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Enantioselective aldol condensation of *O*-silyl dienolates to aldehydes mediated by chiral BINOL–titanium complexes

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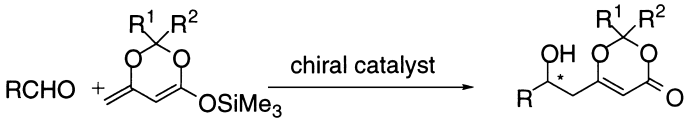
Abstract

Chiral BINOL–titanium complexes have been shown to catalyze enantioselective aldol reactions between dioxinone derivatives and a set of aldehydes. The aldol adducts are isolated in good yields and high enantioselectivities. A range of substitution patterns on the *O*-silyl dienolate is possible: alkyl and benzyl substituents are tolerated. A simple reaction protocol is described and provides an efficient alternative to the well-known methods for conducting enantioselective Mukaiyama aldol reactions.

1. Introduction

The aldol reaction is one of the most important methods for forming carbon–carbon bonds. Particular attention has been recently paid to the use of chiral Lewis acids that activate the aldehyde component toward addition by enol silanes.[1] It has to be noted that in the case of unsuccessful employment of the chiral Lewis acid in catalytic amounts, the stoichiometric process is still quite useful and more advantageous than those requiring the binding and removal of chiral auxiliaries.[2]

Recently, it has been shown that the use of *O*-silyl dienolates of types **1** and **2** (Fig. 1) constitutes an interesting alternative to the classic enantioselective Mukaiyama aldol reaction with silyl enol ethers. The interest in the use of the silyl dienolates is due to the easy manipulation



1: $R^1=R^2=$ Me

2: $R^1,R^2=$ -$(CH_2)_5$-

Figure 1.

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of the dioxinone ring in the aldol adducts to a variety of three-carbon units.[3,4] In fact, the masked acetoacetate aldol adducts serve as versatile precursors to optically active δ-hydroxy-β-keto esters and derived β,δ-diol esters, amides and lactones, key structural subunits in biologically active natural products.[5]

In particular, the enantioselective dienolate addition methodology has been applied in the context of total syntheses both for the preparation of key-intermediates and the introduction of stereocenters with defined configuration.[6–10] Recently, important advances have been made by Evans et al.[10] and Carreira et al.,[5a,11,12] who have reported new catalytic processes, involving the use of chiral Ti(IV) and Cu(II) catalysts, characterized by very high efficiency and enantioselectivity. However, it is noteworthy that recent Evans' procedures based on the use of [Cu((*S*,*S*)-Ph-pybox)](SbF$_6$)$_2$[10] complexes require the presence of a suitable chelating group, α-situated to formyl functionality, to achieve high enantioselectivity. Furthermore, tetrabutyl ammonium triphenyldifluorosilicate (TBAT), one of the reagents involved as a fluoride source in Carreira's procedure,[11,12] can be obtained in the necessary analytical purity only after a laborious sequence performed under carefully controlled reaction conditions.[13]

In the course of investigations devoted to the synthesis of chiral furyl-pyran derivatives utilizing nucleophiles of types **1** and **2**,[14] our attention was attracted by an alternative procedure proposed by Sato[15] involving the use of the well-known chiral Ti(O^{i}Pr)$_4$/BINOL system. Although few examples were reported, moderate yields (usually $<60\%$) and very variable enantiomeric excesses (33–92%) were observed, this procedure proved to be very attractive due to the ready accessibility of the reagents and the simplicity of set-up.

In this paper we report that important improvements of the efficiency and enantiocontrol in this reaction may be obtained under appropriate experimental conditions and changes in the dienolate architecture.

2. Results and discussion

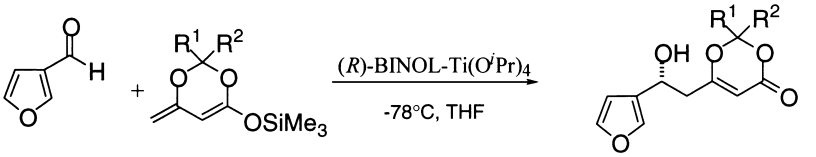
Taking advantage of observations made by Sato in his preliminary survey,[15] a study was initiated to explore the aldol reaction parameters and the influence of the amount of catalyst was initially investigated.

A set of preliminary experiments performed on 3-formyl furan (Table 1) showed that both yields and e.e.s could be noticeably increased by using higher amounts of catalytic system (entries 1–3); the results obtained by using silyloxydiene **2** (entry 4) confirmed the important role played by the structure of the nucleophile: in fact, satisfactory e.e.s were usually obtained in the presence of 0.17 equiv. of the Ti(IV)/(*R*)-BINOL complex, although, once again, significant improvement could be achieved with increased amounts of the catalytic system (entry 5).

In order to evaluate the applicability of the method, a range of aldehydes served as substrates (Table 2). Data reported in Table 2 revealed that the employment of **2** led to chemical yields and enantiomeric excesses very similar to those obtained for the use of **1** but in the presence of lower catalyst loadings (entries 1–5); the reaction performed with *p*-nitrobenzaldehyde and **2** resulted in enhancement of the chemical yield and in an large improvement of the e.e. (entries 6 and 7).

When *trans*-cinnamaldehyde (entry 9) was utilized with **2** the aldol adduct was isolated in poor yield but high enantioselectivity; surprisingly, investigation on the use of aliphatic aldehydes (entries 10 and 11) revealed that the e.e. decreased when using **2**, albeit the low value of conversion remained an unresolved problem with **1**.

Table 1
Enantioselective addition of **1** and **2** to 3-formylfuran



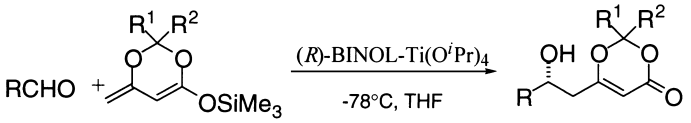
1: R^1=R^2= Me
2: R^1,R^2= -$(CH_2)_5$-

3a: R^1=R^2= Me
4a: R^1,R^2= -$(CH_2)_5$-

Entry	Product	Catalyst Loading	Yield(%)	e.e.(%)[a,b]
1	**3a**	0.17 mol%	42	80
2	**3a**	0.50 mol%	65	89
3	**3a**	1.00 mol%	81	91
4	**4a**	0.17 mol%	59	87
5	**4a**	0.50 mol%	89	94

a.The enantiomeric excess was determined by HPLC analysis of the aldol product using a CHIRALPAK AD column.
b.The absolute configuration of the adducts was established by comparison of the optical rotation to literature values[14b] or by conversion to the corresponding MTPA esters.[16]

Table 2
Enantioselective addition of **1** and **2** to aldehydes RCHO



1: R^1=R^2= Me
2: R^1,R^2= -$(CH_2)_5$-

3b-f: R^1=R^2= Me
4b-f: R^1,R^2= -$(CH_2)_5$-

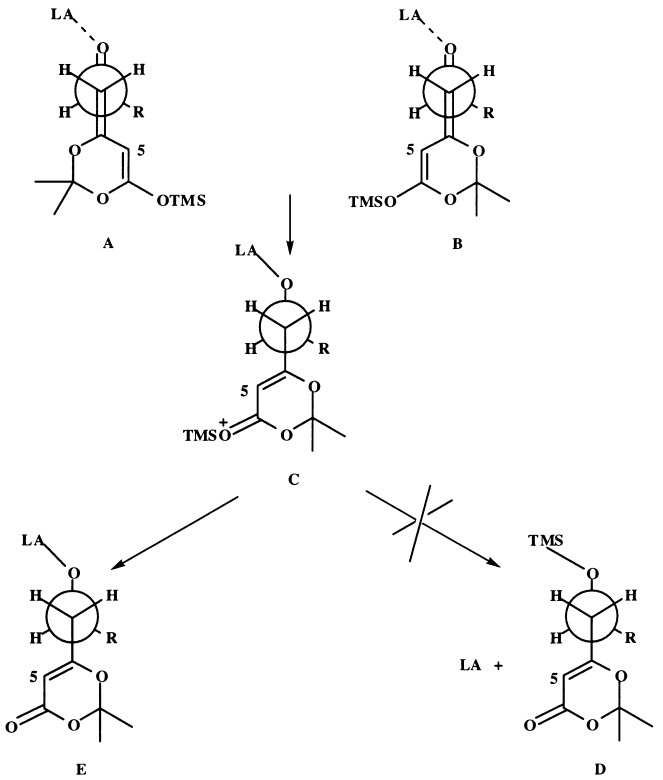
Entry	Product	R (RCHO)	Catalyst Loading	Yield(%)	e.e.(%)[a,b]
1	**3b**	Phenyl	0.50 mol%	63	92
2	**4b**	"	0.17 mol%	69	92
3[c]	**3b**	"	0.20 mol%	24	98
4	**3c**	*p*-Methoxyphenyl	0.50 mol%	59	98
5	**4c**	"	0.17 mol%	55	95
6	**3d**	*p*-Nitrophenyl	0.50 mol%	72	75
7	**4d**	"	0.17 mol%	76	90
8	**3e**	trans-cynnamyl	-	-	-
9	**4e**	"	0.17 mol%	30	90
10	**3f**	Nonyl	0.50 mol%	39	89
11	**4f**	"	0.17 mol%	37	36

a.The enantiomeric excess was determined by HPLC analysis of the aldol product using a CHIRALPAK AD column.
b.The absolute configuration of the adducts was established by comparison of the optical rotation to literature values[11,15] or by conversion to the corresponding MTPA esters.[16]
c.The reaction was performed utilizing 20% mol $Ti(O^iPr)_4$ and 40% mol of (*R*)-BINOL

Additional attempts to increase both conversion and enantioselectivity using the BINOL/Ti(IV) catalyst prepared from the reaction of (*R*)-BINOL and $Ti(O^iPr)_4$ in a 2:1 stoichiometry,[17] respectively, gave very poor chemical yields with considerable improvement in the enantiomeric excess (entry **3**).

In contrast to Evans and Carreira's procedures which afford silylated aldols, in all the experiments free aldols were obtained as the only products so that the usual process of desilylation for the regeneration of hydroxyl functionality could be omitted.

This result can be reasonably explained (Scheme 1) on the grounds of the reaction pathway depicted by Sato,[15] that involves the shielding of *si* face of aldehydes by chiral Ti(IV)/(*R*)-BINOL catalyst (LA) and the attack of the nucleophiles on *re* face through the possible transition states **A** and **B** to afford alkoxide **C**. According to Evans and Carreira's methodologies TMS-transfer (with consequent release of the chiral Lewis acid LA) to give **D** is the determining step for the achievement of an efficient catalytic cycle: the isolation of only free aldols **E** proves the inhibition of this transfer in our procedure and points out the necessity of using higher amounts of catalytic system to enhance yield and e.e.



Scheme 1.

The extension of the above procedure to 5-substituted silyloxydienes[18] of type **5** (Fig. 2) could have allowed a more direct approach to branched diol derivatives.[18,19] No examples are available in literature about the reaction shown in Fig. 2 with the exception of our preliminary report.[14b] The reactivity of nucleophiles **5a**,**b** was investigated (Table 3).

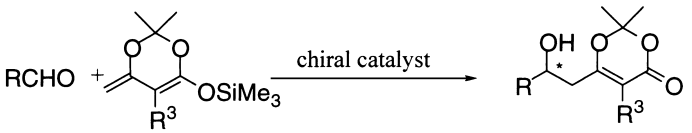


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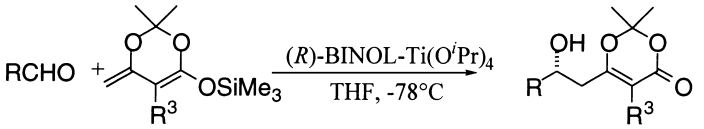
Figure 2.

Table 3
Enantioselective addition of **5a** and **5b** to aldehydes RCHO



5a: R^3= Me
5b: R^3= CH_2Ph

7a-c: R^3= Me
8: R^3= CH_2Ph

Entry	Product	R (RCHO)	Catalyst Loading	Yield(%)	e.e.(%)[a,b]
1	**7a**	3-Furyl	0.17 mol%	40	67
2	**7a**	"	0.50 mol%	41	72
3	**7a**	"	1.00 mol%	50	88
4	**7b**	Phenyl	0.50 mol%	45	73
5	**7b**	"	1.00 mol%	56	88
6	**8**	"	1.00 mol%	45	25[c]
7	**7c**	*p*-Nitrophenyl	0.50 mol%	73	62

a.The enantiomeric excess was determined by HPLC analysis of the aldol product using a CHIRALPAK AD column.
b.The absolute configuration of the adducts was established by conversion to the corresponding MTPA esters.[16]
c.The enantiomeric excess was determined by conversion of the adduct to the corresponding Mosher ester[16] upon treatment with (*S*)-MTPA-Cl and analysis by ^{1}H-NMR spectroscopy.

Although on the grounds of the mechanism proposed by Sato[15] for the Ti(IV)/BINOL-catalyzed aldol condensation of compounds **1** and **2** the presence of substituents in 5-position of the dioxinone ring should have deeply influenced the outcome of the reaction (Scheme 1), promising yields and e.e.s have been obtained with silyloxydiene **5a** (Table 3).

Once again, the best results involved the use of higher catalyst amounts (entries 1–5). For $R^3 = PhCH_2$– (entry 6) a precipitous drop in e.e., to only 25%, could be observed confirming that the steric hindrance of substituents situated in the 5-position of the six-membered ring plays an important role in the assembly of the catalyst–substrate complex. When the reaction with *p*-nitrobenzaldehyde was performed with 0.50 mol% of catalyst (entry 7) the aldol adduct was obtained in good chemical yield and useful levels of enantioselectivity. These results confirm the feasibility of aldol reactions involving the use of 5-substituted silyloxydienes of type **5** and further investigations will be devoted to broaden their synthetic validity.

In conclusion, we have demonstrated that the aldol condensation reaction of *O*-silyl dienolates in the presence of the Ti(O^{i}Pr)$_4$/(*R*)-BINOL complex is a valuable, preparatively simple method for the synthesis of acetoacetate aldols, versatile synthetic intermediates.

The reaction, in fact, can be performed using ordinary laboratory equipment, since no complex preparation of catalyst is required. Moreover, the BINOL ligand is easily recovered and recycled with no decrease in efficiency. The reaction is general for aromatic and heteroaromatic

aldehydes, and employment of substituted dienolate is quite attractive from the viewpoint of the synthesis of branched aldol adducts.

3. Experimental

3.1. General remarks

All reactions were performed using oven dried glassware under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was distilled from CaH_2 and then from $LiAlH_4$, *i*-Pr_2NH was freshly distilled from CaH_2. ^1H NMR and ^{13}C NMR spectra were recorded on solutions in $CDCl_3$ with Bruker DRX 400 (400.135 MHz for ^1H and 100.03 MHz for ^{13}C NMR) spectrometers. Data for ^1H are reported as folllows: chemical shift (δ in ppm), multiplicity (s singlet, d doublet, t triplet, dd doublet of doublets, m multiplet) and coupling constant (J in hertz). Infrared spectra were recorded on a Bruker Vector 22 spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter operating at the sodium D line at room temperature. Concentration is given in g/100 ml. The mass spectra were recorded on a VG TRIO 2000 spectrometer. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). HPLC analyses were performed with Waters Associates equipment and a Hewlett–Packard SP4400 Chromojet integrator using a Chiralpak AD column with a solvent mixture of hexane/isopropanol and flow rates as indicated.

3.2. General procedure for the enantioselective dienolate addition to aldehyde

A mixture of (*R*)-(+)-1,1′-bi-2-naphthol (23 mg, 0.080 mmol, 17% mol), titanium tetra-isopropoxide (23 mg, 0.080 mmol, 17% mol) and molecular sieves 3Å (0.6 g) in 1.0 ml THF was stirred at room temperature under an inert atmosphere for 1 h to yield a red-brown solution. The mixture was cooled to –78°C and the aldehyde (0.47 mmol) was added dropwise followed, after 20 min, by a solution of the dioxinone derivative silyl dienolate[5b,15] (0.94 mmol) in 0.5 ml of THF. The progress of the reaction was monitored by TLC. After 4 h at –78°C, the solution was allowed to warm to room temperature overnight. The reaction mixture was diluted with a saturated aqueous solution of $NaHCO_3$ and after stirring for 30 min it was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography on silica gel using 9:1 $CHCl_3$:Et_2O afforded the aldol adducts. The enantiomeric excess of the products was determined by HPLC analyses using a racemic sample as reference.

The physical and spectroscopic data of compounds **3a** (entry 1, Table 1),[14c] **3b** (entry 1, Table 2),[12,15] **3c** (entry 4, Table 2),[12] **4b** (entry 2, Table 2)[15] and **4e** (entry 9, Table 2)[15] match those described in the literature.

3.2.1. 6-[2-Hydroxy-2-(4-nitro-phenyl)-ethyl]-2,2-dimethyl[1,3]dioxin-4-one **3d** (entry 6, Table 2)

The product was obtained as a pale yellow oil. [Found: C, 57.48; H, 5.05; N, 4.64; $C_{14}H_{15}NO_6$ requires: C, 57.34; H, 5.16; N, 4.78%]; R_f (10% $Et_2O/CHCl_3$) 0.45; ν_{max} ($CHCl_3$) 3600–3300 (bs), 3019, 1721, 1638, 1526, 1393, 1378, 1349, 1276, 1261, 1215; δ_H (400 MHz, $CDCl_3$) 8.19 (d, 2H, J = 7.3 Hz), 7.55 (d, 2H, J = 7.7 Hz), 5.32 (s, 1H), 5.10 (bs, 1H), 3.30 (bs, 1H), 2.61–2.58 (m, 2H),

1.66 (s, 6H); δ_C (100.03 MHz, $CDCl_3$) 167.9, 161.2, 150.3, 147.4, 126.5, 123.8, 106.9, 95.5, 69.8, 43.1, 25.2, 24.6; *m/z* (EIMS) 293 (M^+); $[\alpha]_D^{25} = +21$ (*c* 1.2, $CHCl_3$), e.e. 75% (*R*); HPLC analysis (hexanes:isopropanol, 8:2), 0.8 mL/min; (*S*) enantiomer $t_r = 11.29$ min; (*R*) enantiomer $t_r = 14.23$ min.

3.2.2. 6-(2-Hydroxy-undecyl)-2,2-dimethyl[1,3]dioxin-4-one ***3f*** *(entry 10, Table 2)*

The product was obtained as a yellow oil. [Found: C, 68.51; H, 10.21; $C_{17}H_{30}O_4$ requires: C, 68.42; H, 10.13%]; R_f (10% $Et_2O/CHCl_3$) 0.2; ν_{max} ($CHCl_3$) 3500–3250 (bs), 3020, 2931, 2855, 1721, 1637, 1393, 1376; δ_H (400 MHz, $CDCl_3$) 5.31 (s, 1H), 3.88 (bs, 1H), 2.37 (dd, 1H, J = 3.96, 14.5 Hz), 2.30 (dd, 1H, J = 8.4, 14.5 Hz), 1.68 (s, 6H), 1.49–1.24 (m, 16H), 0.86 (t, 3H, J = 6.1 Hz); δ_C (100.03 MHz, $CDCl_3$) 172.9, 169.4, 161.1, 114.9, 106.6, 95.1, 68.9, 41.7, 37.4, 31.9, 29.5, 29.3, 25.5, 25.3, 24.8, 22.7, 14.1; *m/z* (EIMS) 298 (M^+); $[\alpha]_D^{25} = +13$ (*c* 1.2, $CHCl_3$), e.e. 89% (*R*); HPLC analysis (hexanes:isopropanol, 98:2), 0.5 mL/min; (*R*) enantiomer $t_r = 51.56$ min; (*S*) enantiomer $t_r = 60.04$ min.

3.2.3. 4-[2-Hydroxy-2-(4-methoxy-phenyl)-ethyl]-1,5-dioxa-spiro[5.5]undec-3-en-2-one ***4c*** *(entry 5, Table 2)*

The product was obtained as a yellow oil. [Found: C, 68.03; H, 6.88; $C_{18}H_{22}O_5$ requires: C, 67.91; H, 6.97%]; R_f (10% $Et_2O/CHCl_3$) 0.2; ν_{max} ($CHCl_3$) 3437, 3000, 1712, 1633, 1612, 1512, 1382, 1245; δ_H (400 MHz, $CDCl_3$) 7.25 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 5.19 (s, 1H), 4.92–4.88 (m, 1H), 3.77 (s, 3H), 2.65 (dd, 1H, J = 8.6, 14.6 Hz), 2.62 (partially superimposed, 1H), 2.55 (dd, 1H, J = 4.8, 14.6 Hz), 1.96–1.42 (m, 10H); δ_C (100.03 MHz, $CDCl_3$) 168.4, 161.4, 159.4, 135.1, 127.0, 114.0, 107.3, 95.3, 70.8, 55.3, 43.2, 34.1, 33.3, 24.6, 22.2; *m/z* (EIMS) 318 (M^+); $[\alpha]_D^{25} = +23$ (*c* 1.2, $CHCl_3$), e.e. 95% (*R*); HPLC analysis (hexanes:isopropanol, 8:2), 0.8 mL/min; (*S*) enantiomer $t_r = 12.28$ min; (*R*) enantiomer $t_r = 16.56$ min.

3.2.4. 4-[2-Hydroxy-2-(4-nitro-phenyl)-ethyl]-1,5-dioxa-spiro[5.5]undec-3-en-2-one ***4d*** *(entry 7, Table 2)*

The product was obtained as yellow oil. [Found: C, 61.11; H, 5.82; N, 4.33; $C_{17}H_{19}NO_6$ requires: C, 61.25; H, 5.75; N, 4.20%]; R_f (10% $Et_2O/CHCl_3$) 0.1; ν_{max} ($CHCl_3$) 3605, 3389, 2946, 1719, 1641, 1606, 1525, 1385, 1348; δ_H (400 MHz, $CDCl_3$) 8.21 (d, 2H, J = 8.6 Hz), 7.57 (d, 2H, J = 8.6 Hz), 5.30 (s, 1H), 5.14–5.10 (m, 1H), 3.09 (d, 1H, J = 3.7 Hz), 2.67–2.60 (m, 2H), 1.99–1.45 (m, 10H); δ_C (100.03 MHz, $CDCl_3$) 167.5, 161.3, 150.2, 147.6, 126.6, 123.9, 107.7, 95.8, 70.1, 43.3, 34.1, 33.3, 24.5, 22.2; *m/z* (EIMS) 333 (M^+); $[\alpha]_D^{25} = +26$ (*c* 1.3, $CHCl_3$), e.e. 90% (*R*); HPLC analysis (hexanes:isopropanol, 8:2), 0.8 mL/min; (*S*) enantiomer $t_r = 16.58$ min; (*R*) enantiomer $t_r = 23.36$ min.

3.2.5. 4-(2-Hydroxy-undecyl)-1,5-dioxa-spiro[5.5]undec-3-en-2-one ***4f*** *(entry 11, Table 2)*

The product was obtained as a yellow oil. [Found: C, 71.13; H, 10.01; $C_{20}H_{34}O_4$ requires: C, 70.97; H, 10.12%]; R_f (10% $Et_2O/CHCl_3$) 0.3; ν_{max} ($CHCl_3$) 3400–3250 (bs), 3017, 2937, 2861, 1714, 1634, 1380, 1264; δ_H (400 MHz, $CDCl_3$) 5.28 (s,1H), 3.91 (bs, 1H), 2.42 (dd, 1H, J = 8.3, 14.5 Hz), 2.33 (dd, 1H, J = 8.3, 14.5 Hz), 2.00–1.43 (m, 26H), 0.87 (t, 3H, J = 5.9 Hz); δ_C (100.03 MHz, $CDCl_3$) 169.0, 161.2, 131.5, 107.2, 95.2, 69.0, 41.7, 37.4, 34.0, 33.5, 31.9, 29.5, 29.3, 25.5, 24.6, 22.7, 22.2, 14.1; *m/z* (EIMS) 338 (M^+); $[\alpha]_D^{25} = +33$ (*c* 1.2, $CHCl_3$), e.e. 36% (*R*); HPLC analysis (hexanes:isopropanol, 98:2), 0.5 mL/min; (*R*) enantiomer $t_r = 64.20$ min; (*S*) enantiomer $t_r = 67.94$ min.

3.2.6. 6-(2-Furan-3-yl-2-hydroxy-ethyl)-2,2,5-trimethyl[1,3]dioxin-4-one ***7a*** *(entry* ***1****, Table 3)*

The product was obtained as a yellow oil. [Found: C, 61.77; H, 6.50; $C_{13}H_{16}O_5$ requires: C, 61.90; H, 6.39%]; R_f (10% $Et_2O/CHCl_3$) 0.3; ν_{max} ($CHCl_3$) 3410, 3000, 2350, 1713, 1632, 1389, 1275; δ_H (400 MHz, $CDCl_3$) 7.42 (s, 1H), 7.40 (s, 1H), 6.40 (s, 1H), 4.97 (dd, 1H, J = 5.2, 8.3 Hz), 2.82 (dd, 1H, J = 8.3, 14.2 Hz), 2.62 (dd, 1H, J = 5.2, 14.2 Hz), 1.80 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H); δ_C (100.03 MHz, $CDCl_3$) 162.5, 161.9, 143.6, 139.1, 127.9, 108.2, 105.0, 102.5, 64.2, 39.3, 25.4, 24.6, 10.2; *m/z* (EIMS) 252 (M^+); $[\alpha]_D^{25} = +17$ (*c* 1.5, $CHCl_3$), e.e. 88% (*R*); (*R*)-MTPA ester data: ^1H NMR ($CDCl_3$) furan resonances at δ 6.44 and 6.33 in a ratio of 0.06:1.00.

63.2.7. 6-[2-Hydroxy-2-phenyl-ethyl]-2,2,5-trimethyl[1,3]dioxin-4-one ***7b*** *(entry 4, Table 3)*

The product was obtained as yellow oil. [Found: C, 68.54; H, 7.04; $C_{15}H_{18}O_4$ requires: C, 68.68; H, 6.92%]; R_f (10% $Et_2O/CHCl_3$) 0.3; ν_{max} ($CHCl_3$) 3689, 3617, 3448, 3019, 2974, 2399, 1711, 1646, 1521, 1390, 1375, 1212; δ_H (400 MHz, $CDCl_3$) 7.36–7.28 (m, 5H), 4.98–4.95 (m, 1H), 2.82 (dd, 1H, J = 8.4, 14.1 Hz), 2.60 (dd, 1H, J = 5.1, 14.1 Hz), 2.36 (bs, 1H), 1.73 (s, 3H), 1.61 (s, 6H); δ_C (100.03 MHz, $CDCl_3$) 162.8, 162.2, 156.3, 143.1, 128.7, 128.2, 125.7, 105.0, 102.4, 71.7, 40.5, 25.6, 24.6, 10.2; *m/z* (EIMS) 262 (M^+); $[\alpha]_D^{25} = +25$ (*c* 1.4, $CHCl_3$), e.e. 88% (*R*); HPLC analysis (hexanes:isopropanol, 9:1), 0.8 mL/min; (*S*) enantiomer $t_r = 11.65$ min; (*R*) enantiomer $t_r = 12.93$ min.

3.2.8. 6-[2-Hydroxy-2-(4-nitro-phenyl)-ethyl]-2,2,5-trimethyl[1,3]dioxin-4-one ***7c*** *(entry 7, Table 3)*

The product was obtained as a pale yellow oil. [Found: C, 58.49; H, 5.43; N, 4.68; $C_{15}H_{17}NO_6$ requires: C, 58.63; H, 5.58; N, 4.56%]; R_f (10% $Et_2O/CHCl_3$) 0.2; ν_{max} ($CHCl_3$) 3606, 3404, 3020, 1714, 1650, 1606, 1524, 1393, 1372, 1349, 1222, 1205, 1149; δ_H (400 MHz, $CDCl_3$) 8.21 (d, 2H, J = 8.5 Hz), 7.57 (d, 2H, J = 8.5 Hz), 5.15–5.11 (m, 1H), 2.82 (dd, 1H, J = 8.96, 14.4 Hz), 2.75 (bs, 1H), 2.60 (dd, 1H, J = 4.1, 14.4 Hz), 1.77 (s, 3H), 1.65 (s, 6H); δ_C (100.03 MHz, $CDCl_3$) 162.8, 161.7, 150.9, 147.4, 126.6, 123.8, 105.2, 102.8, 70.4, 64.5, 40.6, 25.6, 25.2, 24.6, 10.2; *m/z* (EIMS) 307 (M^+); $[\alpha]_D^{25} = +21$ (*c* 1.3, $CHCl_3$), e.e. 62% (*R*); HPLC analysis (hexanes:isopropanol 95:5), 0.8 mL/min; (*S*) enantiomer $t_r = 27.05$ min; (*R*) enantiomer $t_r = 28.74$ min.

3.2.9. 5-Benzyl-6-(2-hydroxy-2-phenyl-ethyl)-2,2-dimethyl[1,3]dioxin-4-one ***8*** *(entry 6, Table 3)*

The product was obtained as a pale yellow oil. [Found: C, 74.70; H, 6.68; $C_{21}H_{22}O_4$ requires: C, 74.54; H, 6.55%]; R_f (20% AcOEt/30–50°C light petroleum) 0.3; ν_{max} ($CHCl_3$) 3605, 3448–3278 (bs), 3030, 3012, 1714, 1637, 1389, 1372, 1272; δ_H (400 MHz, $CDCl_3$) 7.36–7.20 (m, 10H), 4.96 (m, 1H), 4.68 (d, 1H, J = 4.6 Hz), 3.62 (AB, 2H, J = 15.7 Hz), 2.88 (dd, 1H, J = 8.9, 14.5 Hz), 2.64 (dd, 1H, J = 4.7, 14.5 Hz), 1.64 (s, 6H); δ_C (100.03 MHz, $CDCl_3$) 164.0, 162.3, 156.3, 143.1, 139.9, 131.3, 128.7, 128.6, 128.2, 126.3, 125.7, 106.7, 105.3, 71.5, 57.0, 40.6, 30.3, 25.8, 24.7; *m/z* (EIMS) 338 (M^+); $[\alpha]_D^{25} = +5$ (*c* 1.3, $CHCl_3$), e.e. 25%(*R*); (*S*)-MTPA ester data: ^1H NMR (C_6D_6) methyl resonances at δ 1.36 and 1.34 in a ratio of 0.59:0.98 (25% e.e.).

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References

1. (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389; (b) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137–1141; (c) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947.
2. Kiyooka, S.; Hena, A. M. *J. Org. Chem.* **1999**, *64*, 5511–5523.
3. Kaneko, C.; Sato, M.; Sakaki, J.; Abe, Y. *J. Heterocyclic Chem.* **1990**, *27*, 25–30.
4. Clemens, R. J.; Witzeman, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186–2193.
5. (a) Singer, A. R.; Carreira, M. E. *J. Am. Chem. Soc.* **1995**, *117*, 12360–12361; (b) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 839–845.
6. Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013–7016.
7. Anné, S.; Yong, W.; Vandewalle, M. *Synlett* **1999**, *9*, 1435–1437.
8. Kim, Y.; Singer, A. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1261–1263.
9. Soriente, A.; De Rosa, M.; Apicella, A.; Scettri, A.; Sodano, G. *Tetrahedron: Asymmetry* **1999**, *10*, 4481–4484.
10. Evans, D. A.; Kozlowski, M. C.; Murry, A. J.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. *J. Am. Chem. Soc.* **1999**, *121*, 669–685.
11. Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837–838.
12. Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124–3126.
13. Handy, J. C.; Lam, Y. F.; Deshong, P. *J. Org. Chem.* **2000**, *65*, 3542–3543.
14. (a) Soriente, A.; De Rosa, M.; Dovinola, P.; Sodano, G.; Scettri, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2197–2199; (b) De Rosa, M.; Dell'Aglio, R.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **1999**, *10*, 3659–3662; (c) De Rosa, M.; Soriente, A.; Sodano, G.; Scettri, A. *Tetrahedron* **2000**, *56*, 2095–2102.
15. Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435–1444.
16. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *112*, 4092–4096.
17. Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363–2364.
18. Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896–1901.
19. De Rosa, M.; Giordano, S.; Scettri, A.; Sodano, G.; Soriente, A.; Pastor, P. G.; Alcaraz, M. J.; Payá, M. *J. Med. Chem.* **1998**, *41*, 3232–3238.