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PAPER

Investigating the reaction mechanism and organocatalytic synthesis of α,α′-dihydroxy ketones†

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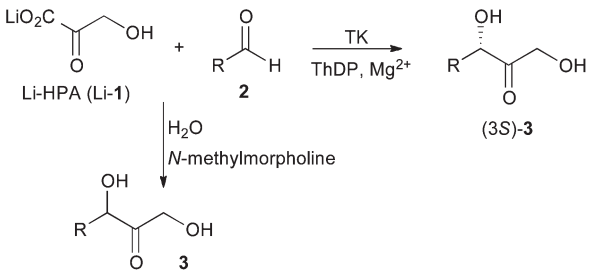
A biomimetic TK one-pot reaction using hydroxypyruvate and aldehydes to generate α,α′-dihydroxy ketones in water has recently been described. To investigate this tertiary-amine mediated reaction mechanism two approaches were used. Firstly, ^{13}C labelled lithium hydroxypyruvate was synthesised and used to establish where hydroxypyruvate is incorporated in the product. In separate experiments reaction intermediates were also successfully intercepted and structurally identified using ESI-MS with tandem mass spectrometry ESI-MS/MS. These studies indicated that two mechanisms appear to be operating, one involving the addition of the tertiary amine catalyst to hydroxypyruvate, the other an aldol-based mechanism. Since the first mechanism may enable facial stereodifferentiation in the addition of intermediates to the aldehyde, a preliminary study on the use of chiral catalysts was performed and the first asymmetric organocatalytic synthesis of α,α′-dihydroxy ketones in aqueous media achieved, in up to 50% *ee*, using a quinine ether catalyst.

Introduction

Transketolase (TK) is a versatile enzyme that requires thiamine diphosphate (ThDP) and magnesium(II) ions as cofactors to reversibly transfer a two carbon ketol unit from D-xylulose-5-phosphate to D-ribose-5-phosphate, in the oxidative branch of the pentose phosphate pathway.[1] To render the reaction irreversible, Srere *et al.* demonstrated *in vitro* the use of β-hydroxypyruvate (HPA **1**) as a ketol donor for TK, with the evolution of carbon dioxide.[2] Since then, TKs have been used by several groups with a range of acceptor aldehydes **2** and HPA **1** for the construction of (3*S*)-α,α′-dihydroxy ketones **3** in moderate to excellent yields and stereoselectivities (Scheme 1).[3–10] Although *in vivo* α-hydroxylated aldehydes are utilised, wild-type TKs have been reported to tolerate non-α-hydroxylated aliphatic aldehydes, but lower activities are observed.[8–10] More recently, *E. coli* TK variants possessing single-point active site mutations have been reported that are able to accept non-α-hydroxylated aliphatic aldehydes and generate either the (3*S*)- or (3*R*)-α,α′-dihydroxy ketone **3** in good yields.[11–13] *E. coli* TK mutants have also been described that are interestingly able to accept aromatic aldehydes such as benzaldehyde, although *ee*s were variable and dependent on the substrate and variant used.[14] In addition, yields were low and side products formed in several cases. However, there is clearly significant interest in the synthesis of compounds possessing the α,α′-dihydroxy ketone functionality, which is found in several natural products and can be readily converted to a range of compounds including ketosugars and 2-amino-1,3-diols.[5,6,15–19]



Scheme 1 Formation of α,α′-dihydroxy ketones using TK or the biomimetic TK reaction using *N*-methylmorpholine.

Non-enzymatic routes to α,α′-dihydroxy ketones have been described, including a five step procedure to aromatic analogues and an enantioselective chiral auxiliary strategy reported by Enders *et al.*, but these are multistep procedures, highlighting the value of the enzyme TK in accessing these compounds using a succinct sustainable approach.[20,21]

Notably, a recent preliminary study has described a non-enzymatic one-pot tertiary amine catalysed reaction in water, using Li-**1** as the ketol donor and aldehyde acceptor to give **3** (Scheme 1).[13,14,22] This biomimetic TK reaction typically used

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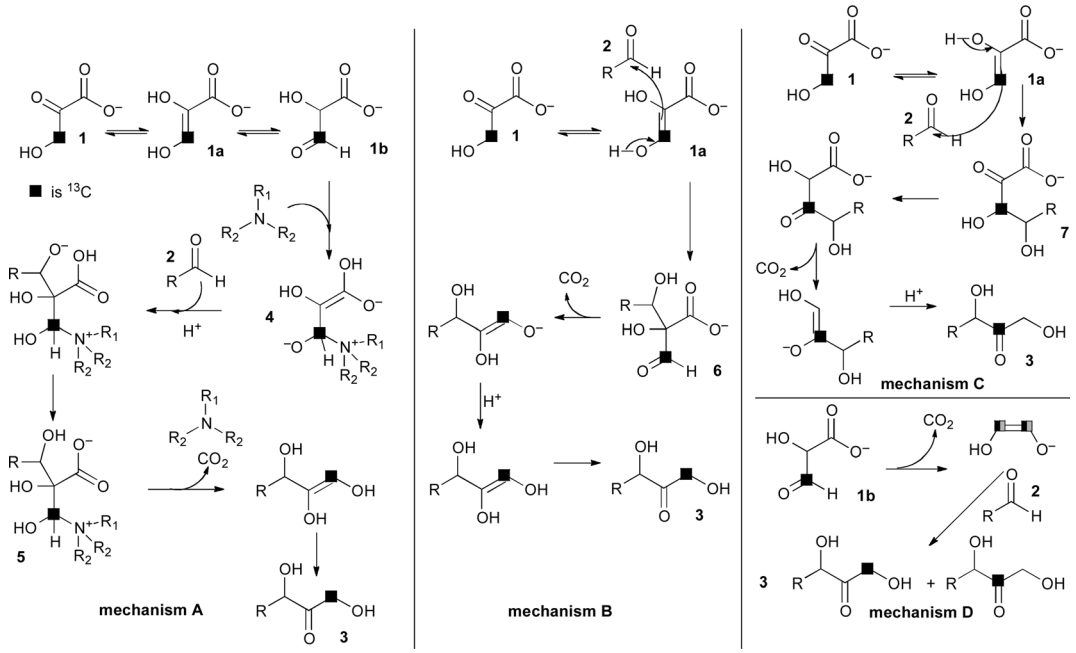
† Electronic supplementary information (ESI) available: Conversion of **3d**, **3e**, **3f**, **3i**, **3k**, **3l** into Mosher's esters. Also spectral data (^1H and ^{13}C NMR) for **3a–3l** and chiral HPLC data where appropriate. See DOI: 10.1039/c2ob06939c



Scheme 2 Proposed mechanisms **A–D** for the formation of **3** from **1** and **2**, and the position of incorporation of [3-^{13}C]-labelled Li-HPA. Intermediates **4–7** are also indicated. For the discussion below **2a**, **2b**, **2c** are where R is cy-C_6H_{11}, Ph and thienyl, respectively.

stoichiometric amounts of *N*-methylmorpholine (NMM) and yields were dependent upon the acceptor aldehyde used, giving variable yields of **3** from 2% to 63%, but in the absence of amine the reaction did not proceed.[13,14,22] More recently, this transformation has been described using HPA in stereoselective decarboxylative aldols, where NMM was identified as the optimal catalyst and was used in sub-stoichiometric or stoichiometric quantities, together with single isomer protected α-hydroxylated aldehydes. *Anti* : *syn* diastereoselectivities were observed of between approximately 1 : 1 and 2 : 1.[23]

There is currently no one-step non-enzymatic asymmetric synthesis of α,α′-dihydroxy ketones using non-chiral aldehydes, only multistep strategies. However, the biomimetic TK reaction requirement for a tertiary amine catalyst might enable development as an asymmetric reaction by the use of chiral catalysts. Herein we report studies to provide mechanistic insights into the reaction, and also investigations to determine whether an asymmetric version of the TK biomimetic reaction can be achieved.

Results and discussion

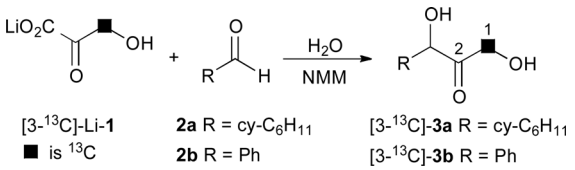
Mechanistic studies using ^{13}C labelled Li-HPA

In a preliminary publication, due to the requirement for the tertiary amine and the ability of the reaction to proceed at pH 7–8 it was proposed that the mechanism could be reminiscent of the Baylis–Hillman reaction, with addition of the amine to carbanion enolate **1a** in a conjugate fashion or tartronic acid semialdehyde **1b** to give a quaternary amine enolate **4** (Scheme 2; mechanism **A**).[22] Then aldol addition of the aldehyde, proton transfer to give **5** and elimination of the tertiary amine and decarboxylation, with subsequent tautomerisation of the enediol, gives **3**.

Alternatively, aldol-based reactions could be envisaged as mentioned by Rohr and Mahrwald, although mechanistic details were not discussed.[23] In principle either the direct aldol addition of **1a** to the aldehyde could occur to give **6** followed by decarboxylation, protonation, and tautomerisation to give **3** (Scheme 2; mechanism **B**). An alternative aldol addition, of **1a** to the aldehyde to give **7**, with subsequent tautomerisation then decarboxylation and tautomerisation would generate the dihydroxy ketone **3** (Scheme 2; mechanism **C**).

Finally, a further mechanism (Scheme 2; mechanism **D**) involving initial decarboxylation of **1b**, generated from **1**, would give a symmetrical enediolate intermediate, which upon an aldol addition to **2** and subsequent tautomerisation would give **3**. To provide insights into the role of the tertiary amine, which may be important in designing an asymmetric version of the reaction, two mechanistic studies were performed: one using ^{13}C-labelled Li-HPA, and in separate experiments mass spectrometry was used to identify any key reaction intermediates. Depending on the mechanism of the reaction there are two positions that [3-^{13}C]-Li-**1** could be incorporated as shown in Scheme 2. If mechanisms **A** or **B** are involved then the ^{13}C-label would be found at [1-^{13}C]-**3**. However, for the aldol mechanism **C** then [2-^{13}C]-**3** would be generated. For mechanism **D** a mixture of ^{13}C labelling would be observed at positions C-1 and C-2. [3-^{13}C]-Li-**1** was prepared *via* the bromination of [3-^{13}C]-sodium pyruvate (99 atom% ^{13}C) using neat bromine at 50 °C to give the monobrominated product [3-^{13}C]-bromopyruvate in 70% yield.[24,25] Then, following a literature protocol to synthesise Li-**1**, 1 M lithium hydroxide was added slowly to [3-^{13}C]-bromopyruvate to afford [3-^{13}C]-Li-**1** in 54% yield.[26]

Cyclohexanecarboxaldehyde **2a** and benzaldehyde **2b** were used as representative aliphatic and aromatic aldehydes in the TK biomimetic reaction with [3-^{13}C]-Li-**1** and NMM, affording [1-^{13}C]-**3a** and [1-^{13}C]-**3b** in 15% and 10% isolated yields, respectively (Scheme 3). The ^{13}C NMR spectra of [1-^{13}C]-**3a** and [1-^{13}C]-**3b** indicated that the ^{13}C label was incorporated at



Scheme 3 Synthesis of [1-^{13}C]-**3a** and [1-^{13}C]-**3b** using [3-^{13}C]-Li-**1**.

C-1 in both cases. This was confirmed from the intensity of the C-1 signal compared to unlabelled natural abundance **3a** and **3b** ^{13}C NMR spectra previously reported.[13,14] In addition, the ^{1}H NMR spectra confirmed this with a $^{1}J_{CH}$ at C-1 of approximately 145 Hz. The [3-^{13}C]-Li-**1** labelling experiment therefore indicated that mechanisms **C** and **D** were not involved in this TK biomimetic reaction, but mechanisms **A** or **B** may occur with addition of the aldehyde at C-2 (Scheme 2; mechanisms **A** and **B**).

ESI-MS studies

ESI-MS and tandem ESI-MS/MS have proven to be useful methods to probe mechanistic studies in solution, by characterising reaction intermediates and the selection and characterisation of specific ions, as well as minor products formed.[27–29] Of particular relevance to our current study, it has been used to investigate organocatalytic reactions including the Baylis–Hillman reaction, the asymmetric intramolecular Michael reaction of aldehydes, and organocatalytic cascades.[30–32] With mechanisms **A** or **B** implicated in the TK biomimetic mechanism ESI-MS (and tandem ESI-MS/MS) was used to intercept and characterise reaction intermediates. Initially, the reaction of cyclohexanecarboxaldehyde **2a** with Li-**1** catalysed by NMM in water was monitored by ESI-MS with the aim of detecting reaction intermediates in solution in the positive or negative ion mode. Unfortunately no intermediary ions were detected, presumably due to instabilities. Alternative aldehydes and tertiary amines were explored and when utilizing 2-thiophenecarboxaldehyde **2c** (which has previously been used with TK variants) Li-**1** and the tertiary amine DABCO in water, intermediates were detected.[14] The reaction was continuously monitored by direct infusion of the aqueous solution into the ESI probe at a flow rate of 3 μL min^{-1}. A high cone voltage (85 V) was used to de-clutter and eliminate intermediate ions defined by non-covalent interactions in the gaseous phase; under these conditions highly charged covalent species were detected (Fig. 1).

The ESI(−)-MS spectra revealed signals at *m*/*z* 215 and 327 which correspond to the covalently bonded anionic intermediates [**6c**]$^{-}$ (mechanism **B**) and [**5c**-H]$^{-}$ (mechanism **A**) respectively, and therefore could potentially be of mechanistic importance. The *m*/*z* of 215 could also correspond to **4c** although later MS/MS studies indicated this was not the case (see below). In addition, an accurate mass of the signal (*m*/*z* 215.0004; calcd for $C_8H_7O_5S$, 215.0014), confirmed it corresponded to the molecular formula of **6c**. The relative abundance of *m*/*z* 215 in comparison with *m*/*z* 327 might suggest pathway **B** is preferred, however the low abundance of *m*/*z* 327 may be due to instability and decomposition of the fragment at the ion source before it is detected. Other ions were considered to be either impurities

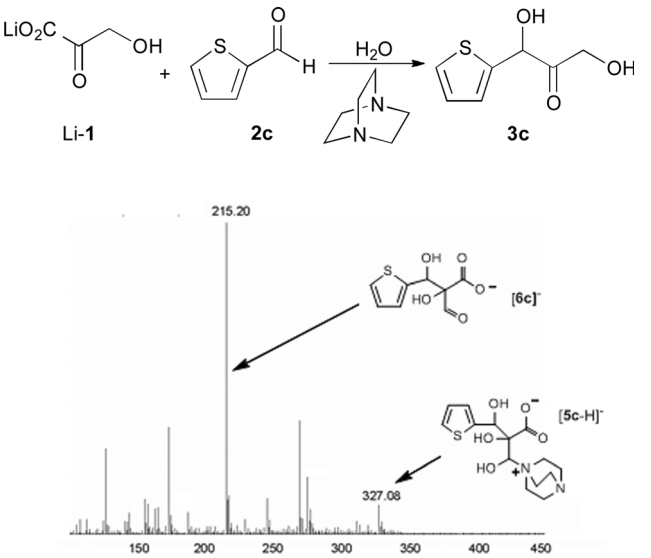


Fig. 1 ESI(−)-MS for the biomimetic TK reaction with **2c** and Li-**1** catalysed by DABCO.

(favoured under the negative-ion ESI), side reaction products or corresponded to fragmentation of the product.

These reactive anionic intermediate ions were individually mass selected and collided with nitrogen at a high collision ionisation dissociation voltage (CID). This lowered the abundance of the intermediate ions with the generation of fragments for further individual structural characterisation in tandem mass spectrometric (MS/MS) analysis. The relatively high CID (17 eV) produced less rearranged products and the elimination of loosely held dimerisation adducts with exclusive higher energy fragments were observed. ESI-(−)MS/MS spectra confirmed [**6c**]$^{-}$ of *m*/*z* 215 as the aldehydic anionic intermediate with a loss of carbon dioxide to form the product ion [**3c**-H]$^{-}$ of *m*/*z* 171. Other fragmented ions resulted from the loss of carbon dioxide and methanol radical to yield [**8**-H]$^{-}$ of *m*/*z* 141 and the loss of carbon dioxide and water to yield [**9**-H]$^{-}$ of *m*/*z* 153. The same CID (17 eV) was also used to fragment intermediate [**5c**-H]$^{-}$ of *m*/*z* 327 by the loss of carbon dioxide to yield [**10**-H]$^{-}$ of *m*/*z* 283. Other dissociation routes revealed the loss of carbon dioxide and water to yield [**11**-H]$^{-}$ of *m*/*z* 265, and the most stable detectable fragment *via* the cleavage of DABCO and methanol radical to yield [**12**-H]$^{-}$ of *m*/*z* 185 (Fig. 2).

Preliminary asymmetric TK biomimetic reactions

These ESI-MS studies therefore indicated that both mechanisms **A** and **B** operate, indeed the predominant mechanism may be dependent on the aldehyde and tertiary amine combination used, together with the reaction conditions. No further mechanistic insights were obtained from NMR experiments to detect reaction intermediates. However, investigating the reaction between **1** and **2a** in D_2O over 24 h by ^{1}H NMR with different mol% of NMM (0, 5, 25, 50, 100) at pH 8 (see ESI†), indicated that the rate of the reaction was proportional to the concentration of NMM used (at <50 mol%), further supporting the involvement of

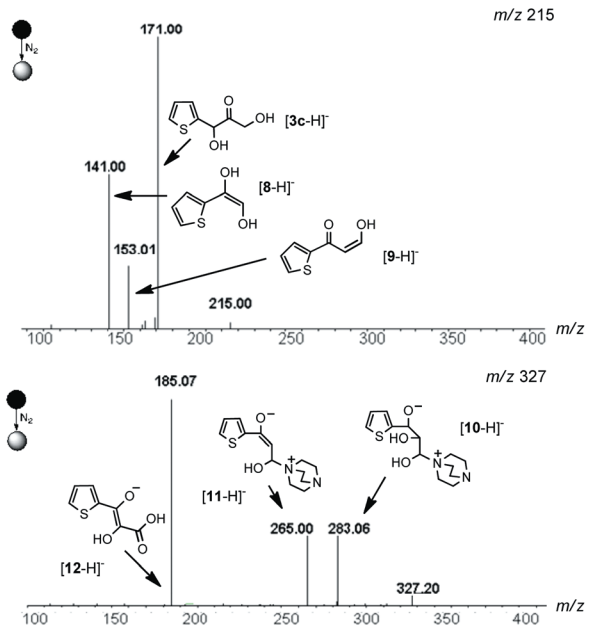


Fig. 2 ESI(−)-MS/MS spectra of *m/z* 215 [**6c**]$^-$ and *m/z* 327 [**5c**-H]$^-$.

mechanism **A**. Studies were then performed to investigate whether an asymmetric TK biomimetic reaction could be established. If the reaction goes *via* mechanism **A**, the use of a single isomer chiral tertiary amine would give an intermediate **4** which could direct *re*- or *si*-addition to the aldehyde by facial stereodifferentiation. For mechanism **B** a chiral tertiary amine cation with an electrostatic interaction to the carboxylate of **1a** might also result in some asymmetric induction. However, asymmetric reactions in water are challenging as water can interrupt ionic and hydrogen bonding interactions critical for stabilising transition states of the reaction or inhibit the catalyst's activity.[33] Initial experiments were performed with Li-**1** and benzaldehyde **2b** and a range of selected chiral catalysts that have previously been successfully used as organocatalysts. Notably the pyrrolidine diamines **13a–d** have recently been used in asymmetric Baylis–Hillman reactions in protic solvents, and asymmetric Michael additions and aldol reactions in aqueous media.[34–38] The cinchona alkaloids are well established asymmetric catalysts and compounds **14** were selected including the hydroquinine analogues **14c** and **14d**.[39–41]

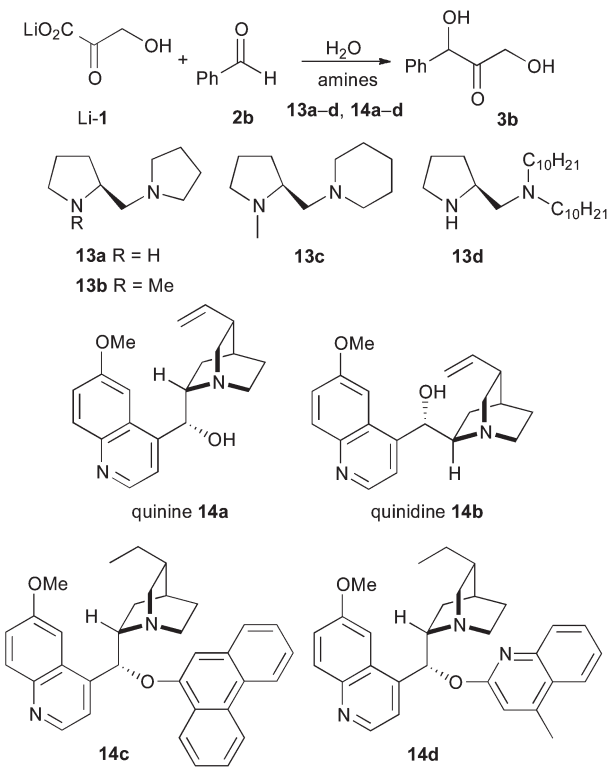
Stereoselectivities were determined *via* dibenzoylation of **3b** and chiral HPLC as previously described for TK reaction products.[14] The pyrrolidine diamines **13** (Table 1; entries 1–4) gave **3b** in poor yields with negligible *ee*s. The addition of water stable Lewis acids $Sc(OTf)_3$ and $Yb(OTf)_3$ to the reactions with **13** resulted in no increase in yield or *ee*. The bulkier catalysts quinine and quinidine (Table 1; entries 5 and 6) gave no asymmetric induction with varied catalyst loading, and water–THF was required as a solvent system to ensure solubilisation of the amine catalysts. Interestingly, the highest selectivities were observed with the quinine ether derivatives **14c** and **14d** when used in a (1 : 1) H_2O–THF solvent system. When the catalyst loading was increased from 5 mol% to one equivalent no *ee* was observed (Table 1; entries 8–10). This is possibly due to the complexation of several catalyst molecules to reaction

Table 1 Use of tertiary amine catalysts **13** and **14** in the biomimetic TK reaction with Li-**1** and **2b**

Entry	Catalyst	Solvent	Time [h]	Yield [%]	*ee* [%]
1	**13a**[a]	H_2O	12	5	3
2	**13b**[a]	H_2O	12	6	2
3	**13c**[a]	H_2O	12	5	2
4	**13d**[a]	H_2O	12	5	0
5	**14a**[a]	H_2O–THF	24	6	0
6	**14b**[a]	H_2O–THF	24	5	0
7	**14c**[a]	H_2O–THF	24	4	18
8	**14d**[a]	H_2O–THF	24	4	22
9	**14d**[b]	H_2O–THF	24	6	16
10	**14d**[c]	H_2O–THF	24	6	0

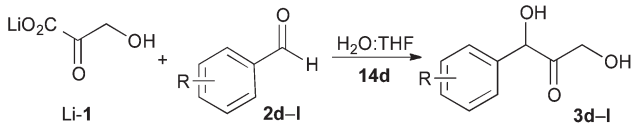
Reaction conditions: **2b** (1.0 equiv) and Li-**1** (1.0 equiv) in THF (1 mL) and H_2O (1 mL). [a] Amine catalyst (5 mol%). [b] Amine catalyst (50 mol %). [c] Amine catalyst (1.0 equiv).

intermediates, altering facial stereoselectivities. The absolute stereochemistry of the major isomer of **3b** generated was established as (3*R*) by formation of the Mosher's ester at the primary hydroxyl with (*S*)-MTPACl as previously described.[42] Having demonstrated some asymmetric induction with the quinine ether catalysts, **14d** was used further with other aromatic aldehydes and the highest *ee*s achieved under a range of reaction conditions explored are presented in Table 2.



In all cases the yields were low, comparable to those observed with the TK mutant enzymes reported,[14] however, the stereoselectivities were promising. The yields observed were lower than those achieved with the less bulky tertiary amine catalyst NMM, perhaps reflecting steric hindrance upon the addition of the amine in mechanism **A**. The *para*-substituted F- and Cl-

Table 2 The asymmetric biomimetic TK reaction with various aldehydes



Entry	Aldehyde	Time [h]	Yield [%]	*ee* [%]
1	**2d**[a] R = 4-Me	12	2	21
2	**2e**[a] R = 4-F	12	3	36
3	**2f**[b] R = 4-Cl	48	2	50
4	**2g**[b] R = 4-OMe	24	3	0
5	**2h**[b] R = 4-Br	72	2	0
6	**2i**[a] R = 3-F	12	2	38
7	**2j**[a] R = 2-F	48	3	0
8	**2k**[c] R = 3-OMe	24	3	36
9	**2l**[c] R = 3-CO_2Me	24	4	25

Reaction conditions: **2d–2l** (1.0 equiv) and Li-**1** (1.0 equiv), solvent (2 mL). [a] **2d**, **2e**, **2i**, **2j** 5 mol% **14d**, 1 : 1 THF–H_2O. [b] **2f**, **2g**, **2h** 20 mol % **14d**, 1 : 2 THF–H_2O. [c] **2k**, **2l** 10 mol% **14d**, 1 : 1 THF–H_2O.

aromatic aldehydes gave moderate *ee*s in comparison to the larger *p*-methoxy- and *p*-bromo-substituents where no *ee* was observed. This decrease in optical purity suggested that the increased size of the *para*-group may detrimentally influence stereoselectivities. The *meta*-substituted aromatic aldehydes containing both electron withdrawing and donating groups, F–, MeO– and MeO_2C–, gave products with *ee*s in the range 25–38%, indicating that the reactivity or the steric bulk of these substituents do not contribute significantly to the asymmetric induction observed. The *ortho*-analogue **2j** gave **3j** in 0% *ee*, and also 2,4-dichlorobenzaldehyde gave no hydroxy ketone product when using amine **14d**, so *ortho*-substituted benzaldehydes were not explored further with these catalysts. Aliphatic aldehydes such as cyclohexanecarboxyaldehyde and hexanal were investigated using amine **14d**. Higher yields of 15–20% were observed, but no enantioselectivities achieved. As for **3b** the optical purities of the dihydroxy ketone products (Table 2) were determined by derivatisation (as the dibenzoate or monobenzoate) and chiral HPLC. The low yields observed when using **14d** may be due to the bulky nature of the quinine catalysts facilitating the stereoselective reaction. As discussed above there are two mechanisms **A** and **B** that both result in the formation of **3**. Route **A** may more readily enable asymmetric inductions to be achieved due to the formation of zwitterion **4** with the tertiary amine covalently bound to HPA, enabling facial stereodifferentiation upon addition to the aldehyde. Mechanism **B** would require a strong electrostatic interaction between **14d** and **1**, which in aqueous media will be disrupted by hydrogen bonding. When considering the zwitterionic intermediate **4** and addition to the aldehyde, as shown in Fig. 3, the lower face of the enolate will not be accessible to the aldehyde. Then addition to the *si*-face of the aldehyde (underside as drawn) may result from a favourable interaction between Ar and methylquinoline ring and would generate the (*R*)-product. Lower or negligible *ee*s may either reflect predominance of mechanism **B** with certain substrate and catalyst combinations or that the aldehyde equally presents the *re*-face to **4** due to unfavourable steric interactions.

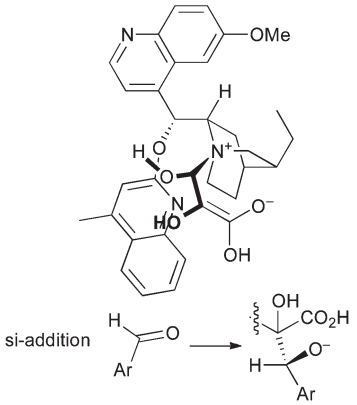


Fig. 3 Proposed rationale for stereoselectivities observed with the addition of **4** to aldehyde **2**.

Conclusions

In conclusion, we have used ^{13}C labelling experiments to provide evidence to support that mechanisms **A** and **B** operate in the tertiary amine catalysed TK biomimetic reaction in aqueous media. Also, some mechanism **A** and **B** reaction intermediates have successfully been intercepted and structurally identified using ESI with tandem mass spectrometry. Finally, we have demonstrated the first asymmetric organocatalytic synthesis of α,α′-dihydroxy ketones in aqueous media catalysed by a quinine ether catalyst **14d** with moderate *ee*s obtained. Further tertiary amine catalyst design that increases the stereoselectivities and yield, and are applicable to a wider range of substrates, can now be investigated.

Experimental

General methods

Unless otherwise noted, solvents and reagents were reagent grade from commercial suppliers (Sigma-Aldrich) and used without further purification. Dry CH_2Cl_2 was obtained using anhydrous alumina columns.[43] All moisture-sensitive reactions were performed under a nitrogen or argon atmosphere using oven-dried glassware. Reactions were monitored by TLC on Kieselgel 60 F_{254} plates with detection by UV, potassium permanganate and phosphomolybdic acid (PMA) [PMA hydrate (12 g) and ethanol (250 mL)] stains. Flash column chromatography was carried out using silica gel (particle size 40–63 μm). ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance-600 MHz machine. Coupling constants are measured in Hertz (Hz) and NMR spectra were recorded at 298 K. Mass spectra (EI/CI) were recorded on a Thermo Finnegan MAT 900XP, ESI data (MS^1 and MS^2) on a Thermo Finnegan LTQ and HR-ESI data on a Waters LCT Premier XE. Infrared spectra were recorded on a Shimadzu FTIR-8700 and Perkin Elmer Spectrum 100 FTIR spectrometer. Chiral HPLC analysis was performed on a Varian Prostar instrument equipped with a Chiracel OD column (Daicel; Chiral Technologies Europe, France) 25 cm × 0.46 cm.

[3-^{13}C]-Bromopyruvate and lithium hydroxypyruvate (^{13}C-labelled and unlabelled) were synthesised as previously

described.[24–26] The pyrrolidine diamines **13a–d** were prepared as previously reported.[38,44,45] The cinchona alkaloids **14a–d** were commercially available (Sigma-Aldrich).

[1-^{13}C]-Cyclohexyl-1,3-dihydroxy-2-propanone [1-^{13}C]-3a.[13] To a stirred solution of [3-^{13}C]-Li-**1** (0.110 g, 0.991 mmol) in water (10 mL) at rt was added cyclohexanecarboxaldehyde (120 μL, 0.991 mmol) and *N*-methylmorpholine (110 μL, 1.00 mmol). The reaction mixture was stirred at rt for 48 h, the solvent was removed *in vacuo* and the crude product dry loaded onto a flash silica chromatography column (EtOAc–hexane, 1 : 1) affording [1-^{13}C]-**3a** (0.026 g, 15%) as a white solid. R_f 0.21 (EtOAc–hexane, 1 : 1); Mp 110–120 °C (EtOAc–hexane, 1 : 1); ^{1}H NMR (600 MHz; $CDCl_3$) δ 1.10–1.31 (5H, m), 1.35–1.85 (6H, m), 4.16 (1H, d, *J* 2.9 Hz, C*H*OH), 4.36 (1H, dd, $^1J_{CH}$ 144 and $^2J_{HH}$ 19.4 Hz, ^{13}C*H*HOH), 4.48 (1H, dd, $^1J_{CH}$ 144 and $^2J_{HH}$ 19.4 Hz, ^{13}CH*H*OH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 25.8 (signals superimposed), 26.4, 28.9, 29.6, 42.3 and 42.7, 66.2 (^{13}CH$_2$OH), 79.3, 211.8 (*C*=O, $^1J_{CC}$ 39.0 Hz); *m*/*z* (CI) 174 (MH^+, 100%), 156 (54), 138 (60), 95 (25); *m*/*z* (HR-CI) calcd for MH^+ $C_8{}^{13}CH_{17}O_3$ 174.12112, found 174.12031.

[1-^{13}C]-3-Dihydroxy-1-phenyl-2-propanone [1-^{13}C]-3b.[14] To a stirred solution of [3-^{13}C]-Li-**1** (0.110 g, 0.991 mmol) in water (10 mL) at rt was added benzaldehyde (102 μL, 1.00 mmol) and *N*-methylmorpholine (110 μL, 1.00 mmol). The reaction mixture was stirred at rt for 48 h, the solvent was removed *in vacuo* and the crude product dry loaded onto a flash silica chromatography column (EtOAc–hexane, 1 : 1) affording [1-^{13}C]-**3b** (0.016 g, 10%) as a white solid. R_f 0.30 (EtOAc–hexane, 1 : 1); Mp 110–120 °C (EtOAc–hexane, 1 : 1); ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.70 (1H, br s, O*H*), 3.83 (1H, br s, O*H*), 4.23 (1H, dd, $^1J_{CH}$ 145 and $^2J_{HH}$ 19.5 Hz, ^{13}C*H*HOH), 4.34 (1H, dd, $^1J_{CH}$ 145 and $^2J_{HH}$ 19.5 Hz, ^{13}CH*H*OH), 5.25 (1H, s, C*H*OH), 7.32–7.42 (5H, m, Ph); ^{13}C NMR (150 MHz; $CDCl_3$) δ 65.2 (^{13}CH$_2$OH), 77.6, 127.0, 129.4 (signals superimposed), 137.4, 208.9 (*C*=O, $^1J_{CC}$ 40.5 Hz); *m*/*z* (CI) 168 (MH^+, 40%), 150 (100), 122 (41); *m*/*z* (HR-CI) calcd for MH^+ $C_8{}^{13}CH_{11}O_3$ 168.07417, found 168.07468.

MS protocols. The reaction between Li-**1** and 2-thiophenecarboxaldehyde **2c** to give 1,3-dihydroxy-1-(thiophen-2-yl)-2-propanone has previously been described.[14] 2-Thiophenecarboxaldehyde **2c** (75 μL, 0.802 mmol) was added to a solution of Li-**1** (110 mg, 1.00 mmol) and DABCO (56 mg, 0.50 mmol) in water (2 mL) for 2 h. The solution was then directly infused at 3 μL min^{-1} for 5 min and was detected by ESI(−)-MS.

Tandem MS/MS. For signal identity confirmation, collision-induced dissociation MS/MS experiments were performed on precursor ions selected from MS^1 using information-dependent acquisition: MS^1 was performed in the full-scan mode (*m*/*z* 100–500). MS^2 was performed on the most intense MS^1 peak at *m*/*z* 215. The MS^1 settings were the same as for MS^2 and were as follows: sheath gas, nitrogen at flow rate of 60 arbitrary units; capillary temperature, 300 °C; source voltage, 5 kV; capillary voltage, 15 V; and tube lens, 85 V. MS^2 was performed on MS^1 peak *m*/*z* 327 with the following conditions: sheath gas, nitrogen at flow rate of 80 arbitrary units; capillary temperature, 300 °C; source voltage, 5 kV; capillary voltage, −1 V; and tube lens, −37.52 V.

Synthesis of racemic α,α′-dihydroxyketones. The corresponding aldehyde **2b–2k** (1.00 mmol) was added to a solution of Li-**1** (110 mg, 1.00 mmol) and *N*-methylmorpholine (110 μL, 1.00 mmol) in water (20 mL) at pH 7 (adjusted with 10% HCl). The reaction was stirred for 24–48 h at rt and monitored by TLC analysis. Upon concentration *in vacuo*, the crude material was dry loaded and purified using flash silica chromatography.

Synthesis of α,α′-dihydroxyketones using catalyst 14d. The corresponding aldehyde **2b**, **2d–2l** (1.00 mmol) was added to a solution of Li-**1** (110 mg, 1.00 mmol) and hydroquinine 4-methyl-2-quinolyl ether **14d** (5–20 mol%) in H_2O–THF at pH 7–8 (Table 2). The reaction was stirred for 24–48 h at rt and monitored by TLC analysis. Upon concentration *in vacuo*, the crude material was dry loaded and the product purified using flash silica chromatography.

Chiral HPLC analysis of 3b, 3d–3l to determine *ee*s. Compounds **3b** and **3k** were dibenzoylated (following a previously reported protocol)[14] and **3d–3j** and **3l** monobenzoylated and the products analysed by chiral HPLC to determine *ee*s, using a Chiralpak OD column and the hexane–2-propanol solvent system given. The absolute stereochemistry of **3** (where appropriate) generated using **14d** was determined using a Mosher's derivatisation method (see ESI†).[42]

1,3-Dihydroxy-1-phenyl-2-propanone (3b).[14] Racemic **3b** was dibenzoylated and HPLC analysis of the product (82 : 18, 1.0 mL min^{-1}) gave retention times of 10.5 min (3*R*-isomer) and 13.4 min (3*S*-isomer). The stereoselective reaction was performed using 5 mol% of **14d** in a 2 mL mixture of H_2O–THF to give **3b** (7 mg, 4%) in 22% *ee* (3*R*-isomer).

1,3-Dihydroxy-1-(4-methylphenyl)-2-propanone (3d). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3d** as a colourless oil (14 mg, 8%); ν_{max}(neat)/cm^{-1} 3403, 2924, 1727, 1513; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.35 (3H, s, CH_3), 4.23 (1H, d, *J* 19.5 Hz, C*H*HOH), 4.34 (1H, d, *J* 19.5 Hz, CH*H*OH), 5.21 (1H, s, C*H*OH), 7.27 (2H, d, *J* 8.0 Hz, ArH), 7.51 (2H, d, *J* 8.0 Hz, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 21.3, 65.3, 77.6, 127.0, 130.1, 134.4, 139.3, 209.2; *m*/*z* (CI) 181 (MH^+, 18%), 163 (100), 145 (25), 135 (36); *m*/*z* (HR-CI) calcd for MH^+ $C_{10}H_{13}O_3$ 181.08592, found 181.08624. Racemic **3d** was monobenzoylated and HPLC analysis of the product (90 : 10, 1.0 mL min^{-1}) gave retention times of 15.1 min (3*S*-isomer) and 16.6 min (3*R*-isomer). The stereoselective reaction was performed using 5 mol% of **14d** in a 2 mL mixture of H_2O–THF to give **3d** (4 mg, 2%) in 21% *ee* (3*R*-isomer).

1-(4-Fluorophenyl)-1,3-dihydroxy-2-propanone (3e). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3e** as a colourless oil (9 mg, 5%); ν_{max}(neat)/cm^{-1} 3377, 2924, 1725, 1603, 1509; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.73 (1H, s, O*H*), 3.85 (1H, s, O*H*), 4.23 (1H, d, *J* 19.5 Hz, C*H*HOH), 4.35 (1H, d, *J* 19.5 Hz, CH*H*OH), 5.24 (1H, s, C*H*OH), 7.09 (2H, m, ArH), 7.32 (2H, m, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ

65.2, 77.4, 116.4 (d, $^{2}J_{CF}$ 21.3 Hz), 128.9 (d, $^{3}J_{CF}$ 8.0 Hz), 133.2, 163.2 (d, $^{1}J_{CF}$ 247 Hz, CF), 208.9; ^{19}F NMR (282 MHz; $CDCl_3$) δ −112.4; *m*/*z* (HR-EI) calcd for M^+ $C_9H_9FO_3$ 184.05302, found 184.05270. Racemic **3e** was monobenzoylated and HPLC analysis of the product (90 : 10, 1.0 mL min^{-1}) gave retention times of 13.0 min (3*S*-isomer) and 15.3 min (3*R*-isomer). The stereoselective reaction was performed using 5 mol % of **14d** in a 2 mL mixture of H_2O–THF to give **3e** (6 mg, 3%) in 36% *ee* (3*R*-isomer).

1-(4-Chlorophenyl)-1,3-dihydroxypropan-2-one (3f). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3f** as a colourless oil (8 mg, 5%); ν_{max}(neat)/cm^{-1} 3344, 2923, 1728, 1598; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.68 (1H, s, O*H*), 3.84 (1H, s, O*H*), 4.24 (1H, d, *J* 19.4 Hz, C*H*HOH), 4.35 (1H, d, *J* 19.4 Hz, CH*H*OH), 5.24 (1H, s, C*H*OH), 7.29 (2H, d, *J* 8.5 Hz, ArH), 7.38 (2H, d, *J* 8.5 Hz, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 65.2, 77.3, 128.4, 129.6, 135.3, 135.8, 208.7; *m*/*z* (HR-EI-) calcd for $[M - H]^-$ $C_9H_8{}^{35}ClO_3$ 199.0162, found 199.0151. Racemic **3f** was monobenzoylated and HPLC analysis of the product (90 : 10, 1.0 mL min^{-1}) gave retention times of 13.6 min (3*S*-isomer) and 15.9 min (3*R*-isomer). The stereoselective reaction was performed using 20 mol% of **14d** in a 2 mL mixture of H_2O–THF to give **3f** (4 mg, 2%) in 50% *ee* (3*R*-isomer).

1,3-Dihydroxy-1-(4-methoxyphenyl)-2-propanone (3g). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3g** as a colourless oil (12 mg, 6%); ν_{max}(neat)/cm^{-1} 3340, 2925, 1720, 1603; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.70 (1H, t, *J* 5.4 Hz, CH_2OH), 3.75 (1H, d, *J* 3.9 Hz, CHO*H*), 3.81 (3H, s, OCH_3), 4.22 (1H, dd, *J* 19.2 and 5.4 Hz, C*H*HOH), 4.33 (1H, dd, *J* 19.2 and 5.4 Hz, CH*H*OH), 5.19 (1H, d, *J* 3.9 Hz, C*H*OH), 6.92 (2H, d, *J* 8.7 Hz, ArH), 7.23 (2H, d, *J* 8.7 Hz, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 55.5, 65.2, 77.3, 114.8, 128.5, 129.4, 160.4, 209.3; *m*/*z* (HR-CI) calcd for MH^+ $C_{10}H_{13}O_4$ 197.08138, found 197.08189.

1-(4-Bromophenyl)-1,3-dihydroxy-2-propanone (3h). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3h** as a colourless oil (7 mg, 3%); ν_{max}(neat)/cm^{-1} 3390, 2923, 1725, 1590; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.69 (1H, s, O*H*), 3.84 (1H, s, O*H*), 4.24 (1H, d, *J* 19.5 Hz, C*H*HOH), 4.35 (1H, d, *J* 19.5 Hz, CH*H*OH), 5.22 (1H, s, C*H*OH), 7.23 (2H, d, *J* 8.4 Hz, ArH), 7.54 (2H, d, *J* 8.4 Hz, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 65.2, 77.3, 123.5, 128.7, 132.5, 136.4, 208.6; *m*/*z* (CI) 247 (M(^{81}Br)$^+$, 3%), 245 (M(^{79}Br)$^+$, 3), 187 (52), 185 (55), 85 (100); *m*/*z* (HR-CI) calcd for MH^+ $C_9H_{10}O_3{}^{79}Br$ 244.98133, found 244.98091.

1-(3-Fluorophenyl)-1,3-dihydroxy-2-propanone (3i). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3i** as a colourless oil (9 mg, 5%); ν_{max}(neat)/cm^{-1} 3345, 2920, 1728; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.68 (1H, t, *J* 4.7 Hz, CH_2OH), 3.85 (1H, d, *J* 3.9 Hz, CHO*H*), 4.26 (1H, dd, *J* 19.5 and 4.7 Hz, C*H*HOH), 4.38 (1H, dd, *J* 19.5 and 4.7 Hz, CH*H*OH), 5.26 (1H, d, *J* 3.9 Hz, C*H*OH), 7.04–7.10 (2H, m, ArH), 7.14 (1H, d, *J* 7.5 Hz, ArH), 7.38 (1H, m, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 65.2, 75.0, 114.0 (d, $^{2}J_{CF}$ 22.1 Hz), 116.3 (d, $^{2}J_{CF}$ 21.0 Hz), 122.7, 131.0 (d, $^{3}J_{CF}$ 8.6 Hz), 139.7 (d, $^{3}J_{CF}$ 6.8 Hz), 163.3 (d, $^{1}J_{CF}$ 247 Hz, *C*F), 208.5; ^{19}F NMR (282 MHz; $CDCl_3$) δ −112.4; *m*/*z* (CI) 185 (MH^+, 35%), 167 (100), 139 (95), 125 (29); *m*/*z* (HR-CI) calcd for MH^+ $C_9H_{10}FO_3$ 185.06140, found 185.06101. Racemic **3i** was monobenzoylated and HPLC analysis of the product (90 : 10, 1.0 mL min^{-1}) gave retention times of 11.8 min (3*S*-isomer) and 14.6 min (3*R*-isomer). The stereoselective reaction was performed using 5 mol% of **14d** in a 2 mL mixture of H_2O–THF to give **3i** (4 mg, 2%) in 38% *ee* (3*R*-isomer).

1-(2-Fluorophenyl)-1,3-dihydroxy-2-propanone (3j). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3j** as a colourless oil (12 mg, 7%); ν_{max}(neat)/cm^{-1} 3350, 2925, 1725; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.78 (1H, t, *J* 4.5 Hz, CH_2OH), 3.93 (1H, d, *J* 4.5 Hz, CHO*H*), 4.28 (1H, dd, *J* 19.5 and 4.5 Hz, C*H*HOH), 4.35 (1H, d, *J* 19.5 and 4.5 Hz, CH*H*OH), 5.52 (1H, d, *J* 4.5 Hz, C*H*OH), 7.12 (1H, m, ArH), 7.19 (1H, m, ArH), 7.35 (2H, m, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 65.2, 71.6, 116.1 (d, $^{2}J_{CF}$ 21.2 Hz), 124.7, 125.2 (d, $^{2}J_{CF}$ 20.3 Hz), 128.8, 131.0 (d, $^{3}J_{CF}$ 8.4), 160.3 (d, $^{1}J_{CF}$ 246 Hz, *C*F), 208.4; ^{19}F NMR (282 MHz; $CDCl_3$) δ −112.4; *m*/*z* (HR-EI) calcd for M^+ $C_9H_9FO_3$ 184.05302, found 184.05270.

1,3-Dihydroxy-1-(3-methoxyphenyl)-propan-2-one (3k). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3k** as a colourless oil (13 mg, 7%); ν_{max}(neat)/cm^{-1} 3325, 2928, 1722; ^{1}H NMR (600 MHz; $CDCl_3$) δ 3.81 (3H, s, OCH_3), 4.24 (1H, d, *J* 19.2 Hz, C*H*HOH), 4.35 (1H, d, *J* 19.2 Hz, CH*H*OH), 5.22 (1H, s, C*H*OH), 6.92 (1H, app. t, *J* 2.1 Hz, ArH), 6.90 (2H, m, ArH), 7.31 (1H, app. t, *J* 8.1 Hz, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 55.5, 65.2, 77.7, 112.4, 114.8, 119.3, 130.5, 138.8, 160.4, 209.0; *m*/*z* (CI) 197 (MH^+, 14%), 279 (100), 151 (28), 84 (31); *m*/*z* (HR-CI) calcd for MH^+ $C_{10}H_{13}O_4$ 197.08138, found 197.08189. Racemic **3k** was dibenzoylated and HPLC analysis of the product (90 : 10, 1.0 mL min^{-1}) gave retention times of 32.6 min (3*S*-isomer) and 37.1 min (3*R*-isomer). The stereoselective reaction was performed using 10 mol% of **14d** in a 2 mL mixture of H_2O–THF to give **3k** (6 mg, 3%) in 36% *ee* (3*R*-isomer).

3-(1,3-Dihydroxy-2-oxo-propyl)-benzoic acid methyl ester (3l). The reaction was carried out for 48 h and the product purified using flash silica chromatography (EtOAc–hexane, 1 : 1) to give **3l** as a colourless oil (11 mg, 5%); ν_{max}(neat)/cm^{-1} 3436, 2954, 1719, 1605; ^{1}H NMR (600 MHz; $CDCl_3$) δ 2.69 (1H, t, *J* 4.8 Hz, CH_2OH), 3.89 (1H, d, *J* 3.9 Hz, CHO*H*), 3.93 (3H, s, OCH_3), 4.24 (1H, dd, *J* 19.5 and 4.8 Hz, C*H*HOH), 4.39 (1H, dd, *J* 19.5 and 4.8 Hz, CH*H*OH), 5.32 (1H, d, *J* 3.9 Hz, C*H*OH), 7.49 (1H, app. t, *J* 7.5 Hz, ArH), 7.54 (1H, m, ArH), 8.03 (2H, m, ArH); ^{13}C NMR (150 MHz; $CDCl_3$) δ 52.5, 65.3, 76.0, 128.2, 129.5, 130.5, 131.3, 131.4, 137.9, 166.5, 208.6; *m*/*z* (CI) 225 (MH^+, 45%), 207 (100), 179 (40), 165 (95); *m*/*z* (HR-CI) calcd for MH^+ $C_{11}H_{13}O_5$ 225.07630, found 225.07563. Racemic **3l** was monobenzoylated and HPLC analysis of the

product (90 : 10, 1.0 mL min^{-1}) gave retention times of 24.5 min (3*S*-isomer) and 28.1 min (3*R*-isomer). The stereoselective reaction was performed using 10 mol% of **14d** in a 2 mL mixture of H_2O–THF to give **3l** (9 mg, 4%) in 25% *ee* (3*R*-isomer).

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