Tetrahedron 64 (2008) 5629–5636

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regio- and diastereoselective conjugate addition of Grignard reagents to aryl substituted α,β-unsaturated carbonyl compounds derived from Oppolzer's sultam

Xiufang Cao, Fang Liu, Wenchang Lu, Gang Chen, Guang-Ao Yu, Sheng Hua Liu *

Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

ARTICLE INFO

Article history:
Received 4 December 2007
Received in revised form 8 April 2008
Accepted 11 April 2008
Available online 15 April 2008

Keywords:
α,β-Unsaturated carbonyl compound
Grignard reagent
Conjugate addition
Regioselectivity
Diastereoselectivity

ABSTRACT

Asymmetric conjugate addition of Grignard reagents to aryl substituted α,β-unsaturated carbonyl compounds (**1**) has been achieved with great regioselectivity (>20:1) and good to excellent diastereoselectivity (de up to 98%). The nucleophilicity and stereospecific blockade of the Grignard reagents play a key role in controlling the regioselectivities and diastereoselectivities of the conjugate addition reaction.

1. Introduction

The addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most versatile synthetic methods for the introduction of a new asymmetric center at the β-position of the carbonyl containing motif.[1] Grignard reagents are among the most widely used organometallic reagents. However, the application of Grignard reagents in the conjugate addition to α,β-unsaturated carbonyl systems has received much less attention in contrast to the application of the other organometallic compounds in the same transformations. This is most probably due to the higher reactivity of Grignard reagents that leads to uncatalyzed 1,2- and 1,4-addition.[2] Several research groups have devised procedures to control the reaction by changing the solvent or using additive such as $CeCl_3$,[3] $InCl_3$,[4] copper(I) salts,[5] $MgBr_2$,[6] $(n\text{-}C_4H_9)_4NBr$,[7] $LiClO_4$,[7] $(i\text{-}C_3H_7O)_3TiC1$,[8] $(n\text{-}C_4H_9O)_3ZrC1$,[8] or organo-aluminum,[9] etc. In addition, the asymmetric 1,4-addition of α,β-unsaturated carbonyl compounds to organometallic reagents has been recently developed with the use of metal complexes, such as copper(I),[10] Rh,[11] and Pd[12] complexes, and chiral ligands[13] as catalyst. However, many of these methods use expensive reagents and are not easy to operate. Thus, it is necessary to develop an alternate synthetic procedure, with the goal of broadening the substrate scope and improving the practicability. In this context, we describe the development of conjugate addition of Grignard reagents based on chiral auxiliary.[14]

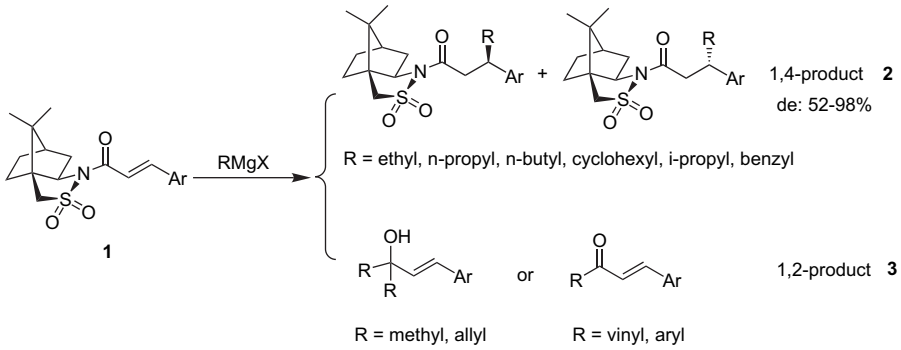
The introduction of chirality using a chiral auxiliary is a useful way of producing a wide variety of optically active organic compounds. Oppolzer reported the diastereoselective conjugate addition of Grignard reagents[15] and organocuprates, Gilman reagents (R_2CuLi),[16] to *N*-enoylsultams. *N*-Enoylsultams were readily obtained by acylation of camphorsultam (as well as its antipode readily prepared from camphor on a kilogram scale) with NaH/acyl chlorides and purified by crystallization. The diastereoselectivity of the conjugate addition with Grignard reagents is high and the chiral auxiliary (D-(−)-camphorsultam) can be recovered with a high yield (>90%) after non-destructive cleavage. However, the scope of substrates reported in the literature is very limited, most of which are alkyl substituents. To the best of our knowledge, relative rare α,β-unsaturated carbonyl compounds with aryl substituents have been employed in such a reaction. Herein, we would like to report a highly regioselective and diastereoselective conjugate addition of a series of aryl substituted α,β-unsaturated carbonyl compounds (**1**) with various Grignard reagents (Scheme 1). The products can be further converted to chiral ketones, alcohols, aldehydes, and carboxylic acids, which are important and useful intermediates in asymmetric synthesis.

2. Results and discussion

N-Enoylsultams **1** were obtained by acylation of camphorsultam with acyl chlorides.[17] The conjugate addition of Grignard reagents

* Corresponding author. Tel./fax: +86 27 67867725.
E-mail address: chshliu@mail.ccnu.edu.cn (S.H. Liu).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.048



Scheme 1. Conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds.

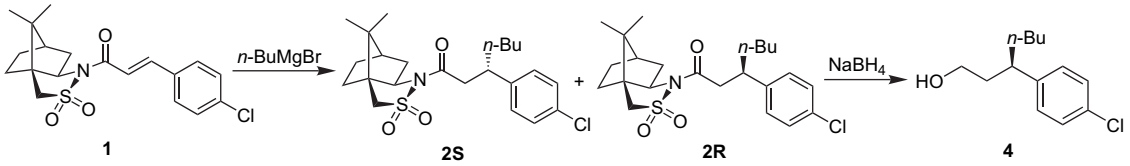
to *N*-enoylsultam **1** at −78 °C gave 1,4-addition product **2** and 1,2-addition product **3** (Scheme 1). Our experiments began with the optimization of the reaction conditions for the conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds **1** (Table 1), and we found that using THF as solvent at −78 °C was the best reaction condition. We examined the scope of this asymmetric conjugate addition to unsaturated *N*-enoylsultams **1** using various Grignard reagents in THF at −78 °C. It was found that the reaction exhibited high regioselectivities (>20:1) and good to excellent diastereoselectivities (52–98% de) (Table 2). Due to the steric hindrance of the camphor skeleton, most of the Grignard reagents gave the 1,4-addition products, except with methyl (entry 18), allyl (entries 19 and 20), vinyl (entries 21 and 22), and aryl (entry 23) Grignard reagents. The proposed mechanism of 1,4-conjugate addition of Grignard reagents is shown in Scheme 2, which is consistent with the mechanism reported by Oppolzer.[15]

The methyl, allyl, vinyl, and aryl Grignard reagents underwent a highly regioselective 1,2-addition to the *N*-enoylsultams **1**. The *N*-enoylsultams **1** were treated with 1 equiv of *p*-methylphenylmagnesium bromide to give a 1,2-addition product (α,β-unsaturated ketone **3w**) and with 2.2 equiv of *p*-methylphenylmagnesium bromide to give a racemic ketone (**3x**) (Scheme 3). However, the *N*-enoylsultams **1** were treated with 1 or 2 equiv of methyl or allyl Grignard reagents to give a product (tertiary alcohol) and the ketone intermediate wasn't observed (Scheme 4), which is consistent with Oppolzer's observation in the reaction of methyl Grignard reagent with *N*-enoylsultam.[15] Vinyl Grignard reagents underwent a continuous 1,2-addition and 1,4-addition to give **3u** or **3v**[18] (Scheme 5). We suggest that strong nucleophilicity of methyl, allyl, vinyl, and aryl Grignard reagents results in the formation of 1,2-addition products. Andersson have reported that the reagent derived from phenylmagnesium bromide and CuBr–Me_2S smoothly underwent a highly regioselective 1,4-addition to the *N*-enoylsultams **1**.[19]

As shown in Table 2, linear aliphatic Grignard reagents provided excellent diastereoselectivities (82–98% de), secondary Grignard regent also worked well to afford the product in moderate diastereoselectivities (60% de and 68% de) (entries 9 and 10), and the more hindered substituted Grignard reagents gave the desired products in high regioselectivities but with low diastereoselectivities (entries 16 and 17). The de and dr in Table 2 were postulated from the ee of **4**, which were obtained by reduction of compounds **2** with $NaBH_4$. The absolute configuration of the major 1,4-addition products **2a–d**, **2i**, **2j**, and **2q**, **2o**, **2p** was confirmed through X-ray crystallography of **2b**,[20] **2j**,[21] and **2p**,[22] respectively, and the absolute configuration of the other compounds **2** was assigned through optical rotation of the corresponding known compound **4**.[23–28]

High levels of asymmetric inductive addition obtained during these studies prompted us to extend our investigation to the addition of different α,β-unsaturated *N*-enoylsultam **1** to the Grignard reagents bearing electron-withdrawing and donating group on the aromatic ring. The results, summarized in Table 2, indicated that most of them gave the addition products in high regioselectivities (>20:1) and diastereoselectivities and high chemical yields. From Table 2, we can conclude that the *N*-enoylsultams **1** have less influence on the regioselectivities, diastereoselectivities, and chemical yields of the conjugate addition reaction. The nucleophilicity and stereospecific blockade of the Grignard reagents play a key role in controlling the regioselectivities and diastereoselectivities of the conjugate addition reaction. As a general trend, linear aliphatic Grignard reagents provided excellent results.

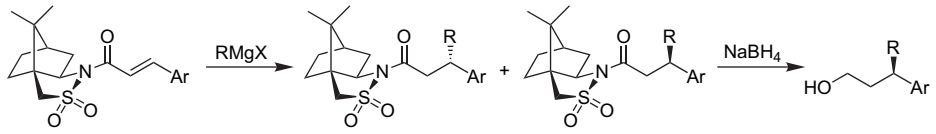
Table 1
Optimization of the reaction conditions for the conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds **1**



Entry	Solvent	Temperature (°C)	Yield[a]	1,4-/1,2-Prod.[b]	ee of 4[c]	1,4-Prod. dr
1	THF	−20	90	>20:1	44	72:28
2	THF	−40	88	>20:1	52	76:24
3	THF	−60	85	>20:1	54	77:23
4	THF	−78	85	>20:1	98	>99:1
5	EtOEt	−78	45	>20:1	66	83:17

All reactions were performed with 1 (1.0 equiv mol) and *n*-BuMgBr (2.2 equiv mol).
[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC (AS-H), eluent: hexane/*i*-PrOH=95:5, 254 nm. The retention time of the *S*-form was 7.3 s and *R*-form was 6.2 s.

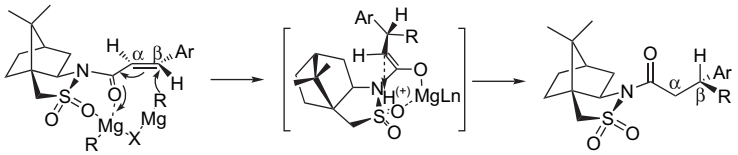
Table 2
Reactions of conjugate addition of Grignard reagents to *N*-enoylsultam **1**



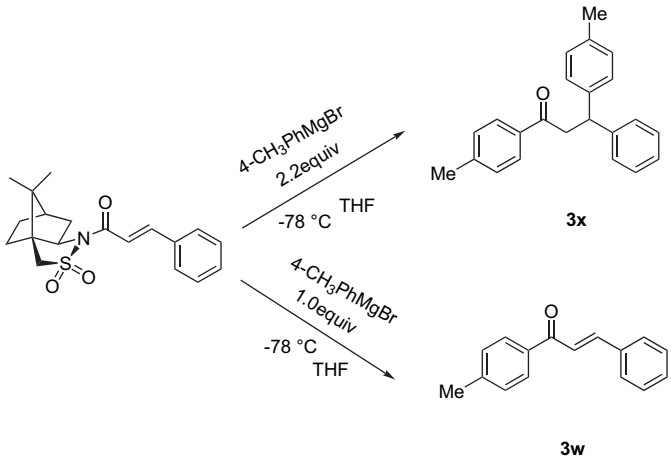
1 **2** **4**

Entry	Ar	RMgX	Yield[a]	Prod.	Configuration of **2a**	1,4-/1,2-Prod.[b]	ee of **4**[c]	1,4-Prod. dr
1	Ph	EtMgBr	83	**2a**	3*R*	>20:1	90	95:5
2	4-FPh	EtMgBr	85	**2b**	3*R*	>20:1	82	91:9
3	4-ClPh	EtMgBr	78	**2c**	3*R*	>20:1	90	95:5
4	4-MePh	EtMgBr	85	**2d**	3*R*	>20:1	88	94:6
5	Ph	*n*-PrMgBr	87	**2e**	3*R*	>20:1	94	97:3
6	4-FPh	*n*-PrMgBr	85	**2f**	3*R*	>20:1	90	95:5
7	4-MePh	*n*-PrMgBr	92	**2g**	3*R*	>20:1	88	94:6
8	4-ClPh	*n*-PrMgBr	88	**2h**	3*R*	>20:1	84	92:8
9	Ph	*i*-PrMgCl	59	**2i**	3*S*	>20:1	60	80:20
10	4-FPh	*i*-PrMgCl	64	**2j**	3*S*	>20:1	68	84:16
11	Ph	*n*-BuMgBr	81	**2k**	3*R*	>20:1	86	93:7
12	4-FPh	*n*-BuMgBr	84	**2l**	3*R*	>20:1	88	94:6
13	4-ClPh	*n*-BuMgBr	85	**2m**	3*R*	>20:1	98	>99:1
14	4-MePh	*n*-BuMgBr	87	**2n**	3*R*	>20:1	88	94:6
15	Ph	BnMgBr	81	**2o**	3*R*	>20:1	68	84:16
16	4-ClPh	BnMgBr	75	**2p**	3*R*	>20:1	52	76:24
17	Ph	Cyclohexyl-MgC	62	**2q**	3*S*	>20:1	56	78:22
18	Ph	MeMgI	77	**3r**		<1:20		
19	4-FPh	Allyl MgBr	98	**3s**		<1:20		
20	Ph	Allyl MgBr	97	**3t**		<1:20		
21	4-FPh	Vinyl MgBr	75	**3u**		<1:20		
22	4-MePh	Vinyl MgBr	73	**3v**		<1:20		
23	4-MePh	4-MePhMgBr	84	**3x**				

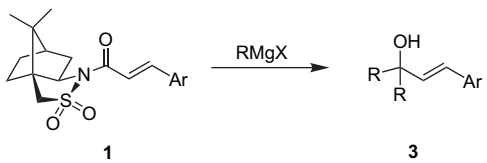
All reactions were performed with **1** (1.0 equiv mol) and RMgBr (2.2 equiv mol) in THF at −78 °C.
[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC (AS-H).



Scheme 2. Mechanism of 1,4-conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds **1**.



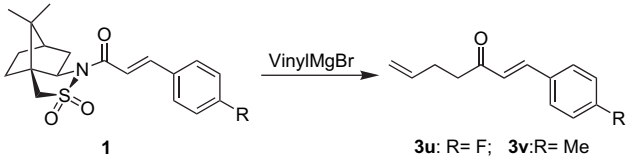
Scheme 3. Conjugate addition of *p*-Me phenyl Grignard reagents to α,β-unsaturated carbonyl compounds.



1 **3**

3r: R=Me, Ar=Ph; 3s: R=Allyl, Ar=4-FPh; 3t: R=Ally, Ar=Ph;

Scheme 4. Conjugate addition of methyl and allyl Grignard reagents to α,β-unsaturated carbonyl compounds.



1 **3u**: R= F; **3v**:R= Me

Scheme 5. Conjugate addition of vinyl Grignard reagents to α,β-unsaturated carbonyl compounds.

3. Conclusion

In summary, we have demonstrated that inexpensive and readily available Grignard reagents can be used to provide excellent stereocontrol in conjugate addition reactions. These reactions provide access to highly valuable building blocks for natural product synthesis and important medicinal intermediate.

4. Experimental section

4.1. General

All reactions were carried out under nitrogen with anhydrous solvents unless otherwise stated. Tetrahydrofuran and diethyl ether were dried by distillation from sodium and benzophenone immediately before use. α,β-Unsaturated *N*-enoylsultams **1a**–**1d** were prepared according to the procedure described in Refs. 29a–d. ^{1}H NMR spectra were recorded at 400 MHz and 600 MHz, and the chemical shifts were reported in parts per million relative to TMS. Enantiomeric excess (ee) determination was carried out with a Chiralcel AS-H (25×4.6 mm) column (Daicel Chemical Industries) on an Agilent 1100 HPLC instrument with UV detector set at 254 nm.

4.2. General procedure for the synthesis of 2 and 3

A solution of **1** (10 mmoL) in anhydrous THF (40 mL) under a nitrogen atmosphere was cooled to −78 °C, to which alkylmagnesium bromide (10 mL, 22 mmol) was added dropwise. The mixture was stirred at −78 °C for 3 h and was then warmed up to −40 °C, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (2×100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The solid residue was purified by crystallization (AcOEt and hexane), and the oil residue was purified by flash chromatography (AcOEt/hexane=1:9 as eluent) to afford the desired product.

*4.2.1. N-[(3R)-3-Phenyl-pentanoyl]bornane-10,2-sultam (**2a**)*

White solid, mp: 98–100 °C; $[\alpha]_D^{20}$ −78.5 (*c* 1.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27–7.30 (m, 2H), 7.18–7.21 (m, 3H), 3.79–3.82 (m, 1H), 3.48 (d, *J*=14 Hz, 1H), 3.40 (d, *J*=13.6 Hz, 1H), 3.07–3.12 (m, 1H), 2.98–3.02 (m, 2H), 2.01–2.02 (m, 2H), 1.87–1.88 (m, 3H), 1.57–1.69 (m, 2H), 1.31–1.36 (m, 2H), 1.17 (s, 3H), 0.96 (s, 3H), 0.77 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.45, 143.56, 128.17, 127.57, 126.20, 65.01, 52.80, 48.14, 47.56, 44.42, 43.05, 41.82, 38.30, 32.60, 29.08, 26.26, 20.75, 19.75, 11.82; MS: *m*/*z*=375. Anal. Calcd for $C_{21}H_{29}NO_3S$: C, 67.17; H, 7.78; N, 3.73; S, 8.54. Found: C, 66.67; H, 7.31; N, 3.53; S, 8.93.

*4.2.2. N-[(3R)-3-(4-Fluorophenyl)-pentanoyl]bornane-10,2-sultam (**2b**)*

White solid, mp: 108–110 °C; $[\alpha]_D^{20}$ −83.9 (*c* 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14–7.18 (m, 2H), 6.94–6.98 (m, 2H), 3.78–3.80 (m, 1H), 3.48 (d, *J*=13.6 Hz, 1H), 3.40 (d, *J*=14 Hz, 1H), 2.99–3.14 (m, 2H), 2.01–2.02 (m, 2H), 1.84–1.89 (m, 3H), 1.58–1.68 (m, 2H), 1.31–1.36 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H), 0.77 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.17, 161.16, 139.16, 128.91, 114.86, 64.93, 52.72, 48.11, 47.50, 44.36, 42.26, 41.83, 38.21, 32.52, 29.17, 26.20, 20.67, 19.66, 11.70; MS: *m*/*z*=393. Anal. Calcd for $C_{21}H_{28}FNO_3S$: C, 64.10; H, 7.17; N, 3.56; S, 8.15. Found: C, 64.36; H, 7.09; N, 3.46; S, 8.37.

*4.2.3. N-[(3R)-3-(4-Chlorophenyl)-pentanoyl]bornane-10,2-sultam (**2c**)*

White solid, mp: 100–102 °C; $[\alpha]_D^{20}$ −54.1 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 3.78–3.81 (m, 1H), 3.49 (d, *J*=13.6 Hz, 1H), 3.40 (d, *J*=14 Hz, 1H), 3.01–3.13 (m, 2H), 2.01–2.02 (m, 2H), 1.85–1.89 (m, 3H), 1.65–1.68 (m, 2H), 1.31–1.34 (m, 2H), 1.16 (s, 3H), 0.97 (s, 3H), 0.77 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.38, 141.81, 131.86, 129.12, 128.30, 64.97, 52.88, 48.14, 47.53, 44.43, 43.14, 41.59, 38.23, 32.65, 29.18, 26.29, 20.78, 19.73, 11.83; MS: *m*/*z*=409. Anal. Calcd for $C_{21}H_{28}ClNO_3S$: C, 61.52; H, 6.88; N, 3.42; S, 7.82. Found: C, 61.88; H, 7.02; N, 3.36; S, 8.06.

*4.2.4. N-[(3R)-3-(4-Methylphenyl)-pentanoyl]bornane-10,2-sultam (**2d**)*

White solid, mp: 117–119 °C; $[\alpha]_D^{20}$ −76.1 (*c* 1.04, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.06–7.11 (m, 4H), 3.79–3.82 (m, 1H), 3.48 (d, *J*=14 Hz, 1H), 3.40 (d, *J*=13.6 Hz, 1H), 2.96–3.13 (m, 3H), 2.30 (s, 3H), 2.01–2.02 (m, 2H), 1.84–1.89 (m, 3H), 1.57–1.68 (m, 2H), 1.30–1.38 (m, 2H), 1.16 (s, 3H), 0.96 (s, 3H), 0.77 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.48, 140.48, 135.49, 128.83, 127.36, 64.96, 52.75, 48.09, 47.52, 44.39, 42.63, 41.86, 38.27, 32.56, 29.10, 26.24, 20.91, 20.70, 19.71, 11.81; MS: *m*/*z*=389. Anal. Calcd for $C_{22}H_{31}NO_3S$: C, 67.83; H, 8.02; N, 3.60; S, 8.23. Found: C, 67.70; H, 8.19; N, 3.53; S, 8.48.

*4.2.5. N-[(3R)-3-Phenyl-hexanoyl]bornane-10,2-sultam (**2e**)*

White solid, mp: 108–109 °C; $[\alpha]_D^{20}$ −79.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26–7.29 (m, 2H), 7.17–7.21 (m, 3H), 3.78–3.81 (m, 1H), 3.49 (d, *J*=14 Hz, 1H), 3.40 (d, *J*=13.6 Hz, 1H), 3.23–3.26 (m, 1H), 2.98–3.10 (m, 2H), 2.01–2.02 (m, 2H), 1.84–1.88 (m, 3H), 1.56–1.62 (m, 3H), 1.30–1.36 (m, 2H), 1.14–1.20 (m, 1H), 1.12 (s, 3H), 0.96 (s, 3H), 0.83 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.41, 143.84, 128.16, 127.49, 126.16, 64.99, 52.78, 48.12, 47.55, 44.41, 42.12, 41.20, 38.41, 38.28, 32.59, 26.26, 20.71, 20.27, 19.74, 13.86; MS: *m*/*z*=389. Anal. Calcd for $C_{22}H_{31}NO_3S$: C, 67.83; H, 8.02; N, 3.60; S, 8.23. Found: C, 68.09; H, 8.30; N, 3.55; S, 8.53.

*4.2.6. N-[(3R)-3-(4-Fluorophenyl)-hexanoyl]bornane-10,2-sultam (**2f**)*

White solid, mp: 96–98 °C; $[\alpha]_D^{20}$ −72.9 (*c* 1.01, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.18 (m, 2H), 6.93–6.98 (m, 2H), 3.77–3.80 (m, 1H), 3.49 (d, *J*=13.6 Hz, 1H), 3.40 (d, *J*=14 Hz, 1H), 3.22–3.24 (m, 1H), 2.98–3.03 (m, 2H), 2.0–2.01 (m, 2H), 1.84–1.88 (m, 3H), 1.54–1.61 (m, 2H), 1.30–1.36 (m, 2H), 1.15 (s, 3H), 1.13–1.14 (m, 2H), 0.96 (s, 3H), 0.83 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.25, 161.2, 139.50, 128.89, 114.94, 65.00, 52.80, 48.17, 47.57, 44.43, 42.19, 40.45, 38.56, 38.27, 32.60, 26.26, 20.71, 20.22, 19.73, 13.81; MS: *m*/*z*=407. Anal. Calcd for $C_{22}H_{30}FNO_3S$: C, 64.84; H, 7.42; N, 3.44; S, 7.87. Found: C, 64.96; H, 7.38; N, 3.42; S, 7.96.

*4.2.7. N-[(3R)-3-(4-Methylphenyl)-hexanoyl]bornane-10,2-sultam (**2g**)*

White solid, mp: 102–103 °C; $[\alpha]_D^{20}$ −79.6 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.08–7.11 (m, 2H), 7.13–7.15 (m, 2H), 3.79–3.82 (m, 1H), 3.48 (d, *J*=13.6 Hz, 1H), 3.40 (d, *J*=14 Hz, 1H), 2.95–3.11 (m, 3H), 2.30 (s, 3H), 2.01–2.02 (m, 2H), 1.84–1.88 (m, 3H), 1.54–1.67 (m, 4H), 1.30–1.36 (m, 2H), 1.16 (s, 3H), 0.96 (s, 3H), 0.77 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.54, 140.83, 135.53, 128.84, 127.43, 65.02, 52.83, 48.15, 47.58, 44.45, 42.23, 40.85, 38.53, 38.32, 32.63, 26.29, 20.97, 20.74, 20.32, 19.77, 13.89; MS: *m*/*z*=403. Anal. Calcd for $C_{23}H_{33}NO_3S$: C, 68.45; H, 8.24; N, 3.47; S, 7.95. Found: C, 68.59; H, 8.36; N, 3.28; S, 8.12.

*4.2.8. N-[(3R)-3-(4-Chlorophenyl)-hexanoyl]bornane-10,2-sultam (**2h**)*

White solid, mp: 129–130 °C; $[\alpha]_D^{20}$ −72.1 (*c* 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23–7.28 (m, 2H), 7.13–7.15 (m, 2H), 3.79–3.80 (m, 1H), 3.49 (d, *J*=13.6 Hz, 1H), 3.40 (d, *J*=14 Hz, 1H), 3.22–3.23 (m, 1H), 3.0–3.03 (m, 2H), 2.00–2.02 (m, 2H),

1.84–1.88 (m, 3H), 1.54–1.60 (m, 2H), 1.30–1.36 (m, 2H), 1.16–1.17 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H), 0.83 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.10, 142.40, 131.68, 129.01, 128.26, 64.98, 52.78, 48.17, 47.56, 44.42, 41.91, 40.55, 38.41, 38.26, 32.59, 26.25, 20.70, 20.20, 19.73, 13.80; MS: m/z=423. Anal. Calcd for $C_{22}H_{30}ClNO_3S$: C, 62.32; H, 7.13; N, 3.30; S, 7.56. Found: C, 62.43; H, 7.05; N, 3.15; S, 7.71.

4.2.9. N-[(3S)-3-Phenyl-4-methyl-hexanoyl]bornane-10,2-sultam (**2i**)

White solid, mp: 82–84 °C; $[\alpha]_D^{20}$ −67.4 (c 1.04, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.28 (m, 5H), 3.75–3.76 (m, 1H), 3.48 (d, J=13.6 Hz, 1H), 3.40 (d, J=14.2 Hz, 1H), 3.19–3.20 (m, 1H), 2.90–3.09 (m, 3H), 1.79–1.96 (m, 5H), 1.26–1.35 (m, 2H), 1.15 (s, 3H), 0.94–0.98 (m, 6H), 0.72–0.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.87, 142.38, 128.32, 127.81, 126.07, 64.86, 52.83, 49.29, 48.09, 47.64, 44.35, 39.15, 38.26, 33.25, 33.15, 26.23, 20.71, 20.29, 19.73, 19.66; MS: m/z=390 $(M+1)^+$. Anal. Calcd for $C_{22}H_{31}NO_3S$: C, 67.83; H, 8.02; N, 3.60; S, 8.23. Found: C, 67.72; H, 8.13; N, 3.48; S, 8.10.

4.2.10. N-[(3S)-3-(4-Fluorophenyl)-4-methyl-hexanoyl]bornane-10,2-sultam (**2j**)

White solid, mp: 108–110 °C; $[\alpha]_D^{20}$ −65.14 (c 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.12–7.16 (m, 2H), 6.89–6.93 (m, 2H), 3.73–3.76 (m, 1H), 3.43 (d, J=13.6 Hz, 1H), 3.37 (d, J=13.6 Hz, 1H), 3.19–3.20 (m, 1H), 2.89–2.90 (m, 1H), 2.85–2.87 (m, 1H), 1.80–1.85 (m, 3H), 1.55–1.61 (m, 2H), 1.42–1.43 (m, 1H), 1.24–1.32 (m, 2H), 0.98 (d, J=6.4 Hz, 3H), 0.88 (s, 3H), 0.73 (d, J=5.6 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.72, 161.21, 138.02, 129.69, 114.59, 64.91, 52.86, 48.83, 48.05, 47.47, 44.37, 39.25, 38.16, 33.2, 32.58, 26.23, 20.72, 20.29, 19.73, 19.63; MS: m/z=407. Anal. Calcd for $C_{22}H_{30}FNO_3S$: C, 64.84; H, 7.42; N, 3.44; S, 7.87. Found: C, 65.00; H, 7.52; N, 3.36; S, 7.98.

4.2.11. N-[(3R)-3-Phenyl-heptanoyl]bornane-10,2-sultam (**2k**)

White solid, mp: 63–64 °C; $[\alpha]_D^{20}$ −72.7 (c 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26–7.29 (m, 2H), 7.18–7.21 (m, 3H), 3.78–3.81 (m, 1H), 3.48 (d, J=13.6 Hz, 1H), 3.40 (d, J=14 Hz, 1H), 3.21–3.23 (m, 1H), 3.05–3.07 (m, 2H), 2.0–2.02 (m, 2H), 1.86–1.88 (m, 3H), 1.63–1.65 (m, 2H), 1.12–1.35 (m, 6H), 1.17 (s, 3H), 0.96 (s, 3H), 0.77–0.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.40, 143.89, 128.15, 127.45, 126.13, 64.95, 52.75, 48.10, 47.52, 44.39, 42.13, 41.43, 38.25, 35.92, 32.56, 29.27, 26.23, 22.44, 20.70, 19.71, 13.81; MS: m/z=403. Anal. Calcd for $C_{23}H_{33}NO_3S$: C, 68.45; H, 8.24; N, 3.47; S, 7.95. Found: C, 68.57; H, 8.16; N, 3.31; S, 8.09.

4.2.12. N-[(3R)-3-(4-Fluorophenyl)heptanoyl]bornane-10,2-sultam (**2l**)

White solid, mp: 93–95 °C; $[\alpha]_D^{20}$ −72.4 (c 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.15–7.18 (m, 2H), 6.93–6.98 (m, 2H), 3.78–3.81 (m, 1H), 3.49 (d, J=13.6 Hz, 1H), 3.42 (d, J=13.6 Hz, 1H), 3.20–3.21 (m, 1H), 3.0–3.03 (m, 2H), 2.0–2.01 (m, 2H), 1.85–1.89 (m, 3H), 1.54–1.63 (m, 2H), 1.05–1.38 (m, 6H), 1.16 (s, 3H), 0.96 (s, 3H), 0.79–0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.27, 161.2, 139.57, 129.0, 114.89, 65.0, 52.81, 48.17, 47.58, 44.44, 42.23, 40.71, 38.27, 36.11, 32.60, 29.26, 26.26, 22.43, 20.73, 19.73, 13.84; MS: m/z=421. Anal. Calcd for $C_{23}H_{32}FNO_3S$: C, 65.53; H, 7.65; N, 3.32; S, 7.61. Found: C, 65.46; H, 7.66; N, 3.22; S, 7.95.

4.2.13. N-[(3R)-3-(4-Chlorophenyl)heptanoyl]bornane-10,2-sultam (**2m**)

White solid, mp: 116–117 °C; $[\alpha]_D^{20}$ −72.1 (c 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 (d, J=7.2 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 3.77–3.80 (m, 1H), 3.49 (d, J=13.6 Hz, 1H), 3.41 (d, J=13.6 Hz, 1H), 3.18–3.20 (m, 1H), 3.00–3.03 (m, 2H), 2.00–2.01 (m, 2H), 1.85–1.89 (m, 3H), 1.54–1.63 (m, 2H), 1.05–1.39 (m, 6H), 1.15 (s, 3H), 0.96 (s, 3H), 0.81 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.09, 142.44, 131.64, 128.87, 128.29, 64.95, 52.75, 48.14, 47.53, 44.40, 41.92, 40.78, 38.24, 35.94, 32.57, 29.19, 26.23, 22.39, 20.69, 19.70, 13.80; MS: m/z=437. Anal. Calcd for $C_{23}H_{32}ClNO_3S$: C, 63.07; H, 7.36; N, 3.20; S, 7.32. Found: C, 63.32; H, 7.42; N, 3.17; S, 7.52.

4.2.14. N-[(3R)-3-(4-Methylphenyl)heptanoyl]bornane-10,2-sultam (**2n**)

White solid, mp: 114–115 °C; $[\alpha]_D^{20}$ −65.6 (c 1.08, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.09 (s, 4H), 3.79–3.80 (m, 1H), 3.48 (d, J=14 Hz, 1H), 3.40 (d, J=14.4 Hz, 1H), 3.18–3.21 (m, 1H), 2.96–3.05 (m, 2H), 2.30 (s, 3H), 2.0–2.02 (m, 2H), 1.84–1.88 (m, 3H), 1.57–1.61 (m, 2H), 1.13–1.36 (m, 6H), 1.15 (s, 3H), 0.96 (s, 3H), 0.81 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.56, 140.91, 135.52, 128.90, 127.33, 65.03, 52.83, 48.14, 47.58, 44.46, 42.28, 41.11, 38.32, 36.06, 32.64, 29.34, 26.30, 22.51, 20.98, 20.75, 19.77, 13.86; MS: m/z=417. Anal. Calcd for $C_{24}H_{35}NO_3S$: C, 69.03; H, 8.45; N, 3.35; S, 7.68. Found: C, 68.99; H, 8.60; N, 3.31; S, 7.82.

4.2.15. N-[(3R)-3-Phenyl-4-phenyltetranoyl]bornane-10,2-sultam (**2o**)

Colorless oil, $[\alpha]_D^{20}$ −46.2 (c 1.04, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14–7.20 (m, 5H), 7.01–7.07 (m, 5H), 3.75–3.77 (m, 1H), 3.54–3.55 (m, 1H), 3.48 (d, J=14 Hz, 1H), 3.40 (d, J=14 Hz, 1H), 3.07–3.12 (m, 2H), 2.90–2.92 (m, 1H), 2.84–2.86 (m, 1H), 1.97–1.98 (m, 2H), 1.88–1.82 (m, 3H), 1.29–1.35 (m, 2H), 1.10 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.05, 142.93, 139.29, 129.0, 127.98, 127.63, 127.53, 126.24, 125.85, 64.87, 52.64, 48.03, 47.44, 44.31, 43.03, 42.82, 40.68, 38.15, 32.46, 26.17, 20.70, 19.65; MS: m/z=437. Anal. Calcd for $C_{26}H_{31}NO_3S$: C, 71.36; H, 7.14; N, 3.20; O, 10.97; S, 7.33. Found: C, 71.25; H, 7.12; N, 3.09; S, 7.43.

4.2.16. N-[(3R)-3-(4-Chlorophenyl)-4-phenyltetranoyl]bornane-10,2-sultam (**2p**)

White solid, mp: 158–160 °C; $[\alpha]_D^{20}$ −58.57 (c 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14–7.22 (m, 5H), 7.05–7.07 (m, 2H), 7.0–7.02 (m, 2H), 3.75–3.78 (m, 1H), 3.54–3.56 (m, 1H), 3.48 (d, J=13.6 Hz, 1H), 3.40 (d, J=13.6 Hz, 1H), 3.07–3.12 (m, 2H), 2.91–2.95 (m, 1H), 2.82–2.86 (m, 1H), 1.95–1.98 (m, 2H), 1.82–1.87 (m, 3H), 1.28–1.37 (m, 2H), 1.12 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.14, 143.98, 139.02, 136.46, 132.63, 132.12, 131.96, 129.71, 129.26, 129.05, 128.25, 126.16, 117.79, 65.03, 52.99, 48.36, 47.71, 44.55, 44.06, 42.76, 40.74, 38.38, 32.72, 26.38, 20.79, 19.76. MS: m/z=471. Anal. Calcd for $C_{26}H_{30}ClNO_3S$: C, 66.16; H, 6.41; N, 2.97; S, 6.79. Found: C, 66.26; H, 6.59; N, 2.93; S, 6.82.

4.2.17. N-[(3S)-3-Phenyl-3-cyclohexyl-propnoyl]bornane-10,2-sultam (**2q**)

White solid, mp: 180–181 °C; $[\alpha]_D^{20}$ −45.3 (c 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.13–7.23 (m, 5H), 3.72–3.75 (m, 1H), 3.43 (d, J=13.6 Hz, 1H), 3.36 (d, J=13.6 Hz, 1H), 3.18–3.24 (m, 1H), 2.90–3.02 (m, 2H), 1.64–1.89 (m, 5H), 0.96–1.59 (m, 13H), 0.87 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.95, 142.46, 128.32, 127.77, 125.98, 64.86, 52.82, 48.34, 48.07, 47.67, 47.16, 44.33, 42.94, 42.58, 38.96, 38.40, 38.02, 32.53, 30.72, 30.38, 26.18, 20.52, 19.67; MS: m/z=429. Anal. Calcd for $C_{25}H_{35}NO_3S$: C, 69.89; H, 8.21; N, 3.26; S, 7.46. Found: C, 69.99; H, 8.39; N, 3.19; S, 7.66.

4.2.18. (E)-2-Methyl-4-phenylbut-3-en-2-ol (**3r**)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38–7.40 (m, 2H), 7.30–7.34 (m, 2H), 7.23–7.26 (m, 1H), 6.59 (d, J=16.4 Hz, 1H), 6.36 (d, J=16.4 Hz, 1H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.69, 134.02, 130.40, 128.51, 128.20, 127.40, 127.31, 126.18, 70.78, 29.51, 27.21; MS: m/z=162. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.35; H, 8.63.

4.2.19. Compound ***3s***

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33–7.36 (m, 2H), 6.99–7.03 (m, 2H), 6.57 (d, J=15.6 Hz, 1H), 6.17 (d, J=15.2 Hz, 1H), 5.79–5.86 (m, 2H), 5.15–5.19 (m, 4H), 2.34–2.47 (m, 4H), 1.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.89, 134.14, 133.03, 132.78, 127.68, 127.09, 118.97, 115.18, 73.73, 45.16; MS: m/z=233 $(M+1)^+$. Anal. Calcd for $C_{15}H_{17}FO$: C, 77.56; H, 7.38. Found: C, 77.42; H, 7.29.

4.2.20. Compound ***3t***

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38–7.40 (m, 2H), 7.30–7.34 (m, 2H), 7.22–7.26 (m, 1H), 6.60 (d, J=16 Hz, 1H), 6.26 (d, J=16 Hz, 1H), 5.80–5.89 (m, 2H), 5.14–5.18 (m, 4H), 2.35–2.48 (m, 4H), 1.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.64, 134.47, 133.17, 128.42, 128.35, 127.28, 126.28, 119.09, 73.72, 45.35; MS: m/z=214. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.98; H, 8.52.

4.2.21. Compound ***3u***

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51–7.56 (m, 3H), 7.09–7.11 (m, 2H), 6.68 (d, J=16 Hz, 1H), 5.84–5.91 (m, 1H), 5.05–5.10 (m, 2H), 2.77 (t, J=7.6 Hz, 2H), 2.41–2.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.26, 163.82, 141.13, 137.03, 130.53, 130.05, 125.62, 116.09, 115.98, 39.82, 27.97; MS: m/z=204. Anal. Calcd for $C_{13}H_{13}FO$: C, 76.45; H, 6.42. Found: C, 76.38; H, 6.54.

4.2.22. Compound ***3v***

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34–7.37 (m, 2H), 6.98–7.03 (m, 2H), 6.60 (d, J=15.6 Hz, 1H), 6.21 (d, J=16.4 Hz, 1H), 6.01–6.08 (m, 2H), 5.36 (d, J=16.8 Hz, 2H), 5.23 (d, J=10.4 Hz, 2H), 2.17 (s, 3H), 1.86 (s, 1H). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.85; H, 8.12.

4.2.23. Compound ***3x***

White solid, mp: 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (d, J=7.6 Hz, 2H), 7.22–7.25 (m, 6H), 7.07 (d, J=7.6 Hz, 2H), 7.15 (d, J=7.2 Hz, 3H), 4.78 (t, J=6.8 Hz, 1H), 3.69 (d, J=6.8 Hz, 2H), 2.39 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.55, 144.37, 143.74, 141.13, 135.70, 134.44, 129.14, 128.42, 128.10, 127.67, 127.58, 126.16, 45.42, 44.49, 21.54, 20.90; MS: m/z=314. Anal. Calcd for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.78; H, 7.14.

4.3. General procedure for the synthesis of 4

A solution of sodium borohydride (40 mmol, 4 equiv) in water (10 mL) was added dropwise to a cooled (ice-water) solution of **2** (10 mmol) in THF (30 mL). The mixture was stirred at room temperature and the completion of the reaction was monitored by TLC. To the reaction mixture was added 2 N HCl at a rate to maintain the internal temperature at 20–25 °C. The reaction mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (50 mL), concentrated under vacuum, and purified by silica gel chromatography (AcOEt/hexane=1:9 as eluent) to get the desired products.

4.3.1. Compound ***4a***

Colorless oil, yield 82%; $[\alpha]_D^{20}$ −6.44 (c 1.16, CH_2Cl_2) [lit. [23]: $[\alpha]_D^{20}$ −2.4 (c 0.8, $CDCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23–7.31 (m, 2H), 7.15–7.21 (m, 3H), 3.48–3.53 (m, 2H), 2.57–2.61 (m, 1H), 1.94–1.98 (m, 1H), 1.79–1.83 (m, 1H), 1.61–1.71 (m, 1H), 1.56–1.59 (m, 1H), 1.12 (s, 1H), 0.78 (t, J=7.6 Hz, 3H). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.28; H, 9.98. Enantiomeric excess 90% (Daicel Chiralcel AS-H, eluent: hexane/i-PrOH=90:10, 254 nm, the retention time of the major was 20.7 min and minor 13.6 min).

4.3.2. Compound ***4b***

Colorless oil, yield 84%; $[\alpha]_D^{20}$ −4.76 (c 1.1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.10–7.12 (m, 2H), 6.97–7.0 (m, 2H), 3.53 (s, 1H), 3.45 (s, 1H), 2.59–2.60 (m, 1H), 1.94–1.95 (m, 1H), 1.74–1.77 (m, 1H), 1.67–1.68 (m, 1H), 1.56–1.60 (m, 1H), 1.16 (s, 1H), 0.77 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{11}H_{15}FO$: C, 72.50; H, 8.30. Found: C, 72.34; H, 8.58. Enantiomeric excess 82% (Daicel Chiralcel AS-H, eluent: hexane/i-PrOH=90:10, 254 nm, the retention time of the major was 20.7 min and minor 13.6 min).

4.3.3. Compound ***4c***

Colorless oil, yield 85%; $[\alpha]_D^{20}$ −5.08 (c 1.0, CH_2Cl_2) [lit. [24]: $[\alpha]_D^{25}$ −4.55 (c 1.34, $CHCl_3$)]; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.26 (d, J=8.4 Hz, 2H), 7.10 (d, J=8.4 Hz, 2H), 3.52–3.54 (m, 1H), 3.43–3.45 (m, 1H), 2.59–2.60 (m, 1H), 1.92–1.96 (m, 1H), 1.75–1.77 (m, 1H), 1.67–1.69 (m, 1H), 1.55–1.56 (m, 1H), 1.22 (s, 1H), 0.77 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{11}H_{15}ClO$: C, 66.49; H, 7.61. Found: C, 66.21; H, 7.56. Enantiomeric excess 90% (Daicel Chiralcel AS-H, eluent: hexane/i-PrOH=95:5, 254 nm, the retention time of the major was 9.0 min and minor 7.4 min).

4.3.4. Compound ***4d***

Colorless oil, yield 81%; $[\alpha]_D^{20}$ −3.31 (c 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.10 (d, J=7.8 Hz, 2H), 7.05 (d, J=7.8 Hz, 2H), 3.52–3.53 (m, 1H), 3.47–3.48 (m, 1H), 2.55–2.56 (m, 1H), 2.32 (s, 3H), 1.93–1.94 (m, 1H), 1.77–1.79 (m, 1H), 1.66–1.67 (m, 1H), 1.58–1.61 (m, 1H), 1.15 (s, 1H), 0.78 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.72; H, 10.01. Enantiomeric excess 88% (Daicel Chiralcel AS-H, eluent: hexane/i-PrOH=90:10, 254 nm, the retention time of the major was 10.8 min and minor 7.1 min).

4.3.5. Compound ***4e***

Colorless oil, yield 89%; $[\alpha]_D^{20}$ −6.16 (c 1.14, CH_2Cl_2) [lit. [25]: $[\alpha]_D^{20}$ −6.7 (c 2.0, $CHCl_3$)]; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.26–7.30 (m, 2H), 7.16–7.20 (m, 3H), 3.52–3.53 (m, 1H), 3.45–3.46 (m, 1H), 2.69–2.70 (m, 1H), 1.92–1.93 (m, 1H), 1.80–1.81 (m, 1H), 1.57–1.61 (m, 2H), 1.14–1.19 (m, 3H), 0.84 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.68; H, 9.98. Enantiomeric excess 94% (Daicel Chiralcel AS-H, eluent: hexane/i-PrOH=95:5, 254 nm, the retention time of the major was 8.7 min and minor 6.7 min).

4.3.6. Compound ***4f***

Colorless oil, yield 88%; $[\alpha]_D^{20}$ −4.58 (c 1.08, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.10–7.13 (m, 2H), 6.96–7.0 (t, J=8.4 Hz, 2H), 3.52–3.53 (m, 1H), 3.43–3.44 (m, 1H), 2.70–2.71 (m, 1H), 1.91–1.93 (m, 1H), 1.74–1.76 (m, 1H), 1.52–1.62 (m, 2H), 1.13–1.18 (m, 3H), 0.84 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{12}H_{17}FO$: C, 73.44; H, 8.73. Found: C, 73.18; H, 8.47. Enantiomeric excess 90% (Daicel Chiralcel AS-H, eluent: hexane/i-PrOH=95:5, 254 nm, the retention time of the major was 7.2 min and minor 6.5 min).

4.3.7. Compound ***4g***

Colorless oil, yield 87%; $[\alpha]_D^{20}$ −5.22 (c 1.16, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.10 (d, J=6.6 Hz, 2H), 7.05 (d, J=7.2 Hz, 2H), 3.52–3.53 (m, 1H), 3.46–3.48 (m, 1H), 2.65–2.66 (m, 1H), 2.32 (s, 3H), 1.90–1.93 (m, 1H), 1.77–1.79 (m, 1H), 1.54–1.60 (m, 2H), 1.13–1.21 (m, 3H), 0.84 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.02; H, 10.56. Enantiomeric excess 88% (Daicel Chiralcel AS-H, eluent: hexane/i-PrOH=95:5, 254 nm, the retention time of the major was 8.7 min and minor 6.2 min).

4.3.8. Compound ***4h***

Colorless oil, yield 90%; $[\alpha]_D^{20}$ −8.96 (c 1.06, CH_2Cl_2) [lit. [26]: $[\alpha]_D^{22}$ −3.3 (c 1.5, $CHCl_3$)]; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.26 (d,

J=6 Hz, 2H), 7.10 (d, J=4.2 Hz, 2H), 3.52–3.53 (m, 1H), 3.42–3.44 (m, 1H), 2.70–2.71 (m, 1H), 1.91–1.93 (m, 1H), 1.74–1.75 (m, 1H), 1.52–1.58 (m, 2H), 1.14–1.18 (m, 3H), 0.84 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{12}H_{17}ClO$: C, 67.76; H, 8.06. Found: C, 67.68; H, 8.28. Enantiomeric excess 84% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 7.8 min and minor 6.5 min).

4.3.9. Compound **4i**

Colorless oil, yield 78%; $[\alpha]_D^{20}$ −6.73 (c 1.14, CH_2Cl_2) [lit.[23]: $[\alpha]_D^{20}$ −5.5 (c 4.0, $CDCl_3$)]; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.27–7.29 (m, 2H), 7.13–7.20 (m, 3H), 3.46–3.47 (m, 1H), 3.38–3.39 (m, 1H), 2.39–2.41 (m, 1H), 2.06–2.08 (m, 1H), 1.80–1.83 (m, 2H), 1.15 (s, 1H), 0.97 (d, J=6.6 Hz, 3H), 0.73 (d, J=7.2 Hz, 3H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.83; H, 10.32. Enantiomeric excess 60% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 12.8 min and minor 7.6 min).

4.3.10. Compound **4j**

Colorless oil, yield 76%; $[\alpha]_D^{20}$ −5.98 (c 1.21, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.07–7.10 (m, 2H), 6.96–7.0 (m, 2H), 3.47–3.49 (m, 1H), 3.37–3.38 (m, 1H), 2.41–2.42 (m, 1H), 2.06–2.08 (m, 1H), 1.77–1.80 (m, 2H), 1.11 (s, 1H), 0.96 (d, J=6.6 Hz, 3H), 0.72 (d, J=6.6 Hz, 3H). Anal. Calcd for $C_{12}H_{17}FO$: C, 73.44; H, 8.73. Found: C, 73.35; H, 8.86. Enantiomeric excess 68% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 9.3 min and minor 7.3 min).

4.3.11. Compound **4k**

Colorless oil, yield 90%; $[\alpha]_D^{20}$ −9.46 (c 1.11, CH_2Cl_2) [lit. [27]: $[\alpha]_D^{25}$ +1.98 (c 1.0, $CHCl_3$) for the *S* isomer]; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.26–7.30 (m, 2H), 7.16–7.21 (m, 3H), 3.52–3.53 (m, 1H), 3.46–3.47 (m, 1H), 2.66–2.69 (m, 1H), 1.93–1.96 (m, 1H), 1.78–1.82 (m, 1H), 1.60–1.65 (m, 2H), 1.20–1.29 (m, 2H), 1.08–1.18 (m, 3H), 0.83 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.05; H, 10.61. Enantiomeric excess 86% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 7.5 min and minor 6.0 min).

4.3.12. Compound **4l**

Colorless oil, yield 92%; $[\alpha]_D^{20}$ −5.17 (c 1.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.09–7.13 (m, 2H), 6.95–7.0 (m, 2H), 3.44–3.52 (m, 2H), 2.65–2.69 (m, 1H), 1.90–1.93 (m, 1H), 1.73–1.77 (m, 1H), 1.51–1.64 (m, 2H), 1.05–1.29 (m, 5H), 0.82 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{13}H_{19}FO$: C, 74.25; H, 9.11. Found: C, 74.33; H, 9.37. Enantiomeric excess 88% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=90:10, 254 nm, the retention time of the major was 5.0 min and minor 4.7 min).

4.3.13. Compound **4m**

Colorless oil, yield 90%; $[\alpha]_D^{20}$ −16.98 (c 1.35, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.26 (d, J=7.8 Hz, 2H), 7.10 (d, J=8.4 Hz, 2H), 3.51–3.52 (m, 1H), 3.43–3.44 (m, 1H), 2.67–2.68 (m, 1H), 1.91–1.93 (m, 1H), 1.74–1.75 (m, 1H), 1.53–1.62 (m, 2H), 1.08–1.28 (m, 5H), 0.82 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{13}H_{19}ClO$: C, 68.86; H, 8.45. Found: C, 68.72; H, 8.63. Enantiomeric excess 98% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 7.3 min and minor 6.2 min).

4.3.14. Compound **4n**

Colorless oil, yield 88%; $[\alpha]_D^{20}$ −13.8 (c 1.07, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.10 (d, J=7.8 Hz, 2H), 7.05 (d, J=7.8 Hz, 2H), 3.51–3.52 (m, 1H), 3.45–3.47 (m, 1H), 2.61–2.64 (m, 1H), 2.32 (s, 3H), 1.90–1.93 (m, 1H), 1.75–1.79 (m, 1H), 1.55–1.61 (m, 2H), 1.20–1.29 (m, 2H), 1.11–1.19 (m, 3H), 0.83 (t, J=7.2 Hz, 3H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.58; H, 10.73. Enantiomeric excess 88% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 7.9 min and minor 5.9 min).

4.3.15. Compound **4o**

Colorless oil, yield 82%; $[\alpha]_D^{20}$ −7.87 (c 0.94, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.25–7.28 (m, 2H), 7.18–7.21 (m, 3H), 7.13–7.17 (m, 3H), 7.04–7.05 (m, 2H), 3.50–3.52 (m, 1H), 3.41–3.43 (m, 1H), 2.99–3.0 (m, 1H), 2.88–2.91 (m, 2H), 1.95–1.98 (m, 1H), 1.83–1.86 (m, 1H), 1.14 (s, 1H). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.78; H, 8.15. Enantiomeric excess 68% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 14.6 min and minor 10.9 min).

4.3.16. Compound **4p**

Colorless oil, yield 84%; $[\alpha]_D^{20}$ −7.97 (c 1.21, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.14–7.23 (m, 5H), 7.05 (d, J=7.8 Hz, 2H), 7.01 (d, J=7.2 Hz, 2H), 3.51–3.52 (m, 1H), 3.40–3.41 (m, 1H), 3.0–3.01 (m, 1H), 2.84–2.91 (m, 2H), 1.96–1.98 (m, 1H), 1.83–1.84 (m, 1H), 1.14 (s, 1H). Anal. Calcd for $C_{16}H_{17}ClO$: C, 73.70; H, 6.57. Found: C, 73.55; H, 6.79. Enantiomeric excess 52% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 25.3 min and minor 22.9 min).

4.3.17. Compound **4q**

Colorless oil, yield 85%; $[\alpha]_D^{20}$ −4.36 (c 0.94, CH_2Cl_2) [lit. [28]: $[\alpha]_D^{22}$ +12.4 (c 1.17, pentane) for the *R* isomer]; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26–7.29 (m, 2H), 7.16–7.20 (m, 1H), 7.11–7.13 (m, 2H), 3.36–3.46 (m, 2H), 2.42–2.46 (m, 1H), 2.07–2.11 (m, 1H), 1.90–1.93 (m, 1H), 1.72–1.83 (m, 2H), 1.58–1.61 (m, 2H), 1.40–1.48 (m, 2H), 1.21–1.25 (m, 1H), 1.05–1.12 (m, 3H), 0.91–0.94 (m, 1H), 0.77–0.80 (m, 1H). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.30; H, 9.92. Enantiomeric excess 56% (Daicel Chiralcel AS-H, eluent: hexane/*i*-PrOH=95:5, 254 nm, the retention time of the major was 22.3 min and minor 15.0 min).

Acknowledgements

The authors acknowledge financial support from National Natural Science Foundation of China (Nos. 20572029 and 20772039), the Science Foundation for the New Teacher at the University of China (No. 20070511006), the National Key Project for Basic Research of China (No. 2004CCA00100), and National Basic Research Program of China (Grant No. 2007CB116302).

References and notes

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series; Pergamon: Oxford, 1992; Vol. 9; (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
2. (a) Reid, G. P.; Brear, K. W.; Robins, D. J. *Tetrahedron: Asymmetry* **2004**, *15*, 793; (b) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103.
3. (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392; (b) Molander, G. *Chem. Rev.* **1992**, *92*, 29.
4. Kelly, B. G.; Gilheany, D. G. *Tetrahedron Lett.* **2002**, *43*, 887.
5. (a) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128; (b) Posner, G. H. *Org. React.* **1972**, *19*, 1; (c) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley-Interscience: New York, NY, 1980; (d) Lipshutz, B. H. *Synthesis* **1987**, 325; (e) Taylor, R. J. K. *Organometallic Reagents*; Oxford University Press: Oxford, 1994.
6. (a) Swain, C. G.; Boyles, H. B. *J. Am. Chem. Soc.* **1951**, *73*, 870; (b) McBee, E. T.; Pierce, O. R.; Higgins, J. F. *J. Am. Chem. Soc.* **1952**, *74*, 1736; (c) Chastrette, M.; Amouroux, R. *Bull. Soc. Chim. Fr.* **1970**, 4348.
7. Chastrett, M.; Amouroux, R. *J. Chem. Soc., Chem. Commun.* **1970**, 470.
8. (a) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31; (b) Seebach, D.; Weidmann, B.; Widler, L. *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag: Frankfurt, 1983; Vol. 3, p 217; (c) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986.

9. Schumann, H.; Kaufmann, J.; Dechert, S.; Schmalz, H. G. *Tetrahedron Lett.* **2002**, *43*, 3507.
10. López, F,; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179; (b) El-Batta, A.; Bergdahl, M. *Tetrahedron Lett.* **2007**, *48*, 1761; (c) Wang, S. Y.; Ji, S. J.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 276.
11. Fujita, N.; Motokura, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Tetrahedron Lett.* **2006**, *47*, 5083; (b) Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D.; Yamamoto, Y.; Miyaura, N. *J. Organomet. Chem.* **2007**, *692*, 428.
12. (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768; (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2003**, *32*, 752; (c) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004**, 1822; (d) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317; (e) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2005**, *34*, 721; (f) Nishikata, T.; Yamamoto, Y.; Gridnev, I. D.; Miyaura, N. *Organometallics* **2005**, *24*, 5025.
13. Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4908.
14. Oppelzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.
15. Oppelzer, W. *Helv. Chim. Acta* **1987**, *70*, 2201.
16. Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.
17. Oppolzer, W.; Barras, J.-P. *Tetrahedron* **1986**, *42*, 4035.
18. Zhang, W.; Matla, A. S.; Romo, D. *Org. Lett.* **2007**, *11*, 2111.
19. Andersson, P. G.; Schink, H. E.; österlund, K. *J. Org. Chem.* **1998**, *63*, 8067.
20. Cao, X. F.; Yu, G.; Liu, S. H.; Hu, M.; Wang, M. *Acta Crystallogr.* **2007**, *E63*, o2034.
21. Cao, X. F.; Yu, G.; Liu, S. H. *Acta Crystallogr.* **2006**, *E62*, o4458.
22. Lin, Y.; Cao, X. F.; Hu, M.; Yu, G.; Liu, S. H. *Acta Crystallogr.* **2007**, *E63*, o1872.
23. Sabbani, S.; Hedenström, E.; Andersson, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1712.
24. Soeta, T.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 297.
25. Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763.
26. Wee, A. G. H.; Shi, Q.; Wang, Z. Y.; Hatton, K. *Tetrahedron: Asymmetry* **2003**, *14*, 897.
27. Pridgen, L. N.; Mokhallalati, M. K.; Wu, M. J. *J. Org. Chem.* **1992**, *57*, 1237.
28. Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299.
29. (a) Kilian, M.; Atsushi, I.; Martin, N. *Chem.—Eur. J.* **2003**, *9*, 5581; (b) Guile, S.; Hardern, D.; Ingall, A.; Springthorpe, B.; Willis, P. WO Patent 2,000,034,283, 2000; (c) Eaudoin S.; Gross, M. F.; Reed, A. D.; Wickenden, A. D.; Zou, A. WO Patent 2,002,008,183, 2002; (d) Jerk, V.; Ulf, A.; Ingeborg, C.; Uli, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 461.