Organocatalytic Domino Michael-Heterocyclization Reaction of α,β-Unsaturated Aldehydes and α–Cyano Ketones. Synthesis of Enantioenriched 4,5,6-Trisubstituted 3,4-Dihydropyranones.

James O. Guevara-Pulido,[a] José M. Andrés,[a] and Rafael Pedrosa*[a]

[a] Instituto CINQUIMA and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Paseo de Belén 7. 47011-Valladolid, Spain

pedrosa@qo.uva.es

Web: http://sintesisasimetrica.blogs.uva.es

Abstract.

α,β-Unsaturated aldehydes with aliphatic, electron-poor aromatic, and electron-withdrawing substituents at β-position easily react with different ketones leading to enantioenriched hemiacetals, which were further oxidized to 4,5,6-trisubstituted-3,4-dihydropyranones, in good yields and excellent enantioselectivities. The behavior of the ketones is dependent on the α-substituent of the carbonyl group, and a fine-tuning of the pKa values is necessary to obtain good results.

Key words: Domino reaction, Asymmetric synthesis, Cyclization, Michael Reaction, One-pot Reaction

Introduction

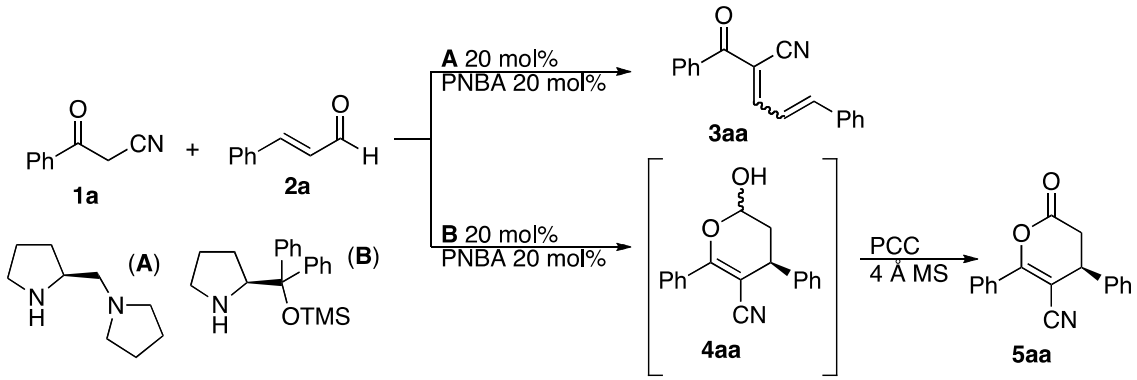
Organocatalytic enantioselective synthesis of pyran derivatives has recently received a lot of attention because of their biological interest, natural occurrence, and their value as intermediates in organic synthesis.[1] Two different approaches have been developed for the organocatalytic synthesis of this class of heterocycles: inverse-electron demand Diels-Alder reaction,[2] and domino Michael Addition heterocyclization processes.[3] A combination of activated ketones, such as β,γ-unsaturated-α-ketoesters[4] or α,β-unsaturated ketones with additional electron-withdrawing substituents at α-position[5] as acceptors and aldehydes or ketones as donors have been used in these transformations. In similar approaches, α,β-unsaturated enals as acceptors and highly acidic β-functionalized ketones[6] as donors, or functionalized nitroalkenes[7] or nitroalkanes,[8] and carbonyl compounds have also been employed in these reactions.

Given the interest of the enantioenriched polysubstituted 3,4-dihydropyranones, we envisaged that they could be obtained by oxidation of the corresponding hemiacetals, which could be easily prepared by organocatalyzed tandem Michael-heterocyclization process. To get this one-pot tandem reaction, the adducts formed in the initial Michael reaction must be able to form an enol, which promotes the hemiacetalization process. Then, we focused our attention on the use of α-functionalized ketones with electron withdrawing groups as nucleophiles because the addition product would also be successfully equilibrated with the enol under the reaction conditions.

Results and Discussion

On the basis of these antecedents, we decided to study the scope of the domino Michael addition-hemiacetalization of α,β-unsaturated aldehydes with different substitution patterns at the double bond (**2a-k**) with functionalized ketones with only one active position (**1a-c**), or two methylene positions with different pKa (**1d-g**). To this end, the reaction of α-cyanoacetophenone **1a** with cinnamaldehyde **2a** was selected as model reaction to establish the ideal reaction conditions. Initially we tested bifunctional organocatalysts (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine (**A**)[9] in the presence of p-nitrobenzoic acid (PNBA) as co-catalyst. This catalyst would be able to activate the electrophile by formation of an iminium ion with the secondary amine, and the nucleophile by deprotonation promoted by the tertiary amine component, but the Knoevenagel condensation compound **3aa** was the only isolated product (Scheme 1). On the contrary, the reactions catalyzed by monofunctional *O*-trimethylsilyl diphenylprolinol (**B**) and PNBA yielded the Knoevenagel product and equimolar mixtures of epimeric hemiacetals **4aa**, which were transformed into 3,4-dihydropyranone **5aa** by oxidation with PCC (Scheme 1).

After extensive work looking for the best reaction conditions, the results summarized in Table 1 show that, at room temperature, the best enantioselection was obtained in dichloromethane (DCM) as solvent (compare entries 1-4), and that the formation of the condensation product **3aa** was not observed at 0^{o} C, increasing the enantiomeric excess (ee) of **5aa** to 78% (entry 5). Both the yield and the ee were raised to 75% and 92%, respectively, when the reaction was carried out at -18^{o} C, although at the expense of increasing the reaction time to 11h (entry 6 in Table 1). It is interesting to note that the intermediate Michael adducts were not detected in any reaction.



Scheme 1. Screening for the conditions of the reaction of cinnamaldehyde and □-cyano acetophenone.

Table 1. Reaction of cyanoketone **1a** and cinnamaldehyde **2a** catalyzed by **B** in different conditions, and subsequent oxidation.

Entry	Solvent	Temp. (^{o} C)	Time (h)[a]	Products (%)[b]	Ee (%)[c]
1	Et_2O	rt	4 + 3	**3aa** (45) **5aa** (55)	46
2	Toluene	rt	4 + 3	**3aa** (60) **5aa** (40)	50
3	MeOH	rt	2 + 3	**3aa** (50) **5aa** (50)	54
4	DCM	rt	3 + 3	**3aa** (50) **5aa** (50)	64
5	DCM	0	7 + 3	**5aa** (65)[d]	78
6	DCM	- 18	11 + 3	**5aa** (75)[d]	92

[a] The first number refers to the reaction time and the second one to the oxidation reaction. [b] Ratio determined by ^{1}HNMR of the reaction mixture. [c] Data refer to product **5aa**, and were determined by chiral HPLC. [d] Yields refer to pure and isolated compounds.

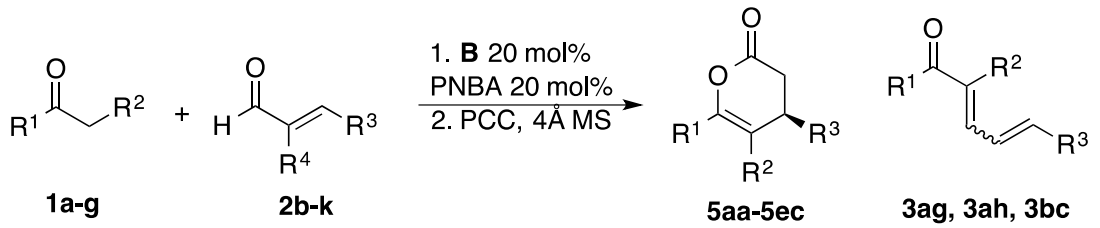
After establishing the best reaction conditions, we studied the scope of the catalyzed enantioselective addition-cyclization reaction using α,β-unsaturated aldehydes with different substitution. To this end, cyanoketone **1a** was reacted with aldehydes **2b-k** in DCM at – 18^{o} C in the presence of diphenyl prolinol derivative **B** (20 mol%) and PNBA (20 mol%), followed by oxidation with PCC of the reaction mixture, and the results are collected in Table 2 (entries 3-9). The reaction worked very well for aldehydes with alkyl (**2b-d**), electron-withdrawing group (**2e**) or electronically-poor aryl substituents (**2f**) at β-position. In all these reactions, 3,4-dihydropyranones **5aa-5af** were obtained as single products in good yields and excellent enantioselectivities (entries 1-7 in Table 2). Surprisingly, electron-rich *p*-methoxy cinnamaldehyde **2g** and heteroaromatic aldehyde **2h** reacted very quickly, but led to the Knoevenagel condensation products **3ag** and **3ah**, respectively (entries 8, 9 in Table 2) as an inseparable mixture of diastereoisomers.[10] α,β-Disubstituted aldehydes **2i-k** did not react with cyano ketone **1a** in the described conditions, and they were recovered unchanged after 240 h of stirring (entries 16-18 in Table 2).

The lack of reactivity of α-substituted aldehydes in Michael additions promoted by prolinol derivatives has been previously observed,[6b,11] although α-branched acroleins participate in different organocatalyzed transformations promoted by chiral primary amines or prolinol derivatives and acidic or basic additives as co-catalysts.[12] This fact has been attributed to the low stability of the α-substituted iminium intermediate due to steric hindrance. It has been reported that cinnamaldehyde **2a** easily forms the iminium triflate by reaction with catalyst **B** and aqueous TfOH after 1 h. in diethyl ether.[13] In our case, 2-methyl cinnamaldehyde (**2i**) was recovered unchanged after 96 h. of stirring at rt in the same conditions. This observation confirms that, under the studied reaction

conditions, the first Michael addition does not occur because the inability of the α-substituted enals to form the activated iminium intermediate.

The influence of the structure of the donor was studied for the reaction of *E*-2-pentenal (**2c**) as acceptor and different activated ketones **1b-g** (Table 2, entries 10-15). In those reactions the results are highly dependent on the nature of the substituent at the carbonyl group and the acidity of the methylene group. For instance, whereas α-cyano acetophenone **1a** yielded 3,4-dihydropyranone **5ac** with high yield and excellent enantioselectivity (entry 4), the trifluoromethylated analog **1c** was unable to react, and it was recovered unchanged after 144 h of stirring in the described conditions (entry 11). The much more acidic α–nitro acetophenone[14] **1b** lead to the Knoevenagel condensation product **3bc** as an inseparable mixture of Z-E diastereoisomers (entry 10).

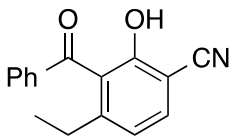
Trying to minimize the Knoevenagel products, the reactions of **1a** with **2g** and **2h** and **1b** with **2g** were carried out at – 35 °C, but the starting materials were recovered unchanged after stirring for 100 h.



1a-g **2b-k** **5aa-5ec** **3ag, 3ah, 3bc**

1	a	b	c	d	e	f	g
R¹	Ph	Ph	CF_3	Et	$PhCH_2$	$PhCOCH_2$	CH_2CO_2Et
R²	CN	NO_2	CN	CN	CN	CN	CN

2	b	c	d	e	f	g	h	i	j	k
R³	Me	Et	n-Pr	CO_2Et	2-O_2NPh	4-MeOPh	2-Furyl	Ph	Ph	Me
R⁴	H	H	H	H	H	H	H	Me	Br	Me



6fc

Scheme 2. Scope for the organocatalyzed reactions of ketones **1a-g** with aldehydes **2b-k**, and subsequent oxidation.

Table 2. Reaction of different aldehydes and ketones catalyzed by (**B**).[a]

Entry	Ketone	Aldehyde	Time (h)[b]	Products (%)[c]	Ee (%)[d]
1	**1a**	**2a**	11 + 3	**5aa** (75)	92
2[f]	**1a**	**2a**	12 + 3	**5aa** (72)	94
3	**1a**	**2b**	12 + 3	**5ab** (67)	88
4	**1a**	**2c**	12 + 3	**5ac** (70)	90
5	**1a**	**2d**	12 + 3	**5ad** (65)	92
6	**1a**	**2e**	4 + 3	**5ae** (70)	96
7	**1a**	**2f**	7 + 3	**5af** (63)	>99[e]
8	**1a**	**2g**	1	**3ag** (70)	-
9	**1a**	**2h**	1,5	**3ah** (65)	-
10	**1b**	**2c**	6	**3bc** (85)	-
11	**1c**	**2c**	144	nr	-
12	**1d**	**2c**	13 + 3	**5dc** (65)	92
13	**1e**	**2c**	14 + 3	**5ec** (73)	94
14	**1f**	**2c**	4	**6fc** (60)	-
15	**1g**	**2c**	4	-	-
16	**1a**	**2i**	240	nr	-
17	**1a**	**2j**	240	nr	-
18	**1a**	**2k**	240	nr	-
19	**1g**	**2c**	12	Complex mixture	-

[a] The reactions were carried out in DCM as solvent, at – 18^{o} C, with 20 mol% of catalyst and 20 mol% of p-NBA, followed by oxidation of the reaction mixture with PCC in DCM. [b] The first number refer to the reaction time and the second one to the

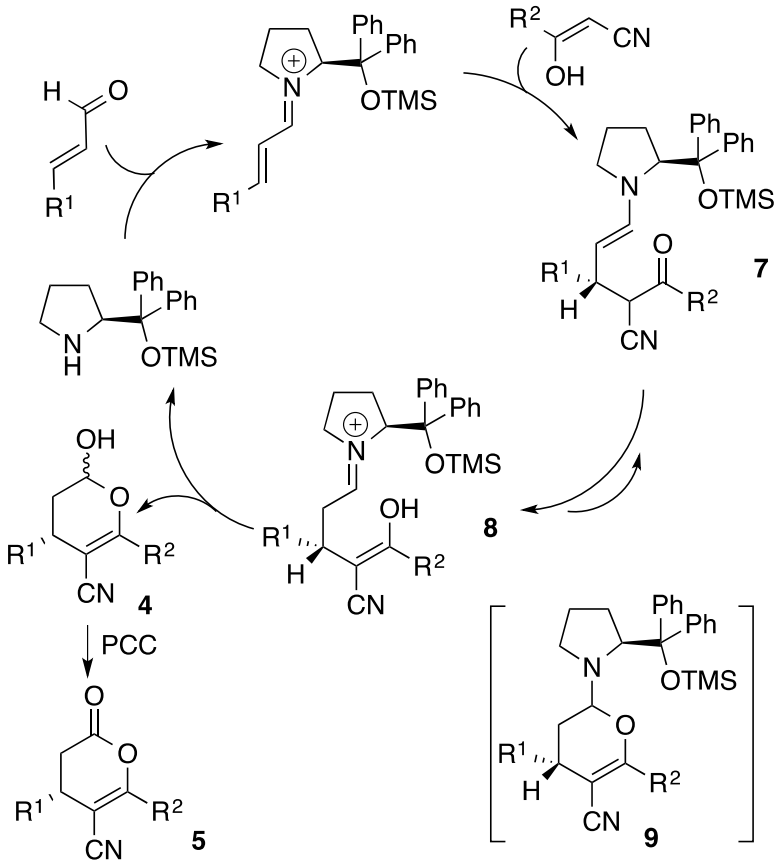
oxidation reaction. [c] Yields refer to pure and isolated compounds. [d] Determined by chiral HPLC. [e] >99 means that only one enantiomer was detected by HPLC. [d] The reaction was scaled up to 3 mmol

Much more interesting are the reactions of **2c** with ketones **1d-g** that could be deprotonated in two different positions. The final products are dependent on the difference in the acidity of the methylene groups α to the carbonyl group. Thus, the reactions of 3-oxo-pentanenitrile **1d**, with a difference of more than 10 pKa units between hydrogens at C-2 and C-4, or 3-oxo-4-phenyl butironitrile **1e** (7 pKa units of difference)[15] with **2c** are not only enantioselective but also regioselective, leading to **5dc** and **5ec**, respectively, in good yield and excellent enantioselection (entries 12, 13 in Table 2). This fact indicates that, as expected, the nucleophile was formed at the more acidic position forming a single enol that reacts with the activated enal leading to the Michael adducts, which cyclize to an equimolar mixture of epimeric hemiacetals **4dc** or **4ec,** converted into lactones **5dc** or **5ec** by oxidation with PCC .

Guided by these results, we decided to extend the reaction to multifunctional α-cyano ketones **1f** and **1g** attempting to prepare 3,4-dihydropyranones with additional functional groups at C-6. Unfortunately, α-cyano diketone **1f** or α-cyano ketoester **1g**, with closer values of pKa (3-4 units of difference) of the hydrogens at both α-positions of the carbonyl group behave in a different way than **1d-e**. 4-Benzoyl-3-oxobutyronitrile (**1f**) reacted very quickly yielding the phenol derivative **6fc**, as a single regioisomer, in moderate yield, (entry 14 in Table 2). This compound was probably formed in a Knoevenagel-cyclization-aromatization sequence.[16] Finally, ethyl 4-cyano-

3-oxo butyrate (**1g**) easily reacted with **2c** but leading to a very complex mixture of products (entry 19).

The described organocatalyzed domino approach consists on an initial Michael addition of the enol derived from the activated ketone to the unsaturated aldehyde, activated as iminium ion, followed by enolization of the adducts and subsequent heterocyclization to yield the final hemiacetal, and the proposed mechanism is summarized in Scheme 3. The activation of the enals and the addition of the nucleophile follows the general path previously described.[17] This means that the stereochemistry of the final product is dictated by the β−attack of the nucleophile from the less hindered Re face in the iminium ion, leading to intermediate **7**. Because the Michael adducts have been never observed, we propose a rapid enolization of **7** to intermediate **8**, which cyclizes to **4** by a fast hemiacetalyzation.[6d,f] The oxidation of hemiaccetal **4** with PCC yields the final enantioenriched trisubstituted 3,4-dihydropyranones **5**. Hemiacetal **4** could also be formed by hydrolysis of the N,O-acetal intermediate **9** resulting from the cyclization of **8**,[18] but we were unable to isolate or detect that intermediate when reacted **1a** and **2a** in the presence of one equivalent of catalyst.[19]



Scheme 3. Proposed pathway for the organocatalyzed formation of hemiacetals.

Conclusions

In summary, we have developed a prolinol ether organocatalyzed enantioselective domino Michael addition-heterocyclization process that yields enantioenriched hemiacetals, which were oxidized to valuable trisubstituted 3,4-dihydropyranones with a stereogenic center at C-5, in high yields and excellent enantioselectivity. In these reactions, α,β-unsaturated aldehydes with aliphatic, electron-deficient aromatic, and electron-withdrawing groups at β-position can be used as electrophiles. Different ketones can also be used as nucleophiles, but a fine-tuning of the pKa values of the hydrogens at α-position is necessary. Cyanoketones worked well, but much more acidic

nitroketones yielded the Knoevenagel product. It has been also demonstrated that the reactions of ketones with two different methylene positions were regioselective whenever the difference in the pKa values of the hydrogens at both □-positions was over 5 units.

Experimental Section

Specific rotations were measured using a 5–mL cell with a 1–dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Melting points were obtained with open capillary tubes and are uncorrected. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass–backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed using different Daicel Chiralcel Columns. UV detection was monitored at 220 nm or at 254 nm. ^{1}H–NMR (400 MHz) and ^{13}C–NMR (100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for protons are reported in ppm from TMS. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet m = multiplet, br = broad), coupling constants in Hertz, and integration.

Organic compounds were used as received. Solvents were dried, if needed, and stored over microwave–activated 4Å molecular sieves

General procedure

A solution of the ketone (0.24 mmol), the corresponding aldehyde (0.29 mmol, 1.2 equivalents) and the catalyst (0.048 mmol, 0.2 equivalents) in 4 mL of DCM was cooled to – 18^{o}C, and stirred for the time given in Table 2. Once the ketone has been

consumed (TLC), solid pyridinium chlorochromate (0.72 mmol, 3 equivalents) and 4Å mol. sieves (500 mg) were added, the reaction mixture was allowed to reach rt and stirred for 3 h. The reaction mixture was filtered though a pad of celite, the solvent evaporated under vacuum and the products purified by flash chromatography on silica gel (Hexane/ethyl acetate, 8:1) to yield the desired lactone.

(S)-2-Oxo-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile (5aa). Colorless oil. $[\alpha]_D^{20}$ = +34.5 (c = 2, $CHCl_3$, 93% ee). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.02 (dd, *J* = 16.1, 4.8 Hz, 1H), 3.16 (dd, *J* = 16.1, 7.2 Hz, 1H), 4.11 (dd, *J* = 7.2, 4.8 Hz, 1H), 8.43 – 6.72 (m, 10H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 35.6; 40.4; 91.5; 117.5; 126.9; 128.0; 128.7; 128.9; 129.7; 132.1; 138.0; 162.2; 164.2. IR. 2920, 2847, 2214, 1768, 1119 cm^{-1}. HPLC (Chiralpak AD-H, hexane/iPrOH=90:10, 1.0 mL/min); t_R = 19.5 min (major); t_R = 18.0 min (minor). HRMS $C_{18}H_{14}NO_2$ (M+H) Calc: 276.1019; Found: 276.1023.

(4R)-4-Methyl-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (5ab). Colorless oil. $[\alpha]_D^{20}$ = +24.2 (c = 1.5, $CHCl_3$, 86% ee). ^{1}H-NMR, (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 7.0 Hz, 3H), 2.59 (dd, *J* = 15.8, 7.3 Hz, 1H), 2.89 (dd, *J* = 15.8, 6.0 Hz, 1H), 3.06 – 2.93 (m, 1H), 7.57 – 7.40 (m, 3H), 8.00 – 7.72 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 19.1; 29.2; 35.3; 93.4; 117.3; 127.9; 128.8; 130.3; 130.5; 131.8; 161.4; 165.0. IR. 2972, 2930, 2209, 1789, 1353, 1124 cm^{-1}. HPLC (Chiralpak AD-H hexane/iPrOH 90:10, 1.0 mL/min); t_R = 13.3 min (major); t_R = 12.5 min (minor). HRMS $C_{13}H_{12}NO_2$ (M+H) Calc: 214.0862; Found: 214.0869.

(4R)-4-Ethyl-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (5ac). Colorless oil. $[\alpha]_D^{20}$ = +19.2 (c = 2, $CHCl_3$, 90% ee). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.4 Hz, 3H), 1.73 – 1.50 (m, 1H), 1.85 (ddd, *J* = 13.6, 7.4, 5.9 Hz, 1H), 2.71 (dd, *J* =

15.2, 4.6 Hz, 1H), 2.86 – 2.73 (m, 1H), 2.87 (dd, *J* = 15.2, 6.2 Hz, 1H), 8.00 – 7.17 (m, 5H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 10.7; 26.7; 32.6; 35.7; 92.2; 117.8; 127.9; 128.8; 129.1; 130.3; 130.5; 131.8; 161.7; 165.2. IR. 2967, 2925, 2209, 1789, 1358, 1124 cm^{-1}. HPLC (Chiralpak AD-H, hexane/iPrOH 90:10; 1.0 mL/min); t_R = 11.4 min (major); t_R = 10.7 min (minor). HRMS $C_{14}H_{14}NO_2$ (M+H) Calc: 228.1019; Found: 228.1022.

(4R)-2-Oxo-6-phenyl-4-propyl-3,4-dihydro-2H-pyran-5-carbonitrile (5ad). Colorless oil. $[\alpha]_D^{20}$ = +36.7 (c = 1, $CHCl_3$, 94% ee). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.66 – 1.29 (m, 3H), 1.83 – 1.67 (m, 1H), 2.70 (dd, *J* = 17.9, 7.0 Hz, 1H), 2.98 – 2.76 (m, 2H), 7.98 – 7.34 (m, 5H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 13.9; 19.6; 33.1; 34.2; 35.7; 92.5; 117.8; 127.9; 128.8; 129.1; 130.3; 130.5; 131.8; 161.6; 165.2. IR. 2962., 2930, 2214, 1789, 1124 cm^{-1}. HPLC (Chiralcel OD hexane/iPrOH = 90:10; 1.0 mL/min) t_R = 16.122 min (major); t_R = 14.821 min (minor). HRMS $C_{15}H_{16}NO_2$ (M+H) Calc: 242.1175; Found: 242.1178.

Ethyl (4R)-5-cyano-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-carboxylate (5ae). Colorless oil. $[\alpha]_D^{20}$ = +15.8 (c = 1.4, $CHCl_3$, 96% ee). ^{1}H-NMR(500 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.1 Hz, 3H), 2.88 (dd, *J* = 16.4, 6.9 Hz, 1H), 3.19 (dd, *J* = 16.4, 3.0 Hz, 1H), 3.70 (dd, *J* = 6.9, 3.0 Hz, 1H), 4.29 (dq, *J* = 7.1, 1.0 Hz, 2H), 7.50 (dt, *J* = 8.6, 7.2 Hz, 3H), 7.97 – 7.83 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 14.2; 29.8; 29.9; 40.0; 62.9; 85.8; 117.0; 128.1; 128.6; 128.9; 129.8; 132.4; 162.9; 163.6; 169.2. IR. 2988, 2936, 2214, 1773, 1721, 1368 cm^{-1}. HPLC (Chiralpak AD-H hexane/iPrOH =90:10; 1.0 mL/min) t_R = 21.7 min (major); t_R = 20.6 min (minor). HRMS: $C_{18}H_{14}N_2O_4$ (M+H) Calc: 272.0917 Found: 272.0918.

(S)-4-(2-Nitrophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (5af). Colorless oil. $[\alpha]_D^{20}$ = +72 (c = 2.5, $CHCl_3$ 99.5% ee). ^{1}H-NMR (500 MHz, $CDCl_3$) δ

3.14 (dd, *J* = 16.4, 4.5 Hz, 1H), 3.32 (dd, *J* = 16.4, 7.7 Hz, 1H), 4.88 (dd, *J* = 7.7, 4.5 Hz, 1H), 8.20 – 7.33 (m, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 35.3; 36.5; 89.9; 117.0; 126.4; 128.1; 128.7; 129.0; 129.7; 130.0; 132.5; 132.7; 134.6; 148.8; 163.4; 163.80. IR. 2925, 2858, 2214, 1789, 1519, 1347 cm^{-1}. HPLC (Chiralpak AD-H hexane/iPrOH 80:20; 1.0 mL/min); t_R = 18.9 min (major); t_R = 20.3 min (minor). HRMS: $C_{18}H_{13}N_2O_4$ (M+H) Calc: 321.0869 Found: 321.0870.

(4R)-4,6-Diethyl-2-oxo-3,4-dihydro-2H-pyran-5-carbonitrile (5dc). Colorless oil. $[\alpha]_D^{20}$ = +19.7 (c = 1, $CHCl_3$ 92% ee). ^{1}H NMR(500 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.51 (dt, *J* = 14.5, 7.4 Hz, 1H), 1.72 (ddd, *J* = 13.3, 7.4, 5.7 Hz, 1H), 2.65 – 2.51 (m, 4H), 2.74 (dd, *J* = 15.3, 6.0 Hz, 1H). ^{13}C-NMR (126 MHz, CDCl3) δ 10.3, 11.2; 26.3; 26.6; 32.6; 33.8; 92.0; 116.6; 165.3; 167.7. IR. 2967, 2936, 2214, 1789, 1649, 1129 cm^{-1}. HPLC (Chiralpak AD-H hexane/iPrOH 97:3; 0.7 mL/min); t_R = 13.5 min (major); t_R = 12.8 min (minor). HRMS: $C_{10}H_{14}NO_2$ (M+H) Calc: 180.1019 Found: 180.1022.

(4R)-6-Benzyl-4-ethyl-2-oxo-3,4-dihydro-2H-pyran-5-carbonitrile (5ec). Colorless oil. $[\alpha]_D^{20}$ = +8.8 (c = 0.5, $CHCl_3$ 94% ee). ^{1}H-NMR(500 MHz, $CDCl_3$,) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.62 – 1.40 (m, 1H), 1.74 (ddd, *J* = 13.5, 7.2, 6.0 Hz, 1H), 2.54 (dd, *J* = 15.3, 5.0 Hz, 1H), 2.79 – 2.59 (m, 2H), 3.81 (q, *J* = 14.5 Hz, 2H), 7.33 (s, 5H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 10.4; 26.6; 32.5; 34.0; 39.0; 93.2; 116.8; 127.6; 128.8; 128.9; 134.6; 164.9; 165.0. HPLC (Chiralpak AD-H hexane/iPrOH 97:3; 0.7 mL/min) t_R = 18.2 min (major); t_R = 19.0 min (minor). HRMS: $C_{15}H_{15}NO_2$ (M+Na) Calc: 240.1238 Found: 240.1240.

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Supporting Information Available: Copies of ^{1}H-NMR and ^{13}C-NMR spectra for all new compounds and copies of the HPLC chromatograms are available as supporting information.

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Table of Contents

One-pot domino enantioselective organocatalytic Michael Addition-heterocyclization followed by oxidation of the hemiacetal intermediate allows the synthesis of enantioenriched 3,4-dihydro pyranone derivatives.