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α-Chloroacetone as a donor in the BINAM-L-prolinamide organocatalyzed aldol reaction: application to the enantioselective synthesis of α,β-epoxy ketones

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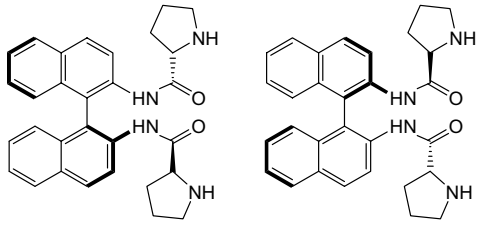
Dedicated to Professor Gerard van Koten on occasion of his 65th birthday

Abstract—Recoverable (S_a)-BINAM-L-prolinamide in combination with benzoic acid catalyzed the direct aldol reaction between α-chloroacetone and several aldehydes in different solvents, including water. It is possible to obtain mainly one of the isomers with good regio-, diastero-, and enantioselectivity by choosing the appropriate solvent and reaction conditions. Thus, α-chloroacetone mainly gives the *anti*-aldol isomer in DMF/H_2O with up to 97% ee. The crude α-chloro-β-hydroxy ketones obtained are transformed stereospecifically into the corresponding enantioenriched *trans*-α,β-epoxy ketones derivatives with up to 97% ee through an S_N2 displacement reaction by treatment with Et_3N.

1. Introduction

Apart from the economic and environmental aspects, the use of small organic molecules[1] as catalysts has shown their attractiveness due to their simplicity. This fact has broadened the application of this synthetic strategy from enantioselective C–C and C–X bond formation[2] to a one-pot multistep processes, achieving chiral molecules with growing molecular complexity.[3] Although organocatalysis is an old tool used for promoting asymmetric transformations,[4] it was not until the pioneering work of Barbas et al., which showed that L-proline acted as a synthetic mimic of aldolases class I or II in the direct aldol reaction,[5] that this field has undergone its revolution. For the aldol reaction,[6] the use of a simple proline permitted access to chiral synthetically useful intermediates by a highly atom efficiency process.[7] The simultaneous control of the regio-, diastereo- and enantioselectivities when unsymmetrical ketones are used as donors, remains as one of the challenges of this type of transformation.

Recently, we and others have reported the use of several BINAM-prolinamides as catalysts in this type of reaction, providing the expected aldol products under several reaction conditions using alkyl[8] and α-chalcogen substituted[9] ketones as donors. The best catalysts were (S_a)-BINAM-L-Pro **1a** and its enantiomer (Fig. 1).[8a] The addition of benzoic acid as a cocatalyst in the reaction led to a great acceleration in the reaction, thus permitting the use of less reactive ketones, such as butanone,[8c] α-alkoxy ketones[9a] and α-(methylsulfanyl)acetone even in water,[8f,9a,b] allowing the synthesis of aldols with a high level of selectivity. We also found that these catalysts can be recovered by simple extractive work-up.[8a,c,9]



1a *ent*-**1a**

Figure 1. BINAM-derived prolinamides.

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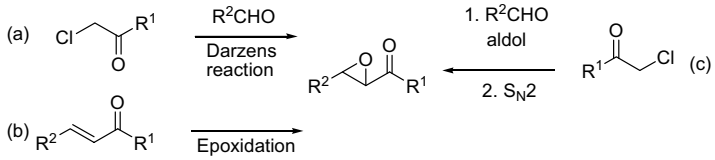


Figure 2. Possible routes for the asymmetric organocatalyzed synthesis of α,β-epoxy carbonyl compounds.

Epoxides are very useful intermediates in organic synthesis,[10] with methods dealing in their enantioselective synthesis being of enormous interest. α,β-Epoxy carbonyl compounds have been synthesized enantioselectively by organocatalytic methods[2] by using either: (a) Darzens reaction[11] or (b) epoxidation of α,β-unsaturated carbonyl compounds.[12] Alternatively, these compounds can be synthesized by (c) a two-step procedure based on an aldol reaction followed by an S_N2 displacement from the chiral α-chlorinated aldols (Fig. 2).[13]

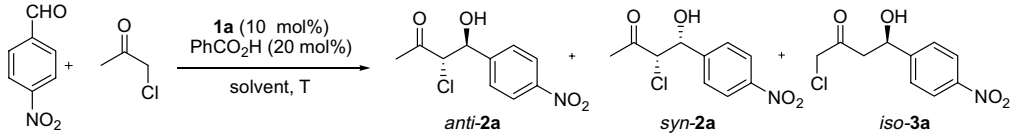
In the case of the last strategy, the chiral intermediate α-chloro-β-hydroxy ketones can be readily synthesized by the direct aldol reaction between α-chloro ketones and aldehydes, although this strategy remains almost unexplored.[13,14] The aldol reaction between α-chloroacetone and aromatic aldehydes has only been performed using proline (50 mol %) as organocatalyst in ionic liquids giving chiral α-chloro-β-hydroxy ketones in moderate yields (21–82%) and diastereomeric ratios (up to 85:15 for the *anti*:*syn*-isomers).[13] By treatment of the obtained products, with Et_3N in the ionic liquid, the corresponding *trans*-α,β-epoxy ketones were obtained with up to 75% ee.[13] Recently, prolinamides derived from simple aromatic amines were evaluated in this aldol reaction with THF as solvent, to mainly afford the expected α-chloro-β-hydroxy ketones with modest yields (18–57%) and moderate to good regio- (4:1–20:1), diastereo- (5:1–31:1) and enantioselectivities (86–98% ee).[14] Here we report a two step synthesis of α,β-epoxy ketones by the aldol reaction of α-chloroacetone with aldehydes using recoverable BINAM-prolinamide **1a** as the organocatalyst followed by Et_3N mediated cyclization.

2. Results and discussion

First, we studied the best reaction conditions in a reaction between α-chloroacetone and *p*-nitrobenzaldehyde using (S_a)-BINAM-L-Pro **1a** as catalyst and comparing the results obtained with those obtained by using L-proline (Table 1).

Initially, DMF was choosen as a solvent based upon our previous work on aldol reactions.[8a,c,9] The reaction took place at 0 °C with good yield and moderate regio- (4:1), diastereo- (*anti*/*syn* dr 10:1) and enantioselectivity (88% ee for *anti*-**2a**). However 108 h was required to achieve complete conversion (Table 1, entry 1). The addition of water to the reaction mixture, led to an increase in the reaction rate (from 108 to 19 h) to mainly give the *anti*-**2a** aldol

Table 1. Optimization of conditions for the reaction of 4-nitrobenzaldehyde with α-chloroacetone catalyzed by **1a**[a]



Entry	Cat.	Solvent	*T* (°C)	*t* (h)	Yield[b] (%)	Isomer ratio[c]		ee[d] (%)		
						Regioselectivity (**2a**/**3a**)	dr (*anti*/*syn*)	*anti*-**2a**	*syn*-**2a**[e]	*iso*-**3a**
1	**1a**	DMF	0	108	94	4:1	10:1	88	27	67
2	**1a**	DMF:H_2O[f]	0	19	90	10:1	6:1	89	58	95
3	**1a**	DMF:H_2O[f]	−20	31	86	>99:1	>99:1	90	—	—
4	**1a**	H_2O	0	20	96	4:1	6:1	85	18	94
5	**1a**[g]	THF	25	168	78	19:1	16:1	88	5	67
6	**1a**	THF	25	96	95	4:1	9:2	80	40	82
7	**1a**[g]	THF:H_2O[f]	25	168	82	6:1	5:1	75	nd	nd
8	L-Pro[h]	DMF:H_2O[f]	0	31	85	2:1	2:3	7	4	82
9	L-Pro[h]	H_2O	0	168	86	3:2	2:1	2	3	88

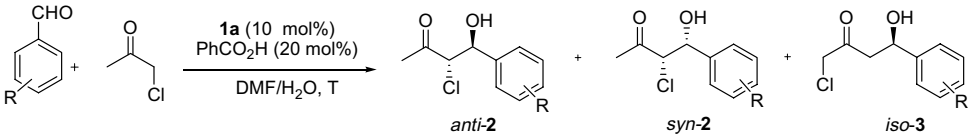
[a] The reaction was carried out using 27.6 equiv of ketone per equivalent of aldehyde in the presence of 10 mol % of catalyst and 20 mol % of acid in 0.5 mL of solvent, otherwise stated.
[b] Calculated from the crude product by ^1H NMR.
[c] Determined by ^1H NMR.
[d] Determined by HPLC, Chiracel OJ.
[e] Tentative absolute configuration assignment based on the intermediate *E*-enamine.
[f] 1:1.
[g] The reaction was performed in the absence of acid.
[h] 20 mol % of catalyst was used.

isomer with a promising 89% ee (Table 1, entry 2). The reaction temperature was then decreased to −20 °C, to give *anti*-**2a** as a unique regioisomer with a nearly quantitative yield and 90% ee (Table 1, entry 3). A high enantioselectivity was also reached when water was the chosen solvent, even at 0 °C (85% ee), with the regioselectivity being lower than those obtained in DMF/H_2O (Table 1, compare entries 2 and 4). As has been reported that THF at rt is a good solvent for carrying out the reaction between α-chloroacetone and aldehydes using an L-prolinamide as catalyst,[14] we used these conditions with catalyst **1a** in the absence or presence of 20 mol % of acid (Table 1, entries 5 and 6). In both cases, the reaction was extremely slow, with nearly 7 d required for completion in the absence of acid and 4 d in the presence of acid, the achieved regio-, diastero- and enantioselectivities being lower than in DMF/H_2O at 0 or −20 °C (Table 1, entries 5 and 6). When the reaction was carried out in THF/H_2O 1:1 at rt in the absence of acid, the reaction time increased to 7 d and the observed regio-, diastereo- and enantioselectivity was lower that in DMF/H_2O (Table 1, entry 7). In order to establish a fair comparison with L-proline, the reaction was performed using this catalyst in the presence of benzoic acid using DMF/H_2O or H_2O as solvent at 0 °C. In both cases the obtained results were worse than those achieved with catalyst **1a** (Table 1, compare entries 2 and 4 with 8 and 9, respectively).

Once the best reaction conditions were established, α-chloroacetone was allowed to react with different aldehydes using catalyst **1a** in the presence of 20 mol % of benzoic acid and DMF/H_2O (1:1) as solvent, the results are summarized in Table 2.

In all cases, the main product observed was the *anti*-**2** isomer. The reaction proceeded with a reasonable rate when *p*-substituted aromatic aldehydes were used as electrophiles with the exception of *p*-methoxycarbonylbenzaldehyde (Table 2, entry 8), where 7 d was needed, even at 0 °C, for the completion of the reaction. In all cases the *anti*-aldol product was obtained with high ee's (83–97%). Conversely, the reactions were very slow when *o*-substituted aldehydes were used (Table 2, entries 2, 3, 10 and 11), especially in the case of *o*-bromobenzaldehyde in which after 14 d, only 27% of the aldehyde was consumed probably due to steric reason (Table 2, entry 10). Also, the main isomer *anti*-**2** was achieved with lower enantioselectivity than those achieved with *p*-substituted aldehydes (ee up to 74%, Table 2, entries 2, 3, 10 and 11). The use of *m*-nitrobenzaldehyde gave the expected *anti*-**2c** product with good diasteroselectivity and high enantioselectivity (93% ee, Table 2, entries 4 and 5). The use of a less electrophilic benzaldehyde gave after 5 d, *anti*-**2i** as a unique product but with a moderate enantiomeric excess (53% ee, Table 2, entry 12). When less reactive aldehydes, such as cyclohexanecarboxaldehyde, were used, the reaction did not take place after 9 d at either −20 or 0 °C. The reaction also failed when other α-chloro ketones such as 3-chloro-2-butanone or 2-chlorocyclohexanone were used as donors and *p*-nitrobenzaldehyde as the acceptor.

Table 2. Reaction of substituted aldehydes with α-chloroacetone catalyzed by **1a**[a]



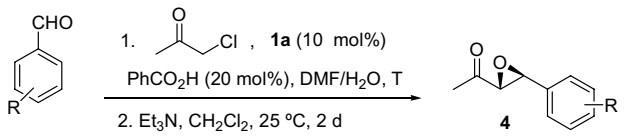
Entry	R	*T* (°C)	*t* (d)	Yield[b] (%)	Isomer ratio[c]			ee[d] (%)	
					Product	Regioselectivity (**2**/**3**)	dr (*anti*/*syn*)	*anti*-**2**	*syn*-**2**[e]
1	4-NO_2	−20	1.5	86	**a**	>99:1	>99:1	90[f]	—
2	2-NO_2	−20	11	75	**b**	5:1	3:1	72[g]	55[g]
3	2-NO_2	0	6	93		5:1	5:1	67[g]	87[g]
4	3-NO_2	−20	1.5	80	**c**	>99:1	27:1	93[g]	70[g]
5	3-NO_2	0	1	91		16:1	8:1	97[g]	98[g]
6	4-NC	−20	3	80	**d**	>99:1	32:1	90[g]	90[g]
7	4-NC	0	1	92		14:1	10:1	92[g]	81[g]
8	4-MeO_2C	0	7	93	**e**	>99:1	16:1	91[h]	49[h]
9	4-F_3C	0	2	77	**f**	3:1	13:1	83[j]	61[j]
10	2-Cl	−20	9	96	**g**	4:1	4:1	74[g]	—
11	2-Br	0	14	27	**h**	3:1	2:1	46[j]	66[j]
12	H	0	5	66	**i**	>99:1	99:1	53[i]	—

[a] The reaction was carried out using 27.6 equiv of ketone per equivalent of aldehyde in the presence of 10 mol % of catalyst and 20 mol % of benzoic acid in DMF/H_2O (1:1, 0.5 mL).
[b] Calculated for the crude product based on the aldehyde.
[c] Determined by ^1H NMR.
[d] Determined by HPLC.
[e] Tentative absolute configuration assignment based on the intermediate *E*-enamine.
[f] Chiracel OJ, hexane/^{i}PrOH: 98/2.
[g] Chiracel OJ, hexane/^{i}PrOH: 97/3.
[h] Chiralpak AD, hexane/^{i}PrOH: 95/5.
[i] Chiralpak AD, hexane/^{i}PrOH: 98/2.
[j] Chiralpak AS, hexane/^{i}PrOH: 90/10.

In our hands, any attempts to purify the obtained products **2** by flash silica gel, alumina, neutral alumina or florisil led to the partial racemization of the mixture.[15] Only when neutral flash silica was employed for the purification of product *anti*-**2c** (Table 2, entry 4), did epimerization occur to give a 2:1 mixture of *anti*/*syn*-**2c** isomers enantioselectivity for the *anti*-**2c** product was kept. In view of these results, we decided to directly transform the crude α-chloro-β-hydroxy ketones **2** to the corresponding α,β-epoxy ketones by an S_N2 displacement reaction. Thus, the crude mixture of the product obtained from the aldol reaction between α-chloroacetone and different aldehydes were dissolved in dry dichloromethane and dry Et_3N was added. The reaction mixture was stirred for 2 d at rt and the obtained *trans*-epoxides **4** purified by column chromatography, with the results summarized in Table 3.

For all cases, the achieved enantioselectivities for products **4** were similar to those obtained for *anti*-**2** isomers with the exception of epoxides **4b** and **4i** derived from *o*-nitrobenzaldehyde and benzaldehyde, respectively. For those examples, the enantioselectivities of the epoxides were higher (93% and 65%, respectively) than those obtained for the corresponding isomers *anti*-**2b** and *anti*-**2i** (67% and 53% ee, respectively) showing that a possible resolution process has taken place in the second reaction step (Table 3, entries 2 and 7). The absolute configuration of the epoxides could be assigned as (3*R*,4*S*) by comparison of the specific rotation values obtained for compound **4i** to that reported in the literature.[13]

Table 3. Formation of chiral α-epoxy ketones by a subsequent aldol condensation-S_N2 displacement[a]



Entry	R	No.	Yield[b] (%)	ee[c,d] (%)
1[e]	4-NO_2	**4a**	45	83 (75)
2[e]	2-NO_2	**4b**	44	96 (67)
3[e]	3-NO_2	**4c**	60	97 (97)
4	4-NC	**4d**	56	93 (92)
5[f]	4-MeO_2C	**4e**	61	87 (91)
6	4-F_3C	**4f**	58	85 (83)
7	H	**4i**	53	65 (53)

[a] The resulting crude mixture isolated from the aldol reaction in Table 2 was diluted in CH_2Cl_2 and Et_3N (1.32 equiv) were added and the resulting mixture stirred at rt for 2 d unless otherwise stated.
[b] For the products isolated by flash column chromatography after two step synthesis based on the starting aldehyde.
[c] Determined by HPLC.
[d] In parentheses ee for the intermediate aldol product *anti*-**2**.
[e] 3 days required to perform the S_N2 reaction.
[f] Only 28 h of reaction required for completion.

3. Conclusion

In conclusion, recoverable BINAM-L-prolinamide **1a** and benzoic acid are adequate catalysts for the aldol reaction between α-chloroacetone and several aldehydes in aqueous DMF as the solvent affording the corresponding *anti*-α-chloro-β-hydroxy ketones with better yields and regio-, diastereo- and enantioselectivies than with other organocatalyts, such as L-Pro[13] or aromatic amine derived prolinamides.[14] For the synthesis of chiral *trans*-α,β-epoxy ketones, dry Et_3N in CH_2Cl_2 at rt were adequate reaction conditions.

4. Experimental

4.1. General

All reactions were carried out under argon. All others reagents were commercially available and used without further purification, with the exception of PhCHO, which was distilled prior to its use. Only the structural, most important peaks of the IR spectra (recorded on a Nicolet 510 P-FT) are listed. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ as the solvent and TMS as the internal standard, unless otherwise stated. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. HPLC analyses were performed on a Shimadzu LC-10AD and on a JASCO AS 2059 PLUS equipped with a chiral column, using mixtures of *n*-hexane/isopropyl alcohol (IPA) as a mobile phase, at 25 °C. High-resolution mass spectra were obtained on a Finnigan VG Platform. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized under UV light ($\lambda = 254$ nm).

4.2. Experimental procedure for the synthesis of the epoxides

To a solution of aldehyde (0.25 mmol), in dry DMF and water (0.25 mL of each) under argon were added benzoic acid (20 mol %, 6.1 mg) and chloroacetone (5.5 mmol, 0.55 mL). To the resulting solution, catalyst **1a** was added (10 mol %, 12.0 mg) in one portion, and the resulting mixture stirred at the corresponding temperature. After completion of the reaction, 6 M aqueous solution of hydrochloric acid (5 mL) and ethyl acetate (5 mL) were added. The mixture was stirred vigorously for 10 min. The emulsion was separated (3 × 5 mL satd NaCl) and the aqueous phase treated with a satd NaOH solution until pH > 9 after which ethyl acetate was added (3 × 15 mL). The organic layer was separated, dried over $MgSO_4$ and evaporated to recover crude catalyst **1a**. The organic phase from the acidic work up was dried ($MgSO_4$) and evaporated to dryness yielding the aldol products. The resulting aldol was treated with dry triethylamine (1.32 equiv) under argon in dry dichloromethane (0.5 mL). The resulting mixture was stirred for 2 days. The reaction was quenched with diethyl ether (5 mL) and an aqueous solution of 1 M hydrochloric acid (5 mL). The mixture was stirred vigorously for 10 min. The emulsion was separated (3 × 5 mL satd NaCl) and the organic layer separated, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography in silica gel with ethyl acetate/hexane mixtures to yield pure epoxides.

4.2.1. *trans*-3,4-Epoxy-4-(4-nitrophenyl)butan-2-one 4a. White solid; mp 38 °C (AcOEt/hexane). $[\alpha]_D^{20} = -15$ (*c* 1.14, $CHCl_3$). R_f 0.43 (AcOEt/hexane 2:3). IR (KBr) $\nu = 2912, 2857, 2581, 2381, 1713, 1609, 1517, 1350, 1250, 1105\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ (ppm) = 2.22 (s, 3H), 3.47 (d, $J = 1.87$ Hz, 1H), 4.12 (d, $J = 1.71$ Hz, 1H), 7.47 (d, $J = 8.58$ Hz, 2H), 8.25 (d, $J = 8.74$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm) = 24.8, 29.7, 56.5, 63.4, 123.6, 123.9, 124.0, 124.8, 126.1, 126.5, 126.6, 196.2. HRMS (*m*/*z*) $C_{10}H_9NO_4$: 207.0532. Found: 207.0514. HPLC: *Chiralpak* AD column, hexane/*i*PrOH: 98/2; 1.25 mL/min; ret. times, 43.9 (major), 53.4 (minor) min.

4.2.2. *trans*-3,4-Epoxy-4-(2-nitrophenyl)butan-2-one 4b. White solid; mp 59 °C (AcOEt/hexane). $[\alpha]_D^{20} = -40$ (*c* 1.2, $CHCl_3$). R_f 0.52 (AcOEt/hexane 2:3); IR (KBr) $\nu = 2918, 2842, 2372, 2317, 1711, 1520, 1334, 1102\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ (ppm) = 2.29 (s, 3H), 3.40 (d, $J = 2.07$ Hz, 1H), 4.61 (d, $J = 1.88$ Hz, 1H), 7.61 (m, 3H), 8.23 (d, $J = 0.94$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm) = 25.2, 56.2, 61.9, 124.9, 127.0, 129.4, 132.3, 134.6, 202.7. HRMS (*m*/*z*) calculated for $C_8H_8NO_3$ ($M^+ - COMe$) 164.1416. Found: 164.0341. HPLC: *Chiralpak* AD column, hexane/*i*PrOH: 98/2; 1.25 mL/min; ret. times, 19.7 (major), 36.0 (minor) min.

4.2.3. *trans*-3,4-Epoxy-4-(3-nitrophenyl)butan-2-one 4c. White solid; mp 35 °C (AcOEt/hexane). $[\alpha]_D^{20} = -17$ (*c* 1.4, $CHCl_3$). R_f 0.66 (AcOEt/hexane 2:3). IR (KBr) $\nu = 2918, 2853, 2361, 1601, 1361, 1132\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ (ppm) = 2.22 (s, 3H), 3.50 (d, $J = 1.88$ Hz), 4.13 (d, $J = 1.70$ Hz, 1H), 7.61 (m, 2H), 8.20 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm) = 29.7, 56.5, 63.3, 120.8, 123.9, 129.9, 131.6, 137.5, 203.1. HRMS (*m*/*z*) calculated for $C_{10}H_9NO_4$: 207.0532. Found: 207,0528. HPLC *Chiralpak* AD column, hexane/*i*PrOH: 98/2; 1.25 mL/min; ret. times, 25.4 (major), 32.6 (minor) min.

4.2.4. *trans*-3,4-Epoxy-4-(4-cyanophenyl)butan-2-one 4d. White solid; mp 49 °C (AcOEt/hexane). $[\alpha]_D^{20} = -50$ (*c* 0.84, $CHCl_3$). R_f 0.66 (AcOEt/hexane 2:3). IR (KBr) $\nu = 3033, 2913, 2852, 2367, 2328, 2219, 1711, 1427, 1366, 1241, 1219\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ (ppm) = 2.21 (s, 3H), 3.45 (d, $J = 1.87$ Hz, 1H), 4.61 (d, $J = 1.72$ Hz, 1H), 7.40 (d, $J = 8.27$ Hz, 2H), 7.67 (d, $J = 8.42$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm) = 24.8, 56.7, 63.3, 112.8, 118.2, 126.3, 132.5, 140.4, 203.1. HRMS (*m*/*z*) calculated for $C_{11}H_9NO_2$: 187.0633. Found: 187.0649. HPLC *Chiralpak* AD column, hexane/*i*PrOH: 98/2; 1.25 mL/min; ret. times, 32.3 (major), 43.2 (minor) min.

4.2.5. *trans*-3,4-Epoxy-4-{4-(methoxycarbonyl)phenyl}-butan-2-one 4e. White solid; mp 62 °C (AcOEt/hexane). $[\alpha]_D^{20} = -63$ (*c* 0.5, $CHCl_3$). R_f 0.52 (AcOEt/hexane 2:3). IR (KBr) $\nu = 2954, 2928, 2844, 1722, 1436, 1282, 1106, 1018\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ (ppm) = 2.21 (s, 3H), 3.92 (s, 3H), 3.96 (s, 1H), 4.06 (d, $J = 1.72$ Hz, 1H), 7.35 (d, $J = 8.26$ Hz, 2H), 8.03 (d, $J = 8.27$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm) = 24.8, 52.3, 57.1, 63.4, 125.6, 129.9, 130.8, 140.1, 166.5, 203.6. HRMS (*m*/*z*) calculated for $C_{12}H_{12}O_4$: 220.0736. Found: 220.0737. HPLC: *Chiralpak* AD column, hexane/*i*PrOH: 98/2; 1.25 mL/min; ret. times, 9.0 (major), 12.0 (minor) min.

4.2.6. *trans*-3,4-Epoxy-4-{4-(trifluoromethyl)phenyl}butan-2-one 4f.[13] Mp 61 °C (AcOEt/hexane). HPLC: *Chiralpak* AD column, hexane/*i*PrOH: 98/2; 1.25 mL/min; ret. times, 11.1 (major), 14.0 (minor) min.

4.2.7. *trans*-(3*R*,4*S*)-Epoxy-4-phenylbutan-2-one 4i.[13] Mp 62 °C (AcOEt/hexane). HPLC: *Chiralpak* AD column, hexane/*i*PrOH: 98/2; 1.25 mL/min; ret. times, 11.1 (major), 13.7 (minor) min.

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References

1. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (b) List, B. *Synlett* **2001**, 1675–1686; (c) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495; (d) Benaglia, M.; Puglivi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401–3440; (e) Houk, K. N.; List, B.; Guest Eds.; *Acc. Chem. Res.* **2004**, 37, 487 (thematic issue on *Asymmetric Organocatalysis*, No. 8); (f) List, B.; Bolm, C.; Issue Eds.; *Adv. Synth. Catal.* **2004**, *346*, 1021–1022 (thematic issue on *Organic Catalysis*, Nos. 9 and 10); (g) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064; (h) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (i) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005; (j) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (k) Kočovský, P.; Malkov, A. V.; Issue Eds.; *Tetrahedron* **2006**, *62*, 255 (thematic issue on *Organocatalysis in Organic Synthesis*, Nos. 2 and 3); (l) Lelais, G.; McMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79–87; (m) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543; (n) List, B. *Chem. Commun.* **2006**, 819–824; (o) Wessig, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2168–2171; (p) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909–3912; (q) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876–7880; (r) Gaunt, M. J.; Johansonn, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8–27.
2. (a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011; (b) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492.
3. (a) Rueping, M. *Nachr. Chem.* **2007**, *55*, 35–37; (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581; (c) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693–700.
4. Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349–354.
5. For the first proline catalyzed intramolecular reaction see: List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
6. For general reviews on the catalytic enantioselective aldol reaction, see: (a) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137–1141; (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389; (c) Carreira, E.

M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Platz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, Chap 29–188 (d) Mahrwald, R. *Chem. Rev.* **1999**, *96*, 1095–1120; (e) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374; (f) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601; (g) *Modern Aldol Reactions*; Marhrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1–2, (h) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Rev. Soc.* **2004**, *33*, 65–75; (i) Mestres, R. *Green Chem.* **2004**, *6*, 583–603; (j) Vicario, J. L.; Badía, D.; Carillo, L.; Reyes, E.; Etxbarria, J. *Curr. Org. Chem.* **2005**, *9*, 219–235; (k) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506–7525.

7. (a) Trost, B. M. *Science.* **1991**, *254*, 1471–1477; (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246; (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705; (d) Trost, B. M.; Frederiksen, M. U.; Mathias, U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630–6666; (e) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358–2364.
8. (a) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 729–733; (b) Gryko, D.; Kowalczyk, B.; Zawadzki, L. *Synlett* **2006**, 1059–1062; (c) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493–1497; Corrigendum: *Tetrahedron: Asymmetry* **2007**, *18*, 1031; (d) Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2754–2760; (e) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197–208; (f) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247–1250.
9. (a) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027–1031; Corrigendum: *Tetrahedron: Asymmetry* **2007**, *18*, 1030; (b) Guillena, G.; Hita, M. C.; Nájera, C. *ARKIVOC* **2007**, *iv*, 260–269; Corrigendum: *ARKIVOC* **2007**, *i*, 146–147.
10. (a) Padwa, A.; Murphree, S. S. *ARKIVOC* **2006**, *iii*, 6–33; (b) Sello, G.; Fumagalli, T.; Orsini, F. *Curr. Org. Synth.* **2006**, *3*, 379–402.
11. Rosen, T. In *Comprehensive Organic Synthesis*; Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 409–439.
12. (a) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2006**, 2001–2011; (b) Berkessel, A. *Pure. Appl. Chem.* **2005**, *77*, 1277–1284; For the distereoselective synthesis of epoxides by sulfur ylide methodology, see: (c) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105–2114.
13. Kitazume, T.; Jiang, Z.; Kasai, K.; Mihara, Y.; Suzuki, M. *J. Fluor. Chem.* **2003**, *121*, 205–212.
14. He, L.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron* **2006**, *62*, 346–351.
15. In Ref. 14, the purification of the achieved products was carried out by using silica gel without any epimerization or racemization problems.