Supporting information

Design and Process Study of Chiral Separation of (2*S*, 4*S*)-1-(*tert*-butoxy carbonyl)-4-(methoxymethyl) pyrrolidine-2-carboxylic acid for Green Manufacturing

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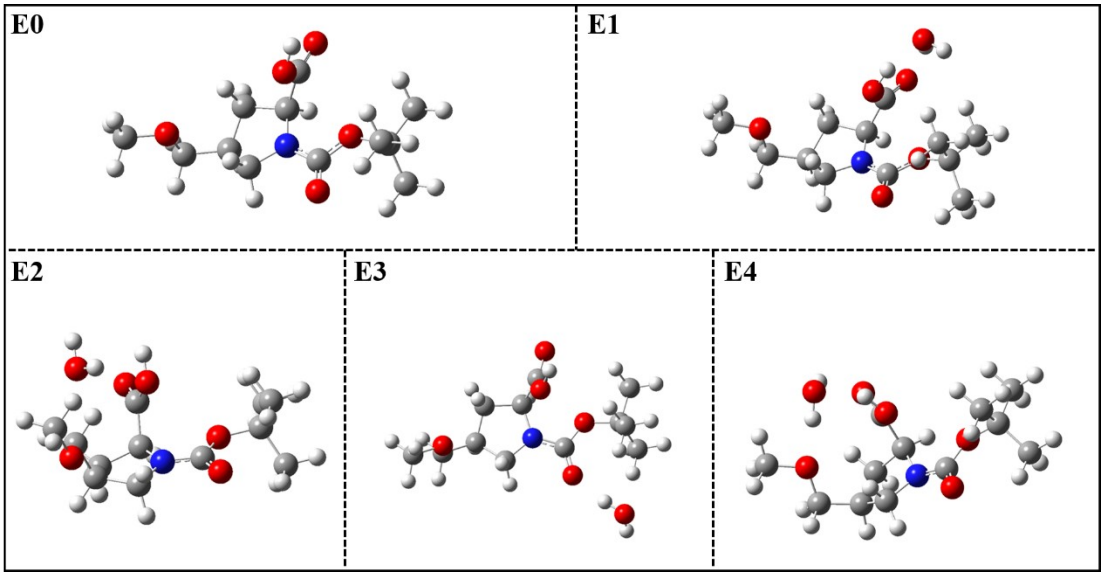


Fig S1. Hydrogen bonds of (2*S*, 4*S*)-TBMP with water at the different positions

Table S1 The hydrogen bonding energy and distances of the (2*S*, 4*S*)-TBMP with water

Energy	E total energy (Hartee)	E correction (Hartee)	E total energy+ E correction (Hartee)	ΔE(kcal/mol)	$D_{H\cdots O}$(Å)
E_0	-900.82462751	0.334076	-900.4905991	/	/
E_{water}	-76.40895332	0.021168	-76.38778532	/	/
E_1	-977.33313321	0.360512	-976.97262121	-59.1345280929	1.739
E_2	-977.31975384	0.359007	-976.96074684	-51.6832421742	1.932
E_3	-977.32076811	0.358917	-976.96185111	-52.3761826419	1.846
E_4	-977.32941487	0.361285	-976.96812987	-56.3161673295	2.085

ΔE(kcal/mol) =(E-E_{water}-E_0) *627.51(kcal/mol)

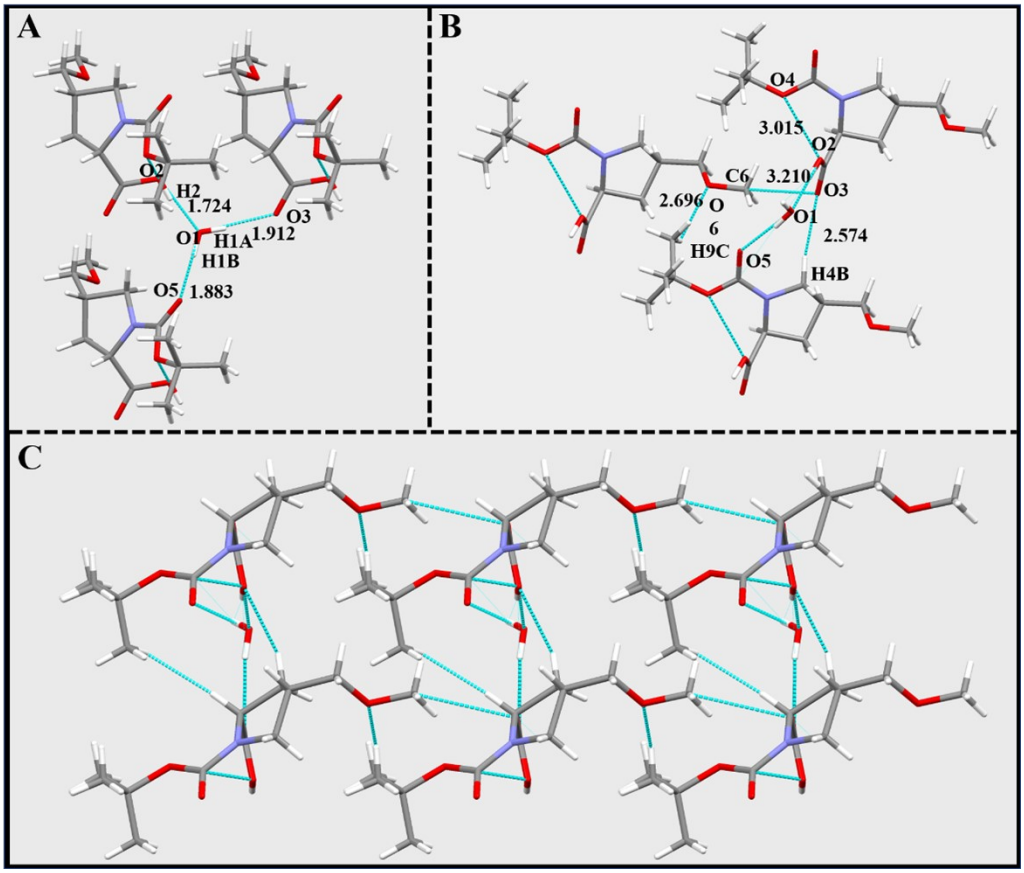


Fig. S2 The map of hydrogen bonds of Crystal **1**, C-grey, N-blue, O-red, H-off-white, **A)** and **B)** The distances of hydrogen bonds in the molecules of Crystal **1**,
C) Crystal **1** packing along the b-axis

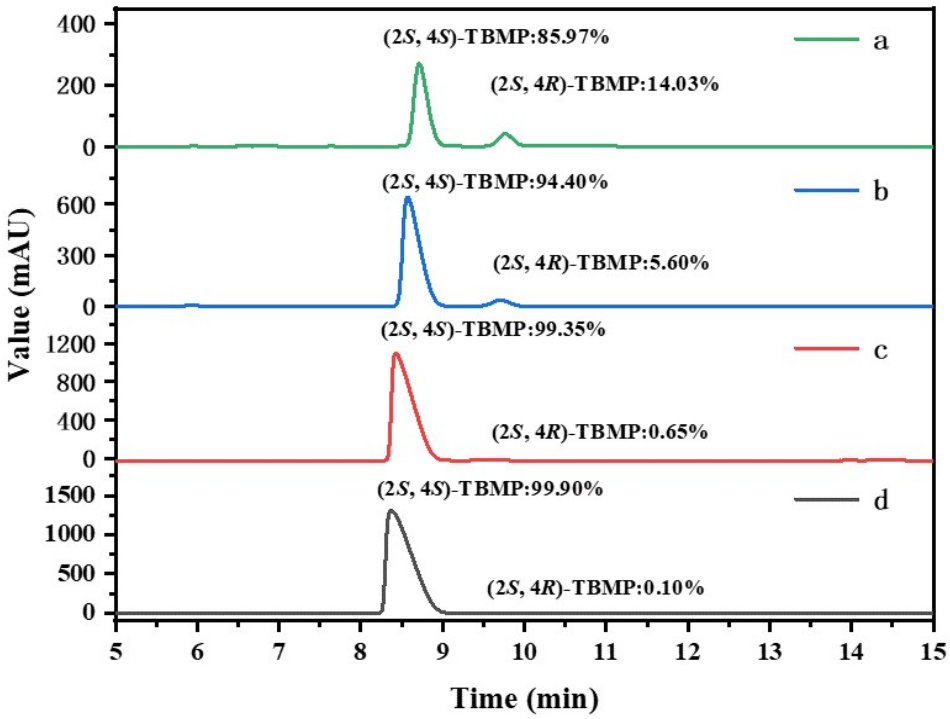


Fig. S3 The HPLC curve of the first batch of (2*S*, 4*S*)-TBMP and (2*S*, 4*R*)-TBMP: a) initial raw material; b) the first crystallization product; c) the second crystallization product; d) the third crystallization product

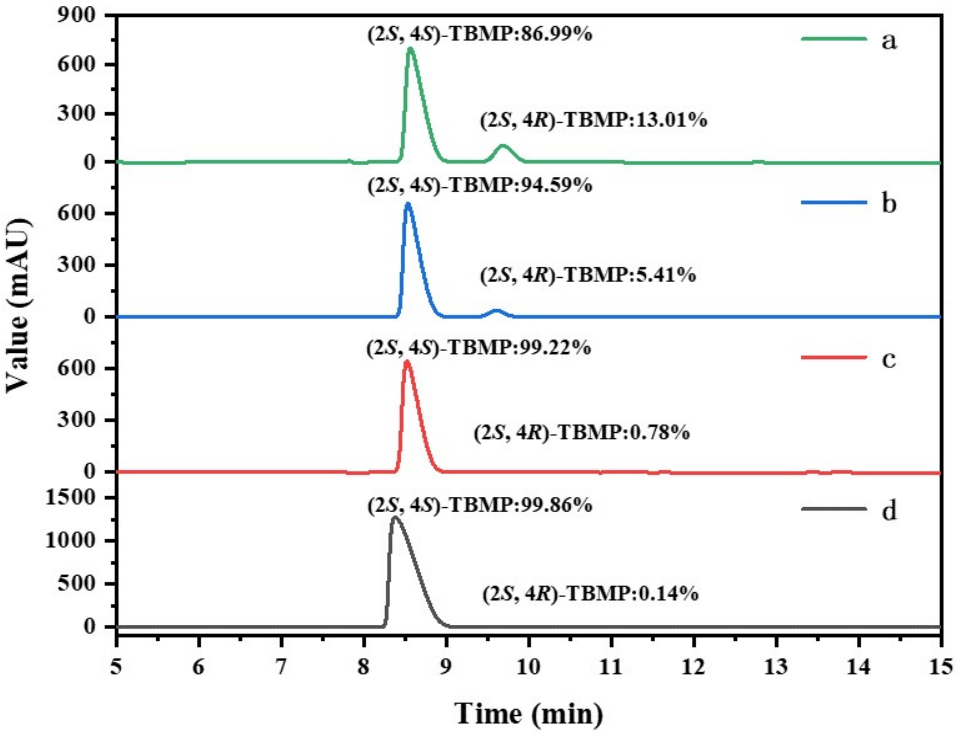


Fig. S4 The HPLC curve of the second batch of (2*S*, 4*S*)-TBMP and (2*S*, 4*R*)-TBMP, a) initial raw material; b) the first crystallization product; c) the second crystallization product; d) the third crystallization product

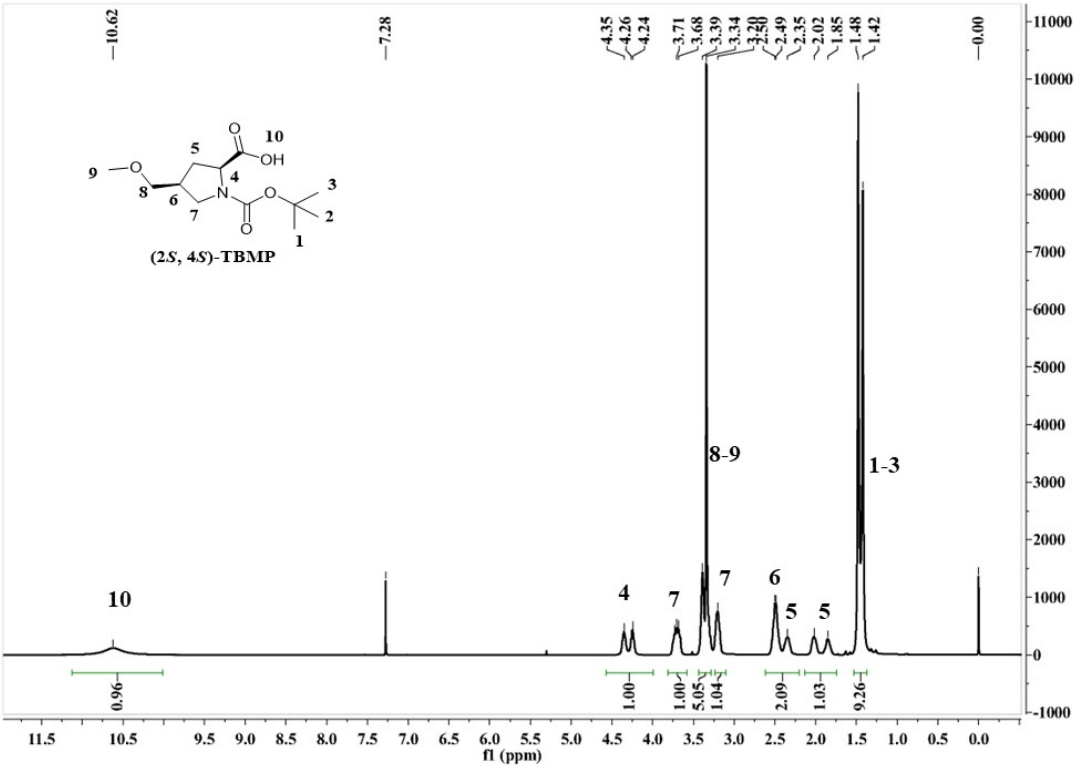


Fig. S5 The ^{1}H NMR spectrum of (2*S*, 4*S*)-TBMP

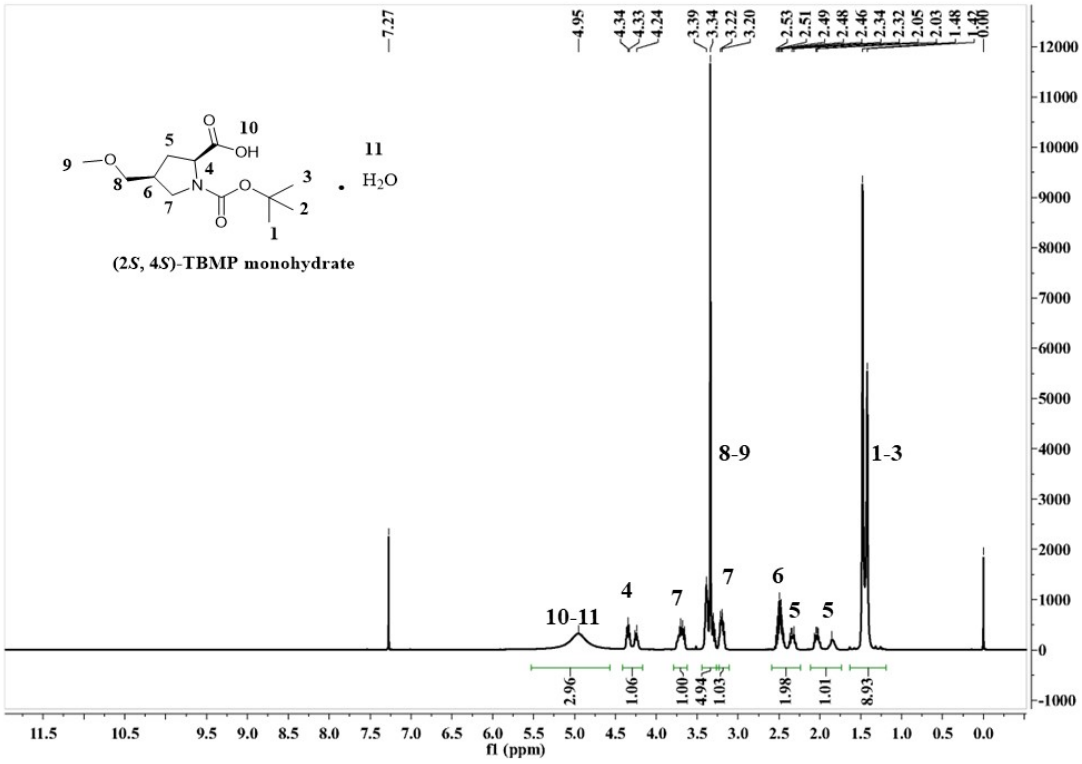


Fig. S6 The ^{1}H NMR spectrum of (2*S*, 4*S*)-TBMP monohydrate

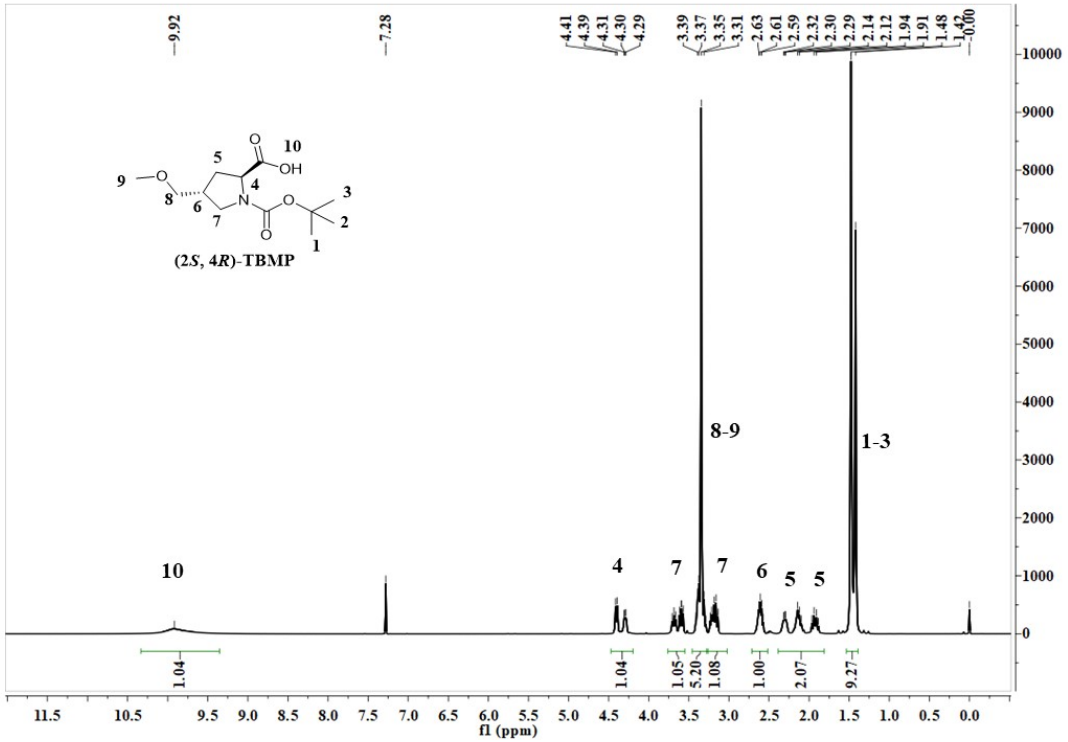


Fig. S7 The ^{1}H NMR spectrum of (2*S*, 4*R*)-TBMP

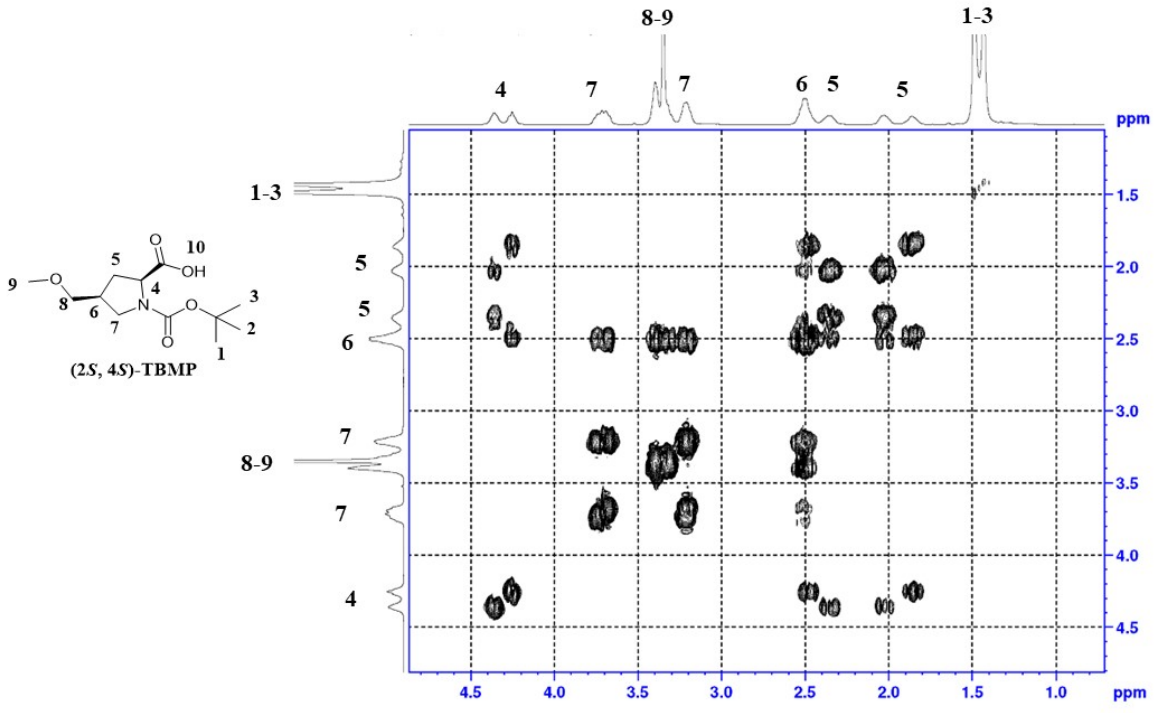


Fig. S8 The HSQC spectrum of (2*S*, 4*S*)-TBMP

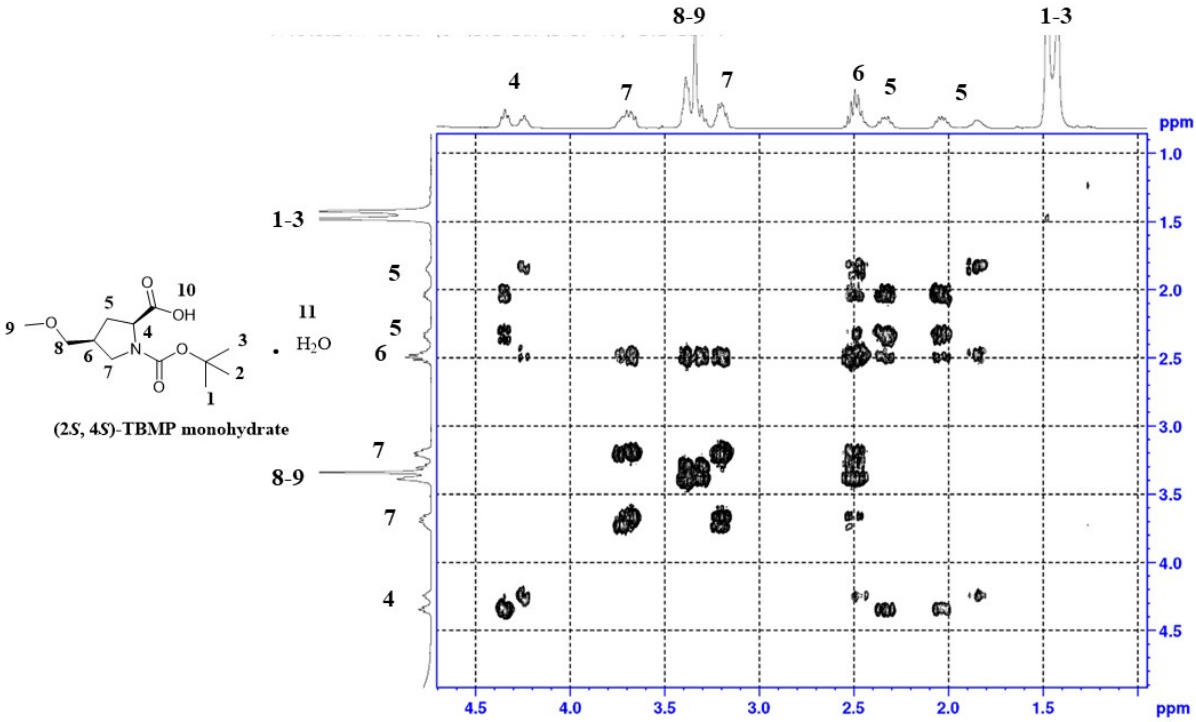


Fig. S9 The HSQC spectrum of (2*S*, 4*S*)-TBMP monohydrate

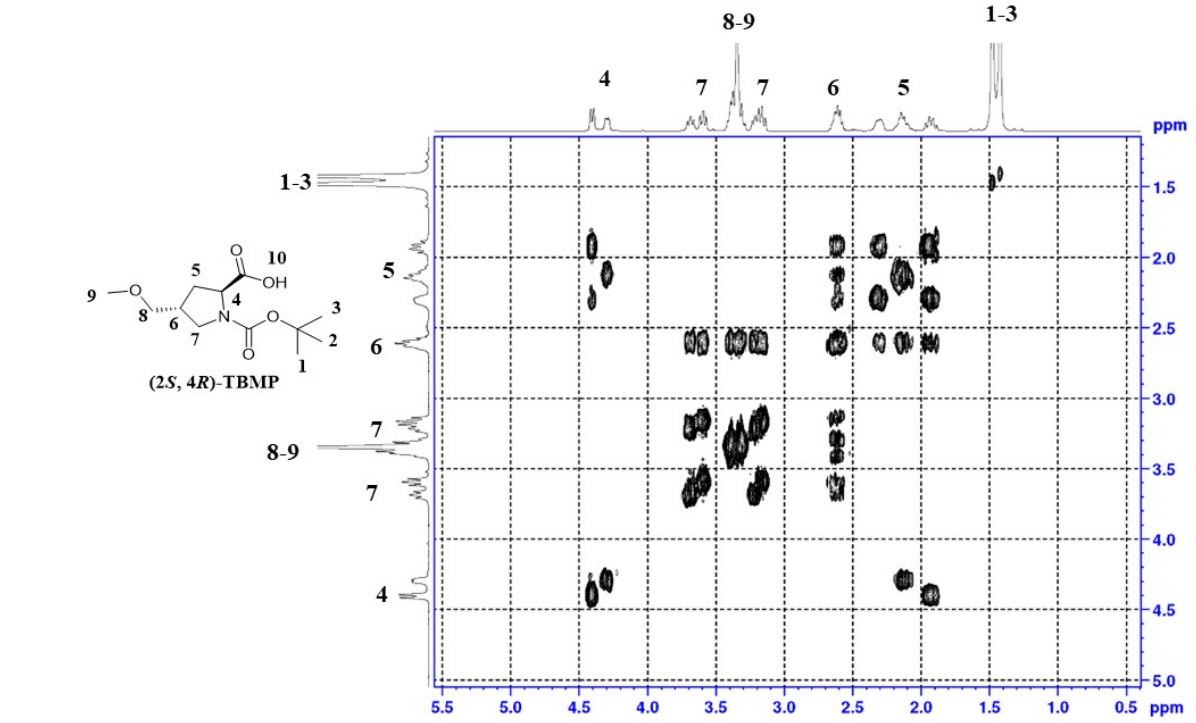


Fig. S10 The HSQC spectrum of (2*S*, 4*R*)-TBMP

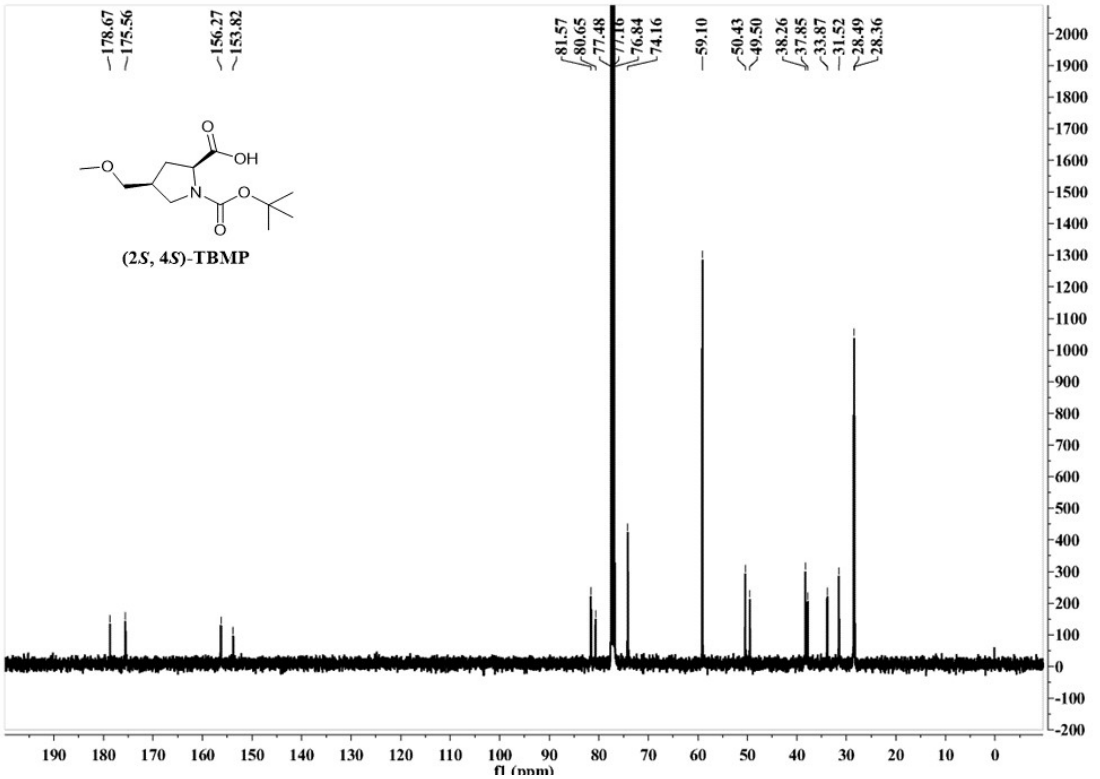


Fig. S11 The ^{13}C NMR spectrum of (2*S*, 4*S*)-TBMP

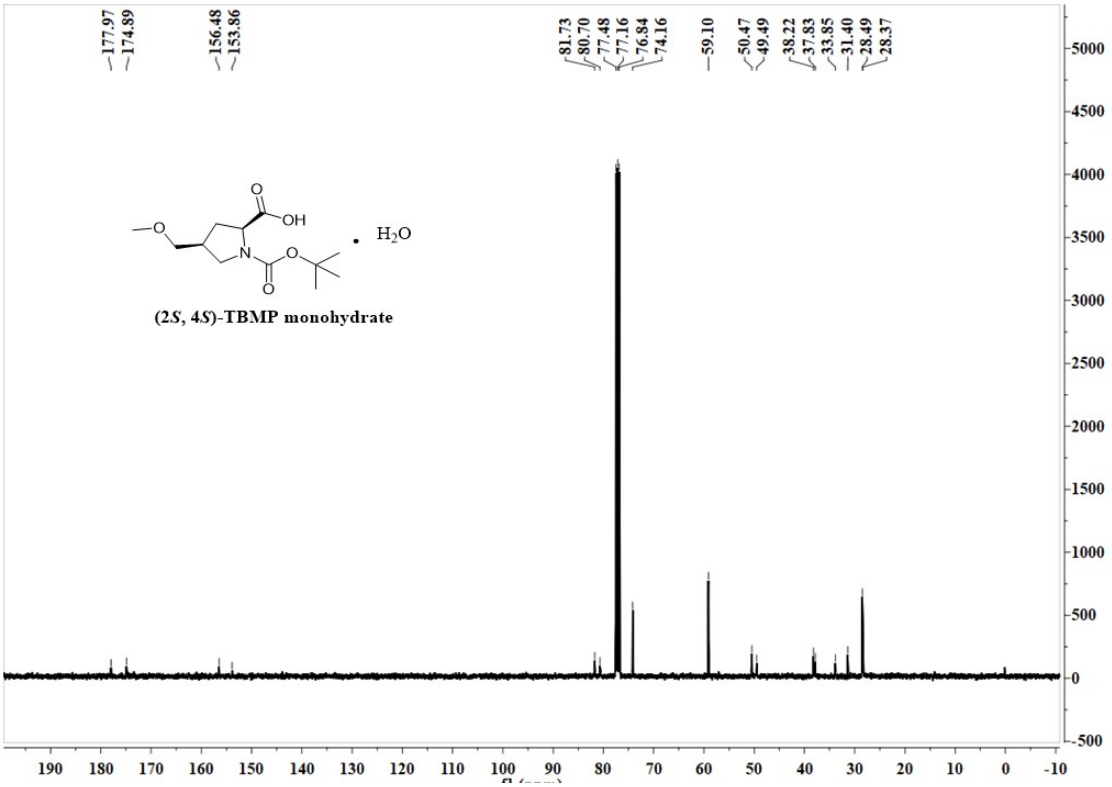


Fig. S12 The ^{13}C NMR spectrum of (2*S*, 4*S*)-TBMP monohydrate

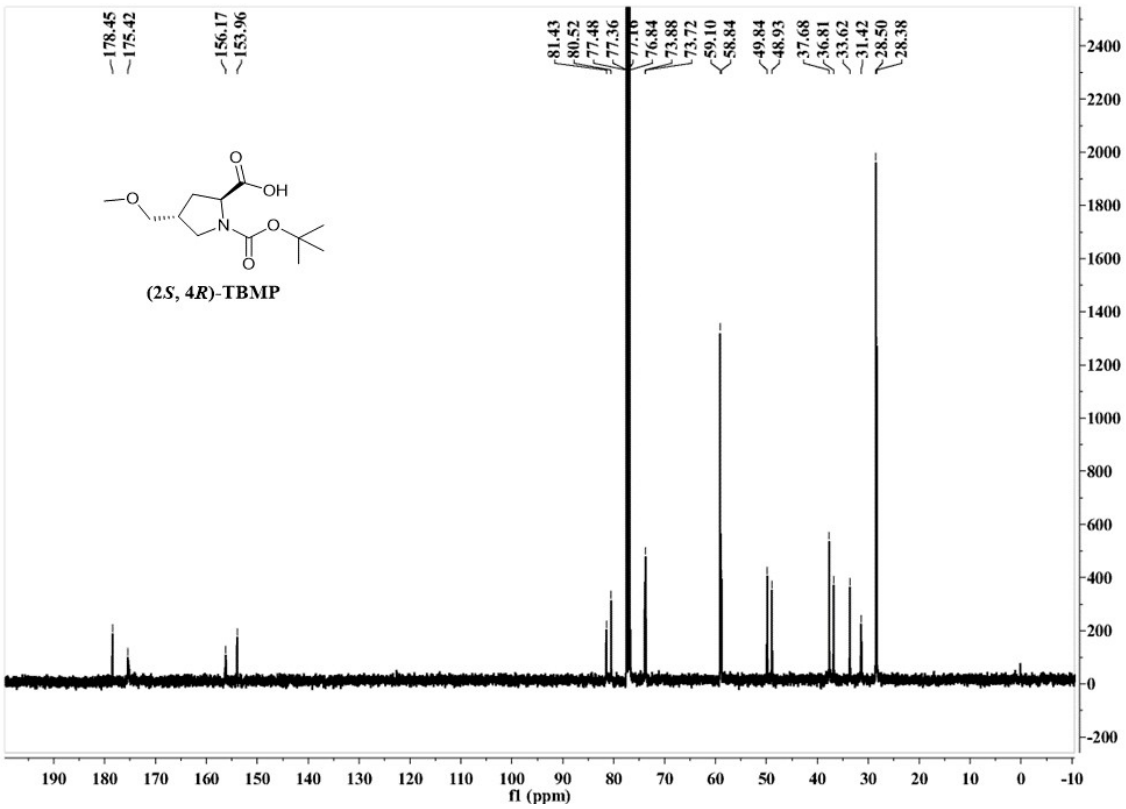


Fig. S13 The ^{13}C NMR spectrum of (2*S*, 4*R*)-TBMP

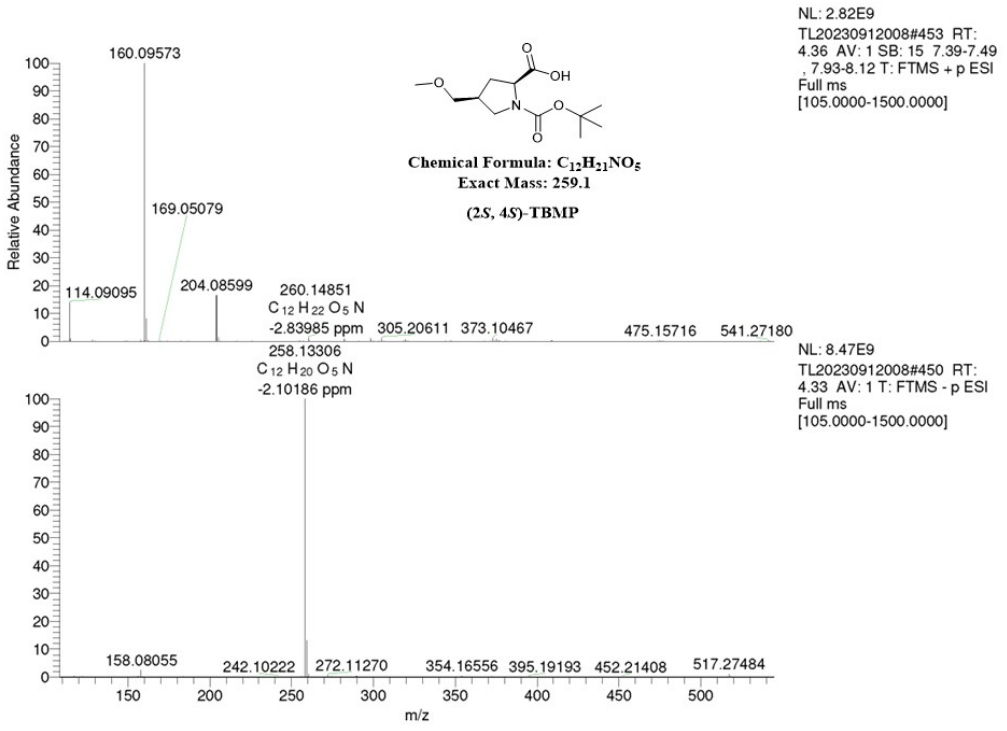


Fig. S14 The HRMS spectrum of (2*S*, 4*S*)-TBMP

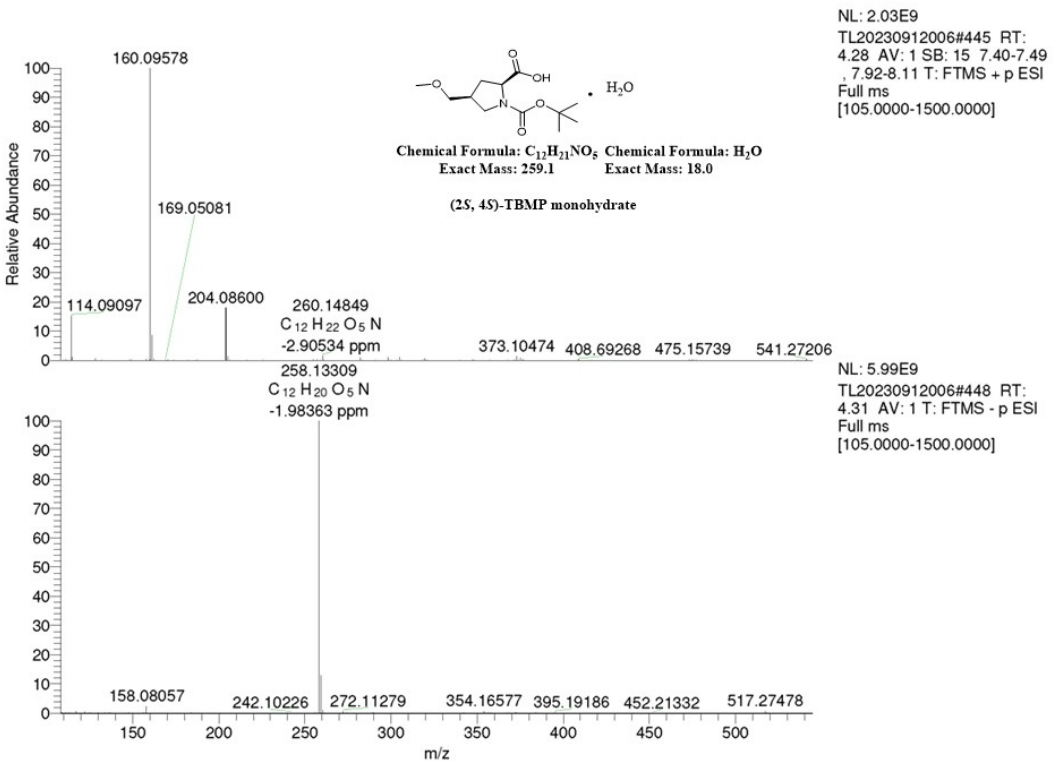


Fig. S15 The HRMS spectrum of (2*S*, 4*S*)-TBMP monohydrate

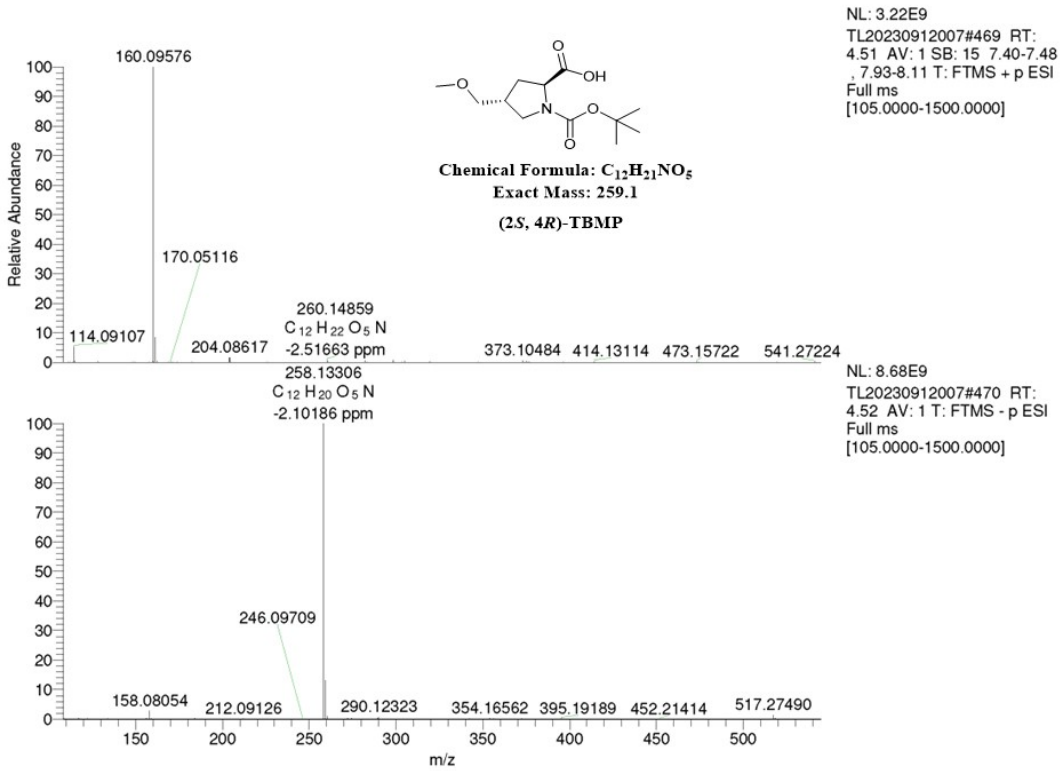


Fig. S16 The HRMS spectrum of (2*S*, 4*R*)-TBMP

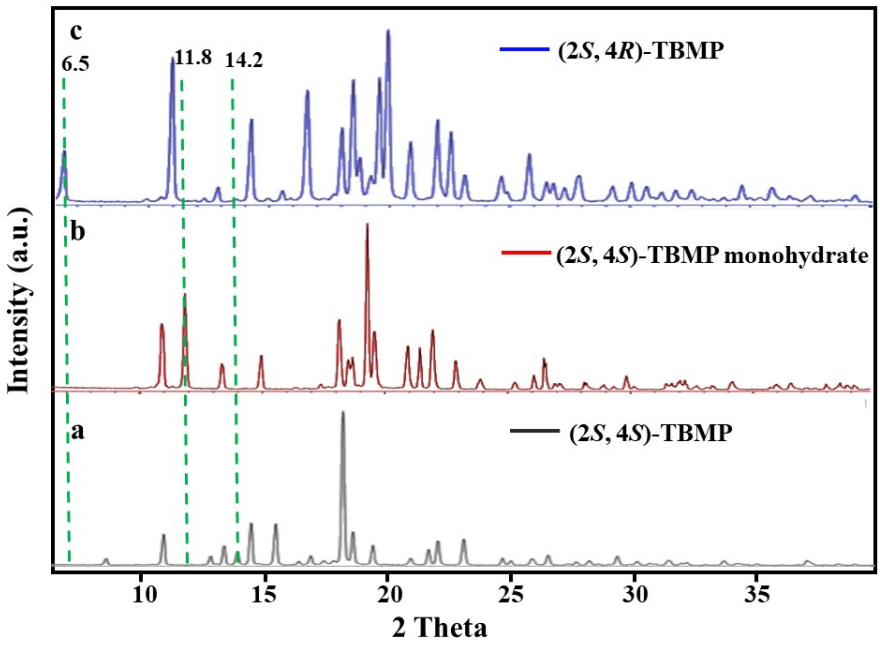


Fig. 17 The XRD of (2*S*, 4*S*)-TBMP, (2*S*, 4*S*)-TBMP monohydrate and (2*S*, 4*R*)-TBMP

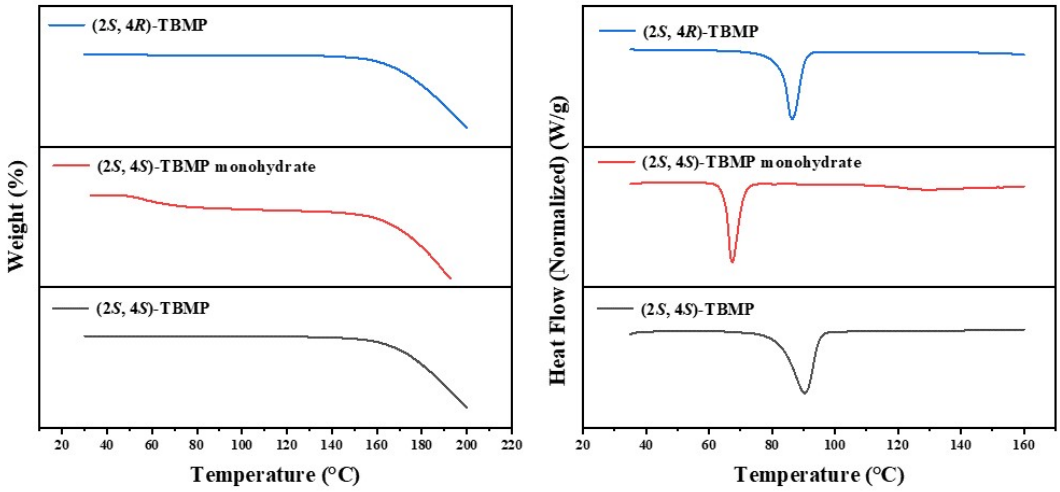


Fig. 18 A) TGA curves of (2*S*, 4*S*)-TBMP, (2*S*, 4*S*)-TBMP monohydrate and (2*S*, 4*R*)-TBMP

B) DSC curves of (2*S*, 4*S*)-TBMP, (2*S*, 4*S*)-TBMP monohydrate and (2*S*, 4*R*)-TBMP

Table S2 Crystal and experiment data for Crystal **1** and Crystal **2**

Compound	Crystal **1**	Crystal **2**
Formula	$C_{12}H_{21}NO_5,H_2O$	$C_{12}H_{21}NO_5$
Formula weight	277.31	259.30
Crystal system	Triclinic	Orthorhombic
Space group	*P*1	*P21 21 21*
a (Å)	5.8953(2)	6.3761(8)
b (Å)	7.8109(2)	9.9644(12)
c (Å)	8.5294(2)	22.622(3)
α (°)	71.666(1)	90.00
β (°)	86.269(1)	90.00
γ (°)	86.169(1)	90.00
V (Å3)	371.586(18)	1437.3(3)
Z	1	4
Dc (Mg·m-3)	1.239	1.198
T (K)	170	296
μ (mm-1)	0.832	0.093
No. of reflns collected	2616	3281
No. of unique reflns	1308	1914
S	1.089	1.079
CCDC Number	2275123	2275122

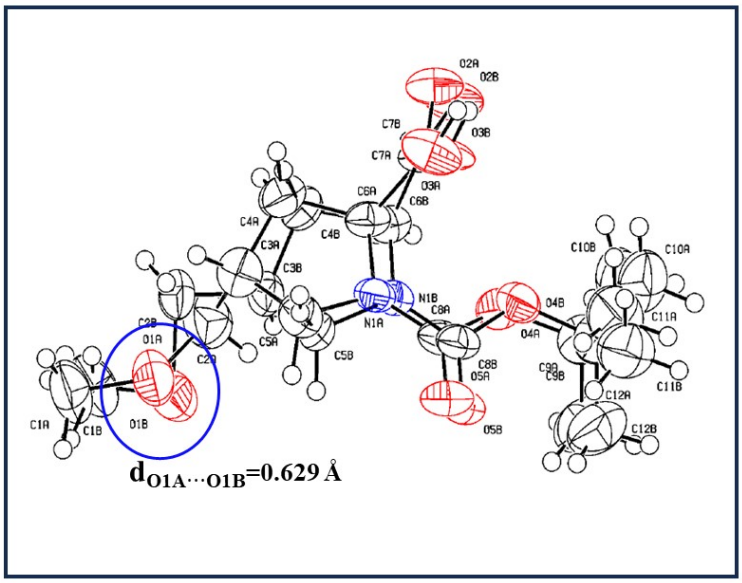


Fig. 19 The distance of (2*S*, 4*S*)-TBMP and (2*S*, 4*R*)-TBMP

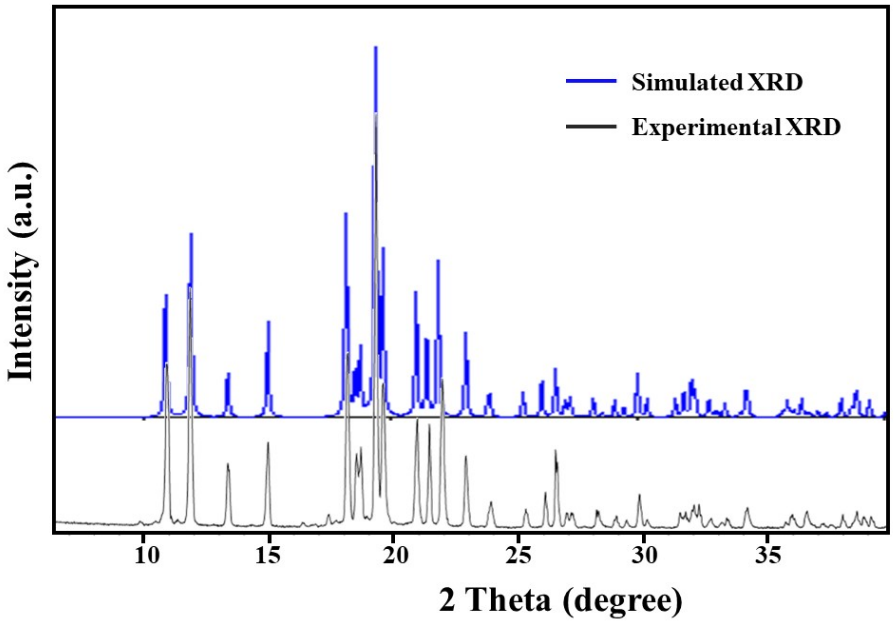


Fig. 20 The XRD of simulated and experimental (2*S*, 4*S*)-TBMP monohydrate

Table S3：The new approach (First Pass CHEM21 green metrics toolkit)

Yield, AE, RME, MI/PMI and OE

Reactant (Umiting Reactant first)	Mass(g)	MW	Mol	Catalyst	Mass(g)	Reagent	Mass(g)	Reaction solvent	Volume(cm^3)	Density(g/ml)	Mass(g)	Work up chemical	Mass(g)	Work up solvent	Volume(cm^3)	Density (g/ml)	Mass(g)
TBMP	20.00	259.30	0.077					H_2O	118.80	1.00	118.80	(2S,4S)-TBMP monohydrate	0.06	water	30.00	1.00	30.00
H_2O	1.20	18.00	0.067														
Total	21.20	277.30			0.00		0.00				118.80		0.06				30.00

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

		Flag
Yield	87.70	87.70
Conversion	100.00	100.00
Selectivity	87.70	87.70
AE	93.51	
RME	71.51	
PMI toal	11.22	
PMI Reaction	9.23	
PMI reactants, reagents, catalyst	1.40	
PMI solvents	7.84	
PMI Workup	1.98	
PMI Workup chemical	0.00	
PMI Workup solvents	1.98	

		OE	76.47
		E_m	-0.99

Product	Mass	Mw	Mol
	15.16	259.30	0.058

Unreacted limiting reactant	Mass

Solvents(First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	water
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac_2O, Acetonitrile, AcOMe, THF, heptane, Mecyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexanewater	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

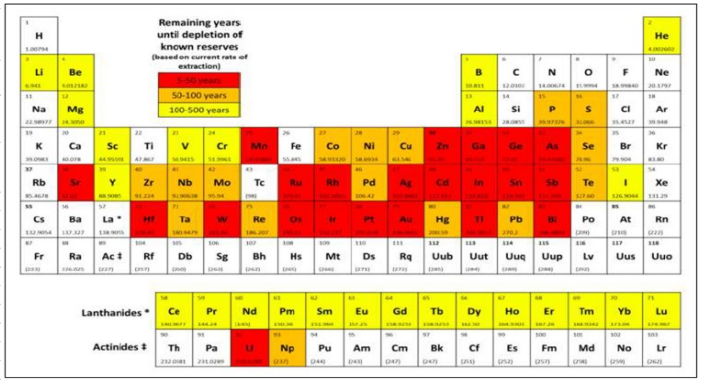
Experimental: In a 100 ml flask, 20.00 g of TBMP (de: 71.94%) was combined with 40 ml of water. The mixture was gently heated to a temperature range of 55-65 °C, allowing for melting. Gradually reduce the temperature to a range of 20-40 °C. Introduce 0.02 g pure monohydrate crystal seeds and allow incubation for 1-3 hours. Further cooling was carried out to reach a temperature of 0-10 °C. The resulting mixture was stirred for a duration of 1 hour. After this, the mixture was subjected to filtration, washed with 10 mL of water, and room temperature volatile drying, yielding 18.65 g of TBMP monohydrate, inclusive of 17.50 g of anhydrous TBMP (de: 88.80%).

A subsequent step involved taking 40 ml of water and 18.65 g of the product and placing it in a 100 ml flask. This was similarly heated to a range of 55-65 °C to enable melting. Gradually reduce the temperature to a range of 20-40 °C. Introduce 0.02 g pure monohydrate crystal seeds and allow incubation for 1-3 hours. Further cooling to 0-10 °C was performed, and the mixture was kept warm while being stirred for 1 hour. This mixture, too, underwent filtration, washed with 10 mL of water, and room temperature volatile drying, providing 16.86 g of TBMP monohydrate, consisting of 15.76 g of anhydrous TBMP (de: 98.70%).

Subsequently, an additional 40 ml of water and 16.86 g of the product were placed in a 100 ml flask. This was also subjected to the same heating and cooling procedures. After reaching a temperature of 0-10 °C and stirring for 1~3 hours, filtration, washed with 10 mL of water, and room temperature volatile drying were employed to yield 16.21 g of TBMP monohydrate. The monohydrate was subjected to initial evaporation at room temperature for a period of 5-10 hours, followed by vacuum drying in the temperature range of 30-50 °C for another 5-10 hours, ultimately resulting in the isolation of 15.16 g of anhydrous (2*S*, 4*S*)-TBMP (de:99.80%).

Critical elements

Supply remaining	Flga colour	Note element
5-50 years	Red flag	
50-500 years	Amber flag	
+ 500 years	Green flag	



Energy(First pass)		Tick
Reaction run between 0 to 70°C	Green flag	x
Reaction run between -20 to 0 or 70 to 140°C	Amber flag	
Reaction run below -20 or ab 140°C	Red flag	

		Tick
Reaction run at reflux	Red flag	
Reaction run 5°C or more below the solvent boiling point	Green flag	x

Batch/flow	Flga colour	Tick
Flow	Green flag	
Batch	Amber flag	x

Work up		list
quenching	Green flag	x
filtration		
centrifugation		
crystallisation		
low temperature distillation/evaporation/sublimation((<140 °C at atmospheric pressure)		
solvent exchange, quenching into aqueous solvent	Amber flag	
chromatograhy/ion exchange	Red flag	
high temperature		
multiple recrystallisation		

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-	List substances and H-
Highly explosvie	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			x
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331				
Long Term toxicity	H340, H350, H3560, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances and H-codes
chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red flag	none

Table S4：The original approach (First Pass CHEM21 green metrics toolkit)

Yield, AE, RME, MI/PMI and OE

Reactant (Umiting Reactant first)	Mass(g)	MW	Mol	Catalyst	Mass(g)	Reagent	Mass(g)	Reaction solvent	Volume(cm^3)	Density(g/ml)	Mass(g)	Work up chemical	Mass(g)	Work up solvent	Volume (cm^3)	Density(g/ml)	Mass(g)
TBMP	15.20	259.30	0.059					tert-Butyl methyl ether	270.00	0.74	199.80	Na_2SO_4	1.60	tert-Butyl methyl ether	60.00	0.74	44.40
Dicyclohexylamine	8.77	181.32	0.048					H_2O	80.58	1.00	80.58						
NaOH	1.76	40.00	0.044					Dichloromethane	5.00	1.33	6.65						
Hydrochloric acid	5.58	36.46	0.153					Heptane	25.00	0.68	17.00						
Total	31.31	517.08			0.00		0.00				304.03		1.60				44.40

		Flag						
Yield	70.33		70.73					
Conversion	100.00		100.00					
Selectivity	70.33		70.73				Mass	Mw	Mol
AE	50.15				Product		8.82	259.30	0.034
RME	28.17	OE	56.17				Mass		
PMI toal	43.24	E_m	-0.96		Unreacted limiting reactant				
PMI Reaction	38.02								
PMI reactants, reagents, catalyst	3.55								
PMI solvents	34.47								
PMI Workup	5.22								
PMI Workup chemical	0.18								
PMI Workup solvents	5.03								

Solvents(First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	water
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac_2O, Acetonitrile, AcOMe, THF, heptane, Mecyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	MTBE
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexanewater	DCM, pentane
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Experimental: 15.20 g of TBMP (de: 65%) were combined with 120 mL of methyl tert-butyl ether (TBME) and 8.77 g of dicyclohexylamine. The mixture was gently heated to 60 °C. After 3 hours, the resulting precipitated solid was allowed to cool slowly to 20 °C and was subsequently stirred overnight. The solid was then separated by filtration, washed with 30 mL of TBME, and carefully dried, yielding 16.00 g of a nearly white solid with a diastereomeric excess of 94%.

For the next step, 16.00 g of the obtained material was combined with 75 mL of water and 75 mL of MTBE. To this mixture, 1.76g of sodium hydroxide was added. After stirring for 20 minutes, the solution was separated, and the aqueous phase was collected. An additional 75 mL of methyl *tert*-butyl ether was added, and the mixture was stirred with 5.58 g of hydrochloric acid and 5.58 g of water. The solution was then separated again. The aqueous phase was subjected to another extraction with 30 mL of methyl tert-butyl ether, and the organic phases were combined. To remove any remaining moisture, 1.60 g of anhydrous sodium sulfate was stirred into the combined organic phase for 1 hour, followed by a spinning dry process, resulting in a final yield of 9.10 g.

In the final step, 16.79 g of hexane and 6.71 g of dichloromethane were heated to 60 °C. 9.10 g of the TBMP were dissolved until the solution was clear. Upon cooling to 5-10 °C, a solid precipitated out, which was subsequently filtered and dried, yielding 9.00 g of TBMP (de: 96%, 8.82 g pure (2*S*, 4*S*)-TBMP).

Critical elements

Supply remaining	Flga colour	Note element
5-50 years	Red flag	
50-500 years	Amber flag	
+ 500 years	Green flag	

Energy(First pass)		Tick
Reaction run between 0 to 70°C	Green flag	x
Reaction run between -20 to 0 or 70 to 140° C	Amber flag	
Reaction run below -20 or ab 140°C	Red flag	

		Tick
Reaction run at reflux	Red flag	
Reaction run 5°C or more below the solvent boiling point	Green flag	

Batch/flow	Flga colour	Tick
Flow	Green flag	
Batch	Amber flag	x

Work up		list
quenching	Green flag	
filtration		
centrifugation		
crystallisation		
low temperature distillation/evaporation/sublimation((<140 °C at atmospheric pressure)		
solvent exchange, quenching into aqueous solvent	Amber flag	x
chromatograhy/ion exchange	Red flag	
high temperature		
multiple recrystallisation		

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosvie	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	dicyclohexylamine:H410 Heptane:H410	DCM:H351 Hydrochloric acid:H331	MTBE water
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331				
Long Term toxicity	H340, H350, H3560, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances and H-codes
chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red flag	none

Table S5：The new approach (Third Pass CHEM21 green metrics toolkit)

Yield, AE, RME, MI/PMI and OE

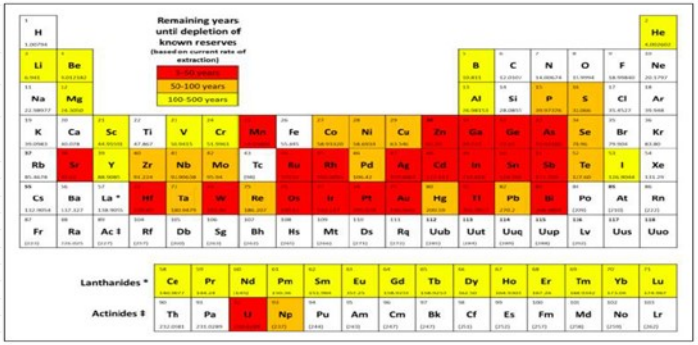
Reactant (Umiting Reactant first)	Mass(kg)	MW	Mol	Catalyst	Mass(kg)	Reagent	Mass(kg)	Reaction solvent	Volume(L^3)	Density(g/ml)	Mass(kg)	Work up chemical	Mass(kg)	Work up solvent	Volume(L^3)	Density (g/ml)	Mass(kg)
TBMP	200.00	259.30	0.771					H_2O	1188.00	1.00	1188.00	(2S,4S)-TBMP monohydrate	0.60	water	300.00	1.00	300.00
H_2O	12.00	18.00	0.667														
Total	212.00	277.30			0.00		0.00				1188.00		0.60				300.00

		Flag					
Yield	91.92	91.92					
Conversion	100.00	100.00					
Selectivity	91.92	91.92				Mass(kg)	Mw	Mol
AE	93.51				Product	158.90	259.30	0.613
RME	74.95	OE	80.16			Mass		
PMI toal	10.70	E_m	-0.99		Unreacted limiting reactant			
PMI Reaction	8.81							
PMI reactants, reagents, catalyst	1.33							
PMI solvents	7.48							
PMI Workup	1.89							
PMI Workup chemical	0.00							
PMI Workup solvents	1.89							

Solvents(Third Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	water
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac_2O, Acetonitrile, AcOMe, THF, heptane, Mecyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexanewater	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Critical elements

Supply remaining	Flga colour	Note element
5-50 years	Red flag	
50-500 years	Amber flag	
• 500 years	Green flag	



Energy(Third pass)		Tick
Reaction run between 0 to 70°C	Green flag	x
Reaction run between -20 to 0 or 70 to 140°C	Amber flag	
Reaction run below -20 or ab 140°C	Red flag	

		Tick
Reaction run at reflux	Red flag	
Reaction run 5°C or more below the solvent boiling point	Green flag	x

Batch/flow	Flga colour	Tick
Flow	Green flag	
Batch	Amber flag	x

Work up		list
quenching	Green flag	x
filtration		
centrifugation		
crystallisation		
low temperature distillation/evaporation/sublimation((<140 °C at atmospheric pressure)		
solvent exchange, quenching into aqueous solvent	Amber flag	
chromatography/ion exchange	Red flag	
high temperature		
multiple recrystallisation		

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-	List substances and H-
Highly explosvie	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			x
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331				
Long Term toxicity	H340, H350, H3560, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances and H-codes
chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red flag	none