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Solvent-free asymmetric vinylogous aldol reaction of Chan's diene with aromatic aldehydes catalyzed by hydrogen bonding

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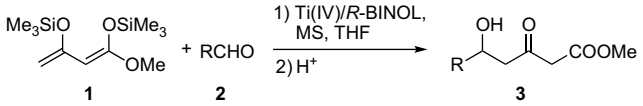
ABSTRACT

Chan's diene proved to react with aromatic aldehydes under organocatalytic conditions in presence of a chiral naphthyl-TADDOL derivative to give vinylogous aldols (up to 65% ee) with complete γ-selectivity. A further process of hetero-Diels–Alder cycloaddition, leading to chiral pyran-4-one derivatives (up to 60% ee), was favoured by electron-withdrawing substituents on the aromatic ring.

1. Introduction

In the last years Chan's diene **1**, a highly oxygenated masked form of an acetoacetate ester, has proven to be a valuable starting material for the synthesis of a notable variety of classes of compounds.[1] Particularly, Chan's diene has been conveniently used in highly enantioselective vinylogous aldol reactions,[2] to afford δ-hydroxy-β-ketoesters, key-intermediates in the preparation of many bio-active compounds. In fact, in the presence of catalytic amounts (2–8 mol %) of chiral Ti(O^{i}Pr)$_4$/BINOL complex, the exclusive formation of products **3** was found to take place in high yields and enantiomeric excesses (Scheme 1, Table 1).[2b,3]



Scheme 1.

As clearly reported in Table 1, a high level of enantioselectivity can be observed with variously substituted aldehydes, indicating a negligible occurrence of a background reaction leading to racemic aldols **3**.

However, a set of experiments performed under solvent-free conditions on benzaldehyde (chosen as the representative substrate) pointed out the relevant nucleophilic properties of Chan's diene **1** (Scheme 2): in fact, in the absence of any added catalyst, the vinylogous aldol reaction leading to the corresponding aldol **3a** was found to take place in significant yield (entries 1–3, Table 2).

Table 1
Ti(O^{i}Pr)$_4$/*R*-BINOL catalyzed vinylogous aldol reaction of **1**

Entry	**2**	R	Conditions	Yield[a] (%)	ee[b] (%)
1	**2a**	Ph	2 h/−78 °C; 16 h/rt	94	>99
2	**2b**	4-MeOC$_6$H$_4$	2 h/−78 °C; 16 h/rt	68	91
3[b]	**2c**	4-NO$_2$C$_6$H$_4$	2 h/−78 °C; 16 h/rt	86	90
4	**2d**	4-CF$_3$C$_6$H$_4$	2 h/−78 °C; 16 h/rt	77	93
5[c]	**2a**	Ph	4 h/rt	—	—
6[d]	**2a**	Ph	4 h/rt	—	—
7[d]	**2a**	Ph	16 h/rt	—	—

[a] Yields refer to isolated chromatographically pure compounds **3**, whose structures were confirmed by spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, IR).
[b] ees were determined by HPLC analysis.
[c] In this entry the reaction was carried out in the absence of Ti(O^{i}Pr)$_4$/*R*-BINOL and MS.
[d] In this entry the reaction was carried out in the absence of Ti(O^{i}Pr)$_4$/*R*-BINOL.

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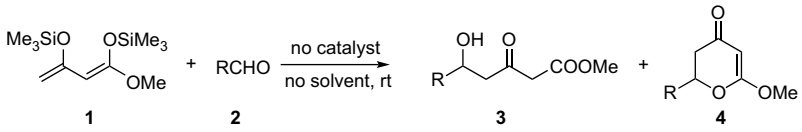


1 2 3 4

Scheme 2.

Table 2
Solvent-free reaction of Chan's diene **1** with aldehydes **2**

Entry	2	R	Reaction time (h)	3 Yield[a] (%)	4 Yield[a] (%)
1	**2a**	Ph	4	36	—
2	**2a**	Ph	24	46	—
3	**2a**	Ph	72	25	—
4	**2b**	4-$MeOC_6H_4$	4	9	—
5	**2c**	4-$NO_2C_6H_4$	4	44	12
6	**2e**	2-$NO_2C_6H_4$	4.5	39	21
7	**2e**	2-$NO_2C_6H_4$	24	50	37

[a] Yields refer to isolated chromatographically pure compounds **3** and **4**, whose structures were confirmed by spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, IR).

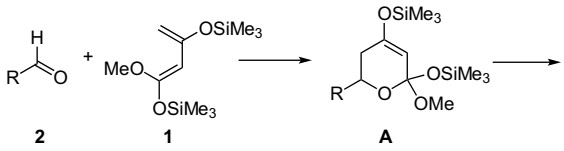
Furthermore, while electron-rich aldehydes, such as 4-MeO-benzaldehyde, exhibited a very poor reactivity (entry 4, Table 2), a quite different result was obtained by using electron-poor aldehydes (entries 5–7), which were converted, under the reported conditions, in rather good overall yield into a mixture of aldols **3** and pyran-4-one derivatives **4**.

The formation of products **4** can be reasonably explained through a hetero-Diels–Alder (HDA) reaction involving the formation of the intermediates **A** and **B** (Scheme 3).

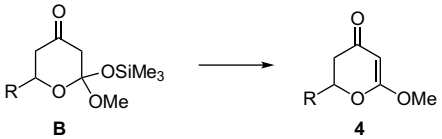
It is noteworthy that the dihydro-pyran-4-one moiety of products **4** represents the main structural feature of a family of pathotoxins isolated from *Alternaria Citri*,[4] a fungus responsible of the damage of rough lemon plants.

Rather interestingly, Brassard's diene **5**,[5] strictly related to Chan's diene from a structural point of view, is characterized by a quite different reactivity exhibiting a very strong tendency to afford the isomeric pyran-2-one derivatives **6** through a [4+2] concerted mechanism (Scheme 4) under a variety of metal-[6] or organocatalyzed[7] processes.

Now, in these last years an even increasing interest has been devoted to the organocatalysis[8] and, particularly, carbonyl activation

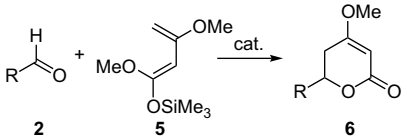


2 1 A



B 4

Scheme 3.



2 5 6

Scheme 4.

by hydrogen bonding has been exploited only in a few procedures both for the vinylogous aldol condensations[9] and HDA reactions[7] of masked acetoacetates.

2. Results and discussion

Therefore the reactivity of Chan's diene was examined under solvent-free conditions in the presence of a set of commercially available hydrogen bond donors.

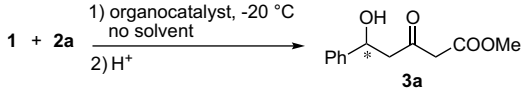
Benzaldehyde **2a** and 2-NO_2-benzaldehyde **2e** were chosen, respectively, as non-activated and activated representative substrates.

As reported in Scheme 5 and Table 3, benzaldehyde was submitted to reaction with Chan's diene **1** in the presence of some commercially available hydrogen bond donors.

The reaction was carried out at −20 °C under solvent-free conditions in order (a) to limit the occurrence of the non-asymmetric background reaction (entry 1, Table 3) and (b) to enhance the level of activation of the aldehydic functionality by hydrogen bonding.

However, most of the used organocatalysts gave rather disappointing results (entries 2–5), while, conversely, naphthyl-TADDOL derivative (*S*,*S*)-**7a** (commercially available, Fig. 1) proved to be a more promising organocatalyst. In fact, although the reaction had to be performed at room temperature in order to have an acceptable stirring of the very dense mixture, the formation of the expected aldol **3a** took place in modest yield and, interestingly, in 61% ee in spite of the competing non-asymmetric pathway (entry 6).

No significant improvement was observed after more prolonged reaction times (entry 7), while slight increase of ee was obtained at 0 °C at the expense of the efficiency of the process (compare entries 6 and 8).



3a

Scheme 5.

Table 3
Asymmetric vinylogous aldol reaction of Chan's diene **1** on PhCHO **2a** promoted by organocatalysts

Entry	Catalyst	Reaction time (h)	3a Yield[a] (%)	3a ee[b] (%)
1	—	72	25	—
2	(2*R*,3*R*)-Butanediol	72	33	0
3	D-Mandelic acid	72	—	—
4	(*R*)-BINOL	72	25	8 (*S*)
5	(*R*,*R*)-**7b**	72	43	11 (*S*)
6[c]	(*S*,*S*)-**7a**	24	42	61 (*R*)
7[c]	(*S*,*S*)-**7a**	72	42	58 (*R*)
8[d]	(*S*,*S*)-**7a**	24	32	65 (*R*)

[a] In all entries 1:1.3:0.1 aldehyde/**1**/catalyst ratios were used under solvent-free conditions. All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, IR).
[b] Determined by chiral-phase HPLC analysis (CHIRALPAK AD, Hexane/EtOH 95:5+0.1% TFA, 1 ml/min, λ=254 nm).
[c] The experiment was performed at room temperature.
[d] The experiment was performed at 0 °C.

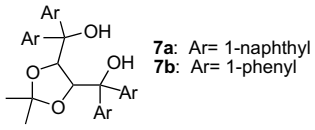
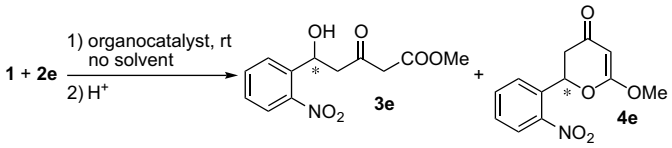


Figure 1.



Scheme 6.

In the case of 2-NO_2-benzaldehyde **2e** (Scheme 6) not only the competing background process seemed to be a serious problem to circumvent (entry 1, Table 4) but the steric bulk of the *ortho* substituent and the Lewis basicity of the nitro group could represent further disadvantages for an asymmetric pathway.

In fact, in the presence of some commercially available hydrogen bonding donors (entries 2–4, Fig. 2) the usual mixture of products **3e** and **4e** was obtained in rather high overall yields but in almost racemic forms. Compound (*S*,*S*)-**7a** again gave an interesting result leading to **3e** and **4e** as enantioenriched compounds (respectively 21% and 53% ees) (entry 5).

Notably, a 30:64 **3e**/**4e** ratio was observed, reversed with respect to the control experiment (entry 1). This different outcome can be explained through a strong intermolecular hydrogen bond through the organocatalyst –OH and the aldehydic carbonyl resulting in the decrease of the LUMO energy, which favours the hetero-Diels–Alder pathway.[9,10]

In order to assess the scope of the procedure a set of non-electron-poor aldehydes was reacted with Chan's diene **1** in the presence of (*S*,*S*)-**7a** (Scheme 7, Table 5) and in all entries 1–5 the vinylogous aldols of type **3** were isolated as exclusive products.

Furthermore, aliphatic aldehydes proved to be unreactive, so that they could be recovered completely unchanged after more prolonged reaction times (entry 6). The results obtained in entries 4 and 5 pointed out a strong dependence both of efficiency and enantioselectivity on the substitution pattern of the aromatic nucleus.

It is noteworthy that *o*-anisaldehyde and *p*-anisaldehyde exhibited a similar difference of reactivity in the Mukaiyama aldol reaction of *O*-silyl-*N*,*O*-ketene acetals promoted by the cyclohexylidene TADDOL derivative of type **7**.[11]

The behaviour of electron-poor aromatic and hetero-aromatic aldehydes was successively examined under the usual conditions (Scheme 8, Table 6).

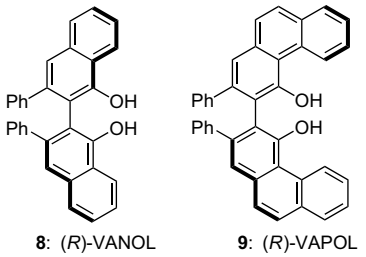
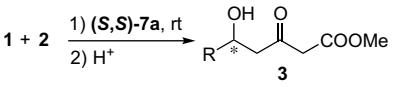


Figure 2.



Scheme 7.

All the tested aldehydes **2** showed an enhanced reactivity with respect to non-activated aldehydes and were converted in good to high yields in the usual mixture of enantioenriched vinylogous aldols **3** and pyran-4-one derivatives **4**.

The choice of the experimental conditions represented a critical factor for the preparative and stereochemical outcome: in fact, when the experiment of entry 2 was carried out at −20 °C for 72 h in the presence of toluene (0.1 ml), **3e** and **4e** were isolated in comparable yields (respectively, 32% and 30%) and a significant increase of ees could be observed (respectively, 46% and 60%) (entry 3).

As regards the mechanistic aspects, it has to be reminded that a general model has been proposed for other related TADDOL-catalyzed processes, such as the asymmetric hetero-Diels–Alder reactions of Rawal's[10,13] and Brassard's[7] dienes, as well as the vinylogous Mukaiyama reaction of dienol silylethers derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one.[9] The main structural feature of the TADDOL derivatives is represented by an intramolecular hydrogen bond between the two –OH groups, while the formation of an intermolecular hydrogen bond between the free –OH and the aldehyde oxygen is responsible for the carbonyl activation through the lowering of its LUMO energy. Furthermore, the sense of the asymmetric induction has been explained in terms of a π–π^* interaction between a naphthyl nucleus and the electron-poor aldehydic carbonyl.

In agreement with this general model, one only TADDOL derivative molecule is involved in the corresponding transition state, consequently no evidence of nonlinear effects should have been detected by performing a set of experiments in the presence of variously enantioenriched organocatalysts. However, taking in mind that the above model was proposed for reactions taking place

Table 4
Vinylogous aldol reaction of Chan's diene **1** on 2-nitrobenzaldehyde **2e** promoted by organocatalysts

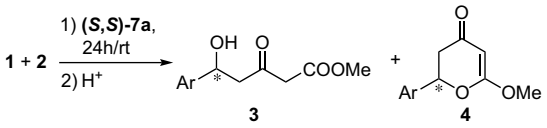
Entry	Catalyst (mol %)	Reaction time (h)	**3e** Yield[a] (%)	**3e** ee[b] (%)	**4e** Yield[a] (%)	**4e** ee[b] (%)
1	—	24	50	—	37	—
2	(*R*)-BINOL (10%)	24	53	2	35	3
3	(*R*)-VANOL (5%)	24	47	4	3	0
4	(*R*)-VAPOL (5%)	24	42	4	26	1
5	(*S*,*S*)-**7a**	4.5	37	19	32	57
6	(*S*,*S*)-**7a**	24	30	21	64	53
7[c]	(*S*,*S*)-**7a**	72	32	46	30	60

[a] In all entries 1:1.3:0.1 aldehyde/**1**/catalyst ratios were used under solvent-free conditions. All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, IR).
[b] Determined by chiral-phase HPLC analysis (CHIRALPAK AD and CHIRALCEL OD).
[c] The experiment was performed at −20 °C in toluene (0.1 ml).

Table 5
Asymmetric vinylogous aldol reaction of Chan's diene **1** to non-activated aldehydes RCHO **2** promoted by **7a**

Entry	R	Product	**3** Yield[a] (%)	**3** ee[b] (%)
1	Ph	**3a**	42	61
2	*p*-Tol	**3f**	39	57
3	2-Furyl	**3g**	40	37
4	*p*-$MeOC_6H_4$	**3b**	18	11
5	*o*-$MeOC_6H_4$	**3h**	57	40
6	*n*-C_9H_{19}	**3i**	—	—

[a] In all entries 1:1.3:0.1 aldehyde/**1**/**7a** ratios were used under solvent-free conditions. All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, IR).
[b] ees were determined by HPLC with a CHIRALPAK AD column. Absolute configuration of compounds **3a**,[3a] **3f**,[12] **3g**[12] and **3b**[3a] was assigned as (*R*) by comparison of the sign of the optical rotation with the one reported in the literature.



Scheme 8.

Table 6
Asymmetric vinylogous aldol reaction of Chan's diene **1** with electron-poor aromatic aldehydes RCHO **2** promoted by **7a**

Entry	Ar	Product **3**	Yield[a] (%)	ee[b] (%)	Product **4**	Yield[a] (%)	ee[b] (%)
1	*p*-$NO_2C_6H_4$	**3c**	39	54	**4c**	32	57
2	*o*-$NO_2C_6H_4$	**3e**	30	21	**4e**	64	53
3[c]	*o*-$NO_2C_6H_4$	**3e**	32	46	**4e**	30	60
4	*p*-$CF_3C_6H_4$	**3d**	52	31	**4d**	38	51
5	*o*-CNC_6H_4	**3j**	46	56	**4j**	39	59
6	*p*-CNC_6H_4	**3k**	35	29	**4k**	26	49
7	5-NO_2-2-Furyl	**3l**	38	ND	**4l**	30	28

[a] In all entries 1:1.3:0.1 aldehyde/**1**/**7a** ratios were used under solvent-free conditions. All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by spectroscopic data (^{1}H NMR, ^{13}C NMR, MS and IR).
[b] Determined by chiral-phase HPLC analysis.
[c] Reaction conditions: 72 h/−20 °C and 0.1 ml of toluene.

in toluene solution, the possibility of different catalytic systems, active under solvent-free conditions, was examined. Therefore, 2-nitro-benzaldehyde was chosen as representative substrate and submitted to the usual treatment with Chan's diene in the presence of enantioenriched (*S*,*S*)-**7a**. The results are reported in Figures 3 and 4 and both for the vinylogous aldol condensation and hetero-Diels–Alder reaction deviations from linearity have been observed, allowing, therefore, to exclude the involvement of the Rawal's model. In our opinion, solvent-free conditions should have favoured the formation of aggregate catalytic species and, consequently, led to the attainment of complex curves from the experiments performed in the presence of enantioenriched organocatalysts. It has to be noted that three-shaped curves, as the ones reported in Figures 3 and 4, have been rationalized on the ground of a ML_4 model.[14,15]

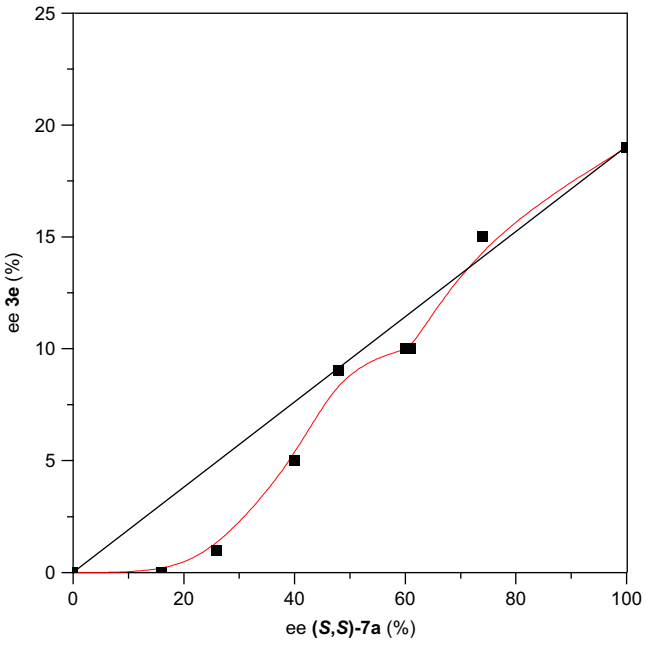


Figure 3.

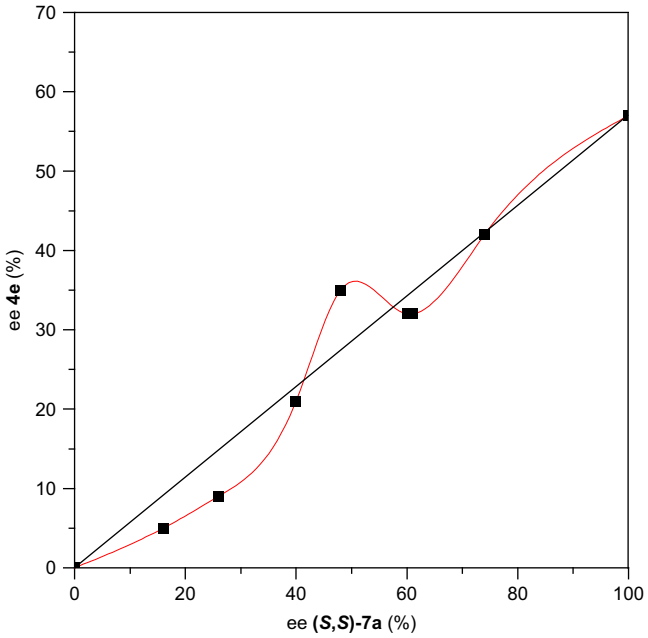


Figure 4.

3. Conclusions

In conclusion, Chan's diene has confirmed its synthetic versatility, being employable in vinylogous aldol reactions proceeding with complete γ-selectivity. In spite of a strongly competing background reaction, acceptable levels of enantioselectivity have been observed by using a chiral naphthyl-TADDOL derivative (up to 65% ee). Furthermore, in the case of electron-poor aldehydes, Chan's diene exhibited an additional unprecedented reactivity affording chiral pyran-4-ones (ees up to 60%) through a hetero-Diels–Alder cycloaddition. Finally, the detection of nonlinear effects suggested the involvement in the transition states of both the processes of naphthyl-TADDOL aggregates, as effective catalytic species.

4. Experimental

4.1. General

All reactions were performed in oven-dried (140 °C) vials. Thin-layer chromatography was performed on Merck Kiesegel 60 F_{254} plates eluting with the solvents indicated, visualized by a 254 nm UV lamp and aqueous ceric sulfate solution. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). All reagents (Aldrich, Fluka and Strem) were used without further purification. Infrared spectra were recorded on a Bruker 22 series FT-IR spectrometer. NMR spectra were recorded on a Bruker DRX 400 (400.135 MHz for ^{1}H and 100.03 MHz for ^{13}C) spectrometer. Chemical shifts are given in parts per million (δ) scale and they were referenced to residual chloroform (δ 7.26 ^{1}H, δ 77.0 ^{13}C). Coupling constants (J) are reported in hertz. HPLC analysis was performed with Waters Associates equipment (Waters 2487 Dual λ absorbance Detector) using a CHIRALPAK AD or a CHIRALCEL OD column with mixtures and flow rates as indicated. Mass spectrometry analysis was carried out using an electrospray spectrometer Waters 4 micro quadrupole.

4.2. General procedure (Table 6)

In a dry vial (*S*,*S*)-**7a** (0.05 mmol), aldehyde (0.5 mmol) and diene **1** (0.65 mmol) were added. The resulting mixture was stirred

for 24 h at room temperature, and then dry THF (2 ml) was added. This solution was cooled at −78 °C and TFA (0.2 ml) was added dropwise, then it was permitted to warm to room temperature and after completion of the desilylation reaction, it was neutralized by addition of saturated aq $NaHCO_3$. The reaction mixture was extracted with AcOEt and the combined organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by non-flash chromatography (petroleum ether/AcOEt from 8:2 to 1:1) to give the products **3** and **4**.

The same procedure was used for the other chiral hydrogen bonding donors (Tables 3 and 4) and for non-asymmetric vinylogous reactions by omitting the employment of the chiral donor (Table 2).

The spectroscopic (IR, ^{1}H NMR and ^{13}C NMR) data of aldols **3a**,[3a] **3b**,[3a] **3c**,[12] **3d**,[17] **3f**,[12] **3g**,[12] **3h**[16] and **3k**[17] matched the ones reported in the literature.

4.3. Spectral data of new compounds

All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. Spectral data of selected compounds: (**3f**):[12] enantiomeric excess was determined by HPLC (Chiralpak AD), hexane/EtOH 95:5+0.1% TFA, 1 ml/min major enantiomer (*R*) t_R=23.3, minor enantiomer (*S*) t_R=30.3; (**3g**):[12] enantiomeric excess was determined by HPLC (Chiralpak AD), hexane/EtOH 95:5+0.1% TFA, 1 ml/min, major enantiomer (*R*) t_R=29.4, minor enantiomer (*S*) t_R=42.3; (**3h**):[16] enantiomeric excess was determined by HPLC (Chiralpak AD), hexane/EtOH 95:5+0.1% TFA, 1 ml/min minor enantiomer t_R=21.2, major enantiomer t_R=23.5; (**3c**):[12] enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 90:10, 0.8 ml/min, minor enantiomer (*S*) t_R=48.0, major enantiomer (*R*) t_R=53.0; (**4c**): yellow oil, *m*/*z*: 250 $[M+H]^+$, 272 $[M+Na]^+$; IR (KBr, neat) 2922, 1656, 1583, 1521, 1450, 1394, 1231; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (2H, d, *J*=8.6 Hz), 7.59 (2H, d, *J*=8.6 Hz), 5.61 (1H, dd, *J*=12.9, 3.9 Hz), 4.98 (1H, s), 3.86 (3H, s), 2.77 (1H, dd, *J*=16.8, 12.9 Hz), 2.68 (1H, dd, *J*=16.8, 3.9 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 190.6, 173.7, 148.0, 144.1, 126.6, 124.1, 82.8, 79.7, 56.2, 42.0; enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 90:10, 0.8 ml/min, minor enantiomer t_R=84.9, major enantiomer t_R=113.6; (**3e**): yellow oil, *m*/*z*: 290 $[M+Na]^+$; IR (KBr, neat) 3507, 2957, 1745, 1716, 1526, 1345–1077; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (1H, d, *J*=8.2 Hz), 7.89 (1H, d, *J*=7.8 Hz), 7.67 (1H, m), 7.44 (1H, m), 5.70 (1H, dd, *J*=9.2, 1.9 Hz), 3.75 (3H, s), 3.55 (2H, s), 3.22 (1H, dd, *J*=17.7, 1.9 Hz), 2.87 (1H, dd, *J*=17.7, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 202.4, 167.1, 147.0, 138.0, 133.8, 128.4, 128.1, 124.4, 65.4, 52.5, 50.7, 49.2; enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 90:10, 0.8 ml/min, minor enantiomer t_R=28.0, major enantiomer t_R=31.4; (**4e**): yellow oil, *m*/*z*: 250 $[M+H]^+$; IR (KBr, neat) 2923, 2853, 1659, 1590, 1527, 1449, 1395–1054; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (1H, d, *J*=8.2 Hz), 7.84 (1H, d, *J*=7.6 Hz), 7.74 (1H, m), 7.56 (1H, m), 6.15 (1H, dd, *J*=13.4, 3.3 Hz), 4.99 (1H, s), 3.83 (3H, s), 2.94 (1H, dd, *J*=16.8, 3.3 Hz), 2.71 (1H, dd, *J*=16.8, 13.4 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 190.9, 173.7, 147.3, 134.7, 134.0, 129.6, 127.9, 124.9, 83.0, 65.4, 56.1, 41.7; enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 90:10, 0.8 ml/min, minor enantiomer t_R=40.4, major enantiomer t_R=44.0; (**3d**):[17] enantiomeric excess was determined by HPLC (Chiralpak AD), hexane/EtOH 95:5+0.1% TFA, 1 ml/min, major enantiomer t_R=15.9, minor enantiomer t_R=17.5; (**4d**): yellow oil, *m*/*z*: 273 $[M+H]^+$; IR (KBr, neat) 2922, 2852, 1653, 1580, 1452, 1326, 1253–1124; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (2H, d, *J*=8.0 Hz), 7.53 (2H, d, *J*=8.0 Hz), 5.56 (1H, dd, *J*=13.4, 3.5 Hz), 4.97 (1H, s), 3.84 (3H, s), 2.79 (1H, dd, *J*=16.7, 13.4 Hz), 2.65 (1H, dd, *J*=16.7, 3.5 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 191.1, 173.8, 145.0, 141.1, 126.2, 125.8, 108.2, 82.8, 80.3, 56.0, 42.0; enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 90:10, 0.8 ml/min, minor enantiomer t_R=22.8, major enantiomer t_R=28.0; (**3j**): yellow oil, *m*/*z*: 248 $[M+H]^+$, 270 $[M+Na]^+$; IR (KBr, neat) 3465, 2955, 2226, 1745, 1716, 1325–1065; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (3H, m), 7.38 (1H, m), 5.52 (1H, dd, *J*=9.5, 2.4 Hz), 3.74 (3H, s), 3.54 (2H, s), 3.08 (1H, dd, *J*=17.7, 2.4 Hz), 2.94 (1H, dd, *J*=17.7, 9.5 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 202.2, 167.0, 145.8, 133.2, 132.8, 128.0, 126.6, 117.1, 109.6, 67.6, 52.5, 50.2, 49.3; enantiomeric excess was determined by HPLC (Chiralpak AD), hexane/^{i}PrOH 80:20, 0.8 ml/min, major enantiomer t_R=11.6, minor enantiomer t_R=14.3; (**4j**): yellow oil, *m*/*z*: 230 $[M+H]^+$, 252 $[M+Na]^+$; IR (KBr, neat) 2923, 2853, 2226, 1658, 1586, 1449, 1254; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (3H, m), 7.51 (1H, m), 5.83 (1H, dd, *J*=13.6, 3.6 Hz), 5.00 (1H, s), 3.85 (3H, s), 2.84 (1H, dd, *J*=16.7, 13.6 Hz), 2.70 (1H, dd, *J*=16.7, 3.6 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 190.5, 173.6, 140.4, 133.4, 129.5, 126.9, 116.5, 110.9, 83.0, 78.8, 56.1, 41.1; enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 95:5, 0.8 ml/min, minor enantiomer t_R=97.0, major enantiomer t_R=101.5; (**3k**):[17] enantiomeric excess was determined by HPLC (Chiralpak AD), hexane/EtOH 95:5+0.1% TFA, 0.5 ml/min, major enantiomer t_R=132.3, minor enantiomer t_R=140.6; (**4k**): yellow oil, *m*/*z*: 230 $[M+H]^+$; IR (KBr, neat) 2923, 2229, 1653, 1586, 1450, 1273–1181; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (2H, d, *J*=8.2 Hz), 7.53 (2H, d, *J*=8.2 Hz), 5.56 (1H, dd, *J*=13.0, 3.9 Hz), 4.97 (1H, s), 3.85 (3H, s), 2.76 (1H, dd, *J*=16.7, 13.0 Hz), 2.66 (1H, dd, *J*=16.7, 3.9 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 190.7, 173.7, 142.3, 132.7, 126.5, 118.1, 112.8, 82.8, 79.9, 56.1, 41.9; enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 90:10, 0.8 ml/min, minor enantiomer t_R=73.8, major enantiomer t_R=83.0; (**3l**): yellow oil, *m*/*z*: 280 $[M+Na]^+$; IR (KBr, neat) 3467, 2956, 2923, 1744, 1716, 1529, 1499, 1357, 1240–1021; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (1H, d, *J*=3.7 Hz), 6.58 (1H, d, *J*=3.7 Hz), 5.25 (1H, m), 3.75 (3H, s), 3.55 (2H, s), 3.18 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 202.2, 167.6, 157.2, 113.1, 110.4, 64.4, 53.3, 49.9, 47.9; (**4l**): yellow oil, *m*/*z*: 240 $[M+H]^+$; IR (KBr, neat) 2924, 2853, 1656, 1586, 1505, 1449, 1393, 1234; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (1H, d, *J*=3.6 Hz), 6.70 (1H, d, *J*=3.6 Hz), 5.61 (1H, dd, *J*=11.5, 4.2 Hz), 4.95 (1H, s), 3.83 (3H, s), 2.99 (1H, dd, *J*=16.8, 11.5 Hz), 2.78 (1H, dd, *J*=16.8, 4.2 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 190.1, 173.5, 152.6, 113.0, 112.2, 83.7, 73.5, 57.0, 38.4; enantiomeric excess was determined by HPLC (Chiralcel OD), hexane/^{i}PrOH 90:10, 0.8 ml/min, minor enantiomer t_R=89.5, major enantiomer t_R=99.1.

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