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Organocatalytic enantioselective multicomponent cascade reaction: facile access to tetrahydropyridines with C3 all-carbon quaternary stereocenters

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ABSTRACT

A novel organocatalytic asymmetric multicomponent cascade reaction for the synthesis of valuable tetrahydropyridines has been developed. The merit of this cascade process is highlighted by its high efficiency of producing five new bonds and an all-carbon quaternary stereocenter in one operation, which otherwise is a big challenge to access by traditional strategies.

1. Introduction

The functionalized piperidine ring systems are not only important starting materials for numerous biologically active compounds, but are also important structural building blocks of many natural products and pharmaceuticals.[1] This fact has stimulated a large number of investigations exploring new methodologies for asymmetric assembly of polysubstituted piperidines.[2] During the last few years, organocatalytic enantioselective cascade reactions[3] have emerged as powerful tools to construct complex molecules from simple and readily available starting materials in only one operation, thereby minimizing waste management as compared to a series of individual stepwise reactions. For example, Terada et al. described an elegant chiral Brønsted acid promoted tandem aza-ene-type reaction to construct piperidines.[4] Hayashi et al. reported a catalytic formal aza [3+3] cycloaddition reactions for the formation of enantioenriched piperidines.[5]

Our group has developed a highly diastereo- and enantioselective synthesis of 2,3-disubstituted tetrahydropyridines in the presence of water from *N*-*p*-methoxyphenyl (*N*-PMP) aldimines and tetrahydro-2*H*-pyran-2,6-diol.[6a] Recently, we have reported a fast and efficient entry into fully substituted piperidines via multiple-organocatalyst-promoted cascade reactions.[6b] Therefore, as a continuous interest in the development of new methodologies for the asymmetric synthesis of this class of six-membered nitrogen-containing heterocycles, we endeavor to develop a more practical, simple-to-perform, and single-operation cascade reaction, which employed commercially available materials directly. Herein, we describe an L-proline catalyzed multicomponent cascade reaction to afford tetrahydropyridines with an all-carbon quaternary stereocenter, which is a big challenge to access in chemical synthesis.[7–9]

2. Results and discussion

To begin this study, we chose commercially available ethyl acetoacetate **1a**, aqueous formaldehyde **2**, and 4-methoxylaniline **3a** as the standard substrates to search for potential catalysts and suitable reaction conditions. First, we used L-proline **5a** as an organocatalyst (Table 1, entry 1) and DMF as a solvent. To our delight, the reaction afforded the desired tetrahydropyridine **4a** in 60% yield with moderate enantioselectivity (51% ee) within 6 h. Encouraged by this result, we then performed a catalyst screening with various chiral amines **5b**–**h**. 4-Hydroxyproline **5b** and siloxyproline **5c** could also catalyze the reaction efficiently to furnish the desired product **4a** albeit with a slight decrease in both yield and enantioselectivity (Table 1, entries 2 and 3). However, when the imidazolidine catalyst **5d** was used, the reaction became sluggish and the enantiomeric excess value obtained was much lower (20%; Table 1, entry 4). Although these catalysts generate only mediocre enantiomeric excess values of the product, diphenylprolinol **5e**, phenylalanine **5f**, diarylprolinol TMS ether **5g**, and

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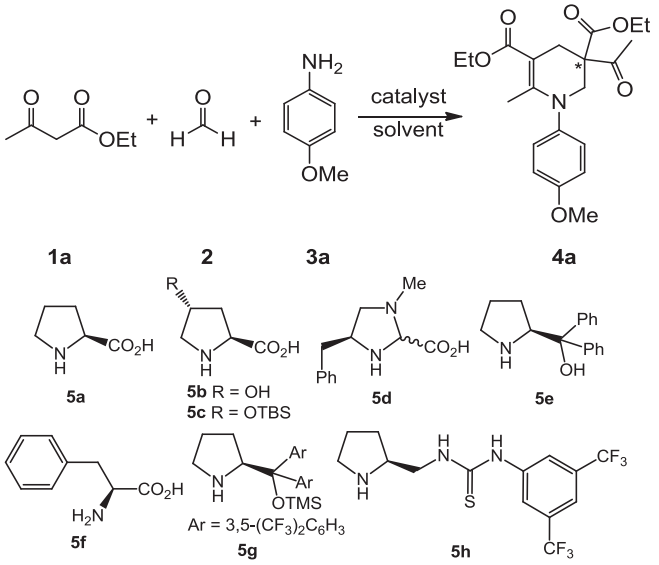
Table 1
Catalyst and solvent screen[a]



Entry	Catalyst	Solvent	Yield[b] [%]	ee[c] [%]
1	**5a**	DMF	60	51
2	**5b**	DMF	58	48
3	**5c**	DMF	54	48
4	**5d**	DMF	38	20
5	**5e**	DMF	64	<10
6	**5f**	DMF	57	<10
7[d]	**5g**	DMF	64	<10
8[e]	**5g**	DMF	45	<10
9	**5h**	DMF	41	<10
10	**5a**	DMSO	61	56
11	**5a**	*i*-PrOH	62	62
12	**5a**	H_2O	59	12
13	**5a**	CH_3CN	60	19
14	**5a**	CH_2Cl_2	32	14
15	**5a**	**THF**	**63**	**65**

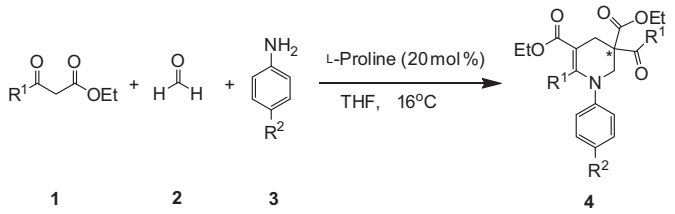
Bold values indicate the optimal condition.
[a] Unless otherwise specified, all reactions were carried out with **1a** (2.0 mmol), **2** (3.0 mmol, 36% aqueous solution), **3a** (0.5 mmol), and organocatalyst (20 mol %) in the indicated solvent (1.0 mL) at 16 °C for 6 h.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral-phase HPLC analysis.
[d] $PhCO_2H$ (20 mol %) was added.
[e] *p*-TSA (20 mol %) was added.

pyrrolidine-thiourea **5h** proved to be even poorer catalysts for this reaction, because poor enantiomeric excess values and/or low yields of the product were obtained (Table 1, entries 5–9).

This screening identified L-proline **5a** as the best catalyst for this reaction. Then, we studied the solvent effects on this reaction by using **5a** as the catalyst. As revealed in Table 1, when DMSO and *i*-PrOH were used as solvents, the enantiomeric excess values obtained were slightly higher (56 and 62%, respectively; Table 1, entries 10 and 11). It is interesting that this reaction could also be performed in water efficiently to furnish the product in 59% yield, but the enantiomeric excess value was much lower (12%; Table 1, entry 12). Acetonitrile and dichloromethane showed a detrimental effect on the enantioselectivity (Table 1, entries 13 and 14). THF proved to be the best solvent (Table 1, entry 15).

Thus, under the optimized conditions, the generality of the reaction was investigated by employing several anilines and β-ketone esters. The results are summarized in Table 2. The electronic nature of the substituent R^2 on the benzene ring was found to have influences on both the reactivity and the enantioselectivity of this reaction. Weak electron-donating group (such as methyl) or unsubstituted phenyl group, diminished slightly the

Table 2
Substrate scope for the organocatalytic multicomponent cascade reaction[a]



Entry	R^1	R^2	Product	*t* [h]	Yield[b] [%]	ee[c] [%]
1	Me	OMe	**4a**	6	63	65
2	Me	Me	**4b**	24	54	63
3	Me	H	**4c**	48	46	63
4	Me	Cl	**4d**	72	42	73
5	Me	Br	**4e**	72	35	74
6	Et	OMe	**4f**	12	65	61
7	*n*-Pr	OMe	**4g**	48	65	61
8	*n*-Hexyl	OMe	**4h**	48	57	51
9	Et	Me	**4i**	48	63	63
10	*n*-Pr	Me	**4j**	48	61	55
11	Et	Cl	**4k**	120	34	72
12	*n*-Pr	Cl	**4l**	120	24	63

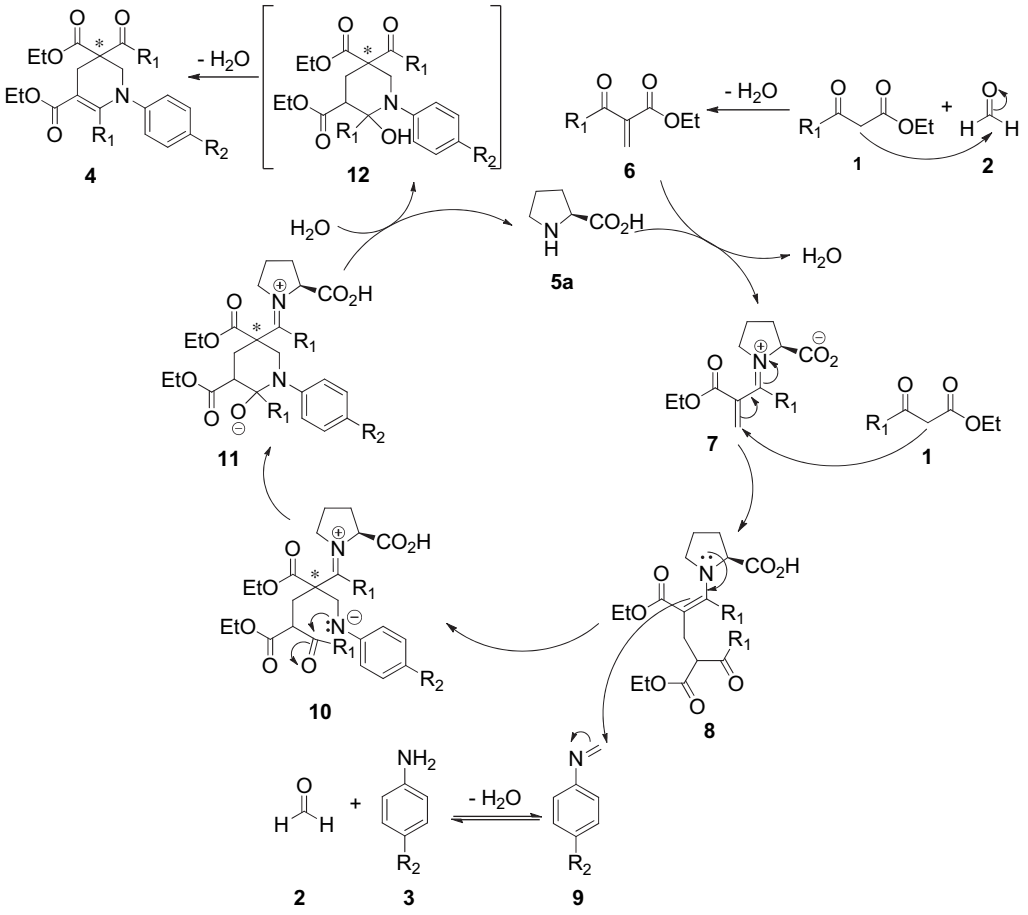
[a] The reactions were carried out with **1** (2.0 mmol), **2** (3.0 mmol, 36% aqueous solution), **3** (0.5 mmol), and L-proline (20 mol %) in THF (1.0 mL) at 16 °C.
[b] Isolated yield after flash chromatography.
[c] Determined by chiral-phase HPLC analysis.

reaction yield and the enantiomeric excess values of this reaction with prolonged reaction time as compared to the strong electron-donating group (Table 2, entries 2 and 3 vs entry 1). Nevertheless, electron-withdrawing groups, such as chlorine or bromine groups, diminished the yield dramatically with much longer reaction time albeit with a slight increase in the enantiomeric excess values (Table 2, entries 4 and 5). On the other hand, the R^1 group of the β-ketone esters had a little influence on both the reactivity and the enantioselectivity of this reaction. The yield of the reaction was essentially not affected and moderate enantiomeric excess values were obtained (Table 2, entries 6–12). It should be noted that the tetrahydropyridines were not obtained when R^1 group was aryl.

The proposed mechanism for the chain of transformation is summarized in Scheme 1. The β-ketone ester **1** would react with an aqueous formaldehyde **2** to form the intermediate **6** via a Knoevenagel reaction, then transformed into the iminium ion **7** by a catalyst **5a**. The β-ketone ester **1** attacked the iminium ion **7** to form the enamine intermediate **8** by a Michael reaction. The enamine **8** then underwent a Mannich reaction with imine **9**, which was formed by the condensation of primary amine **3** with an aqueous formaldehyde **2** to give the intermediate **10**. The intermediate **10** would undergo an intramolecular cyclization to provide the intermediate piperidine **12** with the regeneration of proline **5a**. Under acidic conditions, the unstable intermediate **12** underwent a dehydration reaction to afford the final tetrahydropyridine **4**.

3. Conclusions

In summary, we have developed a novel organocatalytic asymmetric multicomponent cascade reaction to construct tetrahydropyridines with moderate yields and enantioselectivities. In this course, three C–C bonds, two C–N bonds, and an all-carbon quaternary stereocenter are formed. Despite unsatisfactory enantioselectivities, this strategy will easily provide an access to structurally diverse tetrahydropyridines. Further efforts will be spent on applying this methodology to the synthesis of small natural alkaloids and the improvement of stereochemistry.



Scheme 1. A proposed mechanism for the cascade reaction.

4. Experimental section

4.1. General

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 as an indicator and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash column chromatography was carried out using silica gel (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz ^{1}H, 100 MHz ^{13}C). The spectra were recorded in $CDCl_3$ as a solvent at room temperature, ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million relative to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. IR spectra were recorded using Nicolet NEXUS 670 FT-IR instrument and are reported in wavenumbers (cm^{-1}). HRMS was performed on a Bruker Apex II mass instrument (ESI). Enantiomeric excess values were determined by HPLC employing a Daicel Chiralpak OD-H and AD-H on Agilent 1100 series and eluting with *i*-PrOH and *n*-hexane. Optical rotation was measured on the Perkin–Elmer 341 polarimeter with $[\alpha]_D$ values reported in degrees; concentration (*c*) is in g/100 mL.

4.2. General experimental procedure

A mixture of aniline (0.50 mmol), β-ketone ester (2.0 mmol), formaldehyde (230 μL, 3.0 mmol, 36% aqueous solution), and a catalytic amount of L-proline (11.5 mg, 0.10 mmol, 20 mol%) in 1 mL of THF was stirred at 16 °C. After the indicated time, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate. The mixture was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether, a little Et_3N) to afford the corresponding tetrahydropyridine.

*4.2.1. Diethyl 3-acetyl-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-6-methylpyridine-3,5-dicarboxylate (**4a**).* Yellow oil. $[\alpha]_D^{20}$ +93 (*c* 0.80, $CHCl_3$, 65% ee). IR (KBr): 2980, 1713, 1683, 1570, 1510, 1234, 1148, 1066, 839, 766, 583, 527 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.03 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=9.2 Hz, 2H), 4.19–4.13 (m, 4H), 3.86 (d, *J*=12.8 Hz, 1H), 3.81 (s, 3H), 3.79 (d, *J*=12.8 Hz, 1H), 3.04 (d, *J*=16.8 Hz, 1H), 2.99 (d, *J*=16.8 Hz, 1H), 2.24 (s, 3H), 2.07 (s, 3H), 1.29 (t, *J*=7.2 Hz, 3H), 1.19 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.1, 170.0, 168.3, 158.1, 153.8, 138.4, 128.3, 114.4, 93.7, 61.7, 59.2, 58.0, 55.4, 54.5, 29.6, 26.1, 19.1, 14.6, 13.9. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=26.9 min, minor enantiomer t_R=33.2 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{21}H_{28}NO_6$]: 390.1911, found: 390.1915.

*4.2.2. Diethyl 3-acetyl-1,2,3,4-tetrahydro-6-methyl-1-p-tolypyridine-3,5-dicarboxylate (**4b**).* Yellow oil. $[\alpha]_D^{20}$ +136 (*c* 0.70, $CHCl_3$, 63% ee). IR (KBr): 2981, 2931, 1714, 1573, 1512, 1447, 1358, 1234, 1147, 1065, 925, 828, 766, 724, 511 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.15 (d, *J*=8.0 Hz, 2H), 6.97 (d, *J*=7.6 Hz, 2H), 4.19–4.10 (m, 4H), 3.87 (d, *J*=12.4 Hz, 1H), 3.83 (d, *J*=12.4 Hz, 1H), 3.05 (d, *J*=16.4 Hz, 1H), 2.97 (d, *J*=16.4 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.10 (s, 3H), 1.29

(t, J=7.2 Hz, 3H), 1.16 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.9, 169.9, 168.2, 153.4, 142.9, 136.2, 129.8, 126.8, 94.6, 61.6, 59.1, 58.1, 54.3, 29.6, 26.0, 20.9, 19.2, 14.6, 13.8. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=14.2 min, minor enantiomer t_R=16.2 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{21}H_{28}NO_5$]: 374.1962, found: 374.1969.

*4.2.3. Diethyl 3-acetyl-1,2,3,4-tetrahydro-6-methyl-1-phenylpyridine-3,5-dicarboxylate (**4c**).* Yellow oil. $[\alpha]_D^{20}$ +164 (*c* 0.94, $CHCl_3$, 63% ee). IR (KBr): 2981, 1713, 1571, 1495, 1360, 1234, 1148, 1068, 926, 768, 703, 564, 505 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (t, J=7.6 Hz, 2H), 7.22 (t, J=7.6 Hz, 1H), 7.07 (d, J=7.6 Hz, 2H), 4.20–4.12 (m, 4H), 3.89 (t, J=14 Hz, 2H), 3.07 (d, J=16.4 Hz, 1H), 2.93 (d, J=16.4 Hz, 1H), 2.22 (s, 3H), 2.11 (s, 3H), 1.30 (t, J=7.2 Hz, 3H), 1.13 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.0, 169.9, 168.2, 153.1, 145.5, 129.2, 126.8, 126.2, 95.7, 61.7, 59.2, 58.2, 54.3, 29.7, 26.0, 19.4, 14.6, 13.8. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=19.4 min, minor enantiomer t_R=24.0 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{20}H_{26}NO_5$]: 360.1805, found: 360.1809.

*4.2.4. Diethyl 3-acetyl-1-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methylpyridine-3,5-dicarboxylate (**4d**).* Yellow oil. $[\alpha]_D^{20}$ +171 (*c* 0.75, $CHCl_3$, 73% ee). IR (KBr): 2981, 1713, 1570, 1490, 1359, 1235, 1149, 1017, 925, 839, 764, 509 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (d, J=8.8 Hz, 2H), 7.02 (d, J=8.8 Hz, 2H), 4.21–4.06 (m, 4H), 3.85 (s, 2H), 3.06 (d, J=16.8 Hz, 1H), 2.93 (d, J=16.8 Hz, 1H), 2.22 (s, 3H), 2.10 (s, 3H), 1.30 (t, J=7.2 Hz, 3H), 1.14 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.8, 169.7, 168.0, 152.3, 144.0, 131.7, 129.3, 128.0, 96.7, 61.8, 59.3, 58.0, 54.2, 29.6, 26.0, 19.3, 14.5, 13.8. The enantiomeric excess was determined by HPLC with an AD-H column. (*n*-Hexane/*i*-PrOH=97:3), 1.0 mL/min; major enantiomer t_R=23.4 min, minor enantiomer t_R=26.7 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{20}H_{25}ClNO_5$]: 394.1416, found: 394.1419.

*4.2.5. Diethyl 3-acetyl-1-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methylpyridine-3,5-dicarboxylate (**4e**).* Yellow oil. $[\alpha]_D^{20}$ +180 (*c* 0.90, $CHCl_3$, 74% ee). IR (KBr): 2981, 1713, 1570, 1487, 1359, 1235, 1149, 1066, 1013, 836, 765, 563, 506 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.47 (d, J=8.8 Hz, 2H), 6.95 (d, J=8.4 Hz, 2H), 4.21–4.03 (m, 4H), 3.87 (d, J=13.2 Hz, 1H), 3.83 (d, J=13.2 Hz, 1H), 3.06 (d, J=16.8 Hz, 1H), 2.91 (d, J=16.8 Hz, 1H), 2.21 (s, 3H), 2.10 (s, 3H), 1.30 (t, J=7.2 Hz, 3H), 1.14 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.8, 169.7, 168.1, 152.2, 144.6, 132.3, 128.4, 119.5, 97.0, 61.8, 59.4, 58.1, 54.1, 29.7, 26.0, 19.4, 14.6, 13.8. The enantiomeric excess was determined by HPLC with an AD-H column. (*n*-Hexane/*i*-PrOH=97:3), 1.0 mL/min; major enantiomer t_R=25.3 min, minor enantiomer t_R=28.1 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{20}H_{25}BrNO_5$]: 438.0911, found: 438.0921.

*4.2.6. Diethyl 6-ethyl-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-3-propionylpyridine-3,5-dicarboxylate (**4f**).* Yellow oil. $[\alpha]_D^{20}$ +94 (*c* 0.81, $CHCl_3$, 61% ee). IR (KBr): 2979, 1714, 1565, 1509, 1462, 1368, 1229, 1033, 841, 809, 768, 574, 527 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.08 (d, J=7.6 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 4.19–4.10 (m, 4H), 3.85 (d, J=12.8 Hz, 1H), 3.82 (s, 3H), 3.76 (d, J=12.8 Hz, 1H), 3.04 (d, J=16.4 Hz, 1H), 2.98 (d, J=16.4 Hz, 1H), 2.65–2.51 (m, 4H), 1.29 (t, J=7.2 Hz, 3H), 1.19 (t, J=7.2 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H), 0.86 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.9, 170.3, 167.7, 159.9, 158.2, 138.1, 128.8, 114.3, 92.4, 61.6, 59.1, 57.8, 55.4, 55.1, 31.4, 29.6, 23.3, 14.6, 13.9, 13.4, 7.7. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=16.7 min, minor enantiomer t_R=24.5 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{23}H_{32}NO_6$]: 418.2224, found: 418.2226.

*4.2.7. Diethyl 3-butyryl-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-6-propylpyridine-3,5-dicarboxylate (**4g**).* Yellow oil. $[\alpha]_D^{20}$ +92 (*c* 0.81, $CHCl_3$, 61% ee). IR (KBr): 2964, 1713, 1565, 1509, 1461, 1366, 1227, 1037, 840, 767, 575, 537 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.07 (d, J=7.6 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.20–4.10 (m, 4H), 3.83 (d, J=11.2 Hz, 1H), 3.82 (s, 3H), 3.75 (d, J=11.2 Hz, 1H), 3.04 (d, J=16.4 Hz, 1H), 2.97 (d, J=16.4 Hz, 1H), 2.58–2.46 (m, 4H), 1.61–1.56 (m, 2H), 1.31–1.27 (m, 5H), 1.18 (t, J=7.2 Hz, 3H), 0.88 (t, J=7.2 Hz, 3H), 0.68 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.1, 170.2, 167.8, 158.6, 158.1, 138.3, 128.8, 114.3, 92.9, 61.6, 59.1, 58.0, 55.4, 55.1, 39.8, 31.9, 29.5, 22.5, 16.9, 14.6, 14.1, 13.9, 13.5. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=12.8 min, minor enantiomer t_R=17.8 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{25}H_{36}NO_6$]: 446.2537, found: 446.2543.

*4.2.8. Diethyl 3-heptanoyl-6-hexyl-1,2,3,4-tetrahydro-1-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (**4h**).* Yellow oil. $[\alpha]_D^{20}$ +66 (*c* 0.87, $CHCl_3$, 51% ee). IR (KBr): 2929, 2858, 1714, 1565, 1509, 1462, 1366, 1232, 1094, 1046, 840, 767, 575, 538 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.07 (d, J=6.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.19–4.07 (m, 4H), 3.83 (d, J=12.8 Hz, 1H), 3.82 (s, 3H), 3.74 (d, J=12.8 Hz, 1H), 3.03 (d, J=16.4 Hz, 1H), 2.97 (d, J=16.4 Hz, 1H), 2.62–2.48 (m, 4H), 1.54 (br, 2H), 1.30–1.25 (m, 13H), 1.18 (t, J=7.2 Hz, 3H), 1.02 (br, 4H), 0.87 (t, J=6.8 Hz, 3H), 0.77 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.3, 170.3, 167.8, 158.7, 158.1, 138.3, 128.9, 114.3, 92.9, 61.6, 59.1, 58.0, 55.5, 55.1, 38.0, 31.6, 31.2, 30.0, 29.6, 29.2, 28.9, 28.7, 23.4, 22.5, 22.4, 14.7, 14.0, 13.9. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=8.3 min, minor enantiomer t_R=13.0 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{31}H_{48}NO_6$]: 530.3476, found: 530.3483.

*4.2.9. Diethyl 6-ethyl-1,2,3,4-tetrahydro-3-propionyl-1-p-tolylpyridine-3,5-dicarboxylate (**4i**).* Yellow oil. $[\alpha]_D^{20}$ +122 (*c* 0.81, $CHCl_3$, 63% ee). IR (KBr): 2980, 1714, 1564, 1511, 1460, 1368, 1231, 1144, 1026, 829, 767, 725, 575, 510 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.16 (d, J=8.0 Hz, 2H), 7.02 (d, J=7.6 Hz, 2H), 4.20–4.07 (m, 4H), 3.85 (d, J=12.4 Hz, 1H), 3.79 (d, J=12.4 Hz, 1H), 3.05 (d, J=16.4 Hz, 1H), 2.95 (d, J=16.4 Hz, 1H), 2.66–2.52 (m, 4H), 2.35 (s, 3H), 1.29 (t, J=7.2 Hz, 3H), 1.16 (t, J=7.2 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H), 0.87 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.8, 170.2, 167.7, 159.7, 142.7, 136.5, 129.8, 127.4, 93.4, 61.6, 59.1, 58.0, 55.0, 31.4, 29.7, 23.4, 21.0, 14.6, 13.9, 13.5, 7.7. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=9.5 min, minor enantiomer t_R=11.6 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{23}H_{32}NO_5$]: 402.2275, found: 402.2273.

*4.2.10. Diethyl 3-butyryl-1,2,3,4-tetrahydro-6-propyl-1-p-tolylpyridine-3,5-dicarboxylate (**4j**).* Yellow oil. $[\alpha]_D^{20}$ +129 (*c* 0.70, $CHCl_3$, 55% ee). IR (KBr): 2965, 1713, 1685, 1565, 1511, 1459, 1366, 1229, 1145, 1080, 1031, 828, 766, 518 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.15 (d, J=8.4 Hz, 2H), 7.01 (d, J=7.6 Hz, 2H), 4.20–4.03 (m, 4H), 3.84 (d, J=12.4 Hz, 1H), 3.79 (d, J=12.4 Hz, 1H), 3.05 (d, J=16.4 Hz, 1H), 2.94 (d, J=16.4 Hz, 1H), 2.62–2.44 (m, 4H), 2.35 (s, 3H), 1.63–1.53 (m, 2H), 1.34–1.27 (m, 5H), 1.15 (t, J=7.2 Hz, 3H), 0.87 (t, J=7.2 Hz, 3H), 0.68 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.0, 170.2, 167.8, 158.3, 142.9, 136.4, 129.8, 127.3, 93.9, 61.6, 59.1, 58.1, 54.9, 39.9, 31.9, 29.6, 22.5, 21.0, 16.8, 14.6, 14.0, 13.8, 13.5. The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-Hexane/*i*-PrOH=98:2), 1.0 mL/min; major enantiomer t_R=7.8 min, minor enantiomer

t_R=9.3 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{25}H_{36}NO_5$]: 430.2588, found: 430.2584.

*4.2.11. Diethyl 1-(4-chlorophenyl)-6-ethyl-1,2,3,4-tetrahydro-3-propionylpyridine-3,5-dicarboxylate (**4k**).* Yellow oil. $[\alpha]_D^{20}$ +160 (*c* 1.00, $CHCl_3$, 72% ee). IR (KBr): 2982, 1713, 1565, 1490, 1371, 1232, 1145, 1091, 1021, 758, 668, 509 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (d, *J*=8.8 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 2H), 4.20–4.11 (m, 4H), 3.82 (s, 2H), 3.06 (d, *J*=16.4 Hz, 1H), 2.91 (d, *J*=16.4 Hz, 1H), 2.68–2.50 (m, 4H), 1.30 (t, *J*=7.2 Hz, 3H), 1.14 (t, *J*=7.2 Hz, 3H), 1.03 (t, *J*=7.2 Hz, 3H), 0.87 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.6, 170.0, 167.5, 158.6, 143.9, 132.0, 129.3, 128.7, 95.6, 61.7, 59.3, 58.0, 54.9, 31.4, 29.7, 23.3, 14.5, 13.8, 13.4, 7.7. The enantiomeric excess was determined by HPLC with an AD-H column. (*n*-Hexane/*i*-PrOH=97:3), 1.0 mL/min; major enantiomer t_R=15.6 min, minor enantiomer t_R=17.9 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{22}H_{29}ClNO_5$]: 422.1729, found: 422.1733.

*4.2.12. Diethyl 3-butyryl-1-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-propylpyridine-3,5-dicarboxylate (**4l**).* Yellow oil. $[\alpha]_D^{20}$ +136 (*c* 1.00, $CHCl_3$, 63% ee). IR (KBr): 2925, 1711, 1564, 1490, 1368, 1218, 1090, 759, 668, 517 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (d, *J*=8.8 Hz, 2H), 7.05 (d, *J*=8 Hz, 2H), 4.20–3.99 (m, 4H), 3.80 (s, 2H), 3.07 (d, *J*=16.4 Hz, 1H), 2.89 (d, *J*=16.4 Hz, 1H), 2.66–2.41 (m, 4H), 1.60–1.55 (m, 2H), 1.31–1.26 (m, 5H), 1.13 (t, *J*=7.2 Hz, 3H), 0.87 (t, *J*=7.2 Hz, 3H), 0.69 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.9, 170.0, 167.7, 157.2, 144.1, 131.9, 129.3, 128.6, 96.3, 61.7, 59.3, 58.2, 54.9, 39.9, 31.9, 29.6, 22.5, 16.8, 14.6, 13.9, 13.8, 13.5. The enantiomeric excess was determined by HPLC with an AD-H column. (*n*-Hexane/*i*-PrOH=97:3), 1.0 mL/min; major enantiomer t_R=12.2 min, minor enantiomer t_R=15.2 min. HRMS (ESI): [M+H$^+$] calcd for [$C_{24}H_{33}ClNO_5$]: 450.2042, found: 450.2039.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.02.047. This data include MOL file and InChIKey of the most important compound described in this article.

References and notes

1. For a review, see: Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and Its Derivatives*; Elsevier: Amsterdam, 1991.
2. For selected examples of the synthesis of piperidine derivatives, see: (a) Zhang, W.; Franzén, J. *Adv. Synth. Catal.* **2010**, *352*, 499; (b) Zhu, W.; Mena, M.; Jnoff, E.; Sun, N.; Pasau, P.; Ghosez, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5880; (c) Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474; (d) Franzén, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 787; (e) Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222; (f) Zu, L.; Xie, H.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Chem.—Eur. J.* **2008**, *14*, 6333; (g) Franke, P. T.; Johansen, R. L.; Bertelsen, S.; Jørgensen, K. A. *Chem.—Asian J.* **2008**, *3*, 216; (h) Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2008**, *47*, 9971; (i) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836; (j) Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458; (k) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514; (l) Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4534; (m) Kauffman, G. S.; Watson, P. S.; Nugent, W. A. *J. Org. Chem.* **2006**, *71*, 8975; (n) Olofsson, B.; Bogár, K.; Fransson, A.-B. L.; Bäckvall, J.-E. *J. Org. Chem.* **2006**, *71*, 8256; (o) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042; (p) Muthusamy, S.; Krishnamurthi, J.; Suresh, E. *Org. Lett.* **2006**, *8*, 5101; (q) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305.
3. For reviews, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570; (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037; (c) Alba, A.-N.; Companyó, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. For selected examples of organocatalytic cascade reactions, see: (d) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233; (e) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962; (f) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036; (g) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051; (h) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710; (i) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986; (j) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861; (k) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256; (l) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768; (m) Zu, L.-S.; Wang, J.; Li, H.; Xie, H.-X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036; (n) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467; (o) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101; (p) Wang, J.; Li, H.; Xie, H.; Zu, L.; Shen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9050; (q) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946; (r) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425; (s) Cabrera, S.; Aleman, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121; (t) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539; (u) Lu, M.; Zhu, D.; Lu, Y. P.; Hou, Y. X.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187; (v) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699; (w) Schrader, W.; Handayani, P. P.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1463; (x) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892; (y) Wang, Y.; Han, R.-G.; Zhao, Y.-L.; Yang, S.; Xu, P.-F.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9834; (z) McGarraugh, P. G.; Brenner, S. E. *Org. Lett.* **2009**, *11*, 5654.
4. Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336.
5. Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012.
6. (a) Han, R.-G.; Wang, Y.; Li, Y.-Y.; Xu, P.-F. *Adv. Synth. Catal.* **2008**, *350*, 1474; (b) Wang, Y.; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem.—Eur. J.* **2010**, *16*, 3922.
7. For recent reviews on quaternary stereogenic centers, see: (a) Douglas, C. J.; Overmann, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363; (b) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688; (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591; (d) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473; (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369; (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969.
8. For a review on the organocatalytic formation of quaternary stereocenters, see: Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.
9. For selected recent examples regarding the formation of an all-carbon substituted quaternary stereocenter in chiral amine-catalyzed domino reactions, see: (a) Rios, R.; Sunden, H.; Vesely, J.; Zhao, G.-L.; Dziedzic, P.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 1028; (b) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.—Eur. J.* **2008**, *14*, 4788; (c) Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 2437; (d) Ma, A.; Ma, D. *Org. Lett.* **2010**, *12*, 3634.