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Enantioselective synthesis of functionalized 3,4-dihydropyran derivatives organocatalyzed by a novel fluorinated-diphenylprolinolether

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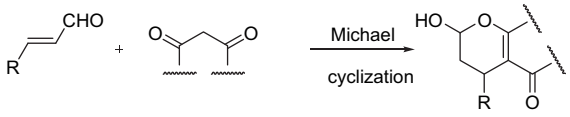
ABSTRACT

A novel fluorinated diarylprolinol silyl ether catalyst have been designed and it successfully applicated in the first asymmetric Michael addition–cyclization reaction between 1,3-dicarbonyl compounds with α,β-unsaturated aldehydes at room temperature. The products were isolated in good yields with high diastereoselectivities and enantioselectivities.

1. Introduction

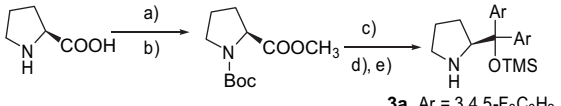
In recent years, the development of asymmetric reactions using small organic molecules as catalysts has grown rapidly and it has become the eminent strategy in contemporary organic synthesis.[1] Particularly, among the various organocatalysts reported recently, the incredibly high efficient diarylprolinols derivatives serve as a reliable and powerful synthetic tool for organocatalytic asymmetric reactions.[2] Moreover, Moorthy et al. successfully applied perfluorophenylamide catalyst to enantioselective Aldol reaction with a broad substrate scope compared to other aryl catalysts.[3] The perfluorophenylamide catalyst can indeed work efficiently with only a marginal sacrifice of the enantioselectivity and diastereoselectivity in various nonpolar and polar solvents. These general and readily available catalysts represent an important starting point for the investigation of new asymmetric processes, due to they often avoid the need for multiple screening processes of catalysts to determine the asymmetric reaction conditions. In recent years, more attention has been paid to optimization of the structure of the chiral catalyst so as to achieve good to excellent selectivity and catalytic activity.[4] Hydrogen bonding plays a vital role in organocatalytic asymmetric reactions. It was found that fluorine engaged in C–H···F hydrogen bonding easily. It prompted us to envision that it might be possible to develop a novel fluorinated diarylprolinol ether and apply them in the first asymmetric Michael addition–cyclization reaction between 1,3-dicarbonyl compounds and α,β-unsaturated aldehydes giving the corresponding 3,4-dihydropyran derivatives.

Pyran derivatives are polyfunctionalized structures that commonly appear in numerous natural products and biologically active compounds.[5] Based on their biological and structural properties, synthetic



Scheme 1. Organocatalytic synthesis of 3,4-dihydropyrans.

methods that yield 3,4-dihydropyrans derivatives have thus received much research interest. The common way to access 3,4-dihydropyrans is, by inverse electron-demand HDA reactions of unsaturated carbonyl compounds with electron- rich alkenes[6] and others methods.[7] However, to the best of our knowledge, few studies have been reported about enantioselective synthesis of 3,4-dihydropyran. Recently,



1 2

3a, Ar = 3,4,5-$F_3C_6H_2$
3c, Ar = 3-FC_6H_4

Scheme 2. The synthesis of the novel fluorinated diarylprolinol ethers. Condition: a) $SOCl_2$, CH_3OH; b) Boc_2O, Et_3N; c) ArMgBr, 2-MeTHF, 5 h, rt, yield: 70.2%; d) HCl/AcOEt, 2 h, rt; e) TMSCl, Et_3N, CH_2Cl_2, 2 h, rt.

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Jøgensen[8] and Gong[9] revealed that the silyl-protected diarylprolinol ethers catalyzed chemoselective and enantioselective synthesis of pyran derivatives (Scheme 1). We herein reported facile synthesis of novel fluorinated diarylprolinol ether and its application in the initial Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes followed by a subsequent cyclization reaction.

2. Results and discussion

2.1. Preparation of fluorinated diarylprolinol ethers

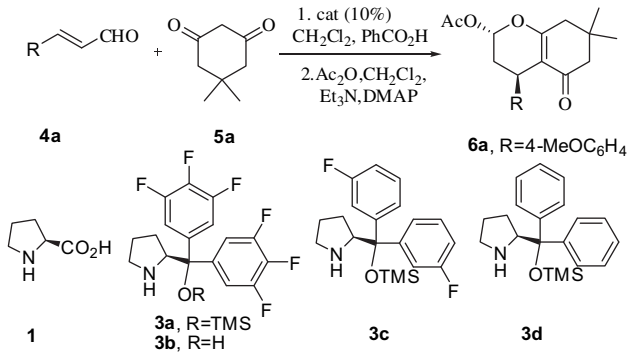
As our primary goal, we designed a broad set of novel fluorinated diarylprolinol ether from L-proline (Scheme 2).

2.2. Enantioselective Michael addition–cyclization reaction

As a model reaction, the reaction of α,β-unsaturated aldehyde **4a** with 1,3-dicarbonyl compound **5a** was investigated in the presence of various chiral secondary amines catalysts, using $PhCO_2H$ as additive in solvent CH_2Cl_2, followed by acetylation to give the 3,4-dihydropyran derivative **6a** as shown in Table 1. To our delight, the results showed that altering the number of fluorine atoms of catalysts plays a critical role in achieving good yields and high level of stereoselectivities. The novel fluorinated diarylprolinol silyl ether catalyst **3a** afforded the 3,4-dihydropyran **6a** in high yield with good enantioselectivity and diastereoselectivity (Table 1, entry 2).

The Michael addition–cyclization reaction can be carried out in various nonpolar and polar solvents (Table 2, entries 1–6), such as CH_2Cl_2, Et_2O, H_2O, DMF, CH_3OH and toluene. Among them, CH_2Cl_2 was the best one. In addition, the primary investigation showed that benzoic acid as additive could give good yield and enantioselectivity up to 84% (Table 2, entry 6). More experiments showed that suitable acid additives were necessary to obtain excellent yield and enantioselectivity.[10] For example, low enantioselectivity was observed when using strongly acid TFA, while slightly weak acid NH_4Cl also induced low yield and enantioselectivity (Table 2, entries 7, 8). Moreover, the influence of some substituted benzoic acids produced on the reaction was also investigated (Table 2, entries 9, 10).

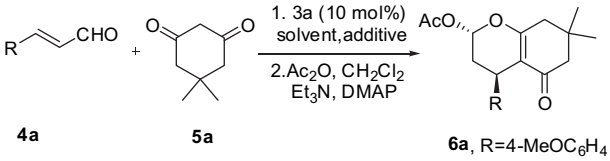
Table 1
Catalyst screening for the reaction of **4a** and **5a**[a]



Entry	Cat	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1**	<5	nd	nd
2	**3a**	89	>25:1	84
3	**3b**	52	nd	15
4	**3c**	75	15:1	67
5	**3d**	85	10:1	35

[a] Reactions conditions: The mixture of **4a** (1.1 mmol), **5a** (1 mmol), 10 mol % catalyst, 10 mol % benzoic acid, 1 mL of CH_2Cl_2 was stirred for 12 h then the acetylation was performed.
[b] Isolated yield based on **5a**.
[c] Diastereomeric ratio was determined by ^1H NMR spectroscopy or HPLC.
[d] Determined by chiralstationary phase HPLC.

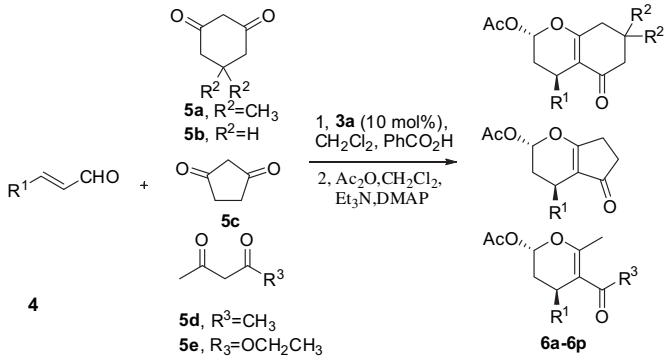
Table 2
Solvent and additive screening for the reaction of **4a** and **5a**[a]



Entry	Solvent	Additive	T °C	Yield[b] (%)	dr[c]	ee[d] (%)
1	H_2O	$PhCO_2H$	RT	50	>25:1	65
2	DMF	$PhCO_2H$	RT	40	>25:1	73
3	Et_2O	$PhCO_2H$	RT	62	10:1	76
4	CH_3OH	$PhCO_2H$	RT	65	15:1	75
5	Toluene	$PhCO_2H$	RT	52	17:1	77
6	CH_2Cl_2	$PhCO_2H$	RT	89	>25:1	84
7	CH_2Cl_2	NH_4Cl	RT	75	20:1	60
8	CH_2Cl_2	CF_3COOH	RT	63	>25:1	59
9	CH_2Cl_2	4-$MeOC_6H_4CO_2H$	RT	80	12:1	67
10	CH_2Cl_2	2,3,4,5-F_4 $C_6H_4CO_2H$	RT	74	>25:1	80
11[e]	CH_2Cl_2	$PhCO_2H$	0	71	>25:1	81
12[f]	CH_2Cl_2	$PhCO_2H$	-50	40	>25:1	83

[a] Reactions conditions: The mixture of **4a** (1.1 mmol), **5a** (1 mmol), 10 mol % **3a** catalyst, 10 mol % additive, 1 mL of solvent was stirred for 12 h, then the acetylation was performed.
[b] Isolated yield based on **5a**.
[c] Diastereomeric ratio was determined by ^1H NMR spectroscopy or HPLC.
[d] Determined by chiralstationary phase HPLC.
[e] Reaction time prolonged to 18 h.
[f] Reaction time prolonged to 36 h.

Table 3
Reaction of α,β-unsaturated aldehydes **4** with 1,3-dicarbonyl compounds **5** catalyzed by **3a**[a]



Entry	R^1	1,3-Dicarbonyl compounds	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	4-$CH_3OC_6H_4$	**5a**	**6a**	89	>25:1	84
2	4-$CH_3C_6H_4$	**5a**	**6b**	74	>25:1	90
3	4-FC_6H_4	**5a**	**6c**	83	>25:1	84
4	4-ClC_6H_4	**5a**	**6d**	76	>25:1	86
5	C_6H_5	**5a**	**6e**	83	11:1	83
6	3-$CH_3C_6H_4$	**5a**	**6f**	73	15:1	90
7	3-ClC_6H_4	**5a**	**6g**	84	>25:1	86
8[e]	2-$CF_3C_6H_4$	**5a**	**6h**	40	>25:1	83
9[e]	2-$CH_3OC_6H_4$	**5a**	**6i**	45	>25:1	90
10	CH_3	**5a**	**6j**	92	8:1	91
11	$CH_2CH_2CH_3$	**5a**	**6k**	94	>25:1	87
12	2-furyl	**5a**	**6l**	80	>25:1	81
13	4-$CH_3OC_6H_4$	**5b**	**6m**	82	>25:1	84
14	4-$CH_3OC_6H_4$	**5c**	**6n**	72	5:1	88
15	4-$CH_3OC_6H_4$	**5d**	**6o**	50	8:1	20
16	4-$CH_3OC_6H_4$	**5e**	**6p**	70	6:1	87

[a] Reactions conditions: The mixture of **4** (1.1 mmol), **5** (1 mmol), 10 mol % **3a** catalyst, 10 mol % benzoic acid, 1 mL of CH_2Cl_2, was stirred at room temperature for 12 h, then the acetylation was performed.
[b] Isolated yield based on **5**.
[c] Diastereomeric ratio determined by ^1H NMR spectroscopy.
[d] Determined by chiralstationary phase HPLC.
[e] 3 equiv α,β-unsaturated aldehydes were used.

However, the reaction was performed at lower temperature (0 or −50 °C) led to some loss of catalytic efficiency, but without any increase in the ee value (Table 2, entries 11, 12). The fluorinated diarylprolinol derivatives could indeed work efficiently at room temperature.

With the optimized reaction conditions, we embarked on a systematic evaluation of the catalytic system in variety of substituted α,β-unsaturated aldehydes and 1,3-dicarbonyl compounds (Table 3). In most cases, aromatic α,β-unsaturated aldehydes afforded good yields and enantioselectivities (Table 3, entries 1–7, 83–90% ee). In the case of *ortho*-substituted aromatic α,β-unsaturated aldehydes lower yields were observed due to 1,2-addition side reaction (Table 3, entries 8, 9). This process was then extended to alkyl and heterocyclic α,β-unsaturated aldehydes. Performing the reaction with alkyl α,β-unsaturated aldehydes increased to 94% yield with good diastereoselectivities and enantioselectivities (Table 3, entries 10, 11). Heteroaromatic substituent also gave satisfactory result (Table 3, entry 12). To explore further the potential of this Michael addition–cyclization reaction other 1,3-dicarbonyl compounds were tested. The acyclic ethyl 3-oxobutanoate **5e** could give good enantioselectivity up to 87% ee (Table 3, entry 16). But entane-2,4-dione **5d** gave enantioselectivity only 20% ee (entry 15), the reversibility of the Michael addition reaction performed with entane-2,4-dione might explain the low enantioselectivity.[11]

Encouraged by the good results of fluorinated substituted diarylprolinol silyl ether catalyst **3a**, we attempted to design perfluoro-diarylprolinol catalyst, but we just obtained the unexpected product **3e** without catalytic activity (Fig. 1).

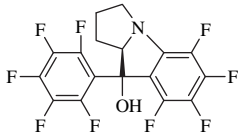
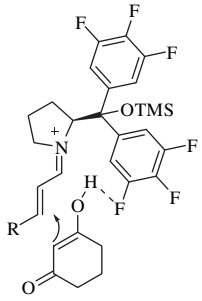


Figure 1. Compound **3e**.

The proposed mechanism for the silyl-protected diarylprolinols catalyzed the reaction course was summarized by Jøgensen et al.[8] The fluorinated catalyst **3a** possibly is attributed to the enhanced catalytic activity and stronger binding of the substrate via hydrogen bonding in the transition state (Scheme 3).



Scheme 3. Possible catalytic transition state for the present catalytic system.

3. Conclusion

In summary, we have developed a novel fluorinated diarylprolinol silyl ether catalyst and applied it to promote the enantioselective synthesis of 3,4-dihydropyran derivatives via Michael addition–cyclization reaction of 1,3-dicarbonyl compounds with α,β-unsaturated aldehydes at mild reaction conditions. The attractive features of this process were the practicability and the mild reaction conditions, which provide a series of 3,4-dihydropyran derivatives in good yields with high enantioselectivities and diastereoselectivities.

4. Experimental

4.1. General details

Analytical grade solvents and commercially available reagents were used without further purification. The flash column chromatography was carried out over silica gel (200–400mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured on a Perkin Elmer Model 341 digital polarimeter, Melting points were determined on a Büchi B-540 capillary melting point apparatus. IR spectra was recorded on an AVATAR-370, samples were prepared as KBr plates. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. ^{1}H NMR and ^{13}C NMR spectra were recorded at VARAIN–400 or BRUKER AVANCE III–500 using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants J are given in Hertz. The low-resolution mass spectra were obtained with the Thermo Trace GC Ultra-DSQ II and Agilent 6120 (Quadrapole LC–MS) mass spectrometer. High resolution mass spectral (HRMS) analyze were measured on an Agilent 6210 TOF LC/MS using ESI or EI (electrospray ionization) techniques. Enantiomeric excesses of products were determined by HPLC using a Daicel Chiralcel AS-H or OD-H column and eluting with *n*-hexane/*i*-PrOH.

4.2. Typical procedure for the catalyzed synthesis of 3,4-dihydropyran derivatives

A mixture of catalyst **3a** (0.1 mmol, 10 mol %), $PhCO_2H$ (0.1 mmol, 10 mol %) and α,β-unsaturated aldehyde **4** (1.1 mmol) in 2 mL CH_2Cl_2 was stirred for 5 min at room temperature. Then the 1,3-dicarbonyl compounds **5** (1 mmol) were added. The reaction mixture was stirred at room temperature for the given time (monitored by TLC). To the reaction mixture was added CH_2Cl_2 (2 mL), Ac_2O (3 mmol), Et_3N (0.2 mL) and DMAP (0.1 mmol, 10 mol %) and stirred at ambient temperature for about 2 h. The reaction mixture was quenched with H_2O (20 mL), extracted with CH_2Cl_2 (3×10 mL), dried over Na_2SO_4, the solvent was evaporated under vacuum, and the residue was purified by flash column chromatography over silica gel (AcOEt/petroleum ether 2:1–8:1) to provide products **6a–k**.

4.3. Experimental data of compound

*4.3.1. (S)-2-[Bis-(3,4,5-trifluoro-phenyl)-trimethylsilanyloxymethyl]-pyrrolidine (**3a**).* Viscous oil; IR (KBr): 2959, 1525, 1339 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.21–7.14 (m, 2H), 7.00–6.94 (m, 2H), 3.93 (t, J=6.8 Hz, 1H), 2.97–2.91 (m, 1H), 2.83–2.77 (m, 1H), 1.67 (s, 1H), 1.63–1.55 (m, 2H), 1.53–1.39 (m, 2H), 0.01(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.9 (dd, J_1=6.8 Hz, J_2=22.7 Hz, 2C), 149.4 (dd, J_1=6.1 Hz, J_2=19.0 Hz, 2C), 142.6 (d, J=4.6 Hz), 141.1 (d, J=4.6 Hz), 140.1 (d, J=14.4 Hz), 137.5 (d, J=14.4 Hz), 112.6–111.5 (m, 4C), 81.5, 64.8, 47.2, 27.4, 24.9, 2.2 (d, J=29.6, 3C); MS (ESI): m/z (%)=434 (100) [M^++1]; HRMS (ESI) Calculated for $C_{20}H_{21}F_6NOSi$ (M^+), 433.1297; found: 433.1298; $[\alpha]_D^{20}$=−28.2 (c 0.75, $CHCl_3$).

*4.3.2. (S)-2-[Bis-(3-fluoro-phenyl)-trimethylsilanyloxymethyl]-pyrrolidine (**3c**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31–7.23(m, 4H), 7.18–7.11 (m, 2H), 6.98–6.95 (m, 2H), 4.04 (t, J=7.6 Hz, 1H), 2.95–2.84 (m, 2H), 1.68 (br s, 1H); 1.65–1.43 (m, 4H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.7 (d, J=8.3 Hz), 161.2 (d, J=7.6 Hz), 149.2 (d, J=6.1 Hz), 148.1 (d, J=6.0 Hz), 129.8–128.9 (m, 2C), 123.3 (d, J=84.2 Hz, 1C), 121.0 (t, J=4.4 Hz, 1C), 115.5–112.4 (m,

4C), 82.4, 65.1, 46.9 (d, J=27.3 Hz), 27.5, 25.4; 2.22 (dd, J_1=29.6 Hz, J_2=19.0 Hz, 3C); MS (ESI): m/z (%)=362 (100) [M^++1], HRMS (ESI) Calculated for $C_{20}H_{25}F_2NOSi$ (M^+): 361.1673, found: 361.61673; $[\alpha]_D^{20}$=−66.1 (c 0.11, $CHCl_3$).

*4.3.3. (9S,9aS)-5,6,7,8-Tetrafluoro-9-(perfluorophenyl)-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indol-9-ol (**3e**).* Yellow solid; mp 98.9–100.2 °C; IR (KBr): 3416, 3161, 1492, 1304 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=4.31–4.26 (m, 1H), 3.70–3.65(m, 1H), 3.30–3.22 (m, 1H), 2.08–1.93 (m, 2H), 1.63–1.58 (m, 1H), 1.04–0.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=146.4–133.2 (m, CH×10), 115.2 (d, J=17.8 Hz), 114.7, 80.0, 77.3–76.7 (m, 1C), 51.8, 28.5, 26.7; ^{19}F NMR (372 MHz, $CDCl_3$): δ=−138.6 (d, J=13.8 Hz, 2F), −143.6 (dd, J_1=21.2 Hz, J_2=13.8 Hz, 1F), −154.7 to −155.0 (m, 1F), −154.7 to −154.8 (m, 1F), −155.0, −160.1 to −160.2(m, 2F), −168.8 to −169.0 (m, 1F); MS (EI): m/z (%)=413 (100) [M^+], MS (EI) Calculated for $C_{17}H_8F_9NO$ (M^+): 413.0462, found: 413.0466; $[\alpha]_D^{20}$=−152.6 (c 0.30, $CHCl_3$).

*4.3.4. (2R,4S)-4-(4-Methoxyphenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6a**).* Yellow solid; mp 131.1–133.5 °C; IR (KBr): 2957, 1759, 11 632, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.06 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 6.11 (dd, J_1=3.2 Hz, J_2=8.8 Hz, 1H), 4.02 (s, 1H), 3.76 (s, 3H), 2.47 (d, J=17.2 Hz, 1H), 2.37 (d, J=17.2 Hz, 1H), 2.29 (d, J=16.0 Hz, 1H), 2.22 (d, J=16.0 Hz, 1H), 2.13–2.11 (m, 1H), 2.11 (s, 3H), 2.10–2.04 (m, 1H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.7, 169.0, 167.7, 158.1, 135.4, 128.2, 114.0, 112.2, 89.9, 55.1, 50.7, 42.0, 34.4, 32.3, 32.0, 28.7, 28.1, 20.8; MS (ESI): m/z (%)=367 (100) [M+Na]$^+$, HRMS (ESI) Calculated for $C_{20}H_{24}O_5$(M+Na)$^+$: 367.1624, found: 367.1615; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; T_{major}=15.3 min, τ_{minor}=10.5 min, 84% *ee*; $[\alpha]_D^{25}$=+56.1, (c 2.4, CH_2Cl_2).

*4.3.5. (2R,4S)-7,7-Dimethyl-5-oxo-4-p-tolyl-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6b**).* Yellow solid; mp 129.4–129.9 °C; IR (KBr): 3128, 2958, 1748, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.09 (d, J=8.0 Hz, 2H), 7.03 (d, J=8.0 Hz, 2H), 6.12 (dd, J_1=2.8 Hz, J_2=8.8 Hz, 1H), 4.03 (s, 1H), 2.48 (d, J=17.6 Hz, 1H), 2.37 (d, J=17.6 Hz, 1H), 2.31–2.20 (m, 5H), 2.18–2.12 (m, 1H), 2.10 (s, 3H), 2.08–2.03 (m, 1H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.4, 169.1, 167.8, 140.5, 136.0, 129.3, 127.1, 112.3, 90.0, 50.8, 42.1, 34.4, 32.8, 32.1, 28.7, 28.2, 22.7, 20.9; MS (ESI): m/z (%)=329 (100) [M^++1], HRMS (ESI) Calculated for $C_{20}H_{24}O_4$ (M^+): 328.1675, found: 328.1670; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=10.6 min, τ_{minor}=7.6 min, 90% *ee*; $[\alpha]_D^{25}$=+122.3, (c 0.52, CH_2Cl_2).

*4.3.6. (2R,4S)-4-(4-Fluorophenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6c**).* Yellow solid; mp 98.7–100.2 °C; IR (KBr): 2964, 1759, 1626, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.11 (dd, J_1=5.2 Hz, J_2=8.4 Hz, 2H), 6.97 (t, J=8.4 Hz, 2H), 6.11(dd, J_1=2.8 Hz, J_2=8.8 Hz, 1H), 4.04 (s, 1H), 2.48 (d J=17.6 Hz, 1H), 2.37 (d, J=18.4 Hz, 1H), 2.38 (d, J=17.2 Hz, 1H), 2.29 (d, J=16.4 Hz, 1H), 2.23 (d, J=16.4 Hz, 1H), 2.20–2.12 (m, 1H), 2.12 (s, 3H), 2.07–2.02 (m, 1H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.4, 169.1, 168.04, 161.6 (d, J=243.4 Hz, 1C), 139.2, 128.7 (d, J=8.3 Hz, 2C), 115.5 (d, J=21.2 Hz, 2C), 112.1, 89.8, 50.8, 42.01, 34.4, 32.5, 32.1, 28.7, 28.2, 20.9; MS (ESI): m/z (%)=333 (100) [M^++1], HRMS (ESI) Calculated for $C_{19}H_{21}FO_4$ (M^+): 332.1424, found: 332.1440; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/iPrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=10.1 min, τ_{minor}=8.4 min, 84% ee; $[\alpha]_D^{25}$=+101.2, (c 0.51, CH_2Cl_2).

*4.3.7. (2R,4S)-4-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6d**).* Viscous oil; IR (KBr): 2965, 1769, 1628, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.25 (d, J=8.4 Hz, 2H), 7.08 (d, J=8.4 Hz, 2H), 6.11 (dd, J_1=2.4 Hz, J_2=8.4 Hz, 1H), 4.02 (br s, 1H), 2.47 (d, J=16.4 Hz, 1H), 2.33 (d, J=17.6 Hz, 1H), 2.28 (d, J=16.4 Hz, 1H), 2.22 (d, J=16.0 Hz, 1H), 2.15 (dd, J_1=6.0 Hz, J_2=8.4 Hz,1H), 2.11 (s, 3H), 2.07–2.02 (m, 1H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.3, 169.0, 168.1, 142.1, 132.3, 128.8, 128.6, 111.9, 89.7, 50.7, 42.0, 34.3, 32.6, 32.1, 28.7, 28.2, 20.9; MS (EI): m/z (%)=348 (10) [M^+], 306 (25), 288 (60), 277 (100), 253 (20); HRMS (EI) Calculated for $C_{19}H_{21}ClO_4$ (M^+): 348.1128, found: 348.1120; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=11.0 min, τ_{minor}=10.1 min, 84% *ee*; $[\alpha]_D^{25}$=+95.1, (c 0.7, CH_2Cl_2).

*4.3.8. (2R,4S)-7,7-Dimethyl-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6e**).* Yellow solid; mp 100.2–102.0 °C; IR (KBr): 2961, 1745, 1360, 700 cm^{-1}; major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ=7.30–7.26 (m, 2H), 7.20–7.13 (m, 3H), 6.12 (dd, J_1=3.2 Hz, J_2=9.2 Hz, 1H), 4.07 (s, 1H), 2.49 (d, J=17.6 Hz, 1H), 2.38 (d, J=17.2 Hz, 1H), 2.30 (d, J=16.0 Hz, 1H), 2.23 (d, J=16.4 Hz, 1H), 2.19–2.13 (m, 1H), 2.10 (s, 3H), 2.10–2.04 (m, 1H), 1.16 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.4, 169.1, 167.9, 143.4, 128.6, 127.2, 126.5, 112.0, 89.9, 50.7, 42.0, 34.3, 33.1, 32.1, 28.2, 28.1, 20.9; MS (ESI): m/z (%)=315 (100) [M^++1]; HRMS (ESI) Calculated for $C_{19}H_{22}O_4$ (M^+): 314.1518, found: 314.1530; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=11.9 min, τ_{minor}=8.0 min, 89% *ee*; $[\alpha]_D^{25}$=−3.1, (c 0.85, CH_2Cl_2).

*4.3.9. (2R,4S)-7,7-Dimethyl-5-oxo-4-m-tolyl-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6f**).* Yellow solid; mp 77.6–80.3 °C; IR (KBr): 2958, 1762, 1618, 765 cm^{-1}; major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$): δ=7.16 (t, J=7.6, 1H), 7.00–6.91 (m, 3H), 6.11 (dd, J_1=2.8 Hz, J_2=8.8 Hz, 1H), 4.03 (s, 1H), 2.43 (d, J=17.6 Hz, 1H), 2.37 (d, J=17.6 Hz, 1H), 2.30 (d, J=7.6 Hz, 1H), 2.31 (s, 3H), 2.29–2.25 (m, 1H), 2.21–2.14 (m, 1H), 2.13 (s, 3H), 2.12–2.05 (m, 1H), 1.16 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.5, 169.1, 168.0, 143.4, 138.2, 128.5, 128.1, 127.9, 124.2, 112.1, 89.9, 50.7, 42.0, 34.3, 33.1, 32.1, 28.7, 28.2, 21.5, 20.9; MS (ESI): m/z (%)=351 (100) [M+Na]$^+$; HRMS (ESI) Calculated for $C_{20}H_{24}O_4$ (M+Na)$^+$: 351.1675, found: 351.1670; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}= 8.0 min, τ_{minor}=15.8 min, 82% *ee*; $[\alpha]_D^{25}$=102.5, (c 0.48, CH_2Cl_2).

*4.3.10. (2R,4S)-4-(3-Chlorophenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6g**).* Yellow viscous oil; IR (KBr): 2960, 1748, 1624, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.24–7.16 (m, 2H), 7.12 (s, 1H), 7.02 (d, J=7.2 Hz, 1H), 6.10 (dd, J_1=2.8 Hz, J_2=8.4 Hz, 1H), 4.02 (t, J=5.2 Hz, 1H), 2.50 (d, J=17.2 Hz, 1H), 2.37 (d, J=18.0 Hz, 1H), 2.31 (d, J=10.4 Hz, 1H), 2.27 (d, J=13.6 Hz, 1H), 2.21–2.16 (m, 1H), 2.14 (s, 3H), 2.12–2.05 (m, 1H), 1.16 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.3, 169.0, 168.3, 145.7, 134.5, 129.9, 127.5, 126.8, 125.4, 111.6, 89.7, 50.7, 42.1, 34.3, 33.0, 32.1, 28.7, 28.2, 20.9; MS (EI): m/z (%)=348 (10) [M^+], 306 (25), 288 (70), 277 (100), 253 (30); HRMS (EI) Calculated for $C_{19}H_{21}ClO_4$ (M^+): 348.1128, found: 348.1120; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=12.9 min, τ_{minor}= 9.0 min, 86% *ee*; $[\alpha]_D^{25}$=+83.4, (c 1.36, CH_2Cl_2).

*4.3.11. (2R,4S)-7,7-Dimethyl-5-oxo-4-(2-(trifluoromethyl)phenyl)-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6h**).* Yellow viscous oil; IR (KBr): 2958, 1758, 1632, 1397, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.67 (d, J=7.6 Hz, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.17 (d, J=7.6 Hz, 1H), 6.27 (dd, J_1=2.8 Hz, J_2=7.2 Hz, 1H), 4.38 (t, J=6.0, 1H), 2.49 (d, J=17.6 Hz, 1H), 2.39 (d, J=17.6 Hz, 1H), 2.36–2.22 (m, 3H), 2.12 (s, 3H), 2.03–1.97 (m, 1H), 1.15 (s, 3H), 1.09 (s,

3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=195.9, 169.2, 168.1, 143.0, 131.9, 127.8, 126.5, 112.6, 89.4, 50.7, 42.1, 34.0, 32.0, 29.3, 28.4, 20.9; MS (ESI): *m*/*z* (%)=383 (100) [M^++1]; HRMS (ESI) Calculated for $C_{20}H_{21}F_3O_4$ (M^+): 382.1392, found: 382.1399, The *ee* was determined by HPLC analysis using a Chiralpak AS-H column [hexane/*i*PrOH (79:21)]; flow rate 1.0 mL/min; τ_{major}=6.3 min, τ_{minor}=7.4 min, 83% *ee*; $[\alpha]_D^{25}$=115.0 (*c* 0.16, CH_2Cl_2).

*4.3.12. (2R,4S)-4-(2-Methoxyphenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6i**).* Yellow solid; mp 89.7–92.0 °C; IR (KBr): 2958, 1762, 1618, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.19–7.15 (m, 1H), 6.89–6.82 (m, 3H), 6.03 (dd, J_1=3.2 Hz, J_2=9.6 Hz, 1H), 4.40 (s, 1H), 3.86 (s, 3H), 2.50 (d, *J*=17.6 Hz, 1H), 2.37 (d, *J*=17.6 Hz, 1H), 2.31 (d, *J*=16.0 Hz, 1H), 2.23 (d, *J*=16.0 Hz, 1H), 2.19–2.14 (m, 1H), 2.10 (s, 3H), 2.08–2.02 (m, 1H), 1.17 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.4, 169.2, 168.4, 156.0, 130.94, 127.8, 120.3, 111.7, 110.5, 90.6, 55.2, 50.8, 42.1, 32.1, 31.8, 29.0, 28.0, 27.5, 21.0; MS (ESI): *m*/*z* (%)=345 (100) [M^++1], HRMS (ESI) Calculated for $C_{20}H_{24}O_5$ (M^+): 344.1624, found: 344.1618; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=15.8 min, τ_{minor}=32.3 min, 83% *ee*; $[\alpha]_D^{25}$=58.2, (*c* 0.44, CH_2Cl_2).

*4.3.13. (2R,4R)-4,7,7-Trimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6j**).* Yellow solid; mp 55.9–57.9 °C; IR (KBr): 3133, 2959, 1759, 1629 cm^{-1}; major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.27 (dd, J_1=2.8 Hz, J_2=9.2 Hz, 1H), 2.90 (br s, 1H); 2.34–2.27 (m, 2H), 2.60–2.19 (m, 2H), 2.15 (s, 3H), 1.95–1.87 (m, 1H), 1.81 (dt, J_1=3.2, J_2=6.8, 1H), 1.16 (d, *J*=6.8 Hz, 3H), 1.07 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.4, 169.4, 166.3, 115.2, 90.0, 51.0, 41.9, 32.9, 32.0, 28.6, 27.8, 22.2, 21.0, 20.5; MS (ESI): *m*/*z* (%)=253 (100) [M^++1], HRMS (ESI) Calculated for $C_{14}H_{20}O_4$ (M^+): 252.1362, found: 252.1355; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=6.2 min, τ_{minor}=5.7 min, 92% *ee*; $[\alpha]_D^{25}$=63.5, (*c* 0.52, CH_2Cl_2).

*4.3.14. (2R,4R)-7,7-Dimethyl-5-oxo-4-propyl-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6k**).* Yellow viscous oil; IR (KBr): 3133, 2959, 1759, 1629 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.25 (dd, J_1=2.8 Hz, J_2=9.6 Hz, 1H), 2.77 (br s, 1H), 2.29–2.17 (m, 3H), 2.15 (s, 3H), 2.02–1.97 (m, 1H), 1.82–1.74 (m, 1H), 1.68–1.62 (m, 1H), 1.42–1.19 (m, 4H), 1.06 (s, 3H), 1.04 (s, 3H), 0.91 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.2, 169.4, 166.4, 114.6, 90.2, 51.0, 41.9, 32.0, 29.3, 28.5, 28.0, 27.0, 21.0, 20.0, 14.0; MS (ESI): *m*/*z* (%)=281 (100) [M^++1], HRMS (ESI) Calculated for $C_{16}H_{24}O_4$ (M^+): 280.1675, found: 280.1678; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=5.8 min, τ_{minor}=6.7 min, 87% *ee*; $[\alpha]_D^{25}$=74.6, (*c* 0.59, CH_2Cl_2).

*4.3.15. (2R,4R)-4-(Furan-2-yl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate (**6l**).* Yellow viscous oil; IR (KBr): 2958, 1758, 1632, 1397, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.28 (d, *J*=6.0 Hz, 1H), 6.25–6.22 (m, 2H), 5.97 (d, *J*=3.2 Hz, 1H), 4.16 (s, 1H), 2.43–2.29 (m, 4H), 2.14 (s, 3H), 2.04–1.97 (m, 2H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.3, 169.1, 168.0, 155.3, 141.4, 110.3, 106.3, 90.6, 50.7, 42.0, 32.2, 30.7, 28.6, 28.1, 27.3, 20.9; MS (EI): *m*/*z* (%)=304 (20) [M^+], 262 (35), 244 (100), 215(30), HRMS (EI) Calculated for $C_{17}H_{20}O_5$ (M^+): 304.1311, found: 304.1309; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/iPrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=8.6 min, τ_{minor}=7.7 min,81% *ee*; $[\alpha]_D^{25}$=81.9, (*c* 0.52, CH_2Cl_2).

*4.3.16. (2R,4S)-4-(4-Methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl acetate(**6m**).* Yellow viscous oil; IR (KBr): 2944, 1754, 1633, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.06 (d, *J*=8.8 Hz, 2H), 6.82 (d, *J*=8.0 Hz, 2H), 6.09 (dd, J_1=2.8 Hz, J_2=8.8 Hz, 1H), 4.03 (s, 1H), 3.76 (s, 3H), 2.62–2.48 (m, 2H), 2.41–2.33 (m, 2H), 2.17–2.11 (m, 1H), 2.16 (s, 3H), 2.08–2.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 169.6, 169.1, 158.3, 135.4, 128.2, 114.1, 113.6, 89.9, 55.2, 36.6, 34.4, 32.4, 28.4, 20.9, 20.8; MS (EI): *m*/*z* (%)=316 (40) [M^+], 274 (35), 256 (95), 245 (100), 231 (45), HRMS (EI) Calculated for $C_{18}H_{20}O_5$ (M^+): 316.1311, found: 316.1312; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=22.5 min, τ_{minor}=15.5 min, 84% *ee*; $[\alpha]_D^{25}$=70.8, (*c* 0.5, CH_2Cl_2).

*4.3.17. (2R,4S)-4-(4-Methoxyphenyl)-5-oxo-2,3,4,5,6,7-hexahydrocyclopenta[b]pyran-2-yl acetate (**6n**).* Yellow viscous oil; IR (KBr): 2925, 1754, 1637, 869 cm^{-1}; major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.07 (d, *J*=8.8 Hz, 2H), 6.84 (d, *J*=8.8 Hz, 2H), 6.37 (dd, J_1=2.4 Hz, J_2=6.4 Hz, 1H), 3.81 (br s, 1H), 3.78 (s, 3H), 2.70–2.65 (m, 2H), 2.51–2.47 (m, 2H), 2.22–2.17 (m, 1H), 2.15 (s, 3H), 2.05–1.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.1, 181.8, 168.9, 158.3, 132.8, 128.2, 116.9, 114.0, 91.3, 55.1, 34.5, 33.3, 31.1, 25.8, 20.8; MS (EI): *m*/*z* (%)=302 (20) [M^+], 242 (100), 231 (40), 216 (65); HRMS (EI) Calculated for $C_{17}H_{18}O_5$ (M^+): 302.1154, found: 302.1158; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (82:18)]; flow rate 1.0 mL/min; τ_{major}=32.7 min, τ_{minor}=30.1 min, 88% *ee*; $[\alpha]_D^{25}$=+40.4 (*c* 0.53, CH_2Cl_2).

*4.3.18. (2R,4S)-5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydro-2H-pyran-2-yl acetate (**6o**).* Yellow viscous oil; IR (KBr): 2932, 1758, 1677, 836 cm^{-1}; major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.14–7.09 (m, 2H), 6.86–6.81 (m, 2H), 6.04 (dd, J_1=2.8 Hz, J_2=7.6 Hz, 1H), 3.98 (t, *J*=5.2 Hz, 1H), 3.78 (s, 3H), 2.27 (s, 3H), 2.23–2.21 (m, 1H), 2.12 (s, 3H), 2.05–1.96 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=199.6, 169.3, 160.8, 158.5, 135.5, 128.5, 114.4, 90.3, 89.0, 55.3, 36.3, 34.8, 29.7, 21.1, 20.1; MS (ESI): *m*/*z* (%)=305 (100) [M^++1], HRMS (ESI) Calculated for $C_{17}H_{20}O_5$ (M^+): 304.1311, found: 304.1315; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major}=18.7 min, τ_{minor}=19.9 min, 20% *ee*; $[\alpha]_D^{25}$=−36.2, (*c* 0.26, CH_2Cl_2).

*4.3.19. (2R,4S)-Ethyl 2-acetoxy-4-(4-methoxyphenyl)-6-methyl-3,4-dihydro-2H-pyran-5-carboxylate (**6p**).* Yellow viscous oil, IR (KBr): 2932, 1758, 1708, 1249 cm^{-1}, major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.12–7.08 (m, 2H), 6.83 (m, 2H), 6.09 (dd, J_1=2.8 Hz, J_2=7.6 Hz, 1H), 4.00–3.92 (m, 3H), 3.78 (s, 3H), 2.31 (s, 3H), 2.27–2.13 (m, 1H), 2.11 (s, 3H), 2.01–1.99 (m, 1H), 0.97 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.3, 167.5, 161.2, 158.2, 136.5, 128.3, 113.9, 105.4, 89.3, 59.8, 55.2, 35.4, 34.5, 21.0, 19.5, 13.9; MS (EI): *m*/*z* (%)=334 (5) [M^+], 289 (10), 274 (100), 245(60), HRMS (EI) Calculated for $C_{18}H_{22}O_6$ (M^+): 334.1416, found: 334.1418; The *ee* was determined by HPLC analysis using a Chiralpak OD-H column [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major}=11.6 min, τ_{minor}=10.8 min, 88% *ee*; $[\alpha]_D^{25}$=119.0, (*c* 0.42, CH_2Cl_2).

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