by examining the effect of altering the ring size of the ketone. Cyclopentanone (**17a**) was found to react at a similar rate to cyclohexanone, and gave the *anti*-aldol product **18a** in high ee. However, when the reaction was performed using the same conditions as used for cyclohexanone, substantial amounts of bis-aldol product (25–30%) was obtained. Fortunately formation of this by-product could be suppressed simply by lowering the concentration of aldehyde. Under optimized conditions, the *anti*-aldol product **15a** was isolated in 76% yield, 80:20 dr and 97% ee In contrast, cycloheptanone (**17b**) was found to react at a much slower rate and no bis-aldol by-product was produced. In this case the reaction conditions used for cyclohexanone gave the *anti*-aldol product **18b** with good diastereoselectivity, but relatively low ee (72% ee). It was found that addition of 2 equiv of water to the reaction mixture increased the ee to 87% ee. Adding more water simply led to a reduction in the rate of reaction.

Table 4
Effect of ketone structure



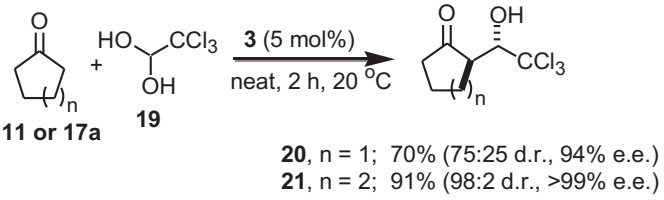
Entry	R^1	R^2	Time (h)	Yield (%)[a]	*anti*:*syn*[b]	ee[c] (%)
a[d]	$-(CH_2)_2-$		3.5	76[e]	80:20	97
b[f]	$-(CH_2)_4-$		13	99	90:10	87[g]
c[h,i]	H	H	22	86[j]	—	88
d[h]	CH_3	CH_3	30	93	20:80	98
e[f,h]	H	OBn	10	92	17:83	98

[a] Isolated yield after purification.
[b] Determined by ^{1}H NMR spectroscopy.
[c] ee of major diastereoisomer.
[d] Aldehyde added in three batches to minimize formation of bis-aldol adduct.
[e] 14% Bis-aldol product also obtained.
[f] Ketone (3 equiv) was used.
[g] Water (2 equiv) was added.
[h] 3-Nitrobenzoic acid (5 mol %) was added.
[i] Reaction performed at 10 °C.
[j] 6% Bis-aldol product also obtained.

Next we examined three acyclic ketones **17c**–**e** possessing different levels of substitution. These substrates were found to react at a significantly slower rate than cyclohexanone. It was found that addition of 5 mol % of 3-nitrobenzoic acid[6c] increased the rate of reaction for all three of these ketones. In contrast, addition of 3-nitrobenzoic acid had no beneficial effect on reactions involving cyclic ketones. When acetone (**17c**) was used, the bis-aldol by-product was again formed. In this case it was more convenient to suppress this by performing the reaction at 10 °C. Under these conditions, the aldol product **18c** could be isolated in 86% yield and 88% ee. With diethylketone (**17d**), the *syn*-aldol product **18d** was obtained as the major diastereoisomer in high ee. *syn*-Selectivity has also been reported for this reaction using a related primary-tertiary diamine catalyst[6c] and presumably arises due to reaction proceeding predominantly via the *Z*-enamine. Benzyloxyacetone (**17e**) was also found to favour the *syn*-aldol product, again in high ee. In this case only the branched aldol products (*syn*- and *anti*-**18e**) could be detected by ^{1}H NMR indicating that this reaction proceeds with high regioselectivity. This is again consistent with observations reported for related primary-tertiary diamine catalysts.[6c]

Finally, in an effort to further investigate the utility of catalyst **3** we examined the aldol reactions between cyclohexanone **11** and cyclopentanone **17a**, and chloral hydrate **19**. As far as we are aware, there has only been one previous report of enantioselective amine-catalyzed aldol reactions involving these ketones and chloral hydrate.[11] In this study it was shown that reaction of cyclohexanone **11** with chloral hydrate **19** in the presence of a proline tetrazole catalyst gave the *anti*-aldol product (92% de, 98% ee), whereas reaction of cyclopentanone **17a** with chloral hydrate **19** gave the *syn*-

aldol product (76% de, 82% ee). Such a dramatic switch in diastereoselectivity on going from cyclopentanone to cyclohexanone is unusual. Consequently we were interested to see whether the same switch would occur using catalyst **3**. It was found that both aldol reactions were complete within 3 h at 20 °C (Scheme 3) and in both cases the *anti*-aldol product (**20** and **21**) was obtained. For each ketone, the enantioselectivity and diastereoselectivity observed was in line with that obtained with other aldehydes, suggesting that chloral hydrate does not behave in an anomalous fashion when catalyst **3** is used.



Scheme 3. Aldol reactions involving chloral hydrate **19**.

3. Conclusion

In conclusion, we have been able to demonstrate that a simple *tropos* dibenz[*c*,*e*]azepinium salt **3** derived from *trans*-1,2-diaminocyclohexane can be prepared in four steps and 69% overall yield. This salt is able to promote stereoselective cross-aldol reactions between ketones and aldehydes. When cyclic ketones are used, *anti*-aldol products are obtained with high diastereo- and enantioselectivity. In contrast acyclic ketones were found to favour *syn*-aldol products. These observations are consistent with cyclic ketones reacting via an *E*-enamine intermediate and acyclic ketones reacting preferentially via a *Z*-enamine intermediate. High conversions and isolated yields are obtained when electron-deficient aromatic aldehydes and chloral hydrate are used. With electron-neutral and electron-deficient aromatic aldehydes the reactions do not proceed to completion, but in most cases reasonable isolated yields (60–65%) of the aldol products can be obtained.

4. Experimental

4.1. General information

All solvents and chemicals were used as provided by the supplier. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} pre-coated glass TLC plates, visualized using UV light and then basic potassium permanganate solution. Flash chromatography was performed using Merck silica gel (230–400 mesh) as the stationary phase. Melting points were determined using a Kopfler hot-stage apparatus and are uncorrected. Infrared spectra were recorded using either a Perkin–Elmer FT 1600 or a Nicolet Avatar 360 FT-IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV3400 or DPX400 spectrometer at ambient temperature. Chemical shifts are quoted relative to residual solvent and *J* values are given in hertz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Diastereoisomer ratios (dr) were measured by integration of the CHOH proton signals on expanded spectra. Mass spectra were obtained on a Micromass Autospec or Micromass LCT instruments using electron impact (EI) or electrospray (ES) ionization. Specific rotations were measured using a Bellingham and Stanley ADP440 polarimeter at ambient conditions and are given in units of deg cm^2 g^{-1}; *c* is in g/100 ml of solvent. HPLC analysis was performed on a Varian Pro-Star 210 machine fitted with a diode array detector. All ees were determined by HPLC comparison with racemates using Chiralcel OD-H or Chiralpak AD-H columns. HPLCs were run in duplicate and the ratio of integrals checked for consistency at four separate wavelengths (220 nm, 232 nm, 254 nm, 280 nm). All DFT calculations were performed using B3LYP/6-31G** as implemented in Spartan'10 v1.1.0.[12] Relative energies quoted are based on total energies (gas phase) at 298 K and have ZPE corrections applied. All transition states were verified by frequency calculations and by confirming that the imaginary frequency vibration was consistent with the C–C bond forming process depicted in Scheme 2.

Salt **5** was prepared as previously reported. The absolute stereochemistry of the *anti*-aldol products **13a**,[5] **13d**,[13] and **13i**,[14] **21**[11] was determined to be (2*R*,1′*S*) by comparison of HPLC retention times or sign of optical rotation with known compounds. The absolute stereochemistry of *anti*-aldol products **13b**,[6a] **13c**,[15] **13e**,[6a] **13f**,[16] **13g**,[17] **13h**,[6a] **13j**,[18] **13l**,[19] **18a**,[18] **18b**[20] is assumed to be (2*R*,1′*S*). These compounds all have HPLC retention times or sign of optical rotation consistent with those previously reported for compounds assumed to have this stereochemistry. The absolute stereochemistry of *syn*-aldol products **18d**,[6c] **18e**[6c] is assumed to be (1*S*,2*S*). These compounds all have HPLC retention times or sign of optical rotation consistent with those previously reported for compounds assumed to have this stereochemistry.

4.2. 2,2′-Bis-bromomethylbiphenyl, 8

Finely powdered 2,2′-biphenyldimethanol (2.40 g, 11.2 mmol) was dissolved in 33% HBr in acetic acid (30 ml) and the mixture was heated at reflux for 30 min. The reaction was then allowed to cool to room temperature and the precipitate collected by filtration. The filtrate was dissolved in chloroform (50 ml) and washed sequentially with saturated aqueous $NaHCO_3$ (50 ml) and brine (50 ml). The organic layer was dried (Na_2SO_4), then activated charcoal (1 g) added. After standing for 5 min the solution was filtered through a pad of Celite® and then concentrated under reduced pressure to give dibromide **8** (3.06 g, 80%) as a colourless solid, mp 85–86 °C (lit., mp 91–93 °C[21]). R_f 0.6 (9:1, petroleum ether/diethyl ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3067, 3022, 2990, 2933, 2878, 1475; δ_H (400 MHz, $CDCl_3$) 7.57 (2H, dd, *J* 7.5, 1.5 Hz, ArH), 7.44 (2H, ddd, *J* 7.5, 7.5, 1.5 Hz, ArH), 7.40 (2H, ddd, *J* 7.5, 7.5, 1.5 Hz, ArH), 7.30 (2H, dd, *J* 7.5, 1.5 Hz, ArH), 4.37 (2H, d, *J* 10.0 Hz, C*H*$_a$H$_b$), 4.22 (2H, d, *J* 10.0 Hz, CH$_a$*H*$_b$); δ_C (100 MHz, $CDCl_3$) 139.4 (C), 135.9 (C), 130.7 (CH), 130.2 (CH), 128.7 (CH), 128.3 (CH), 32.0 (CH_2); *m*/*z* (EI) 340 (M^+, $^{79}Br^{81}Br$, 6%), 261 (35), 259 (37), 179 (100), 178 (44), 76 (39), 51 (32); *m*/*z* (EI) found [M, $^{79}Br^{81}Br]^+$ 339.9282, $C_{14}H_{12}^{79}Br^{81}Br$ requires 339.9285.

4.3. DAB protected amine, 9[3]

A solution of (*R*,*R*)-1,2-diaminocyclohexane (0.69 g, 6.0 mmol) in dry tetrahydrofuran (120 ml) was placed under an argon atmosphere. 1,3-Dimethyl-5-acetylbarbituric acid (1.19 g, 6.0 mmol) was added and the reaction stirred at room temperature for 5 h over which time a white precipitate formed. The precipitate was collected by filtration and dried in air to afford amine **9** (1.71 g, 97%) as a colourless solid, mp 231–233 °C. $[\alpha]_D^{24}$ −63.0 (*c* 0.9, $CHCl_3$); R_f 0.3 (1:9 methanol/dichloromethane); $\nu_{max}(CHCl_3)/cm^{-1}$ 3675, 3378, 3009, 2942, 2863, 1702, 1638, 1593, 1523, 1478, 1382; δ_H (400 MHz, $CDCl_3$) 12.76 (1H, br d, *J* 7.5 Hz, NH), 3.48–3.37 (1H, m, NHC*H*), 3.33 (3H, s, NCH_3), 3.32 (3H, s, NCH_3), 2.87–2.79 (1H, m, NH_2CH), 2.75 (3H, s, CCH_3), 2.04–1.91 (2H, m, NHCHCH_2), 1.87–1.73 (2H, m, NH_2CHCH_2), 1.56 (2H, br s, NH_2), 1.48–1.15 (4H, m, 2× CH_2); δ_C (100 MHz, $CDCl_3$) 173.9 (C), 166.7 (C), 163.1 (C), 151.5 (C), 90.3 (C), 60.7 (CH), 54.9 (CH), 34.8 (CH_2), 32.4 (CH_2), 27.9 (CH_3), 27.6 (CH_3), 24.6 (CH_2), 24.5 (CH_2), 18.4 (CH_3); *m*/*z* (ES) 295 (M+H$^+$, 100%); *m*/*z* (ES) found $[M+H]^+$ 295.1769. $C_{14}H_{23}N_4O_3^+$ requires 295.1765.

4.4. DAB protected (1′*R*, 2′*R*)-6-(2′-aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine, 10

A solution of amine **9**[3] (1.73 g, 5.88 mmol) and dibromide **8** (2.00 g, 5.88 mmol) in acetonitrile (150 ml) was placed under an argon atmosphere. Anhydrous K_2CO_3 (5.36 g, 38.8 mmol) was added and the mixture stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, then filtered, washing through with dichloromethane (100 ml). The filtrand was concentrated under reduced pressure and the residue purified by chromatography on silica gel to give amine **10** (2.67 g, 96%) as a colourless solid, mp 106–108 °C. $[\alpha]_D^{22}$ −177.6 (*c* 0.8, $CHCl_3$); R_f 0.2 (69:30:1, petroleum ether/ethyl acetate/triethylamine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3692, 3676, 3606, 3067, 3009, 2941, 2862, 2813, 1731, 1700, 1637, 1597, 1478, 1383; δ_H (400 MHz, $CDCl_3$) 12.90 (1H, br d, *J* 7.0 Hz, NH), 7.48–7.44 (2H, m, ArH), 7.44–7.38 (2H, m, ArH), 7.38–7.31 (4H, m, ArH), 3.81–3.71 (1H, m, CHN), 3.60 (2H, d, *J* 12.5 Hz, NCH_aH_b), 3.48 (2H, d, *J* 12.5 Hz, NCH_aH_b), 3.37 (3H, s, NCH_3), 3.31 (3H, s, NCH_3), 2.90–2.81 (1H, m, CHN), 2.73 (3H, s, CCH_3), 2.22–2.14 (1H, m, CH_aH_b), 2.01–1.93 (1H, m, CH_aH_b), 1.89–1.78 (2H, m, CH_2), 1.60–1.23 (4H, m, 2× CH_2); δ_C (100 MHz, $CDCl_3$) 172.8 (C), 166.4 (C), 163.2 (C), 151.6 (C), 140.8 (C), 135.9 (C), 129.6 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 90.0 (C), 68.5 (CH), 55.6 (CH), 52.4 (CH_2), 33.5 (CH_2), 27.8 (CH_3), 27.8 (CH_2), 27.6 (CH_3), 25.4 (CH_2), 24.6 (CH_2), 18.6 (CH_3); *m*/*z* (ES) 473 (M+H^+, 100%); *m*/*z* (ES) found $[M+H]^+$ 473.2537. $C_{28}H_{33}N_4O_3^+$ requires 473.2547.

4.5. (1′*R*,2′*R*)-6-(2′-Aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine[22]

A solution of the azepine **10** (2.67 g, 5.64 mmol) in ethanol (100 ml) was placed under an argon atmosphere. Powdered KOH (1.90 g, 33.9 mmol) was added and the mixture was stirred at 50 °C for 24 h. The resulting solution was allowed to cool to room temperature, then diluted with water (150 ml) and dichloromethane (150 ml). The aqueous layer extracted with dichloromethane (2×150 ml), and the combined organics were then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the product (1.49 g, 90%) as a colourless oil. $[\alpha]_D^{25}$ −39.8 (*c* 0.8, $CHCl_3$); R_f 0.1 (97:2:1, dichloromethane/methanol/triethylamine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3374, 2933, 2859, 1602, 1450, 1080; δ_H (400 MHz, $CDCl_3$) 7.49–7.36 (8H, m, ArH), 3.61 (2H, d, *J* 12.5 Hz, NCH_aH_b), 3.54 (2H, d, *J* 12.5 Hz, NCH_aH_b), 2.83 (1H, ddd, *J* 10.5, 10.5, 4.0 Hz, CHN), 2.47–2.38 (1H, m, $CHNH_2$), 2.07–2.00 (3H, m, CH_aH_b and NH_2), 1.82–1.68 (3H, m, CH_aH_b and CH_2), 1.39–1.14 (4H, m, 2× CH_2); δ_C (100 MHz, $CDCl_3$) 140.9 (C), 136.7 (C), 129.8 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 72.1 (CH), 52.1 (CH_2), 52.0 (CH), 35.3 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 25.1 (CH_2); *m*/*z* (ES) 293 (M+H^+, 100%); *m*/*z* (ES) found $[M+H]^+$ 293.1995. $C_{20}H_{25}N_2^+$ requires 293.2012.

4.6. Triflate salt of (1′*R*,2′*R*)-6-(2′-aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (3)

A solution of triflic acid (765 mg, 5.09 mmol) in dichloromethane (40 ml) was added to a solution of (1′*R*,2′*R*)-6-(2′-aminocyclohexyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (1.49 g, 5.09 mmol) in dichloromethane (40 ml). The solution was stirred at room temperature for 1 h, then concentrated under reduced pressure to afford ammonium salt **3** (2.26 g, 100%) as an off-white solid, mp 74–76 °C. $[\alpha]_D^{25}$ −6.0 (*c* 1.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3690, 3674, 3606, 3069, 3043, 2946, 2866, 1603, 1451, 1374, 1287, 1241, 1175, 1028; δ_H (400 MHz, $CDCl_3$) 7.57–7.32 (8H, m, ArH), 5.48 (3H, br s, NH_3^+), 3.63 (2H, d, *J* 12.5 Hz, 2× NCH_aH_b), 3.54 (2H, d, *J* 12.5 Hz, 2× NCH_aH_b), 3.24–3.13 (1H, m, CHN), 2.93–2.80 (1H, m, $CHNH_2$), 2.38–2.27 (1H, m, CH_aH_b), 1.95–1.86 (1H, m, CH_aH_b), 1.86–1.73 (2H, m, CH_2), 1.71–1.53 (1H, m, CH_aH_b), 1.52–1.22 (3H, m, CH_aH_b and CH_2); δ_C (100 MHz, $CDCl_3$) 140.8 (C), 135.0 (C), 129.9 (CH), 128.2 (2× CH), 127.6 (CH), 120.2 (q, *J* 319 Hz, CF_3), 66.9 (CH), 52.4 (CH), 51.7 (br, 2× CH_2), 29.9 (CH_2), 26.6 (CH_2), 25.1 (CH_2), 24.1 (CH_2); *m*/*z* (ES) 293 (M−TfO^-, 100%), 242 (54); *m*/*z* (ES) found [M−TfO^-] 293.2002. $C_{20}H_{25}N_2^+$ requires 293.2012.

4.7. DAB protected (1*R*,2*R*)-*N*,*N*-dibenzyldiaminocyclohexane

A solution of benzaldehyde (309 mg, 2.91 mmol) and amine **9** (171 mg, 0.58 mmol) in acetonitrile (4 ml) and water (0.2 ml) was stirred for 45 min until the reaction was homogeneous. $NaCNBH_3$ (76.8 mg, 1.22 mmol) was added and the reaction stirred for a further 30 min. Acetic acid (0.2 ml) was then added and the mixture concentrated under reduced pressure. The residue was dissolved in chloroform (10 ml), washed with 1 M aqueous NaOH (2×5 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the product (185 mg, 83%) as a colourless oil. $[\alpha]_D^{24}$ −9.9 (*c* 1.0, $CHCl_3$); R_f 0.3 (65:33:1 petroleum ether/ethyl acetate/triethylamine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3013, 2943, 1639, 1478, 1384; δ_H (400 MHz, $CDCl_3$) 12.81 (1H, d, *J* 7.0 Hz, NH), 7.37–7.35 (4H, m, ArH), 7.30–7.23 (6H, m, ArH), 3.79 (2H, d, *J* 14.0 Hz, 2× NCH_aH_b), 3.58 (2H, d, *J* 14.0 Hz, 2× NCH_aH_b), 3.56–3.51 (1H, m, CHN), 3.47 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 2.84 (1H, ddd, *J* 11.0, 11.0, 3.5 Hz, CHN), 2.40 (3H, s, CCH_3), 2.20–2.17 (1H, m, CH_aH_b), 1.98–1.95 (1H, m, CH_aH_b), 1.91–1.87 (1H, m, CH_aH_b), 1.76–1.72 (1H, m, CH_aH_b), 1.52–1.42 (1H, m, CH_aH_b), 1.34–1.16 (3H, m, CH_aH_b and CH_2); δ_C (100 MHz, $CHCl_3$) 172.7 (C), 165.0 (C), 163.0 (C), 151.6 (C), 139.2 (C), 128.7 (CH), 128.3 (CH), 127.1 (CH), 89.8 (C), 63.0 (CH), 55.1 (CH), 54.5 (CH_2), 34.1 (CH_2), 27.8 (CH_3), 27.5 (CH_3), 25.0 (CH_2), 24.7 (CH_2), 23.6 (CH_2), 18.0 (CH_3); *m*/*z* (ES) 497 (M+Na^+, 100%), 304 (60); *m*/*z* (ES) found $[M+Na]^+$ 497.2524. $C_{28}H_{34}N_4O_3Na^+$ requires 497.2523.

4.8. (1*R*,2*R*)-*N*,*N*-dibenzyldiaminocyclohexane[3]

A solution of DAB protected (1*R*,2*R*)-*N*,*N*-dibenzyldiaminocyclohexane (132 mg, 0.26 mmol) in ethanol (4 ml) was placed under an argon atmosphere. Finely ground KOH (72.7 mg, 1.30 mmol) was added and the reaction heated to 50 °C for 25 h. The mixture was allowed to cool to room temperature, then diluted with water (15 ml) and dichloromethane (15 ml). The aqueous layer was extracted with dichloromethane (2×10 ml) and the combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the product (53.0 mg, 70%) as a pale orange oil. $[\alpha]_D^{25}$ −61.3 (*c* 1.0, $CHCl_3$); R_f 0.1 (97:2:1 dichloromethane/methanol/triethylamine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3373, 3352, 2933, 2859, 1452; δ_H (400 MHz, $CDCl_3$) 7.37–7.24 (10H, m ArH), 3.87 (2H, d, *J* 13.5 Hz, 2× NCH_aH_b), 3.43 (2H, d, *J* 13.5 Hz, 2× NCH_aH_b), 2.73 (1H, ddd, *J* 10.5, 10.5, 4.0 Hz, CHN), 2.20 (1H, ddd, *J* 11.5, 10.5, 3.5 Hz, CHN), 2.04–2.00 (4H, m, NH_2 and 2× CH_aH_b), 1.87–1.82 (1H, m, CH_aH_b), 1.69–1.65 (1H, m, CH_aH_b), 1.33–1.09 (3H, m, CH_aH_b and CH_2), 1.03–0.92 (1H, m, CH_aH_b); δ_C (100 MHz, $CHCl_3$) 140.1 (C), 128.8 (CH), 128.3 (CH), 126.8 (CH), 64.6 (CH), 53.7 (CH_2), 51.1 (CH), 34.7 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 22.5 (CH_2); *m*/*z* (ES) 295 (M+H^+, 100%); *m*/*z* (ES) found $[M+H]^+$ 295.2172. $C_{20}H_{27}N_2^+$ requires 295.2169.

4.9. Triflate salt of (1′*R*,2′*R*)-*N*,*N*-dibenzyldiaminocyclohexane (4)

A solution of triflic acid (18.9 mg, 0.13 mmol) in dichloromethane (1 ml) was added to a solution of (1*R*,2*R*)-*N*,*N*-dibenzyldiaminocyclohexane (37.0 mg, 0.13 mmol) in dichloromethane (1 ml). The solution was stirred at room temperature for 1 h, then concentrated under reduced pressure. The residue was dissolved in

diethyl ether (0.5 ml) then petroleum ether (0.5 ml) was added and the mixture filtered. The filtrand was concentrated under reduced pressure to give **4** (46.3 mg, 83%) as a colourless solid, mp 49 °C. $[\alpha]_D^{22}$ −34.3 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2941, 1603, 1454, 1240, 1028; δ_H (400 MHz, $CDCl_3$) 7.37–7.24 (10H, m, ArH), 3.79 (2H, d, *J* 13.5 Hz, 2× NCH_aH_b), 3.47 (2H, d, *J* 13.5 Hz, 2× NCH_aH_b), 2.89 (1H, ddd, *J* 11.0, 11.0, 4.0 Hz, CHN), 2.49 (1H, ddd, *J* 11.5, 11.0, 3.5 Hz, NCH), 2.16–2.13 (1H, m, CH_aH_b), 2.00–2.04 (1H, m, CH_aH_b), 1.86–1.84 (1H, m, CH_aH_b), 1.74–1.71 (1H, m, CH_aH_b), 1.41–1.18 (4H, m, 2× CH_2); δ_C (100 MHz, $CHCl_3$) 138.6 (C), 128.9 (CH), 128.7 (CH), 127.5 (C), 120.1 (q, *J* 319 Hz, CF_3), 61.8 (CH), 53.9 (CH_2), 51.3 (CH), 30.6 (CH_2), 24.8 (CH_2), 24.1 (CH_2), 23.1 (CH_2); *m*/*z* 295 (M−TfO^-, 100%); *m*/*z* (ES) found [M−TfO^-] 295.2164. $C_{20}H_{27}N_2^+$ requires 295.2169.

4.10. General procedure used to investigate effect of solvent (Table 2)

Cyclohexanone (0.60 ml, 6.4 mmol) was added to a solution of diamine salt **3** (8.9 mg, 20 μmol) in the solvent (0.7 ml). A solution of 4-nitrobenzaldehyde (60 mg, 0.40 mmol) in the solvent (0.7 ml) was then added and the mixture stirred at 20 °C. Aliquots (0.1 ml) were taken after 1 h, 2 h, 3 h, 4 h, 8 h and 15 h. The catalyst was removed by passing the aliquots through a short plug of silica, using ethyl acetate (5 ml) to elute. They were then concentrated under reduced pressure and immediately assayed by ^1H NMR and chiral HPLC. Reactions were stopped after >97% consumption of 4-nitrobenzaldehyde.

4.11. General procedure used to investigate effect of aldehyde structure (Table 3)

Aldehyde (0.40 mmol) in cyclohexanone (118 mg, 1.20 mmol) was added to a reaction tube containing diamine salt **3** (8.9 mg, 0.02 mmol). The mixture was stirred for 3–30 h at 20 °C, then purified by chromatography on silica gel to give the aldol products. ees and drs were measured on unpurified samples.

4.12. General procedure used to investigate effect of ketone structure (Table 4)

The appropriate ketone (4.0 mmol) was added to a reaction tube containing diamine salt **3** (8.9 mg, 0.02 mmol) and any additives specified. 4-Nitrobenzaldehyde (60.4 mg, 0.40 mmol) was then added and the mixture stirred for 3–30 h at 20 °C, then purified by chromatography on silica gel to give the aldol products. drs were measured on unpurified samples, ees were measured on both unpurified and purified samples.

4.13. (2*R*,1′*S*)-2-(1′Hydroxy-1′-(fur-3-yl)methyl)cyclohexan-1-one 13k

Colourless oil; $[\alpha]_D^{29}$ −11.4 (*c* 1.0, $CHCl_3$, 98% ee); ν_{max} ($CHCl_3$)/cm^{-1} 3528, 3009, 2944, 1697, 1504, 1450, 1239, 1023, 874; R_f 0.3 (1:4 ethyl acetate/petroleum ether); δ_H (400 MHz, $CDCl_3$) 7.42–7.41 (2H, m, ArH), 6.45–6.42 (1H, m, ArH), 4.83 (1H, dd, *J* 8.0, 3.0 Hz, CHOH), 3.86 (1H, d, *J* 3.0 Hz, OH), 2.63 (1H, dddd, *J* 13.0, 8.0, 5.0, 1.0 Hz, CHCO), 2.52–2.47 (1H, m, CH_aH_b), 2.43–2.34 (1H, m, CH_aH_b), 2.17–2.10 (1H, m, CH_aH_b), 1.90–1.83 (1H, m, CH_aH_b), 1.74–1.60 (2H, m), 1.41–1.30 (1H, m, CH_aH_b); δ_C (100 MHz, $CDCl_3$) 215.3 (C), 143.4 (CH), 140.1 (CH), 125.6 (C), 108.7 (CH), 67.1 (CH), 56.5 (CH), 42.7 (CH_2), 30.8 (CH_2), 27.8 (CH_2), 24.8 (CH_2); *m*/*z* (ES) 217 (M+Na^+, 100%); *m*/*z* (ES) Found 217.0839. $C_{11}H_{14}O_3Na^+$ requires 217.0835; HPLC: Chiralcel OD-H; mobile phase, hexane/2-propanol (90:10 v/v); flow rate, 0.8 ml/min; retention times, 10.3 min (1.0%), 13.6 min (99.0%), 98% ee.

Acknowledgements

Financial support for this work was provided by AstraZeneca, EPSRC and the Leverhulme Trust.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.101.

References and notes

1. (a) Lygo, B.; Allbutt, B.; Beaumont, D. J.; Butt, U.; Gilks, J. A. R. *Synlett* **2009**, 675–680; (b) Lygo, B.; Beaumont, D. J. *Chimia* **2007**, *61*, 257–262; (c) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461–4464; (d) Melville, J. L.; Lovelock, K. J. R.; Wilson, C.; Allbutt, B.; Burke, E. K.; Lygo, B.; Hirst, J. D. *J. Chem. Inf. Model* **2005**, *45*, 971–981; (e) Lygo, B.; Humphreys, L. D. *Synlett* **2004**, 2809–2811; (f) Lygo, B.; Allbutt, B. *Synlett* **2004**, 326–328; (g) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525; (h) Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629–5632.
2. Peng, F.-Z.; Shao, Z.-H.; Pu, X.-W.; Zhang, H.-B. *Adv. Synth. Catal.* **2008**, *350*, 2199–2204.
3. Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978–5981.
4. For recent reviews on application of amine organocatalysis in aldol chemistry see: Bhanushali, M.; Zhao, C.-G. *Synthesis* **2011**, 1815–1830; Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632; Zlotin, S. G.; Kucherenko, A. S.; Beletskaya, I. P. *Russ. Chem. Rev.* **2009**, *78*, 737–784.
5. The absolute stereochemistry of **13a** was established by comparison of HPLC retention times with those previously reported: Inoue, H.; Kikuchi, M.; Ito, J.-I.; Nishiyama, H. *Tetrahedron* **2008**, *64*, 493–499.
6. (a) Lin, J.-H.; Zhang, C.-P.; Xiao, J.-C. *Green Chem.* **2009**, *11*, 1750–1753; (b) Luo, S.; Li, J.; Zhang, L.; Xu, H.; Cheng, J.-P. *Chem.—Eur. J.* **2008**, *14*, 1273–1281; (c) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075.
7. Liu, Q.-Z.; Wang, X.-L.; Luo, S.-W.; Zheng, B.-L.; Qin, D.-B. *Tetrahedron Lett.* **2008**, *49*, 7434–7437; Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177; Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245–1248.
8. Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561–1578.
9. For a discussion on the utility of B3LYP/6-31G** calculations for comparison of relative transition state energies of organocatalysed aldol processes see: Allemann, C.; Um, J. M.; Houk, K. N. *J. Mol. Catal. A: Chem.* **2010**, *324*, 31–38 and references therein.
10. Luo, S.; Zhou, P.; Li, J.; Cheng, J.-P. *Chem.—Eur. J.* **2010**, *16*, 4457–4461.
11. Torii, H.; Masakazu, N.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986.
12. Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio, R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C. P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172–3191.
13. Doherty, S.; Knight, J. G.; McRae, A.; Harrington, R. W.; Clegg, W. *Eur. J. Org. Chem.* **2008**, 1759–1766.
14. Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991.
15. Lei, M.; Shi, L.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892–7898.
16. Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Liu, W.; Tao, J.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 2649–2656.
17. Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. *Tetrahedron* **2008**, *64*, 9585–9591.
18. Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649–4652.
19. Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593–2595.
20. Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420.
21. Hall, D. M.; Lesslie, M. S.; Turner, E. E. *J. Chem. Soc.* **1950**, 711–713.
22. For an alternative approach to this compound see, Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431–8434.