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TBD/Al₂O₃: a novel catalytic system for dynamic intermolecular aldol reactions that exhibit complex system behaviour[†]

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The heterogeneous system TBD/Al_2O_3 is an efficient catalyst for the intermolecular aldol reaction between ketones and aromatic aldehydes. This system operates with low catalysts loading (10%), in water or organic solvents, and with short reaction times. The desired aldol products are rendered cleanly. Experiments confirmed that this aldol protocol is reversible, and allowed for the preparation of dynamic combinatorial libraries (DCLs) of interconverting aldols. Analysis of these DCLs showed up how properties such as diastereoselectivity can emerge unpredictably from the library when it is considered as a whole.

Introduction

In recent years, the chemistry of the reversible covalent bond (dynamic covalent chemistry $(DCC)^1$) has been exploited in the generation of dynamic combinatorial libraries (DCLs).² DCLs can be defined as mixtures of different interconverting compounds operating under thermodynamic control. That is, the entire distribution of library components is governed by their relative free energies, and so, processes that are capable of altering the free energy relationships within the DCL can ultimately influence the distribution (population) of the integrating library members. Nowadays the utility of DCLs cannot be questioned: these libraries have shown considerable potential in the development of sensors,³ the preparation of interlocked chemical architectures⁴ and the discovery of ligands for artificial receptors and large biomolecules,⁵ among others.

An obvious condition to create a DCL is to find an appropriate reversible process, which has to fulfil a number of prerequisites. Firstly, it has to be reversible on a reasonable time scale under mild experimental conditions (considering the slow kinetics of the covalent bond formation it is often necessary to make use of catalysts) and, it cannot interfere with other processes of the library or destroy the chemical integrity of the library members. Accordingly, the reversible reactions suitable for DCC are rare compared to the large number of irreversible processes found in classical synthetic chemistry. To our knowledge, disulfide exchange reactions, acyl transfer reactions (from esters, thioesters, and amides), acetal exchange reactions, C=N exchange

reactions (imines, hydrazones, oximes, nitrones), alkene and alkyne metathesis, Diels–Alder/retro-Diels–Alder reactions, Michael addition/retro-Michael reactions, and very few others only have been used to generate DCLs to date. In this communication we report an efficient catalytic system that promotes fast and efficient dynamic aldol reactions between ketones and aromatic aldehydes allowing for the preparation of DCLs of aldols in water or, alternatively, in non-polar organic solvents.⁶ Although organocatalyzed⁷ aldol reactions are admittedly reversible, known to proceed through aldol/retro-aldol reaction channels, only recent contributions⁸ have exploited this character.

Results and discussion

Initially, we looked for a simple and mild system capable of catalyzing the direct aldol reaction between ketones and aromatic aldehydes to full conversion. The reaction between cyclohexanone, 1, and 4-chlorobenzaldehyde, 2a, a not too reactive aldehyde, was used as a model system to screen different reaction conditions. Inspired by the work of Mioskowski and Baati⁹ on triazabicyclo[4.4.0]dec-5-ene (TBD)-catalyzed intramolecular 5and 6-enolexo aldolizations of ketoaldehydes in THF, and based on our recent finding of TBD-derived guanidinium salts as suitable additives for proline-catalyzed aldol reactions,¹⁰ we turned our attention to this inexpensive, readily available, guanidine base.¹¹ Early experiments showed that aldol **3a** was rendered in 71% conversion when a solution of aldehyde 2a and cyclohexanone, 1, in THF, was stirred for 5 days in the presence of 10 mol % TBD (Table 1, entry 1). After several trials toluene turned out to be a better solvent for this reaction. When a solution of aldehyde 2a (1 equiv.) and cyclohexanone (10 equiv.) containing 10 mol% of TBD was stirred for 5 days in toluene (0.2 M for 2a) at room temperature, the desired aldol adduct 3a was obtained cleanly in 98% conversion as a mixture of

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Table 1Initial screening of conditions for the formation of aldol $3a^a$



^{*a*} General conditions: **1** (10 equiv.), **2a** (1 equiv.), solvent (0.2 M for **2a**). ^{*b*} Determined by ¹H NMR analysis from crude reaction mixtures. *Anti* and *syn* diastereoisomers were identified by comparison with similar compounds previously described in the literature. ^{*c*} Neutral Al₂O₃ (10 mol%) was used as co-catalyst. ^{*d*} Neutral Al₂O₃ (10 mol%) was used as co-catalyst. The reaction mixture was sonicated.

diastereoisomers, with no significant diastereoselectivity (Table 1, entry 2). Aiming to shorten the reaction time we investigated the effect of incorporating a Lewis acid (l.a.) to our catalytic system. Whereas most of the l.a. explored led to dehydration products (α , β -unsaturated ketones), addition of 10 mol% of neutral alumina (Al₂O₃), a rather mild heterogeneous l.a., quantitatively afforded aldol **3a** in 3 h (Table 1, entry 3). Moreover, when this reaction was performed under sonic waves a strong acceleration was observed, the desired aldol **3a** being quantitatively formed in 45 min (Table 1, entry 4). To our surprise, the catalytic system TBD-Al₂O₃ was also effective when distilled water was used as solvent (Table 1, entries 5–7). Blank experiments confirmed that Al₂O₃ itself, with no TBD, was unable to catalyze the aldol reaction in any solvent and under neither of the conditions experienced.

Following this methodology, employing toluene as solvent, a collection of aldols 3a-f (derived from cyclohexanone, Table 2, entries 1–6), 4e (from cyclopentanone, Table 2, entry 7) and 5e (from 3-pentanone, Table 2, entry 8), could be prepared in optimum yield after purification by flash chromatography. All these aldols were isolated as a mixture of diastereoisomers with low levels of diastereoselectivity, the *syn*-disposition being slightly favoured. In general, the reaction tolerates a wide diversity of electron-donating or electron-withdrawing functional groups anchored on either position of the aromatic ring. Reactions carried out on electron poor aldehydes (Table 2, entries 3–5) do not tolerate sonication, leading to complex crude reaction mixtures.

Similarly, TBD-Al₂O₃-catalyzed aldol reactions were performed in water (Table 3). Products **3a–c**, **3e**, **3g**, **4c** and **4e** were obtained in high yields in a process where purification is no longer required. It is significant to point out that the *anti*configuration of these aldols was slightly favoured (except for **4e**, Table 3, entry 7), as opposed to those presented in Table 2.

Table 2 Scope of the TBD/Al₂O₃-catalyzed intermolecular aldol reaction in toluene^a

0 L		TBD (10 mol%) Al ₂ O ₃ (10 mol%) Toluene, r.t. 45 min., sonic waves		о он Ц Ц
R R	+ ArCHO 2a-f			R R
				3a-f, 4e, 5e
Entry	Ar	Product	Anti/syn ^b	Yield (%) ^c
1^d	4-ClC ₆ H ₄	3a	47:53	85
2^d	C ₆ H ₅	3b	50:50	97
$3^{d,e}$	$4-FC_6H_4$	3c	50:50	95
$4^{d,e}$	4-CF ₃ C ₆ H ₄	3d	44:56	98
$5^{d,e}$	$4-NO_2C_6H_4$	3e	42:58	70
6^d	3-ClC ₆ H ₄	3f	45:55	92
7^{f}	$4-NO_2C_6H_4$	4e	38:62	75
8^g	$4-NO_2C_6H_4$	5e	50:50	78

^{*a*} General reaction conditions: ketone (10 equiv.), **2a–f** (1 equiv.), toluene (0.15 M for **2a–f**), 45 min, rt, sonic waves. ^{*b*} Determined by ¹H NMR on crude reaction mixtures. ^{*c*} Isolated yield of pure products **3**, **4** and **5** purified by flash chromatography on silica gel. Products **3**, **4** and **5** were isolated as a mixture of diastereoisomers. ^{*d*} Cyclohexanone was used as ketone. ^{*e*} Reaction was carried out for 3 h at rt without sonication. ^{*f*} Cyclopentanone was employed as ketone. ^{*g*} 3-Pentanone was employed as ketone.

Table 3 Scope of the TBD/Al₂O₃-catalyzed intermolecular aldol reaction in water^a

			3a-c. 3e. 3g. 4c. 4e
 R R	2a-c, 2e, 2g	H ₂ O, r.t. 45 min., sonic waves	^' R R
o	+ ArCHO	TBD (10 mol%) Al ₂ O ₃ (10 mol%)	● OH

Entry	Ar	Product	Anti/syn ^b	Yield (%) ^c
1^d	4-ClC ₆ H ₄	3a	52:48	98
2^d	C ₆ H ₅	3b	58:42	97
3^d	$4 - FC_6H_4$	3c	59:41	95
4^d	$4-NO_2C_6H_4$	3e	57:43	98
5^d	4-CO ₂ MeC ₆ H ₄	3g	60:40	92
6 ^e	$4-FC_6H_4$	4c	57:43	98
7^e	4-NO ₂ C ₆ H ₄	4e	43:57	98

^{*a*} General reaction conditions: ketone (10 equiv.), **2a–f** (1 equiv.), distilled water (0.15 M for **2a–f**), 45 min, rt, sonic waves. ^{*b*} Determined by ¹H NMR on crude reaction mixtures. ^{*c*} Isolated yield of pure products **3** and **4**. Products **3** and **4** were isolated as a mixture of diastereoisomers. ^{*d*} Cyclohexanone was used as ketone. ^{*e*} Cyclopentanone was employed as ketone.

Aldol **3g**, equipped with an ester group, does not suffer from hydrolysis during the course of the reaction.

Aldols **6c** and **6e**, prepared from acetone, were also rendered in good yield by means of our methodology (Table 4). In this occasion, acetone has to be used as reagent and solvent under sonication. This type of aldol adduct are known to suffer rapid dehydration to afford the corresponding enones. In this respect, aldol **6c** was prepared in 79% yield in a significant 4.0 mmol scale.

In order to study the reversibility of the aldol reaction under our experimental conditions, thus the ability to give rise to

Table 4 TBD/Al₂O₃-catalyzed intermolecular aldol reaction with acetone^{α}

Entry	Ar	Product	Yield (%) ^l
$\frac{1}{2^{c}}$	$\begin{array}{l} 4\text{-NO}_2\text{C}_6\text{H}_4\\ 4\text{-FC}_6\text{H}_4 \end{array}$	6e 6c	60 79

^{*a*} General reaction conditions: aromatic aldehyde (1 equiv.), in neat acetone (0.2 M for **2**), 45 min, rt, sonic waves. ^{*b*} Isolated yield of pure products **6** after flash chromatography. ^{*c*} Reaction carried out on a scale of 4.0 mmol.

DCLs, we designed and implemented the following experiment: equimolar mixtures of the cyclohexanone-containing aldol **3e** (0.15 mmol, *anti/syn* 57:43), and cyclopentanone-containing aldol **4c** (0.15 mmol, *anti/syn* 57:43), were stirred for 5 h, in toluene (2 mL), or sonicated for 2 h in water (2 mL), in the presence of cyclohexanone (1.5 mmol, 10 equiv.), cyclopentanone (1.5 mmol, 10 equiv.), TBD (0.03 mmol) and Al_2O_3 (0.03 mmol) to generate libraries LB1 and LB2, respectively (Scheme 1). Excess of ketones must be added to guarantee full conversion to the desired aldol products. To "freeze" the exchanging process, and the population of the different library components, the catalysts were removed by a standard work up. Analysis of LB1 and LB2 by ¹H and ¹⁹F NMR spectroscopy (samples reconstituted in $CDCl_3$ ¹² confirmed the presence of the eight possible aldol products expected to occur from recombination through an aldol/ retro-aldol mechanism. It is important to point out that the presence of undesired side products is negligible amid the mixtures of aldols. Deconvolution of the appropriate resonances allowed identification, calculation (Table 5), and plotting the concentration of each aldol featured in both of the libraries (Fig. 1). Experiments carried out for longer reaction times (overnight for LB1, and 5 h for LB2) showed up an identical distribution of library members in each library. It confirms that the ratios outlined in Table 5 correspond to truly equilibrium positions (energy minimums) for LB1 and LB2. Decomposition of the aldol products was not observed in the reaction times experienced.



Scheme 1 Preparation of dynamic libraries LB1 and LB2 through an aldol/retro-aldol process mediated by catalytic amounts of TBD-Al₂O₃.

Table 5 Distribution of components in dynamic libraries LB1 and LB2^a

Compound	[] in LB1 (mM) ^b	[] in LB2 (mM) ^b
4-NO₂-C₄H₄-CHO	0	0.04
4-F-C ₆ H ₄ -CHO	2.5	0.5
Anti-3e	7.4	19.1
Syn-3e	11.7	28.0
Anti-3c	8.8	8.0
Syn-3c	9.6	5.0
Anti-4e	19.3	8.9
Syn-4e	36.6	18.5
Ånti- 4c	23.3	21.0
Syn-4c	30.8	40.5
-		

^{*a*} Libraries **LB1** and **LB2** were prepared as detailed in the experimental section. ^{*b*} Volumes of cyclohexanone and cyclopentanone were ignored for calculating the concentration of aldols.



Fig. 1 (a) Pie-chart graphic representing the percentage and mmols (in brackets, of a maximum of 0.3 mmol) of cyclopentyl aldols (dark grey) *versus* cyclohexyl aldols (light grey) in DCLs **LB1** (left) and **LB2** (right), respectively. (b) Pie-chart graphic representing the percentage and mmols (in brackets, of a maximum of 0.3 mmol) of *syn* aldols (dark grey) *versus anti* aldols (light grey) in DCLs **LB1** (left) and **LB2** (right), respectively.

A look at Table 5, gathering the results from the previous experiments, confirms that the concentrations of aldols in libraries **LB1** and **LB2** are unlike. Firstly, it is important to note the preference of **LB1** for selecting cyclopentyl aldols, which are populated in a 3-fold excess with respect to the cyclohexyl ones (Fig. 1a). It reveals the larger thermodynamic stability in toluene of structures **4c** and **4e** with respect to the cyclohexyl aldols **3c** and **3e**.

Although in both libraries the *syn* aldols are favoured at expense of those with an *anti* configuration (Fig. 1b), particularly in **LB2**, the cyclopentyl aldols **4c** and **4e** present an *anti/syn*

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Fig. 2 (a) Bar-chart graphic comparing the percentage of *anti* (dark grey) and *syn* (light grey) diastereoisomers of aldol 4c obtained as indicated in Table 3 (top bar) or in library LB2 (bottom bar), respectively. (b) Bar-chart graphic comparing the percentage of *anti* (dark grey) and *syn* (light grey) diastereoisomers of aldol 4e obtained as indicated in Table 3 (top bar) or in library LB2 (bottom bar), respectively.

ratio of around 1:2 (Fig. 2). For 4c, this relationship is significantly different from that obtained for the same aldol when it is prepared separately under analogous reaction conditions, as in Table 3, entry 6 (Fig. 2a). This selectivity for 4c shows how properties (i.e. diastereoselectivity), which could not be predicted in principle by taking into account the subcomponents of the network in isolation, can emerge even from small system/ network of interconverting molecules, interacting through supramolecular contacts,¹³ competing for a catalyst and for molecular building blocks. Accordingly, the system of aldols 3c, 3e, 4c, 4e, involved in thermodynamically controlled reactions, approaches equilibrium in a complex way to render the most stable set of products from the network as a whole. We believe that this kind of approach, a Systems Chemistry strategy,¹⁴ the deliberate creation of mixtures/collections of compounds, commonly avoided in classical organic synthesis, may open untrodden paths for hot areas such as organocatalysis.

Conclusion

Summarizing, herein we have developed a novel catalytic system (TBD/Al_2O_3) , which is rather straightforward and effective for the synthesis of aldols in water and non-polar organic solvents (toluene). The transformation is fast, allowing the preparation of pools of aldols interconverting through an aldol/retro-aldol sequence, a reaction that has not yet been broadly considered in the construction of DCLs. We have demonstrated how moderate levels of diastereoselectivity, which unfortunately could not be

anticipated, can emerge from basic thermodynamically-controlled network of molecules when supramolecular interactions between the library members, and competition for the catalyst and for molecular building blocks come to play. The interconverting library members approach equilibrium in a complex way to render the thermodynamically most stable set of products from the network as a whole entity. This manuscript discloses a comprehensible proof of principle showing that a Systems Chemistry approach is workable. Experiments aiming to couple an irreversible reaction to our DCLs, capable of selecting¹⁵ specific library members, are currently being investigated in our laboratory.

Experimental

All commercially available reagents and solvents were used without further purification. Samples of TBD were taken from a Schlenk flask stored in the dark under argon atmosphere. Flash chromatography of reaction products, when required, was carried out using Silica 60A, particle size 230-400 micron (Merck). Analytical thin layer chromatography (TLC) was performed on DC-Alufolien Kieselgel 60F254 0.2 mm plates (Merck) and compounds were visualised by UV fluorescence or 5% phosphomolybdic acid in methanol. ¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were recorded on a Bruker AC-300 or a Bruker DPX-300 spectrometer, using deuterated solvents and were referenced internally to the residual solvent peak ($\delta_{\rm H} = 7.26$ ppm, $\delta_{\rm C} =$ 77.36 ppm) signal,¹⁶ or to CFCl₃ ($\delta_{\rm F} = 0.00$ ppm) for ¹⁹F spectra. Coupling constants (J-values) are given in Hertz (Hz). The DEPT 135 technique was used to assign methylene (CH_2) signals if necessary. NMR spectra assignation was aided by comparison with literature values for similar compounds.

Standard procedure for the synthesis of aldols (as in Tables 2 and 3)

A suspension of triazabicyclo[4.4.0]dec-5-ene (TBD, 4.2 mg, 0.03 mmol) and neutral Al_2O_3 (3.1 mg, 0.03 mmol) in toluene (2 mL), or alternatively distilled water (2 mL), was prepared inside a closed test tube. The corresponding aromatic aldehyde (0.3 mmol) and ketone (3.0 mmol) were added sequentially to the former suspension. The reaction mixture was then sonicated for 45 min before it was poured onto NH₄Cl aq. sat. (10 mL) and extracted with CH₂Cl₂ (2 × 15 mL). The organic liquors were dried (MgSO₄), and the solvents and volatiles evaporated under reduced pressure to afford crude material, which were purified further, only if required, by a brief filtration through a plug of silica gel.

Standard procedure for the synthesis of acetone-derived aldols (as in Table 4)

Either 4-nitrobenzaldehyde (0.4 mmol), or 4-fluorobenzaldehyde (0.4 mmol), was added to a suspension of triazabicyclo[4.4.0] dec-5-ene (TBD, 5.6 mg, 0.04 mmol) and neutral Al_2O_3 (4.1 mg, 0.04 mmol) in acetone (2 mL) inside a closed test-tube. The reaction mixture was then sonicated for 45 min before it was poured onto NH₄Cl aq. sat. (10 mL) and was extracted with

 CH_2Cl_2 (2 × 15 mL). The organic liquors were dried (MgSO₄), and the solvents and volatiles evaporated under reduced pressure to afford crude material, which were purified further by flash chromatography on silica gel.

Standard procedure for the synthesis of dynamic library LB1

A mixture of cyclohexanone-derived aldol **3e** (37.4 mg, 0.15 mmol, *anti/syn* 57:43) and cyclopentanone-derived aldol **4c** (31.2 mg, 0.15 mmol, *anti/syn* 57:43), weighed in closed a test tube, were dissolved in toluene (2 mL). Cyclohexanone (148 mg, 156 μ L, 1.5 mmol), cyclopentanone (126 mg, 132 μ L, 1.5 mmol), triazabicyclo[4.4.0]dec-5-ene (TBD, 4.2 mg, 0.03 mmol) and neutral Al₂O₃ (3.1 mg, 0.03 mmol) were added to the former solution and it was vigorously stirred for 5 h at room temperature. The reaction mixture was quenched with NH₄Cl aq. sat. (10 mL), and extracted with CH₂Cl₂ (2 × 15 mL). The organic liquors were dried (MgSO₄), and the solvents and volatiles evaporated under reduced pressure to afford a solid material, which was redissolved in CDCl₃ and analyzed by ¹H and ¹⁹F NMR spectroscopy.

Standard procedure for the synthesis of dynamic library LB2

To a suspension of cyclohexanone-derived aldol **3e** (37.4 mg, 0.15 mmol, *anti/syn* 57:43) and cyclopentanone-derived aldol **4c** (31.2 mg, 0.15 mmol, *anti/syn* 57:43), in distilled water (2 mL), cyclohexanone (148 mg, 156 μ L, 1.5 mmol), cyclopentanone (126 mg, 132 μ L, 1.5 mmol), triazabicyclo[4.4.0]dec-5ene (TBD, 4.2 mg, 0.03 mmol) and neutral Al₂O₃ (3.1 mg, 0.03 mmol) were added sequentially. This mixture was sonicated for 2 h before it was quenched with NH₄Cl aq. sat. (10 mL), and extracted with CH₂Cl₂ (2 × 15 mL). The organic liquors were dried (MgSO₄), and the solvents and volatiles evaporated under reduced pressure to afford a solid material, which was redissolved in CDCl₃ and analyzed by ¹H and ¹⁹F NMR spectroscopy.

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References

- (a) J.-M. Lehn, Chem.-Eur. J., 1999, 5, 2455–2463; (b) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, Angew. Chem., Int. Ed., 2002, 41, 898–952; (c) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, Chem. Rev., 2006, 106, 3652–3711; (d) S. Ladame, Org. Biomol. Chem., 2008, 6, 219–226; (e) V. del Amo and D. Philp, Chem.-Eur. J., 2010, 16, 13304–13318.
- 2 J.-M Lehn, Chem.-Eur. J., 1999, 5, 2455-2463.
- 3 For recent selected examples, see: (a) S. Rochat and K. Severyn, J. Comb. Chem., 2010, **12**, 595–599; (b) J. Gao, A. Granzhan, X. Qian and K. Severin, Chem. Commun., 2010 (30), 5515–5517; (c) S. Rochat, J. Gao, X. Qian, F. Zaubitzer and K. Severin, Chem.–Eur. J., 2010, **16**, 104–113; (d) T. Zhang, N. Y. Edwards, M. Bonizzoni and E. V. Anslyn,

J. Am. Chem. Soc., 2009, **131**, 11976–11984; (*e*) M. Kitamura, S. H. Shabbir and E. V. Anslyn, *J. Org. Chem.*, 2009, **74**, 4479–4489.

- 4 For recent selected examples, see: (a) F. B. L. Cougnon, H. Y. Au-Yeung, G. Dan Pantos and J. K. M. Sanders, J. Am. Chem. Soc., 2011, 133, 3198–3207; (b) H. Y. Au-Yeung, G. Dan Pantos and J. K. M. Sanders, J. Org. Chem., 2011, 76, 1257–1268; (c) M.-K. Chung, P. S. White, S. J. Lee and M. R. Gagné, Angew. Chem., Int. Ed., 2009, 48, 8683; (d) K. R. West, R. F. Ludlow, P. T. Corbett, P. Besenius, F. M. Mansfeld, P. A. G. Cormack, D. G. Sherrington, J. M. Goodman, M. C. A. Stuart and S. Otto, J. Am. Chem. Soc., 2008, 130, 10834–10835; (e) R. T. S. Lam, A. Belenguer, S. L. Roberts, C. Naumann, T. Jarrosson, S. Otto and J. K. M. Sanders, Science, 2005, 308, 667.
- 5 For recent selected examples, see: (a) M.-K. Chung, K. Severin, S. J. Lee, M. L. Waters and M. R. Gagné, *Chem. Sci.*, 2011, **2**, 744–747; (b) V. T. Bhat, A. M. Caniard, T. Luksch, R. Brenk, D. J. Campopiano and M. F. Greaney, *Nat. Chem.*, 2010, **2**, 490–497; (c) P.-K. Müller-Graff, H. Szelke, K. Severin and R. Krämer, *Org. Biomol. Chem.*, 2010, **8**, 2327–2331; (d) L. A. Ingerman, M. E. Cuellar and M. L. Waters, *Chem. Commun.*, 2010, **46**, 1839–1841.
- 6 N. Mase and C. F. Barbas III, Org. Biomol. Chem., 2010, 8, 4043–4050, and references therein.
- 7 For some recent reviews on organocatalyzed transformations, with special emphasis to the aldol reaction, see: (a) W. Notz, F. Tanaka and C. F. Barbas, Acc. Chem. Res., 2004, 37, 580; (b) J. Seayad and B. List, Org. Biomol. Chem., 2005, 3, 719; (c) B. List, Chem. Commun., 2006, 819; (d) G. Lelais and D. W. C. MacMillan, Aldrichimica Acta, 2006, 39, 79; (e) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, Chem. Rev., 2007, 107, 5471; (f) A. Dondoni and A. Massi, Angew. Chem., Int. Ed., 2008, 47, 4638; (g) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, Angew. Chem., Int. Ed., 2008, 47, 6138; (h) C. F. Barbas, Angew. Chem., Int. Ed., 2008, 47, 42; (i) Z. Shao and H. Zhang, Chem. Soc. Rev., 2009, 38, 2178; (k) X. Liu, L. Lin and X. Feng, Chem. Commun., 2009, 6145.

- 8 A. M. Flock, C. M. M. Reucher and C. Bolm, *Chem.-Eur. J.*, 2010, 16, 3918–3921.
- 9 C. Ghobril, C. Sabot, C. Mioskowski and R. Baati, *Eur. J. Org. Chem.*, 2008, 4104.
- 10 A. Martínez-Castañeda, B. Poladura, H. Rodríguez-Solla, C. Concellón and V. del Amo, Org. Lett., 2011, 13, 3032–3035.
- 11 For some recent reviews on the chemistry of guanidines, see: (a) T. Ishikawa and T. Kumamoto, *Synlett*, 2006, 737; (b) D. Leow and C.-H. Tan, *Chem.–Asian J.*, 2009, **4**, 488; (c) M. P. Coles, *Chem. Commun.*, 2009, 3659; (d) D. Leow and C.-H. Tan, *Synlett*, 2010, 1589; (e) X. Fu and C.-H. Tan, *Chem. Commun.*, 2011, **47**, 8210–8222.
- 12 Mixtures of aldols in CDCl₃ are inert, exchange processes were not observed in the absence of the catalysts.
- 13 (a) G. Gasparini, M. Martin, L. J. Prins and P. Scrimin, *Chem. Commun.*, 2007, 1340; (b) A. G. Orrillo and R. L. E. Furlan, *J. Org. Chem.*, 2010, 75, 211.
- 14 For a discussion on the chemistry and possibilities of complex systems (Systems Chemistry), see: (a) M. Kindermann, I. Stahl, M. Reimold, W. M. Pankau and G. von Kiedrowski, Angew. Chem., Int. Ed., 2005, 44, 6750; (b) R. F. Ludlow and S. Otto, Chem. Soc. Rev., 2008, 37, 101–108; (c) J. R. Nitschke, Nature, 2009, 462, 736–738; (d) G. von Kiedrowski, S. Otto and P. Herdewijn, J. Syst. Chem., 2010, 1, 1; (e) R. A. R. Hunt and S. Otto, Chem. Commun., 2011, 47, 847–858.
- (a) S. M. Turega, C. Lorenz, J. W. Sadownik and D. Philp, Chem. Commun., 2008, 4076; (b) J. W. Sadownik and D. Philp, Angew. Chem., Int. Ed., 2008, 47, 9965; (c) P. Vongvilai, M. Angelin, R. Larsson and O. Ramström, Angew. Chem., Int. Ed., 2007, 46, 948; (d) M. Angelin, P. Vongvilai, A. Fischer and O. Ramström, Chem. Commun., 2008, 768; (e) P. Vongvilai and O. Ramström, J. Am. Chem. Soc., 2009, 131, 14419; (f) P. Vongvilai, M. Linder, M. Sakulsombat, M. S. Humble, P. Berglund, T. Brinck and O. Ramström, Angew. Chem., Int. Ed., 2011, 50, 6592.
- 16 H. E. Gottlieb, V. Kotlyar and A. Nudelman, J. Org. Chem., 1997, 62, 7512.