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Quinine catalysed asymmetric Michael additions in a sustainable solvent

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Diethyl carbonate is shown to be a suitable, sustainable solvent in which to carry out quinine catalysed asymmetric Michael additions of malononitriles to enones. Both malonitrile and α-substituted malononitriles can be used as substrate and the results suggest that π-π stacking interactions between the (hetero)aromatic rings of the catalyst and substrates are important in determining the degree of asymmetric induction.

Introduction

Over the last decade there has been an explosion of interest in asymmetric organocatalysis.[1] Whilst the initial advances in this area were made using unmodified natural products such as proline,[2] other amino acids[3] and cinchona alkaloids[4] as catalysts, the recent trend has been towards the use of highly modified natural products or totally synthetic catalysts.[1,5] These non–natural catalysts often offer improved solubility and enhanced reactivity compared to the direct use of natural products as catalysts, but sacrifice the green characteristics associated with using unmodified natural products[6] due to the need to carry out multi–step transformations to prepare the catalyst.

Another aspect of organocatalysis that has been rather neglected is the reaction solvent, even though this usually constitutes the bulk of the reaction mass. Amino acid catalysed reactions are often carried out in solvents such as DMF or DMSO to facilitate the solubility of the zwitterionic catalyst.[1–3,7] Other organocatalysed reactions have been carried out in solvents such toluene, acetonitrile, dichloromethane or chloroform.[1–7] However, these solvents are petrochemically derived and have hazards associated with their toxicity; potential to generate contaminated aqueous waste and potential to generate NO_x / SO_x on incineration.[8] In some cases, organocatalysed reactions can be carried out under solvent–free conditions,[9] and water[10] and ionic liquids[11] have both been used as alternative solvents for organocatalysed reactions. However, the green credentials of these solvents have been questioned[12] and water is known to inhibit some proline catalysed reactions.[13]

To overcome the solvent limitations associated with the use of unmodified natural products as organocatalysts, we have recently reported the use of ethylene **1** or propylene **2** carbonate as green polar aprotic solvents for amino acid catalysed reactions.[14] Cyclic carbonates **1** and **2** have high dielectric constants (90 and 65 respectively[15]). In contrast, acyclic carbonates such as dimethyl **3** and diethyl **4** carbonate have a much lower dielectric constant (3.1[16]) and so can be considered as apolar solvents. Carbonates **1–4** have also been used as solvents for uncatalysed and metal catalysed reactions[17] and are used as electrolytes for lithium ion batteries.[18] The green credentials of carbonates **1–4** are supported by their low toxicities,[16,17] facile hydrolysis to innocuous by–products[19] and green syntheses[16,20] with the potential to utilize waste carbon dioxide in their syntheses.[21] Compounds **1–3** were included in a recent listing of industrially recommended green solvents.[22] In this manuscript we show that acyclic carbonate **4** can be used as a green solvent for quinine catalysed Michael additions.

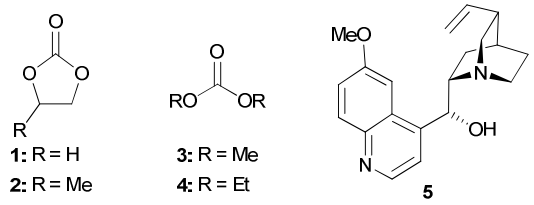
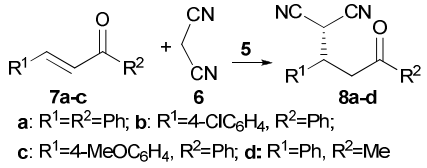


Figure 1 Structures **1–5**



Scheme 1 Quinine catalysed asymmetric Michael additions

Results and discussion

In 2009,[23] Lattanzi and coworkers reported that unmodified quinine **5** would catalyse the asymmetric addition of malononitrile **6** to aryl vinyl ketones **7** to give Michael adducts **8** with 74–95% enantiomeric excess under optimized conditions (-18 °C and 10 mol% catalyst) as shown in Scheme 1.[24] Whilst this 100% atom economical reaction is synthetically attractive as it produces richly functionalised products, it does have two drawbacks: the reaction times were 60–186 hours and high yields and enantioselectivities were only obtained in

petrochemically derived aromatic hydrocarbon solvents (toluene or xylene) which are less than ideal solvents, especially from an environmental impact perspective.[22] Therefore, we felt that this reaction would allow us to extend our previous work on carbonate solvents for organocatalysed reactions to a different class of catalysts and reactions. The choice of solvent for asymmetric organocatalysed reactions is a non–trivial undertaking as efficient asymmetric induction often relies on non–covalent interactions and hydrogen bonds.[1–5] These are easily disrupted by polar solvents or even by non–polar solvents which can act as hydrogen bond acceptors. Thus, even though diethyl carbonate has low polarity there was still the possibility that it would act as a Lewis base, disrupting any hydrogen bonds between the quinine and substrates.

Initial studies were carried out using chalcone **7a** as the Michael acceptor with 1.2 equivalents of malonitrile **6** and with 20 mol% of quinine to increase the reaction rate. The results of this study are shown in Table 1. Entries 1 and 2 confirm the results of Lattanzi and coworkers showing that high chemical yields are obtained in both toluene and methanol, but high levels of asymmetric induction are only obtained in the very non–polar solvent. Entries 3–5 then show that the use of polar cyclic carbonates as solvents give product **8a** in high yield, but with greatly reduced enantiomeric excess compared to reactions carried out in toluene. The use of enantiomerically pure propylene carbonate was also not advantageous in this case (compare entries 4 and 5). In addition, a minor side product was observed in these reactions. This was isolated and determined to be cyclohexanol derivative **9a** (Figure 2) resulting from a tandem double Michael addition of malonitrile to two molecules of chalcone **7a** followed by an intramolecular aldol reaction. The structure and formation of racemic **9a** in related racemic Michael additions has been reported before, as has the relative stereochemistry of its four stereocentres.[25]

Table 1 Michael addition of malononitrile **6** to chalcone **7a**

Entry	Solvent	t (h)	T (°C)	**7a:6**	Yield (%)[a]	**8a:9a**	ee (%)[b]
1	toluene	20	18	1:1.2	98	1:0	87
2	MeOH	20	18	1:1.2	90	1:0	0
3	**1**	20	18	1:1.2	82	4.4:1	11
4	*RS*–**2**	20	18	1:1.2	80	11.6:1	12
5	*R*–**2**	20	18	1:1.2	80	13.5:1	12
6	**3**	20	18	1:1.2	98	8.8:1	48
7	**3**	72	0	1:1.2	98	4.3:1	31
8	**4**	20	18	1:1.2	95	21:1	56
9	**4**	72	0	1:1.2	98	1:1	52
10	**4**	72	-20	1:1.2	98	1:1.7	47
11	**4**	20	30	1:5	98	1:0	58
12	**4**	20	18	1:5	98	1:0	60
13	**4**	20	0	1:5	98	1:0	62
14	**4**	48	-10	1:5	96	1:0	64
15	**4**	72	-20	1:5	90	1:0	64
16	**4**	72	-40	1:5	80	1:0	65

[a] Isolated yield of **8a**+**9a** after purification by flash chromatography. Compounds **8a** and **9a** were not readily separable. [b] Ee of compound **8a** determined by chiral HPLC on a Chiralpak AD-H column.

The mode of action of quinine in this reaction likely involves it acting as a Brønsted base to remove one of the acidic protons from malonitrile. Thus, to get efficient asymmetric induction during the Michael addition of the resulting malonitrile anion, it is necessary for the chiral cation and achiral anion to form a tight ion pair. It is also likely that π–π interactions between the aromatic rings of quinine and enone **7** are important to organise the reaction components and maximise the asymmetric induction, since only aryl enones form effective substrates for this reaction.[23] A polar solvent (such as cyclic carbonates **1** and **2**) would disrupt both the tight ion pair and any π–π interactions, thus resulting in the significantly reduced asymmetric induction. To overcome this problem, the use of much less polar, acyclic carbonate solvents **3** and **4** was therefore investigated. The use of dimethyl carbonate as solvent at either 18 or 0 °C (entries 6 and 7) gave the same chemical yield as a reaction in toluene, but whilst the enantioselectivity increased relative to the use of cyclic carbonates as solvent, it was still only around half that observed in toluene. The use of diethyl carbonate as solvent gave even better results (entry 8), with a high yield and a high ratio of **8a:9a**, though the enantiomeric excess of product **8a** was still only moderate. Attempts to increase the enantioselectivity of the reaction by lowering the reaction temperature (entries 9 and 10) were unsuccessful as not only did the enantiomeric excess of compound **8a** decrease as the temperature was lowered, but the amount of by–product **9a** formed increased significantly and at -20 °C it became the major product (entry 10). The reduction in enantioselectivity at lower temperature was traced to an uncatalysed Michael addition occurring upon addition of water and warming the reaction mixture. This could be avoided by quenching the reactions with dilute hydrochloric acid rather than water.

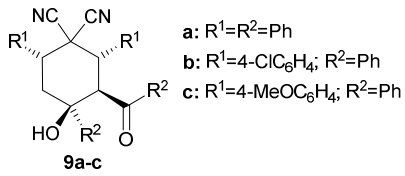


Figure 2 Structure **9a–c**

The use of other cinchona alkaloids as catalysts was briefly investigated under the conditions of Table 1, entry 9. However, under these conditions quinidine, cinchonine and cinchonidine gave compound **9a** as the only product in 84, 55 and 59% chemical yield respectively.

To avoid the formation of by–product **9**, the ratio of malononitrile **6** to chalcone **7a** was increased to 5:1. As shown in Table 1, entry 11, this resulted in the exclusive formation of product **8a** in excellent chemical yield and with further improved enantiomeric excess even from a reaction carried out at 30 °C. It was then possible to further increase the enantioselectivity to 64% by lowering the reaction temperature to -20 °C (entries 12–16). Reactions carried out with 30 mol% of quinine did not result in higher enantioselectivities.

The quinine catalysed Michael addition of malononitrile to three other α,β-unsaturated ketones **7b–d** was also investigated in diethyl carbonate and the results are shown in Table 2. For substrates **7b** and **7c** the enantioselectivities at -20 °C were essentially identical to those obtained using substrate **7a** (compare Table 1, entry 15 with Table 2, entries 4 and 8). The chemical yields obtained using substrates **7a** and **7b** were also very similar, whilst electron–rich substrate **7c** was less reactive. Benzylidene acetone **7d** was not a substrate for the reaction. These results suggest the importance of π–π interactions involving an aromatic ring at the R^2 position of substrate **7** in obtaining good levels of asymmetric induction.

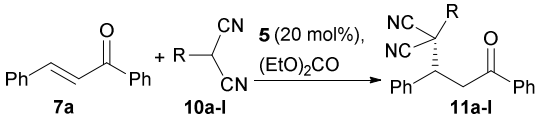
Table 2 Michael addition of malononitrile **6** to enones **7b–d**

Entry	Enone	t (h)	T (°C)	**7b–d:6**	Yield (%)[a]	**8:9**	ee (%)[b]
1	**7b**	24	18	1:1.2	72	8.5:1	45
2	**7b**	72	-20	1:1.2	81	5.2:1	44
3	**7b**	24	18	1:5	73	1:0	58
4	**7b**	72	-20	1:5	91	1:0	64
5	**7c**	24	18	1:1.2	90	10.8:1	54
6	**7c**	72	-20	1:1.2	41	0.2:1	54
7	**7c**	24	18	1:5	79	1:0	54
8	**7c**	72	-20	1:5	72	1:0	65

[a] Isolated yield of **8b–c+9b–c** after purification by flash chromatography. [b] Ee of compounds **8b,c** determined by chiral HPLC on a Chiralpak AD-H column.

If steric factors were responsible for the asymmetric induction, then we reasoned that increasing the size of the malonitrile enolate would increase the facial discrimination between the enantiotopic faces of the enone and result in higher levels of asymmetric induction. Therefore, we investigated the Michael addition of α-monosubstituted malonitrile derivatives **10a–l** to chalcone **7a** to give ketones **11a–l** as shown in Scheme 2. The results of this study are given in Table 3. Initially a series of arylmethyl substituted malonitriles **10a–i** were used to see if π–π interactions involving the aryl ring would improve the enantioselectivity. Dinitrile **10a** was however not encouraging, giving compound **11a**[26] with only moderate enantiomeric excess and in very low yield after a reaction carried out for 72 hours at room temperature (entry 1). However, introducing a halogen substituent into the 4-position of dinitrile **10** had a highly beneficial effect on both the yield and enantioselectivity of the reactions, giving compounds **11b,c** with 94 and 89% enantiomeric excess respectively (entries 2,3). Moving the halogen to the 3–position of the aromatic ring (**10d**) retained the improved yield, but not the enhanced enantioselectivity (entry 4), whilst moving it to the 2–position of the aromatic ring (**10e**) lowered both the yield and enantioselectivity to values similar to those seen for unsubstituted substrate **10a**.

Other substituents at the 4-postion of the aromatic ring of substrates **10** were also beneficial with the most positive effects being seen with strongly electron withdrawing groups such as nitro (**10f**) and trifluoromethyl (**10h**) whilst an electron donating methoxy substituent had a beneficial effect on the enantioselectivity, but not on the yield (entries 6–8). Substrate **10i** with fluorine substituents at all positions of the aromatic ring gave product **11i** in good chemical yield but with very low enantiomeric excess (entry 9).



a: R = CH_2Ph; **b:** R = 4-$BrC_6H_4CH_2$; **c:** R = 4-$ClC_6H_4CH_2$; **d:** R = 3-$ClC_6H_4CH_2$; **e:** R = 2-$ClC_6H_4CH_2$; **f:** R = 4-$O_2NC_6H_4CH_2$; **g:** R = 4-$MeOC_6H_4CH_2$; **h:** R = 4-$F_3CC_6H_4CH_2$; **i:** R = $C_6F_5CH_2$; **j:** R = CH_3; **k:** R = $CH_2CH{=}CH_2$; **l:** R = CH_2CCH

Scheme 2 Quinine catalysed asymmetric Michael additions of α-monosubstituted malononitriles

Table 3 Quinine catalysed Michael addition of α-substituted malononitriles **10a–i** to enone **7a**

Entry	**10**	solvent	t (h)	T (°C)	Yield (%)[a]	ee (%)[b]
1	**a**	**5**	72	18	12	46
2	**b**	**5**	72	18	41	94
3	**c**	**5**	72	18	39	89
4	**d**	**5**	72	18	32	47
5	**e**	**5**	72	18	19	50
6	**f**	**5**	72	18	47	91
7	**g**	**5**	72	18	22	77
8	**h**	**5**	72	18	52	80
9	**i**	**5**	72	18	65	20
10	**a**	**5**	168	18	54	40
11	**b**	**5**	168	18	63	50
12	**c**	**5**	168	18	56	77
13	**d**	**5**	168	18	46	50
14	**e**	**5**	168	18	68	33
15	**f**	**5**	168	18	72	78
16	**h**	**5**	168	-20	33	46
17	**i**	**5**	168	-20	63	21
18[c]	**b**	**5**	72	18	57	50
19	**j**	**5**	72	18	44	48
20	**j**	**5**	168	18	61	48
21	**k**	**5**	72	18	57	46
22	**k**	**5**	168	18	73	50
23	**l**	**5**	72	18	88	38
24	**b**	toluene	72	18	62	76
25	**b**	acetone	72	18	24	11
26	**b**	EtOAc	72	18	31	61
27	**b**	cymene	72	18	49	68

[a] Isolated yield of **11a–i** after purification by column chromatography. [b] Ee determined by chiral HPLC on a Chiralpak AD-H column. [c] Using 5 equivalents of **10b**.

In an attempt to improve the chemical yields of these reactions, the reaction times were extended to 168 hours with substrates **10a–f**. This was successful in raising the chemical yields of products **11a–f** (entries 10–15), but also resulted in a decrease in the enantiomeric excess of products **11a–f**, except for product **11d**. This suggests that compounds **11a–i** can undergo slow racemisation under the reaction conditions, presumably by a retro–Michael/Michael addition process. In the case of substrates **10h,i** the extended reaction time experiments were carried out at -20 °C in an attempt to improve the enantioselectivity of the reactions since these two substrates had given reasonable chemical yields after 72 hours at room temperature. However, for substrate **10h** this had a negative impact on both the yield and enantiomeric excess of product **11h** (entry 16), whilst for product **11i**, there was no significant difference in the yield or enantiomeric excess (entry 17). An attempt was also made to increase the chemical yield by using five equivalents of malononitrile **10b** (entry 18). However, whilst this did result in a modest increase in chemical yield (compare entries 2 and 18), this was at the expense of a major reduction in enantioselectivity. It may be that the large excess of **10b** present in this reaction increases the polarity of the reaction solvent and hence destabilises π– π interactions between the catalyst and substrates.

The study was then extended to non–aromatic malononitriles **10j–l** to investigate if the aryl group present in substrates **10a–I** was important for asymmetric induction. The results (entries 19–23) showed that for these substrates which lack an aromatic ring, the enantiomeric excess of the products was 38–50%, values which are comparable with the worst

performing aromatic substrates under the same conditions (entries 1,4,5,9–11,13,14,16,17), but much lower than the best of the aryl methyl malonitriles (entries 2,3,6–8,12,15).

Finally, we screened a number of other solvents using substrate **10b** at 18 °C for 72 hours (entries 24–27). Toluene gave product **11b** with inferior enantiopurity compared to a reaction carried out in diethyl carbonate (compare entries 2 and 24). Other green solvents were also tested, but acetone and ethyl acetate both gave product **11b** in low yield and in the case of acetone with very low enantiopurity (entries 25 and 26). Cymene (4-isopropyl-toluene) which is available from limonene gave **11** in lower yield and enantiomeric purity than the reaction carried out in toluene (compare entries 24 and 27).

The above results are not consistent with simple steric or electronic effects being responsible for the magnitude of the asymmetric induction, though they do suggest that substituents at the 4-position of substrate **10** will be beneficial whilst those at other positions of the aromatic ring will be detrimental. In particular, both electron donating (**10g**) and electron withdrawing (**10b,c,h**) substituents gave products with higher enantiomeric excesses than that of the unsubstituted substrate **10a**. It may be that π–π stacking between substrate **10** and quinine **5** and/or enone **7a** are important for the asymmetric induction, and substituents at the 2– or 3–positions of the aryl ring of substrates **10** disrupt this π–π stacking. This is consistent with the results obtained with substrates **10j–l** which lack an aromatic ring and so cannot benefit from these favourable π–π interactions.

Conclusions

We have shown that diethyl carbonate can replace toluene as a solvent for quinine catalysed Michael additions of malonitrile derivatives to enones. The chemical yields and enantioselectivities were highly variable which may be due to the complex nature of the intermolecular interactions in this system as the degree of asymmetric induction is likely to be influenced by both the tightness of an ion pair and the nature of the π–π interactions between the enone, malononitrile and quinine. Most solvents have the potential to disrupt these interactions, but it appears that diethyl carbonate is better than other green solvents in this respect.

Experimental

Instrumentation.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or Jeol Oxford 400 spectrometer at resonance frequencies of 300/400 and 75/100 MHz respectively. ^{19}F NMR spectra were recorded on the Oxford 400 spectrometer at a resonance frequency of 367 MHz. Electrospray ionization (ESI) mass spectra were recorded on a Bruker Daltronics microTOF spectrometer. Infrared spectra were recorded on a Bruker Vertex 70 instrument equipped with "Specac" Golden Gate Single Reflection Diamond ATR accessories. Chiral HPLC was performed using an Agilent 1220 Infinity LC series system comprising binary pumping modules, a diode array detector and autosampler. The column, solvent and flow rate are given for each compound. Automated flash chromatography was carried out on a Biotage isolera four system. Melting points were obtained using a Gallenkamp melting point apparatus. Optical rotations were measured at 20 °C on a Jasco DIP-370 polarimeter using a 10 cm curvette. The sample concentration is reported in g/100 mL of the specified solvent.

General procedure for the preparation of racemic samples of compounds 8a–d and 11a–i.

Enone **7a–d** (0.2 mmol) and DABCO (5.0 mg, 0.04 mmol) were dissolved in MeOH (2 mL). Malononitrile **6** or **10a–i** (0.24 mmol) was added and the reaction mixture was stirred at 20 °C for 20 h. The solvent was then removed in vacuo and the residue recrystallized from Et_2O to give racemic samples of compounds **8a,b,d** and **11a–i**. Compound **8c** is an oil and was used without purification.

General procedure for the Michael addition of malononitrile to enones 7a–c.

Enone **7a–c** (0.2 mmol) and quinine (12.9 mg, 0.04 mmol) were dissolved in diethyl carbonate (3 mL). Malononitrile **6** (66.7 mg, 1.0 mmol) was added and the reaction mixture was stirred at between 30 and -40 °C for 20–72 h. Then, 2M HCl was added, the organic layer separated, washed with deioninsed water, then dried with magnesium sulphate. The solvent was then removed in vacuo and the residue purified by flash chromatography (CH_2Cl_2) to give compound **8a–c**. The enantiomeric excess of compounds **8a–c** was determined by chiral HPLC using a Chiralpak AD-H column (hexane/^{i}PrOH 80:20, 1 mL min^{-1}, detection at 254 nm).

(*S*)-2-Cyano-3,5-diphenyl-5-oxo-pentanonitrile 8a[23,27,28] Obtained as a white solid (49.3 mg, 90%) with 64% enantiomeric excess (t_R = 5.9 (minor) and 7.9 (major) minutes). Mp 109–113 °C (lit[27] 109–111 °C); $[\alpha]_D^{20}$ -7.8 (c = 0.2, $CHCl_3$) (lit[28] $[\alpha]_D^{25}$ -12.5 (c = 0.2, $CHCl_3$)); ν_{max}(ATR) 3048, 2984, 2911, 2400 and 1627 cm^{-1}; δ_H 7.99 (2H, d *J* 8.6 Hz, ArH), 7.64 (1H, t *J* 7.4 Hz, ArH), 7.6–7.4 (7H, m, ArH), 4.67 (1H, d *J* 5.0 Hz, CHCN), 3.97 (1H, dt *J* 8.4, 5.3 Hz, PhCH), 3.74 (1H, dd *J* 18.4, 8.3 Hz, CH_2); 3.66 (1H, dd *J* 18.6, 5.6 Hz, CH_2); δ_C 196.8, 136.6, 135.8, 134.3, 129.4, 129.3, 129.0, 128.2, 128.1, 111.9, 111.8, 41.3, 40.2, 28.9; m/z (ESI) Found 297.1004, $C_{18}H_{14}N_2ONa$ $(M+Na)^+$ requires 297.0998.

(*S*)-3–(4–Chlorophenyl)–2-cyano-5-phenyl-5-oxo-pentano-nitrile 8b[23] Obtained as a white solid (56.1 mg, 91%) with 64% enantiomeric excess (t_R = 5.6 (minor) and 8.3 (major) minutes). Mp 124–127 °C (lit[23] 132–134 °C); $[\alpha]_D^{20}$ -8.1 (c = 0.2, $CHCl_3$) (lit[23] $[\alpha]_D^{25}$ -9.0 (c = 0.3, $CHCl_3$) for sample with 92% ee); ν_{max}(ATR) 2884, 1681 and 1597 cm^{-1}; δ_H 7.98 (2H, d *J* 7.2 Hz, ArH), 7.65 (1H, t *J* 7.4 Hz, ArH), 7.52 (2H, t *J* 7.8 Hz, ArH), 7.5–7.4 (4H, m, ArH), 4.64 (1H, d *J* 5.0 Hz, CHCN), 3.96 (1H, dt *J* 8.2, 5.4 Hz, PhCH), 3.71 (1H, dd *J* 18.5, 8.3 Hz, CH_2); 3.62 (1H, dd *J* 18.4, 5.5 Hz, CH_2); δ_C 193.6, 135.6, 135.3, 134.9, 134.3, 129.6, 129.4, 129.0, 128.1, 111.6, 111.4, 40.7, 40.0, 28.7; m/z (ESI) Found 331.0605, $C_{18}H_{13}N_2O^{35}ClNa$ $(M+Na)^+$ requires 331.0605.

(*S*)-3–(4–Methoxyphenyl)–2-cyano-5-phenyl-5-oxo-pentano-nitrile 8c[23,28] Obtained as a colourless oil (43.7 mg, 72%) with 65% enantiomeric excess (t_R = 7.9 (minor) and 12.7 (major) minutes). $[\alpha]_D^{20}$ -7.0 (c = 0.2, $CHCl_3$) (lit[28] $[\alpha]_D^{25}$ -11.0 (c = 0.2, $CHCl_3$)); ν_{max}(ATR) 3377, 2224, 1731, 1681 and 1581 cm^{-1}; δ_H 7.98 (2H, dd *J* 8.5, 1.4 Hz, ArH), 7.64 (1H, tt *J* 7.4, 1.4 Hz, ArH), 7.51 (2H, t *J* 7.3 Hz, ArH), 7.38 (2H, d *J* 8.7 Hz, ArH), 6.96 (2H, d *J* 8.8 Hz, ArH), 4.63 (1H, d *J* 5.0 Hz, CHCN), 3.93 (1H, dt *J* 8.3, 5.3 Hz, ArCH), 3.83 (3H, s, OCH_3), 3.72 (1H, dd *J* 18.4, 8.4 Hz, CH_2); 3.62 (1H, dd *J* 18.5, 5.5 Hz, CH_2); δ_C 196.9, 160.2, 135.9, 134.3, 129.3, 129.0, 128.5, 128.2, 114.7, 112.1, 111.8, 55.4, 40.7, 40.3, 29.2; m/z (ESI) Found 327.1102, $C_{19}H_{16}N_2O_2lNa$ $(M+Na)^+$ requires 327.1104.

General procedure for the Michael addition of α-substituted malononitriles 10a–i to enone 7a

Enone **7a** (41.6 mg, 0.2 mmol) and quinine (12.9 mg, 0.04 mmol) were dissolved in diethyl carbonate (3 mL). α-Substituted malononitrile[29] **10a-i** (0.24 mmol) was added and the reaction mixture was stirred at 18 or -20°C for 72 or 168 h. Then, the organic layer was washed with 2M HCl (2 x 4 mL) and deionised water (1 x 4 mL), and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by automated column chromatography (6:1 cyclohexane / EtOAc) to give compounds **11a–i** as white solids. The enantiomeric excess of compounds **11a–i** was determined by chiral HPLC using a chiralpak AD-H column (hexane/^{i}PrOH 80:20, 1 mL min^{-1}, detection at 254 nm).

(*S*)-4,4–Dicyano–1,3,5–triphenylpentan–1–one 11a[26] Obtained as a white solid (8.8 mg, 12%) with 46% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 10.1 (minor) and 19.5 (major) minutes). Mp 119–124 °C; $[\alpha]^{23}_D$ -10.2 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2390 and 1690 cm^{-1}; δ_H 7.95 (2H, dd *J* 8.5, 1.4 Hz, ArH), 7.7–7.3 (13H, m, ArH), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.8–3.6 (1H, m, CH_2CO), 3.06 (1H, d *J* 13.7, $PhCH_2$), 2.85 (1H, d *J* 13.6, $PhCH_2$); δ_C 195.1, 136.0. 135.7, 133.8, 132.2, 130.1, 129,2, 129.1, 128.94, 128.87, 128.8, 128.7, 128.1, 115.3, 114.4, 47.3, 45.2, 42.4, 41.4; m/z (ESI) Found 387.1469, $C_{25}H_{20}N_2ONa$ $(M+Na)^+$ requires 387.1468.

(*S*)-5-(4-Bromophenyl)-4,4–dicyano–1,3–diphenylpentan–1–one 11b Obtained as a yellow solid (36.3 mg, 41%) with 94% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 13.9 (minor) and 29.4 (major) minutes). Mp 172–177 °C; $[\alpha]^{23}_D$ -2.4 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2400 and 1700 cm^{-1}; δ_H 7.95 (2H, d *J* 8.5 Hz, ArH), 7.6–7.2 (10H, m, ArH), 7.20 (2H, d *J* 8.4 Hz, ArH), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.73 (1H, dd *J* 23.0, 8.9 Hz, CH_2CO), 3.03 (1H, d *J* 13.7, $ArCH_2$), 2.80 (1H, d *J* 13.7, $ArCH_2$); δ_C 195.0, 136.5, 135.9, 133.7, 132.2, 131.8, 131.4, 129.3, 129.2, 129.1, 128.8, 128.1, 123.3, 115.2, 114.3, 47.7, 45.1, 42.1, 41.7; m/z (ESI) Found 467.0599, $C_{25}H_{19}N_2O^{81}BrNa$ $(M+Na)^+$ requires 467.0553.

(*S*)-5-(4-Chlorophenyl)-4,4–dicyano–1,3–diphenylpentan–1–one 11c Obtained as a white solid (31.1 mg, 39%) with 89% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 12.8 (minor) and 27.7 (major) minutes). Mp 129–132 °C; $[\alpha]^{23}_D$ -8.8 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2390 and 1688 cm^{-1}; δ_H 7.96 (2H, dd *J* 8.5, 1.5 Hz, ArH), 7.6–7.3 (12H, m, ArH), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.77 (1H, dd *J* 15.7, 1.1 Hz, CH_2CO), 3.36 (1H, d *J* 14.0, $ArCH_2$), 3.08 (1H, d *J* 14.0, $ArCH_2$); δ_C 195.1, 136.6, 136.0, 135.4, 133.6, 131.6, 130.3, 130.1, 129.2, 129.1, 128.8, 128.1, 127.3, 115.2, 114.4, 48.0, 44.1, 41.6, 38.7; m/z (ESI) Found 421.1082, $C_{25}H_{19}N_2O^{35}ClNa$ $(M+Na)^+$ requires 421.1078.

(*S*)-5-(3-Chlorophenyl)-4,4–dicyano–1,3–diphenylpentan–1–one 11d Obtained as a yellow solid (36.6 mg, 46%) with 50% enantiomeric excess from a reaction at 18 °C for 168 h (t_R = 11.1 (minor) and 18.9 (major) minutes). Mp 130–132 °C; $[\alpha]^{23}_D$ -8.4 (c = 0.5, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2390 and 1690 cm^{-1}; δ_H 7.95 (2H, d *J* 7.6 Hz, ArH), 7.7–7.2 (12H, m, ArH), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.8–3.6 (1H, m, CH_2CO), 3.03 (1H, d *J* 13.7, $ArCH_2$), 2.81 (1H, d *J* 13.8, $ArCH_2$); δ_C 194.9, 136.0, 135.4, 134.7, 134.1, 133.8, 130.2, 130.1, 129.3, 129.2, 129.1, 128.9, 128.8, 128.3, 128.1, 115.1, 114.1, 47.4, 44.9, 41.9, 41.5; m/z (ESI) Found 421.1106, $C_{25}H_{19}N_2O^{35}ClNa$ $(M+Na)^+$ requires 421.1078.

(*S*)-5-(2-Chlorophenyl)-4,4–dicyano–1,3–diphenylpentan–1–one 11e Obtained as a white solid (9.9 mg, 19%) with 50% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 9.5 (minor) and 17.1 (major) minutes). Mp 161–165 °C; $[\alpha]^{23}_D$ +1.6 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2390 and 1665 cm^{-1}; δ_H 7.95 (2H, d *J* 7.3 Hz, ArH), 7.7–7.2 (12H, m, ArH), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.73 (1H, dd *J* 22.5, 8.2 Hz, CH_2CO), 3.03 (1H, d *J* 13.7, $ArCH_2$), 2.81 (1H, d *J* 13.8, $ArCH_2$); δ_C 194.9, 136.0, 135.5, 135.0, 133.8, 131.5, 130.6, 129.3, 129.2, 129.1, 128.9, 128.8, 128.1, 115.1, 114.2, 47.3, 45.1, 41.7, 41.5; m/z (ESI) Found 421.1081, $C_{25}H_{19}N_2O^{35}ClNa$ $(M+Na)^+$ requires 421.1078.

(*S*)-4,4–Dicyano–5-(4-nitrophenyl)-1,3–diphenylpentan–1–one 11f Obtained as an orange solid (38.4 mg, 47%) with 91% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 27.5 (minor) and 52.8 (major) minutes). Mp 140–146 °C; $[\alpha]^{23}_D$ -6.0 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2340 and 1687 cm^{-1}; δ_H 8.26 (2H, d *J* 8.8 Hz, ArH), 7.96 (2H, d *J* 8.5 Hz, ArH), 7.7–7.3 (10H, m), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.75 (1H, dd *J* 16.3, 1.9 Hz, CH_2CO), 3.17 (1H, d *J* 13.6, $ArCH_2$), 2.93 (1H, d *J* 13.6, $ArCH_2$); δ_C 194.8, 148.2, 139.3, 135.9, 135.2, 133.9, 131.2, 129.4, 129.3, 128.9, 128.8, 128.1, 124.1, 114.8, 113.8, 47.5, 44.7, 41.9, 41.5; m/z (ESI) Found 432.1355, $C_{25}H_{19}N_3O_3Na$ $(M+Na)^+$ requires 432.1319.

(*S*)-4,4–Dicyano–5-(4-methoxyphenyl)-1,3–diphenylpentan–1–one 11g Obtained as a yellow solid (17.3 mg, 22%) with 77% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 12.5 (minor) and 28.4 (major) minutes). Mp 167–169 °C; $[\alpha]^{23}_D$ +2.6 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2350 and 1690 cm^{-1}; δ_H 7.96 (2H, d *J* 8.5 Hz, ArH), 7.7–7.3 (8H, m, ArH), 7.27 (2H, d *J* 8.6 Hz, ArCH), 6.92 (2H, d *J* 8.7 Hz, ArH), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.82 (3H, s, OCH_3), 3.8–3.7 (1H, m, CH_2CO), 3.06 (1H, d *J* 13.8, $ArCH_2$), 2.84 (1H, d *J* 13.8, $ArCH_2$); δ_C 195.1, 159.9, 136.0, 135.7, 133.7, 131.3, 129.2, 129.0, 128.9, 128.8, 128.1, 124.1, 115.5, 114.5, 114.2, 55.2, 47.1, 45.6, 41.7, 41.4; m/z (ESI) Found 418.1598, $C_{26}H_{22}N_2O_2Na$ $(M+Na)^+$ requires 417.1573.

(*S*)-4,4–Dicyano–1,3–diphenyl-5-(4-trifluoromethylphenyl) pentan–1–one 11h Obtained as a white solid (45.1 mg, 52%) with 2% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 14.2 (minor) and 28.6 (major) minutes). Mp 146–148 °C; $[\alpha]^{23}_D$ -5.2 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2390 and 1690 cm^{-1}; δ_H 7.96 (2H, d *J* 7.3 Hz, ArH), 7.7–7.3 (12H, m, ArH), 4.2–4.0 (2H, m, CH_2CO+CHPh), 3.73 (1H, dd *J* 25.0, 10.3 Hz, CH_2CO), 3.12 (1H, d *J* 13.6, $ArCH_2$), 2.89 (1H, d *J* 13.6, $ArCH_2$); δ_C 195.0, 136.5, 136.3, 135.8, 133.7, 131.4 (q *J* 33.0 Hz), 130.7, 129.4, 129.3, 129.1, 128.9, 128.1, 125.9 (q *J* 3.5 Hz), 47.8, 45.0, 42.3, 41.7; δ_F -62.7; m/z (ESI) Found 455.1371, $C_{26}H_{19}N_2OF_3Na$ $(M+Na)^+$ requires 455.1342.

(*S*)-4,4–Dicyano–5-(pentafluorophenyl)-1,3–diphenyl–pentan–1–one 11i Obtained as a white solid (57.2 mg, 63%) with 21% enantiomeric excess from a reaction at -20 °C for 168 h (t_R = 6.7 (minor) and 10.3 (major) minutes). Mp 139–143 °C; $[\alpha]^{23}_D$ -9.2 (c = 1, $CHCl_3$); ν_{max}(ATR) 3030, 2981, 2390 and 1690 cm^{-1}; δ_H 7.96 (2H, d *J* 7.3 Hz, ArH), 7.7–7.3 (8H, m, ArH), 4.3–4.0 (2H, m, CH_2CO+CHPh), 3.75 (1H, dd *J* 16.8, 2.0 Hz, CH_2CO), 3.28 (1H, d *J* 14.4, $ArCH_2$), 3.03 (1H, d *J* 14.4, $ArCH_2$); δ_C 194.7, 144.9, 135.8, 135.0, 133.9, 129.5, 129.0, 128.8, 128.6, 128.5, 128.1, 122.1, 114.4, 113.5, 113.0, 47.7, 43.0, 41.5, 30.1; δ_F -159.7 (2F, tt *J* 17.8, 12.0 Hz), -150.8 (1F, t *J* 22.0 Hz), -137.9 (2F, dd *J* 25.5, 11.6 Hz); m/z (ESI) Found 477.0988, $C_{25}H_{15}N_2OF_5Na$ $(M+Na)^+$ requires 477.0997.

(*S*)-4,4–Dicyano–1,3–diphenylpentan–1–one 11j Obtained as a white solid (35 mg, 61%) with 48% enantiomeric excess from a reaction at 18 °C for 168 h (t_R = 7.4 (minor) and 9.7 (major) minutes). Mp 93–95 °C; $[\alpha]^{20}_D$ -3.2 (c = 0.5, $CHCl_3$); ν_{max}(ATR) 2970, 2850, 1690 and 1680 cm^{-1}; δ_H 7.92 (2H, d *J* 8.6 Hz, ArH), 7.6–7.3 (8H, m, ArH), 4.05–3.85 (2H, m, CH_2CO+CHPh), 3.64 (1H, dd *J* 16.9, 2.7 Hz, CH_2CO), 1.64 (3H, s, CH_3); δ_C 193.0, 136.0, 135.4, 133.8, 129.1, 129.0, 128.8, 128.1, 123.5, 116.3, 115.3, 47.4, 40.9, 36.8, 23.8; m/z (ESI) Found 311.1160, $C_{19}H_{16}N_2ONa$ $(M+Na)^+$ requires 311.1155.

(*S*)-4,4–Dicyano–1,3–diphenylhept-6-en–1–one 11k[30] Obtained as a white solid (46 mg, 73%) with 50% enantiomeric excess from a reaction at 18 °C for 168 h (t_R = 7.8 (minor) and 12.1 (major) minutes). Mp 90–93 °C; $[\alpha]^{20}_D$ -2.4 (c = 0.5, $CHCl_3$); ν_{max}(ATR) 3090, 2980 and 1688 cm^{-1}; δ_H 7.91 (2H, d *J* 7.0 Hz, ArH), 7.6–7.3 (8H, m, ArH), 5.90 (1H, ddt *J* 17.0, 10.1, 7.2 Hz, =CH), 5.41 (1H, dd *J* 10.0, 0.6 Hz, $=CH_2$), 5.32 (1H, dd *J* 16.9, 1.3 Hz, $=CH_2$), 4.1–3.9 (2H, m, CH_2CO+CHPh), 3.7–3.5 (1H, m, CH_2CO), 2.51 (1H, dd *J* 14.0, 7.5 Hz, CH_2CH=), 2.40 (1H, dd *J* 14.0, 7.1 Hz, CH_2CH=); δ_C 193.0, 136.0, 135.5, 133.8, 129.1, 129.0, 128.9, 128.8, 128.6, 128.1, 123.4, 115.2, 114.5, 46.1, 43.1, 41.3, 40.4; m/z (ESI) Found 337.1301, $C_{21}H_{18}N_2ONa$ $(M+Na)^+$ requires 337.1311.

(*S*)-4,4–Dicyano–1,3–diphenylhept-6-yn–1–one 11l Obtained as a white solid (55 mg, 88%) with 38% enantiomeric excess from a reaction at 18 °C for 72 h (t_R = 8.9 (minor) and 12.8 (major) minutes). Mp 104–108 °C; $[\alpha]^{20}_D$ -1.8 (c = 0.5, $CHCl_3$); ν_{max}(ATR) 3350, 3050, 3040, 2982 and 1710 cm^{-1}; δ_H 7.92 (2H, d *J* 7.2 Hz, ArH), 7.6–7.3 (8H, m, ArH), 4.20 (1H, dd *J* 10.6, 3.0 Hz, CHPh), 4.05 (1H, dd *J* 17.4, 10.6 Hz, CH_2CO), 3.67 (1H, dd *J* 17.3, 3.1 Hz, CH_2CO), 2.78 (1H, dd *J* 16.8, 2.7 Hz, CH_2CC), 2.56 (1H, dd *J* 16.9, 2.7 Hz, CH_2CC), 2.46 (1H, t *J* 2.6 Hz, CCH); δ_C 194.8, 136.0, 134.5, 133.8, 129.2, 129.1, 128.8, 128.7, 128.1, 114.6, 113.9, 75.9, 74.6, 45.1, 42.0, 40.9, 27.3; m/z (ESI) Found 335.1144, $C_{21}H_{16}N_2ONa$ $(M+Na)^+$ requires 335.1155.

Notes and references

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1 For recent reviews see: Ł. Albrecht, H. Jiang, K. A. Jorgensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 8492; L. Zhang, S. Luo, J.-P. Cheng, *Catal. Sci. Technol.*, 2011, **1**, 507; G. Valero, X. Companyó, R. Rios, *Chem. Eur. J.*, 2011, **17**, 2018; W. Raimondi, D. Bonne, J. Rodriguez, *Angew. Chem. Int. Ed.*, 2012, **51**, 40; E. Arceo, P. Melchiorre, *Angew. Chem. Int. Ed.*, 2012, **51**, 5290; J. Mlynarski, B. Gut, *Chem. Soc. Rev.*, 2012, **41**, 587; F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev.*, 2012, **41**, 2406; X. Bugaut, F. Glorius, *Chem. Soc. Rev.*, 2012, **41**, 3511; R. C. Wende, P. R. Schreiner, *Green Chem.*, 2012, **14**, 1821; Y. Zhao, Y. Pan, S.–B. D. Sim, C.–H. Tan, *Org. Biomol. Chem.*, 2012, **10**, 479; L. Bernardi, M. Fochi, M. C. Franchini, A. Ricci, *Org. Biomol. Chem.*, 2012, **10**, 2911; L.–Q. Lu, X.–L. An, J.–R. Chen, W.–J. Xiao, *Synlett*, 2012, 490.

2 For recent reviews see: C. F. Barbas (III), *Angew. Chem. Int. Ed.*, 2008, **47**, 42; S. K. Panday, *Tetrahedron: Asymmetry*, 2011, **22**, 1817.

3 For recent reviews see: S. Pizzarello, A. L. Weber, *Science*, 2004, **303**, 1151; L.–W. Xu, J. Luo, Y. Lu, *Chem. Commun.*, 2009, 1807.

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5 For recent reviews of specific catalyst types see: X. Liu, L. Lin, X. Feng, *Acc. Chem. Res.*, 2011, **44**, 574; J. Yu, F. Shi, L.–Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156; J. N. Johnston, *Angew. Chem. Int. Ed.*, 2011, **50**, 2890; M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, I. Atodiresei, *Angew. Chem. Int. Ed.*, 2011, **50**, 6706; L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.*, 2011, **50**, 11860; S. Gladiali, E. Alberico, K. Junge; M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 3744; M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539; S. Schenker, A. Zamfir, M. Freund, S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2011, 2209; A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* 2011, **44**, 1182; H. Wennemers, *Chem. Commun.*, 2011, **47**, 12036; M. Bhanushali, C.–G. Zhao, *Synthesis*, 2011, 1815; W.–Y. Siau, J. Wang, *Catal. Sci. Technol.*, 2011, **1**, 1298; J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.*, 2011, **17**, 6890; Q.–Y. Zhao, Z. Lian, Y. Wei, M. Shi, *Chem. Commun.*, 2012, **48**, 1724; Y. Sohtome, K. Nagasawa, *Chem. Commun.*, 2012, **48**, 7777; J.–F. Brière, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.*, 2012, **41**, 1696; J. E. Taylor, S. D. Bull, J. M. J. Williams, *Chem. Soc. Rev.*, 2012, **41**, 2109; A.–M. Caminade, A. Ouali, M. Keller, J.–P. Majoral, *Chem. Soc. Rev.*, 2012, **41**, 4113; H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.*, 2012, **354**, 1617; A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.*, 2012, **51**, 314; D. Enders, T. V. Nguyen, *Org. Biomol. Chem.*, 2012, **10**, 5327; L. Zhang, S. Luo, *Synlett*, 2012, 1575; K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jorgensen, *Acc. Chem. Res.* 2012, **45**, 248; Z. Chai, G. Zhao, *Catal. Sci. Technol.*, 2012, **2**, 29; R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nature Chemistry*, 2012, **4**, 603.

6 For a review of sustainable organocatalysis see: J. G. Hernández, E. Juaristi, *Chem. Commun.*, 2012, **48**, 5396.

7 B. List, *Synlett*, 2001, 1675; H. Gröger, J. Wilken, *Angew. Chem. Int. Ed.*, 2001, **40**, 529; B. List, *Tetrahedron*, 2002, **58**, 5573; E. R. Jarvo, S. J. Miller, *Tetrahedron,* 2002, **58**, 2481; B. List, *Acc. Chem. Res.*, 2004, **37**, 548; U. Kazmaier, *Angew. Chem. Int. Ed.,* 2005, **44**, 2186

8 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaksh, T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.

9 B. Rodríguez, T. Rantanen, C. Bolm, *Angew. Chem. Int. Ed.*, 2006, **46**, 6924; B. Rodríguez, A. Bruckmann, C. Bolm, *Chem. Eur. J.*, 2007, **13**, 4710.

10 A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem. Int. Ed.*, 2006, **45**, 8100; M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.*, 2009, **351**, 33; J. Paradowska, M. Stodulski, J. Mlynarski, *Angew. Chem. Int. Ed.*, 2009, **48**, 4288; M. Raj, V. K. Singh, *Chem. Commun.*, 2009, 6687; N. Mase, C. F. Barbas (III), *Org. Biomol. Chem.*, 2010, **8**, 4043; S. Bhowmick, K. C. Bhowmick, *Tetrahedron:*

Asymmetry, 2011, **22**, 1945; M.–C. Simon, C.–J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415.
11 Š. Toma, M. Mečiarova, R. Šebesta, *Eur. J. Org. Chem.*, 2009, 321.
12 D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem. Int. Ed.*, 2007, **46**, 3798; B. Wu, W. Liu, Y. Zhang, H. Wang, *Chem. Eur. J.*, 2009, **15**, 1804.
13 N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.*, 2007, **129**, 15100.
14 M. North, F. Pizzato, P. Villuendas, *ChemSusChem*, 2009, **2**, 862; W. Clegg, R. W. Harrington, M. North, F. Pizzato, P. Villuendas, *Tetrahedron: Asymmetry*, 2010, **21**, 1262; M. North, P. Villuendas, *Org. Lett.*, 2010, **12,** 2378; M. Morcillo, M. North, P. Villuendas, *Synthesis*, 2011, 1918; C. Beattie, M. North, P. Villuendas, *Molecules*, 2011, **16**, 3420.
15 L. B. Silva, L. C. G. Freitas, *J. Mol. Structure THEOCHEM.*, 2007, **806**, 23.
16 P. Tundo, M. Selva, *Acc. Chem. Res.*, 2002, **35**, 706; C. Wohlfarth 'Static Dielectric Constants of Pure Liquids and Binary Liquid Mixtures', Springer Verlag, 2008.
17 B. Schäffner, F. Schäffner, S. P. Verevkin, A. Börner, *Chem. Rev.*, 2010, **110**, 4554; C. Fischmeister, H. Doucet, *Green Chem.*, 2011, **13**, 741.
18 K. Xu, *Chem. Rev.*, 2004, **104**, 4303; S. S. Zhang, *J. Power Sources*, 2006, **162**, 1379; V. Etacheri, R. Marom, R. Elazari, G. Salitra, D. Aurbach, *Energy Environ. Sci.*, 2011, **4**, 3243; B. Scrosati, J. Hassoun, Y.–K. Sun, *Energy Environ. Sci.*, 2011, **4**, 3287.
19 Y. Katrib, G. Deiber, P. Mirabel, S. Le Calvé, C. George, A. Mellouki, G. Le Bras, *J. Atmospheric Chem.*, 2002, **43**, 151.
20 S. Fukuoka, M. Kawamura, K. Komiya, M. Tojo, H. Hachiya, K. Hasegawa, M. Aminaka, H. Okamoto, I. Fukawad, S. Konno, *Green Chem.*, 2003, **5**, 497.
21 M. North, P. Villuendas, C. Young, *Chem. Eur. J.* 2009, **15**, 11454; I. S. Metcalfe, M. North, R. Pasquale, A. Thursfield, *Energy Environ. Sci.*, 2010, **3**, 212; J. Meléndez, M. North, P. Villuendas, C. Young, *Dalton Trans.*, 2011, **40**, 3885; M. North, B. Wang, C. Young, *Energy Environ. Sci.*, 2011, **4**, 4163; M. North, *Arkovic* **2012**, (i), 610.
22 R. K. Henderson, C. Jiménez–González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.*, 2011, **13**, 854.
23 A. Russo, A. Perfetto, A. Lattanzi, *Adv. Synth. Catal.*, 2009, **351**, 3067.
24 For subsequent related work see: C. De Fusco, A. Lattanzi, *Eur. J. Org. Chem.*, 2011, 3728; Z.–P. Hu, W.–J. Wang, X.–G. Yin, X.–J. Zhang, M. Yan, *Tetrahedron: Asymmetry*, 2012, **23**, 461.
25 P. Victory, J. I. Borrell, A. Vidal–Ferran, C. Seoane, J. L. Soto, *Tetrahedron Lett.*, 1991, **32**, 5375; A.–Q. Wang, T.–S. Jin, L.–B. Liu, Z.–L. Cheng, T.–S. Li, *Asian J. Chem.*, 2010, **22**, 1977; G.–p. Lu, C. Cai, *J. Chem. Res.*, 2011, 147.
26 M. Varma, C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1981, 553.
27 W. Yang, Y. Jia, D.–M. Du, *Org. Biomol. Chem.*, 2012, **10**, 332.
28 X. Li, L. Cun, C. Lian, L. Zhong, Y. Chen, J. Liao, J. Zhu, J. Deng, *Org. Biomol. Chem.*, 2008, **6**, 349.
29 B. Zhang, X.–Q. Zhu, J.–Y. Lu, J. He, P. G. Wang, J.–P. Cheng, *J. Org. Chem.,* 2003, **68**, 3295; F. Tayyari, D. E. Wood, P. E. Fanwick, R. E. Sammelson, *Synthesis* 2008, 279; L. Jedinák, V. Kryštof, P Cankař, *Heterocycles,* 2011, **83**, 371; J. Wu, H. Jiang, *Synth. Commun.*. 2011, **41**, 1218; Y.–S. Feng, C.–Y. Yang, Q. Huang, H.–J. Xu, *Tetrahedron*, 2012, **68**, 5053.
30 C. Wang, J. A. Tunge, *Org. Lett.* 2005, **7**, 2137.

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