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Highly enantioselective synthesis of α-trichloromethyldihydropyrans catalyzed by bifunctional organocatalysts

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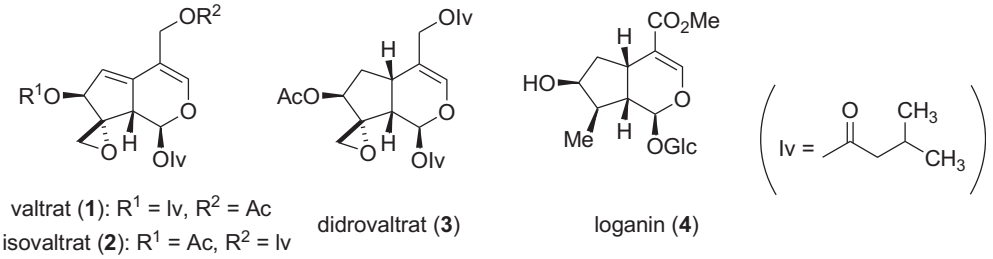
ABSTRACT

The enantioselective Michael addition of α-cyanoketones to α,β-unsaturated trichloromethyl ketones was firstly reported. With a phenylalanine-derived bifunctional piperazine/thiourea catalyst, a series of α-trichloromethyldihydropyrans were obtained with up to 95% ee and 99% yield.

1. Introduction

Dihydropyrans are an important heterocyclic structure extensively present in many biologically active compounds.[1] For examples, the isolated natural products valtrat (**1**), isovaltrat (**2**), and didrovaltrat (**3**) as sedatives exhibited weak to moderate cytotoxicity against lung adenocarcinoma (A549), metastatic prostate cancer (PC-3M), colon cancer (HCT-8), and hepatoma (Bel7402) cell lines;[2] loganin (**4**) exhibited significant anti-HCV entry and anti-infectivity activities (Fig. 1).[3] Consequently, numerous efforts have been done for the construction of this kind of structures.[4]

Recently, our group have developed catalytic asymmetric Michael additions[5] of α-cyanoketones to α,β-unsaturated ketoesters[6d] and CF_3-substituted α,β-unsaturated ketones,[6e] providing facile accesses to a series of chiral dihydropyrans. On the other hand, trichloromethyl ketones are a kind of synthetically highly useful structure, which could be easily converted to carboxylic acids,[7] esters,[8] and amides[8,9] due to the good leaving ability of the trichloromethyl group. However, the reactions of α,β-unsaturated trichloromethyl ketones as an electrophile have rarely been studied. As an extension of our previous works, we herein report the reaction of α-cyanoketones with α,β-unsaturated trichloromethyl



valtrat (**1**): R^1 = Iv, R^2 = Ac
isovaltrat (**2**): R^1 = Ac, R^2 = Iv

didrovaltrat (**3**)

loganin (**4**)

Fig. 1. Several natural compounds with a chiral dihydropyran structure.

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ketones catalyzed by cinchona alkaloids or chiral thioureas, affording a series of novel chiral α-trichloromethyldihydropyrans in high yields and with excellent enantioselectivities.

2. Results and discussion

The Michael addition of 3-oxo-3-phenylpropanenitrile (**7a**) to (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one (**8a**) was selected as a model reaction for catalyst evaluation. First, a series of bifunctional cinchona alkaloid catalysts, with which we have obtained good results in an intramolecular oxa-Michael reaction,[10] were evaluated (Fig. 2 and Table 1). The quinine-derived catalyst **5b** was found to be the best one, providing the desired product **9a** with 68% ee (Table 1, entry 2). The ^{1}H and ^{13}C NMR spectra of **9a** revealed a rapid equilibrium[11] between the cyclic hemiketal **9a** and the Michael-type product **9a**′ with a ratio of around 5:1 (**9a**:**9a**′) (Table 1), which is similar to the result of our previous work.[6d] In order to improve the enantioselectivity, some bifunctional thiourea catalysts derived from chiral α-amino acids previously developed by us and others[6,12] were next evaluated (Fig. 2 and Table 1). For catalysts **6a**–**e** with different amino acid skeletons, comparable or higher enantioselectivities were observed than that obtained with the cinchona alkaloid catalyst**s** with 10 mol % catalyst loading, except for the L-phenylglycine-derivated **6a** (Table 1, entries 14–18). Further variation in the tertiary amine moiety led to the piperazine/thiourea catalyst **6j** as the best one, with which the product **9a** was obtained with up to 78% ee. Notably, thioureas **I**–**IV** derived from cinchona alkaloids and Takemoto's catalyst **V** all gave inferior results (Table 1, entries 22–26), indicating the advantages of amino acids as chiral skeletons in this reaction. In all the cases examined, only one diastereoisomer of the product **9a** was observed.

Subsequent optimization efforts including screens of solvent, catalyst loading, and temperature were then done with the optimal catalyst **6j** (Table 2). It was found that the reaction proceeded well in many other solvents and the best result of 99% yield and 83% ee was obtained in xylenes (Table 2, entry 2). Interestingly, when the reaction was conducted in any one of the three pure isomers of xylenes, both the reaction rate and ee value were significantly reduced (Table 2, entries 3–5). Pleasingly, reducing the catalyst loading from 10 mol % to 5 mol % or 2 mol % increased the ee value to 87% while maintaining the same excellent yield (Table 2, entries 16–17). Lowering the reaction temperature to −10 °C could enhance the ee value to 90% with a similar yield, albeit with an apparently prolonged reaction time (Table 2, entry 18). To summarize, the present reaction was best performed with 2 mol % of **6j** in xylenes at −10 °C.

Having established the optimal conditions, we next explored the scope of the reaction and representative results are listed in Table 3. Generally, with cyanoketone **7a**, for α,β-unsaturated trichloromethyl ketones **8a**–**i**, in which R^1 were differently substituted benzene rings, excellent yields and high ee values were obtained irrespective of the electronic nature of the substituents on the benzene ring (Table 3, entries 1–9). However, when the substituent was on the *ortho* position of the benzene ring, a slight drop in the ee value was observed (Table 3, entries 7, 9). For the heterocyclic substrate **8k** (R^1=furan-2-yl), good results were also achieved (Table 3, entry 11). Notably, when R^1 was an *n*-propyl group, the reaction still proceeded efficiently to give the desired

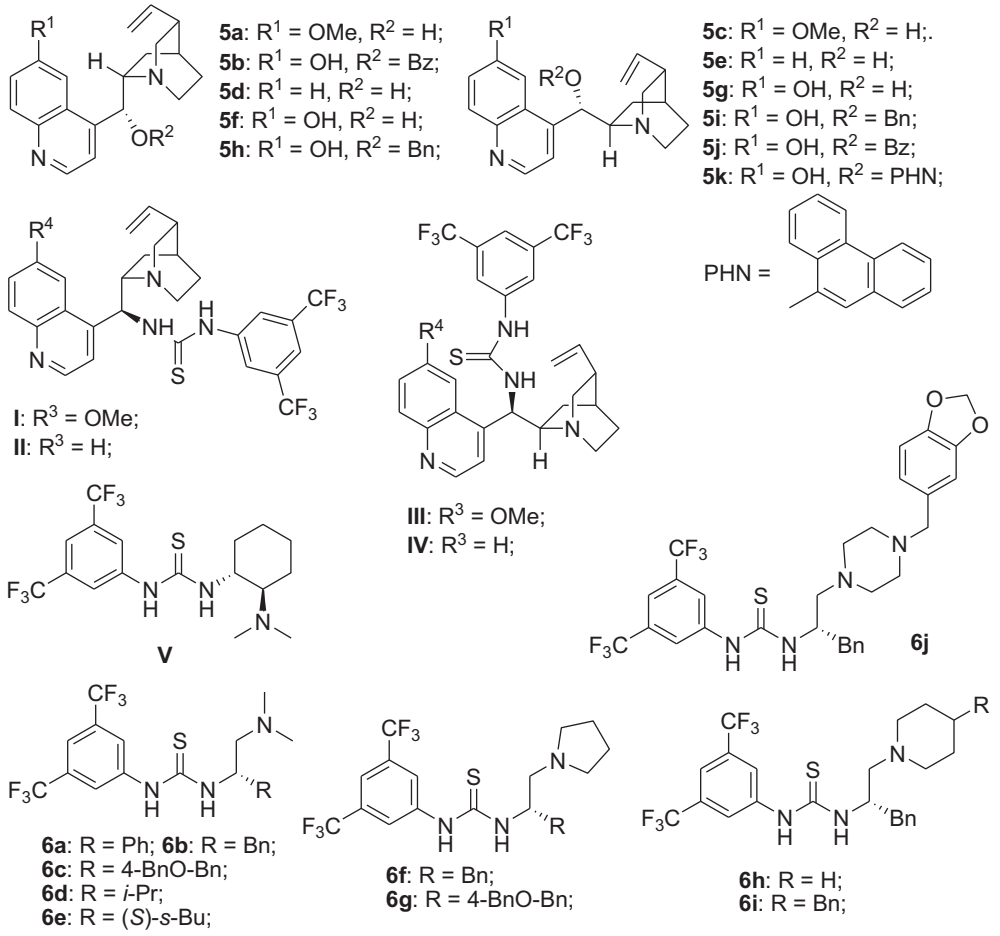
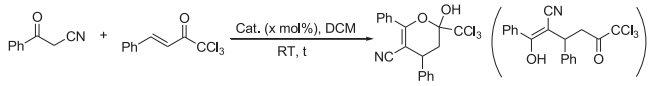


Fig. 2. Bifunctional catalysts screened in this study.

Table 1
Screening of cinchona alkaloid catalysts[a]

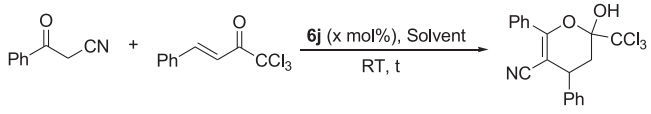


7a 8a 9a 9a'

Entry	Catalyst (x)	t/h	Yield(%)[b]	ee(%)[c]
1	**5a** (20)	9	91	44
2	**5b** (20)	12	96	68
3	**5c** (20)	9	84	−36
4	**5d** (20)	9	81	15
5	**5e** (20)	9	89	0
6	**5f** (20)	9	98	1
7	**5g** (20)	13	84	−10
8	**5h** (20)	11	89	51
9	**5i** (20)	11	81	−43
10	**5j** (20)	22	66	−61
11	**5k** (20)	12	86	−67
12	**6a** (10)	12	91	6
13	**6b** (10)	12	86	70
14	**6c** (10)	12	91	72
15	**6d** (10)	24	96	64
16	**6e** (10)	24	81	60
17	**6f** (10)	16	95	46
18	**6g** (10)	12	86	63
19	**6h** (10)	12	86	67
20	**6i** (10)	24	94	68
21	**6j** (10)	24	95	78
22	**I** (10)	12	94	64
23	**II** (10)	17	96	44
24	**III** (10)	17	94	−29
25	**IV** (10)	17	89	−32
26	**V** (10)	12	86	−42

[a] Unless otherwise noted, the reaction was carried out with **7a** (0.15 mmol), **8a** (0.1 mmol), catalyst, and DCM (1.0 mL) at room temperature for appropriate time.
[b] Yield of the isolated product after column chromatography on silica gel.
[c] Determined by HPLC analysis on a chiral column. Only a single diastereoisomer was observed by ^{1}H NMR analysis of the crude product.

Table 2
Optimization of reaction conditions with catalyst **6j**[a]

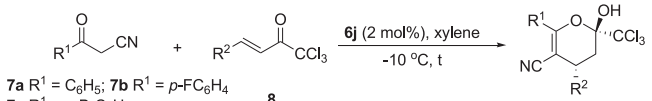


7a 8a 9a

Entry	x	Solvent	t/h	Yield(%)[b]	ee(%)[c]
1	10	Toluene	10	98	78
2	10	Xylenes	6	99	83
3	10	*o*-Xylene	10	97	56
4	10	*m*-Xylene	10	97	57
5	10	*p*-Xylene	10	99	52
6	10	$PhCF_3$	10	99	75
7	10	CH_2Cl_2	24	95	78
8	10	$CHCl_3$	45	97	83
9	10	CCl_4	10	98	80
10	10	$ClCH_2CH_2Cl$	45	97	77
11	10	Et_2O	16	99	81
12	10	THF	72	97	57
13	10	*n*-Hexane	72	98	60
14	10	MTBE	12	98	70
15	10	MeOH	12	98	3
16	5	Xylenes	9	97	84
17	2	Xylenes	9	96	87
18[d]	2	Xylenes	67	94	90

[a] Unless otherwise noted, the reaction was carried out with **7a** (0.15 mmol), **8a** (0.1 mmol), **6j** and solvent (1.0 mL) at room temperature for appropriate time.
[b] Yield of the isolated product after column chromatography on silica gel.
[c] Determined by HPLC analysis on a chiral column. Only a single diastereoisomer was observed by ^{1}H NMR analysis of the crude product.
[d] The reaction was carried out at −10 °C.

Table 3
Examination of the reaction scope with catalyst **6j**[a]



7a R^1 = C_6H_5; **7b** R^1 = *p*-FC_6H_4
7c R^1 = *p*-BrC_6H_4
7d R^1 = *p*-$MeOC_6H_4$
7e R^1 = *n*-Pr; **7f** R^1 = *t*-Bu

8 9

Entry	7	R^2, 8	t/h	9	Yield(%)[b]	ee(%)[c]
1	**7a**	C_6H_5, **8a**	67	**9a**	94	90
2	**7a**	*p*-FC_6H_4, **8b**	66	**9b**	92	90
3	**7a**	*p*-ClC_6H_4, **8c**	60	**9c**	95	90
4	**7a**	*p*-BrC_6H_4, **8d**	36	**9d**	99	90(>99 [d])
5	**7a**	*p*-$NO_2C_6H_4$, **8e**	36	**9e**	98	95
6	**7a**	*p*-MeC_6H_4, **8f**	96	**9f**	93	90
7	**7a**	*o*-ClC_6H_4, **8g**	40	**9g**	98	82[e]
8	**7a**	*m*-ClC_6H_4, **8h**	35	**9h**	99	90
9	**7a**	2,4-diClC_6H_3, **8i**	36	**9i**	97	84[e]
10	**7a**	1-Naphthyl, **8j**	48	**9j**	97	90
11	**7a**	Furan-2-yl, **8k**	96	**9k**	87	86[e]
12	**7a**	*n*-Pr, **8l**	96	**9l**	96	72[e]
13	**7b**	C_6H_5, **8a**	96	**9m**	94	89
14	**7c**	C_6H_5, **8a**	96	**9n**	84	88
15	**7d**	C_6H_5, **8a**	144	**9o**	66	90
16	**7e**	C_6H_5, **8a**	168	**9p**	64	87
17	**7f**	C_6H_5, **8a**	96	–––	Trace	–––

[a] Unless otherwise noted, the reaction was carried out with **7** (0.15 mmol), **8** (0.1 mmol), **6j** (0.002 mmol), and xylenes (1.0 mL) at −10 °C for an appropriate time.
[b] Yield of the isolated product after column chromatography on silica gel.
[c] Determined by HPLC analysis on a chiral column. Only a single diastereoisomer was observed by ^{1}H NMR analysis of the crude product. The absolute configuration of **9d** was determined as 4R, 6S by X-ray crystallographic analysis, and the other products, **9a**–**c** and **9e**–**p** ere assigned by assuming that a similar catalytic mechanism was followed.
[d] The enantioselectivity was determined after a single recrystallization.
[e] The absolute configuration was assigned as 4*S*, 6*S*.

product in excellent yield, though a decrease in enantioselectivity was observed (Table 3, entry 12). Next, various cyanoketones **7** were investigated with α,β-unsaturated trichloromethyl ketone **8a**. When R^1 was an aromatic group, both electron-donating and electron-withdrawing substituents on the benzene ring were tolerated to give the desired products in high ees, though reduced yields and longer reaction times were observed for electron-donating ones (Table 3, entry 13–15). When R^1 was an alkyl group, it was found that the steric hindrance of the substituent displayed a dramatic influence on the reaction: while high ee and moderate yield were obtained for **7e** (R^1=*n*-propyl), the reaction hardly occurred in the case of **7f** bearing a bulky *tert*-butyl group (Table 3, entries 16–17). The absolute configuration of product **9d**, the ee value of which could be increased to >99% after a single recrystallization (Table 3, entry 4), was determined as 4*R*, 6*S* by X-ray crystallographic analysis (Fig. 3).[13]

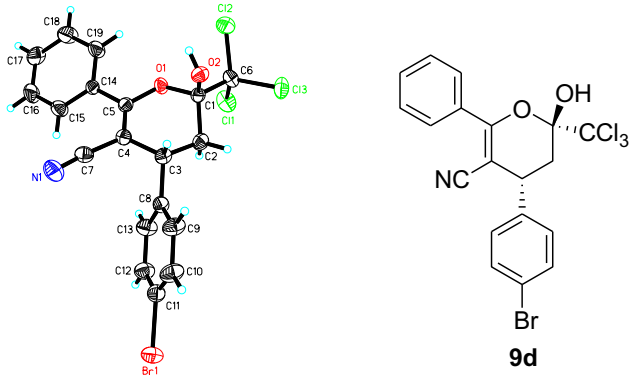
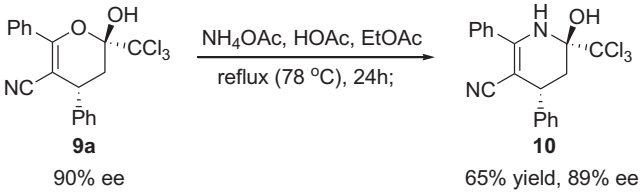


Fig. 3. ORTEP structure of compound **9d**.

Tetrahydropyridine derivatives have exhibited hypotensive, analgesic, anti-inflammatory, and antipyretic activities,[14] even with no observed toxicity at high doses.[15] Studies also revealed that some tetrahydropyridines could increase the cardiac output and reduce the pulmonary and peripheral oedema at a low concentration without changes of heart rate,[16] which may aid in the treatment of congestive heart failure, a widespread and severe disease with character of reduced myocardial contractility. After being treated with NH_4OAc and HOAc in EtOAc at reflux, dihydropyran **9a** could be converted directly to tetrahydropyridine **10** in 65% yield with almost no loss in ee value, which demonstrated the utility of the reaction (Scheme 1).



Scheme 1. Conversion of **9a** to **10**.

3. Conclusion

In conclusion, we have developed a highly enantioselective organocatalytic Michael addition of α-cyanoketones to α,β-unsaturated trichloromethyl ketones using a bifunctional piperazine/thiourea catalyst. With a low catalyst loading of 2.0 mol %, a series of synthetically useful chiral α-trichloromethyldihydropyrans bearing a CCl_3-substituted quaternary stereocenter were obtained with excellent yields and up to 95% ee. Efforts towards applications of the reaction to the synthesis of related biologically active natural products are in progress in our laboratories.

4. Experimental

4.1. General

Unless otherwise indicated, chemicals, and solvents were purchased from commercial suppliers and purified by standard techniques. Flash column chromatography was performed using silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. The ^1H NMR and ^{13}C NMR spectra were recorded on a DPX-400 (100 MHz) with TMS as the internal standard. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as the external standard. All chemical shifts (δ) are given in parts per million. Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, q=quartet, br=broad, and m=multiplet) and coupling constants (Hertz), integration. Analytical high-performance liquid chromatography (HPLC) was carried out on WATERS equipment using a chiral column. Melting points were determined on an SGW X-4 apparatus, and are uncorrected. Optical rotations were measured on a JASCO P-1030 Polarimeter at λ=589 nm. IR spectra were recorded on a Perkin–Elmer 983G instrument. Elementary analysis was taken on a Vario EL III elementary analysis instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd).

4.2. Typical procedure for substrates 8f, 8i–l preparation

To a 25 mL RBF was added α,β-unsaturated aldehyde (5 mmol), $CHCl_3$ (20 mmol, 1.6 mL), and DMF (4 mL), the mixture was stirred at room temperature for about 10 min, then a solution of KOH (5 mmol, 280 mg) in MeOH (4 mL) was added dropwise at 0 °C and the reaction was carried out at this temperature for 2 h (monitored by TLC). The mixture was acidated to pH 4–7 and extracted with ethyl acetate (20 mL). The organic phase was washed with brine (10 mL) and dried over Na_2SO_4, and concentrated in vacuo. This crude secondary alcohol was used without further purification. Under argon atmosphere, the solution of crude secondary alcohol, MnO_2 (15 equiv), DCM (25 mL) was stirred at room temperature for 24–48 h. The residue was filtrated by Celite, concentrated in vacuo, and purified by flash column chromatography on silica gel (petroleum ether) to give the substrates **8**.

*4.2.1. (E)-1,1,1-Trichloro-4-p-tolylbut-3-en-2-one (**8f**).* Yellow solid. Yield: 32%. Mp: 86–88 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.24–7.27 (m, 3H), 7.55 (d, J=7.6 Hz, 2H), 7.98 (d, J=16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 96.6, 114.8, 129.1, 129.9, 131.2, 142.7, 149.8, 180.2; MS (EI): m/z 262 (M^+, 4%), 146 (11), 145 (100), 117 (20), 116 (7), 115 (29), 91 (11), 65 (5); HRMS (EI): m/z calcd for $C_{11}H_9OCl_3$ (M^+): 261.9719, found: 261.9715; IR (KBr) ν 2912, 1708, 1599, 1566, 1513, 1446, 1184, 999 cm^{-1}.

*4.2.2. (E)-1,1,1-Trichloro-4-(2,4-dichlorophenyl)but-3-en-2-one (**8i**).* White solid. Yield: 30%. Mp: 96–98 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.35 (m, 2H), 7.49 (d, J=2.1 Hz, 1H), 7.69 (d, J=8.4 Hz, 1H), 8.33 (d, J=15.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.1, 118.5, 127.7, 128.8, 130.3, 130.6, 136.6, 137.8, 143.8, 179.4; MS (EI): m/z 318 (M^+, 3%), 201 (65), 200 (11), 199 (100), 173 (16), 171 (24), 136 (28), 135 (20), 99 (19); HRMS (EI): m/z calcd for $C_{10}H_5OCl_5$ (M^+): 315.8783, found: 315.8788; IR (KBr) ν 1716, 1610, 1582, 1469, 1386, 1314, 1100, 980 cm^{-1}.

*4.2.3. (E)-1,1,1-Trichloro-4-(naphthalen-1-yl)but-3-en-2-one (**8j**).* Yellow solid. Yield: 26%. Mp: 107–109 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J=15.2 Hz, 1H), 7.52–7.64 (m, 3H), 7.90–7.97 (m, 2H), 7.98 (d, J=8.0 Hz, 1H), 8.25 (d, J=8.0 Hz, 1H), 8.87 (d, J=15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.5, 118.2, 123.1, 125.4, 126.0, 126.6, 127.5, 129.0, 131.0, 131.7, 132.2, 133.8, 146.4, 180.0; MS (EI): m/z 300 (6%), 298 (M^+, 6), 182 (14), 181 (100), 153 (18), 152 (40), 151 (13), 76 (6); HRMS (EI): m/z calcd for $C_{14}H_9OCl_3$ (M^+): 297.9719, found: 297.9724; IR (KBr) ν 2923, 1705, 1602, 1569, 1347, 1123, 978, 790 cm^{-1}.

*4.2.4. (E)-1,1,1-Trichloro-4-(furan-2-yl)but-3-en-2-one (**8k**).* Yellow solid. Yield: 10%. Mp: 42–44 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 1H), 6.83 (d, J=2.8 Hz, 1H), 7.22 (d, J=15.6 Hz, 1H), 7.59 (s, 1H), 7.73 (d, J=15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.5, 113.2, 113.4, 118.5, 134.8, 146.3, 150.9, 180.3; MS (EI): m/z 240 (7%), 238 (M^+, 7), 177 (6), 175 (8), 122 (8), 121 (100), 65 (25), 63 (6); HRMS (EI): m/z calcd for $C_8H_5O_2Cl_3$ (M^+): 237.9355, found: 237.9354; IR (KBr) ν 2855, 1705, 1606, 1546, 1470, 1388, 1269, 986 cm^{-1}.

*4.2.5. (E)-1,1,1-Trichlorohept-3-en-2-one (**8l**).* Colorless liquid. Yield: 7%. ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J=7.2 Hz, 3H), 1.53–1.62 (m, 2H), 2.31–2.37 (m, 2H), 6.75 (d, J=15.6 Hz, 1H), 7.31–7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 21.1, 35.0, 96.4, 119.8, 155.6, 179.7; MS (EI): m/z 179 ([M–Cl]$^+$, 2%), 98 (7), 97 (100), 69 (8), 68 (6), 55 (81), 53 (5), 41 (21), 40 (4); HRMS (EI): m/z calcd for $C_7H_9OCl_3$ (M^+): 213.9719, found: 213.9718; IR (KBr) ν 2963, 1724, 1677, 1628, 1460, 1101, 978, 830 cm^{-1}.

4.3. Typical procedure for Michael reaction

A mixture of cyanoketone **7** (0.15 mmol), α,β-unsaturated trichloromethyl ketone **8** (0.1 mmol), and catalyst **6j** (0.002 mmol) in 1.0 mL of xylene was stirred at −10 °C for the appropriate times until the disappearance of **8** (monitored by TLC). The reaction

mixture was then concentrated, and the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether=1:10) to give the desired products **9**.

*4.3.1. (4R, 6S)-6-Hydroxy-2,4-diphenyl-6-(trichloromethyl)-5,6-dihydro-4H-pyran-3-carbonitrile (**9a**).* White solid (37.3 mg, 94% isolated yield, 90% ee). $[\alpha]_D^{25}$ −5.0 (*c* 0.93, $CHCl_3$). Mp: 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (dt, J_1=3.2 Hz, J_2=13.2 Hz, 1H), 2.80 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 3.96 (d, J=3.2 Hz, 1H), 4.03 (dd, J_1=6.0 Hz, J_2=12.8 Hz, 1H), 7.35–7.50 (m, 8H), 7.87 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.7, 38.4, 90.0, 101.3, 102.9, 118.2, 128.1, 128.2, 128.6, 129.3, 131.3, 132.0, 139.7, 162.0; MS (ESI): *m*/*z* 417.9 ($[M+Na]^+$); HRMS (MALDI): *m*/*z* calcd for ($[C_{19}H_{14}Cl_3NO_2+Na]^+$): 415.9970, found: 415.9982; IR (KBr) ν 3296, 2214, 1612, 1576, 1494, 1338, 1141, 827 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=19.86 min, t_R (major)=23.22 min, λ=254 nm.

*4.3.2. (4R,6S)-4-(4-Fluorophenyl)-6-hydroxy-2-phenyl-6-(trichloromethyl)-5,6-dihydro-4H-pyran-3-carbonitrile (**9b**).* White solid (37.8 mg, 92% isolated yield, 90% ee). $[\alpha]_D^{28}$ −6.8 (*c* 0.95, $CHCl_3$). Mp: 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (t, J=13.2 Hz, 1H), 2.76 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 4.00 (dd, J_1=5.6 Hz, J_2=12.4 Hz, 1H), 4.35 (br s, 1H), 7.10 (t, J=8.4 Hz, 2H), 7.31–7.35 (m, 2H), 7.42–7.51 (m, 3H), 7.84 (d, J=7.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −114.34 (s, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 37.7, 89.8, 101.2, 102.8, 116.2 (d, J=21.1 Hz), 118.1, 128.0, 128.6, 129.7, 129.8, 131.4, 131.9, 135.3 (d, J=3.0 Hz), 162.1 (d, J=2.9 Hz), 162.5 (d, J=245.7 Hz); MS (ESI): *m*/*z* 434.1 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{19}H_{13}FCl_3NO_2+Na]^+$): 433.9888, found: 433.9898; IR (KBr) ν 3245, 2224, 1617, 1577, 1509, 1338, 1158, 829 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=25.10 min, t_R (major)=29.29 min, λ=254 nm.

*4.3.3. (4R, 6S)-4-(4-Chlorophenyl)-6-hydroxy-2-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9c**).* White solid (40.6 mg, 95% isolated yield, 90% ee). $[\alpha]_D^{29}$ −7.3 (*c* 1.00, $CHCl_3$). Mp: 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (t, J=13.2 Hz, 1H), 2.75 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 3.99 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 4.31 (br s, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.42–7.51 (m, 3H), 7.83 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 37.9, 89.4, 101.2, 102.8, 118.0, 128.0, 128.6, 129.4, 129.5, 131.4, 131.8, 134.0, 138.1, 162.3; MS (ESI): *m*/*z* 450.1 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{19}H_{13}Cl_4NO_2+Na]^+$): 449.9593, found: 449.9590; IR (KBr) ν 3344, 2217, 1615, 1576, 1491, 1338, 1154, 827 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=28.39 min, t_R (major)=34.34 min, λ=254 nm.

*4.3.4. (4R, 6S)-4-(4-Bromophenyl)-6-hydroxy-2-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9d**).* White solid (47.0 mg, 99% isolated yield, 90% ee). $[\alpha]_D^{29}$ −6.4 (*c* 0.94, $CHCl_3$). Mp: 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (t, J=12.8 Hz, 1H), 2.74 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 3.97 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 4.33 (br s, 1H), 7.23 (d, J=8.4 Hz, 2H), 7.41–7.50 (m, 3H), 7.54 (d, J=8.0 Hz, 2H), 7.83 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 38.0, 89.3, 101.2, 102.8, 118.0, 122.1, 128.1, 128.6, 129.8, 131.5, 131.8, 132.4, 138.7, 162.3; MS (ESI): *m*/*z* 495.8 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{19}H_{13}BrCl_3NO_2+Na]^+$): 493.9088, found: 493.9089; IR (KBr) ν 3350, 2214, 1616, 1576, 1487, 1339, 1150, 824 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=33.61 min, t_R (major)=42.00 min, λ=254 nm.

*4.3.5. (4R, 6S)-6-Hydroxy-4-(4-nitrophenyl)-2-phenyl-6-(trichloromethyl)-5,6-dihydro-4H-pyran-3-carbonitrile (**9e**).* White solid (43.1 mg, 98% isolated yield, 95% ee). $[\alpha]_D^{26}$ −0.7 (*c* 0.86, EtOH). Mp: 152–154 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 2.83 (d, J=5.6 Hz, 1H), 3.37 (s, 1H), 4.26 (d, J=5.2 Hz, 1H), 5.54 (s, 1H), 7.53–7.59 (m, 3H), 7.76 (d, J=7.6 Hz, 2H), 7.95 (d, J=7.2 Hz, 2H), 8.36 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 36.9, 51.9, 86.5, 100.4, 101.4, 116.5, 122.4, 126.6, 126.7, 127.8, 129.6, 130.9, 146.2, 146.5, 162.2; MS (ESI): *m*/*z* 461.0 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{19}H_{13}Cl_3N_2O_4+Na]^+$): 460.9833, found: 460.9874; IR (KBr) ν 3328, 2219, 1619, 1577, 1519, 1347, 1154, 833 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 4/1, flow rate: 0.75 mL/min, t_R (minor)=23.37 min, t_R (major)=33.91 min, λ=254 nm.

*4.3.6. (4R, 6S)-6-Hydroxy-2-phenyl-4-p-tolyl-6-(trichloromethyl)-5,6-dihydro-4H-pyran-3-carbonitrile (**9f**).* White solid (38.0 mg, 93% isolated yield, 90% ee). $[\alpha]_D^{29}$ −8.0 (*c* 0.95, $CHCl_3$). Mp: 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34–2.38 (m, 4H), 2.74 (dd, J_1=6.4 Hz, J_2=13.6 Hz, 1H), 3.96 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 4.31 (br s, 1H), 7.20–7.25 (m, 4H), 7.40–7.49 (m, 3H), 7.83 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 33.7, 38.0, 90.3, 101.3, 103.0, 118.2, 128.0, 128.1, 128.6, 130.0, 131.2, 132.1, 136.6, 137.9, 161.9; MS (ESI): *m*/*z* 430.1 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{20}H_{16}Cl_3NO_2+Na]^+$): 430.0139, found: 430.0143; IR (KBr) ν 3204, 2226, 1617, 1514, 1448, 1337, 1138, 836 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=16.48 min, t_R (major)=19.47 min, λ=254 nm.

*4.3.7. (4S, 6S)-4-(2-Chlorophenyl)-6-hydroxy-2-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9g**).* Yellowish solid (42.1 mg, 98% isolated yield, 82% ee). $[\alpha]_D^{29}$ +31.8 (*c* 0.84, $CHCl_3$). Mp: 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16–2.22 (m, 1H), 2.85–2.87 (m, 1H), 4.36 (s, 1H), 4.67–4.69 (m, 1H), 7.22–7.50 (m, 7H), 7.84 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 34.5, 88.9, 101.3, 102.8, 118.0, 127.8, 128.1, 128.6, 128.7, 129.3, 130.1, 131.4, 132.0, 134.2, 137.2, 163.0; MS (ESI): *m*/*z* 450.0 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{19}H_{13}Cl_4NO_2+Na]^+$): 449.9593, found: 449.9599; IR (KBr) ν 3232, 2225, 1610, 1568, 1474, 1341, 1141, 824 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 19/1, flow rate: 0.75 mL/min, t_R (minor)=33.30 min, t_R (major)=37.55 min, λ=254 nm.

*4.3.8. (4R, 6S)-4-(3-Chlorophenyl)-6-hydroxy-2-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9h**).* White solid (42.5 mg, 99% isolated yield, 90% ee). $[\alpha]_D^{28}$ −6.2 (*c* 0.85, $CHCl_3$). Mp: 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (t, J=12.8 Hz, 1H), 2.76 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 3.98 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 4.37 (br s, 1H), 7.23–7.24 (m, 1H), 7.24–7.37 (m, 3H), 7.41–7.51 (m, 3H), 7.83 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 38.2, 89.1, 101.2, 102.7, 118.0, 126.4, 128.1, 128.3, 128.5, 128.6, 130.6, 131.5, 131.8, 135.0, 141.7, 162.5; MS (ESI): *m*/*z* 450.0 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{19}H_{13}Cl_4NO_2$ $Na]^+$): 449.9593, found: 449.9589; IR (KBr) ν 3244, 2220, 1596, 1573, 1497, 1335, 1139, 841 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=13.21 min, t_R (major)=15.97 min, λ=254 nm.

*4.3.9. (4S, 6S)-4-(2,4-Dichlorophenyl)-6-hydroxy-2-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9i**).* White solid (44.9 mg, 97% isolated yield, 84% ee). $[\alpha]_D^{26}$ +20.2 (*c* 0.90, EtOH). Mp: 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ 2.15–2.20 (m, 1H), 2.80–2.83 (m, 1H), 4.65 (s, 1H), 7.30–7.47 (m, 8H), 7.88 (d, J=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 32.6, 34.3, 87.9, 101.7, 103.0, 118.3, 126.8, 128.1, 128.5, 129.6, 129.8, 131.3, 132.1, 134.2, 134.8, 163.8; MS (ESI): *m*/*z* 484.0 ($[M+Na]^+$); HRMS (ESI): *m*/*z* calcd for ($[C_{19}H_{12}Cl_5NO_2+Na]^+$): 483.9203, found: 483.9187; IR (KBr) ν 3247, 2225, 1620, 1589, 1496, 1387, 1146, 823 cm^{-1}. The ee was

determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 19/1, flow rate: 0.75 mL/min, t_R (minor)=30.96 min, t_R (major)=35.47 min, λ=254 nm.

*4.3.10. (4R, 6S)-6-Hydroxy-4-(naphthalen-1-yl)-2-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9j**).* White solid (43.0 mg, 97% isolated yield, 90% ee). $[\alpha]_D^{28}$ +71.7 (*c* 0.87, $CHCl_3$). Mp: 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (t, *J*=12.8 Hz, 1H), 2.94 (dd, J_1=6.0 Hz, J_2=13.2 Hz, 1H), 4.35 (s, 1H), 4.97 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 7.41–7.61 (m, 7H), 7.84–7.99 (m, 4H), 8.12 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 33.6, 90.0, 101.4, 102.9, 122.1, 125.2, 125.8, 126.0, 126.9, 128.2, 128.6, 129.3, 131.4, 134.1, 136.0, 163.0; MS (ESI): *m*/*z* 466.0 ([M+Na]$^+$); HRMS (ESI): *m*/*z* calcd for ([$C_{23}H_{16}Cl_3NO_2$+Na]$^+$): 466.0139, found: 466.0143; IR (KBr) ν 3191, 2226, 1621, 1598, 1448, 1396, 1140, 819 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=16.67 min, t_R (major)=19.41 min, λ=254 nm.

*4.3.11. (4S, 6S)-4-(Furan-2-yl)-6-hydroxy-2-phenyl-6-(trichloromethyl)-5,6-dihydro-4H-pyran-3-carbonitrile (**9k**).* White solid (33.4 mg, 87% isolated yield, 86% ee). $[\alpha]_D^{28}$ −21.6 (*c* 0.84, $CHCl_3$). Mp: 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (t, *J*=12.8 Hz, 1H), 2.76 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 4.17 (dd, J_1=6.0 Hz, J_2=12.8 Hz, 1H), 4.34 (br s, 1H), 6.39 (s, 2H), 7.40–7.49 (m, 4H), 7.80 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 32.1, 88.1, 101.3, 108.6, 110.7, 128.1, 128.5, 128.9, 129.3, 131.3, 131.9, 142.9, 151.3, 161.8; MS (ESI): *m*/*z* 406.0 ([M+Na]$^+$); HRMS (ESI): *m*/*z* calcd for ([$C_{17}H_{12}Cl_3NO_3$+Na]$^+$): 405.9775, found: 405.9767; IR (KBr) ν 3267, 2220, 1619, 1577, 1448, 1336, 1142, 822 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=16.58 min, t_R (major)=20.20 min, λ=254 nm.

*4.3.12. (4S, 6S)-6-Hydroxy-2-phenyl-4-propyl-6-(trichloromethyl)-5,6-dihydro-4H-pyran-3-carbonitrile (**9l**).* White solid (34.5 mg, 96% isolated yield, 72% ee). $[\alpha]_D^{28}$ −4.0 (*c* 0.86, $CHCl_3$). Mp: 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J*=7.2 Hz, 3H), 1.37–1.59 (m, 3H), 1.92–2.05 (m, 2H), 2.58–2.76 (m, 1H), 2.77–2.82 (m, 1H), 4.11 (s, 1H), 7.40–7.46 (m, 3H), 7.78 (d, *J*=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.5, 29.7, 30.2, 35.1, 90.7, 101.5, 103.3, 118.3, 128.0, 128.5, 131.0, 132.2, 161.5; MS (ESI): *m*/*z* 382.0 ([M+Na]$^+$); HRMS (ESI): *m*/*z* calcd for ([$C_{16}H_{16}Cl_3NO_2$+Na]$^+$): 382.0139, found: 382.0145; IR (KBr) ν 3319, 2223, 1611, 1575, 1446, 1378, 1146, 821 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=10.77 min, t_R (major)=14.58 min, λ=254 nm.

*4.3.13. (4R, 6S)-2-(4-Fluorophenyl)-6-hydroxy-4-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9m**).* Yellowish solid (39.0 mg, 94% isolated yield, 89% ee). $[\alpha]_D^{28}$ −4.5 (*c* 0.99, $CHCl_3$). Mp: 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (t, *J*=12.8 Hz, 1H), 2.77 (dd, J_1=6.0 Hz, J_2=13.2 Hz, 1H), 3.99 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 4.35 (br s, 1H), 7.11 (t, *J*=8.4 Hz, 2H), 7.34–7.41 (m, 5H), 7.83–7.87 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.94 (s, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 38.4, 90.0, 101.3, 102.9, 115.8 (d, *J*=21.9 Hz), 118.1, 128.1, 128.2, 129.3, 130.3, 130.4, 139.5, 161.0, 164.3 (d, *J*=251.6 Hz); MS (ESI): *m*/*z* 434.0 ([M+Na]$^+$); HRMS (ESI): *m*/*z* calcd for ([$C_{19}H_{13}FCl_3NO_2$+Na]$^+$): 433.9888, found: 433.9877; IR (KBr) ν 3394, 2211, 1654, 1604, 1508, 1338, 1152, 836 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD-H column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=41.98 min, t_R (major)=54.25 min, λ=254 nm.

*4.3.14. (4R, 6S)-2-(4-Bromophenyl)-6-hydroxy-4-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9n**).* White solid (39.7 mg, 84% isolated yield, 88% ee). $[\alpha]_D^{28}$ −0.3 (*c* 0.99, $CHCl_3$). Mp: 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (t, *J*=13.2 Hz, 1H), 2.77 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 3.98 (dd, J_1=6.0 Hz, J_2=12.0 Hz, 1H), 4.32 (br s, 1H), 7.33–7.43 (m, 5H), 7.56 (d, *J*=8.8 Hz, 2H), 7.71 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 38.4, 90.6, 101.4, 102.8, 117.9, 125.8, 128.1, 128.3, 129.3, 129.6, 130.8, 131.9, 139.3, 160.9; MS (ESI): *m*/*z* 493.9 ([M+Na]$^+$); HRMS (ESI): *m*/*z* calcd for ([$C_{19}H_{13}BrCl_3NO_2$+Na]$^+$): 493.9088, found: 493.9080; IR (KBr) ν 3234, 2224, 1616, 1589, 1487, 1331, 1160, 829 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AD-H column, hexane/2-propanol: 9/1, flow rate: 0.75 mL/min, t_R (minor)=15.61 min, t_R (major)=19.46 min, λ=254 nm.

*4.3.15. (4R, 6S)-6-Hydroxy-2-(4-methoxyphenyl)-4-phenyl-6-(trichloromethyl)-5,6-di-hydro-4H-pyran-3-carbonitrile (**9o**).* White solid (28.0 mg, 66% isolated yield, 90% ee). $[\alpha]_D^{28}$ +6.7 (*c* 0.93, $CHCl_3$). Mp: 77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (t, *J*=12.8 Hz, 1H), 2.76 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 3.84 (s, 3H), 4.00 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 4.19 (br s, 1H), 6.94 (d, *J*=8.8 Hz, 2H), 7.35–7.43 (m, 5H), 7.83 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 38.4, 55.5, 88.4, 101.2, 103.1, 113.9, 114.5, 114.6, 127.6, 128.1, 129.2, 129.7, 131.4, 140.0, 161.9; MS (ESI): *m*/*z* 448.0 ([M+Na]$^+$); HRMS (ESI): *m*/*z* calcd for ([$C_{20}H_{16}Cl_3NO_3$+Na]$^+$): 446.0088, found: 446.0077; IR (KBr) ν 3368, 2210, 1608, 1511, 1455, 1338, 1176, 832 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AS-H column, hexane/2-propanol: 4/1, flow rate: 0.75 mL/min, t_R (minor)=15.81 min, t_R (major)=32.35 min, λ=254 nm.

*4.3.16. (4R, 6S)-6-Hydroxy-4-phenyl-2-propyl-6-(trichloromethyl)-5,6-dihydro-4H-pyran-3-carbonitrile (**9p**).* Colorless liquid (23.0 mg, 64% isolated yield, 87% ee). $[\alpha]_D^{25}$ −3.6 (*c* 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, *J*=7.2 Hz, 3H), 1.66–1.72 (m, 2H), 2.19 (t, *J*=12.4 Hz, 1H), 2.48–2.63 (m, 2H), 2.67 (dd, J_1=6.0 Hz, J_2=13.6 Hz, 1H), 3.84 (dd, J_1=6.0 Hz, J_2=12.4 Hz, 1H), 3.97 (br s, 1H), 7.25–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 20.1, 33.6, 35.2, 37.0, 90.2, 100.8, 102.9, 117.5, 127.9, 128.0, 129.2, 139.7, 166.9; MS (EI): *m*/*z* 359 (M$^+$, 2%), 131 (48), 129 (11), 104 (10), 103 (16), 77 (12), 71 (100), 43 (48), 41 (12); HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}NO_2Cl_3$ (M$^+$): 359.0247, found: 359.0249; IR (KBr) ν 3352, 2217, 1651, 1538, 1456, 1384, 1265, 739 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AS-H column, hexane/2-propanol: 4/1, flow rate: 0.75 mL/min, t_R (minor)=8.78 min, t_R (major)=12.10 min, λ=254 nm.

4.4. General procedure for synthesis of compound 10

A mixture of compound **9a** (0.1 mmol, 90% ee), NH_4OAc (1.2 mmol, 92 mg), and HOAc (1.0 mL) in EtOAc (1.0 mL) was stirred at 78 °C (reflux condition) for 24 h (monitored by TLC). Then the reaction mixture was dissolved in EtOAc (10 mL), washed with saturated $NaHCO_3$ (10 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether=1:6) to give the desired products **10**.

*4.4.1. (4R)-6-Hydroxy-2,4-diphenyl-6-(trichloromethyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**10**).* White solid (24.0 mg, 65% isolated yield, 89% ee). $[\alpha]_D^{25}$ −8.6 (*c* 1.00, $CHCl_3$). Mp: 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (t, *J*=13.2Hz, 1H), 2.54 (dd, J_1=4.4 Hz, J_2=13.2 Hz, 1H), 3.86 (s, 1H), 3.92 (dd, J_1=4.4 Hz, J_2=13.2 Hz, 1H), 5.36 (s, 1H), 7.30–7.49 (m, 8H), 7.58 (d, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 38.6, 83.9, 87.3, 105.3, 119.6, 127.8, 127.9, 128.2, 129.0, 129.1, 130.8, 134.7, 140.6, 153.6; MS (ESI): *m*/*z* 415.0 ([M+Na]$^+$); HRMS (EI): *m*/*z* calcd for $C_{19}H_{15}N_2OCl_3$ (M$^+$): 392.0250, found: 392.0251; IR (KBr) ν 3418, 2198, 1616, 1576, 1487, 1339, 1265, 739 cm^{-1}. The ee was determined by HPLC analysis using a chiralcel AS-H column, hexane/2-propanol: 4/1, flow rate:

0.75 mL/min, t_R (minor)=19.14 min, t_R (major)=27.32 min, λ=254 nm.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.043.

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