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A novel and concise synthetic access to chiral 2-substituted-4-piperidone

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A novel and concise synthetic access to enantiopure chiral 2-aryl/alkyl substituted 4-piperidone has been demonstrated. This new route features two key steps: the highly diastereoselective conjugate addition of homochiral lithium amides to *trans*-β-substituted-α,β-unsaturated methyl esters guaranteed the enantiopurity at 2 position (de >19:1) and the intramolecular attacking of carbanions to methyl esters led to the formation of the piperidone ring. A wide range of substrates, including chiral 2-aryl and 2-alkyl-4-piperidones, were successfully synthesized with modest to high yield. Moreover, some non-chiral 3-substituted-4-piperidones were also synthesized with enhanced ring-formation yield, implicating the versatility of this method in construction of various piperidine rings.

chiral 2-substituted-4-piperidone, homochiral lithium amide, diastereoselective conjugate addition, lithium-iodine exchange, intramolecular carbonyl formation

1 Introduction

Piperidine remains as one of the most common and important structures in natural products and pharmaceutical active moleculars, implicating its fundamental and important role in organic synthesis [1–3]. Chiral 2,4-disubstituted piperidines constitute an important category of piperidine derivatives that appear in many drugs and drug candidates [4–6]. For example, Selfotel (CGS-19755) is a competitive NMDA antagonist which exhibits anticonvulsant, anxiolytic, analgesic and neuroprotective effects [7]. Palinavir is regarded as a potent inhibitor of the human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) proteases and may be beneficial to the treatment of HIV [8] (Figure 1).

Considering that the carbonyl group lies in the center of organic synthetic network and can be easily transformed to various specific functional groups, it is undoubtedly believed that chiral 2-substituted-4-piperidones would be an attractive precursor of chiral 2,4-disubstituted piperidine during the synthetic work. The most frequent method used in the synthesis of chiral 2-substituted-4-piperidones was the asymmetric addition of nucleophiles to 2,3-dihydro-4-pyridones in cooperation with chiral ligands and metal catalysts. In 2004, Hayashi first reported the asymmetric addition of arylzinc reagents to 2,3-dihydro-4-pyridones in a rhodium-catalyzed manner and up to 100% yield and 99% ee value were obtained [9]. After that, various aryl and alkyl nucleophiles, including arylboron reagents [10–13], ar-

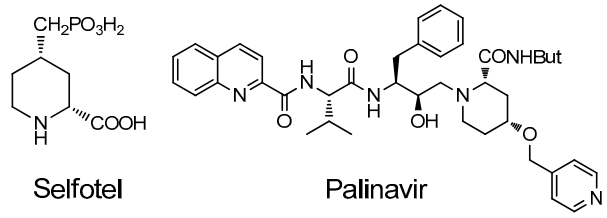

Figure 1 Chemical structures of selfotel and palinavir.

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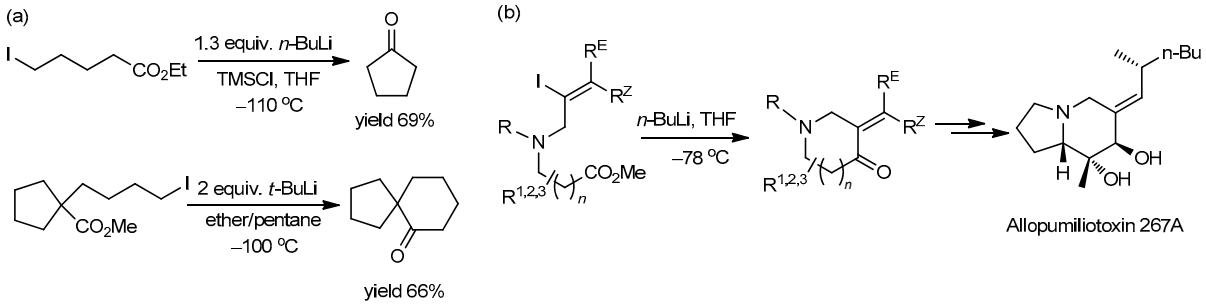
ylsilanes reagents [14, 15], alkylzinc [16, 17] and alkyaluminum reagents [18], were successfully introduced, affording highly enantioenriched chiral 2-aryl/alkyl-4-piperidones. In 2012, high enantioselective synthesis of chiral 2-alkenyl-4-piperidones was also realized via asymmetric addition of alkenyl alanes to 2,3-dihydro-4-pyridones with the aid of copper catalysts (ee up to 97%) [19]. However, none of these methods can enable the high enantioselective production of chiral 2-aryl and 2-alkyl-4-piperidones simultaneously. Another major approach to chiral 2-substituted-4-piperidones is the Aza Diels-Alder reactions between imines and Danishefski's diene [20–24]. Though modest to high ee value (up to 95%) can be achieved, most reactions can only give rise to chiral 2-aryl-4-piperidones.

In the 1980s, Houpis [25] and Schakel [26] developed a cyclization method via carbanion generated by lithiumiodine exchange attacking ester group intramolecularly at low temperature, leading to the formation of cyclopentanone and cyclohexanone with acceptable yield (Scheme 1). Later our group completed the total synthesis of Allopumiliotoxin 267A using the similar strategy as the key ring-formation step [27] (Scheme 1). These results prompted us to develop a similar access to 4-piperidones. On the other hand, careful literature search revealed that Davis's pioneering work in diastereoselective conjugate addition of homochiral lithium amides to *trans*-β-substituted-α, β-unsaturated esters proved to be a powerful tool in establishment of the chirality at 2 position [28]. The retrosynthetic analysis was shown below. However, we also should note here that the deprotonation at α-position of ester by lithium reagent and the addition of lithium reagent to carbonyl group formed in product will account for the main side reactions and the control of regioselectivity will be challengeable in this novel route (Scheme 2).

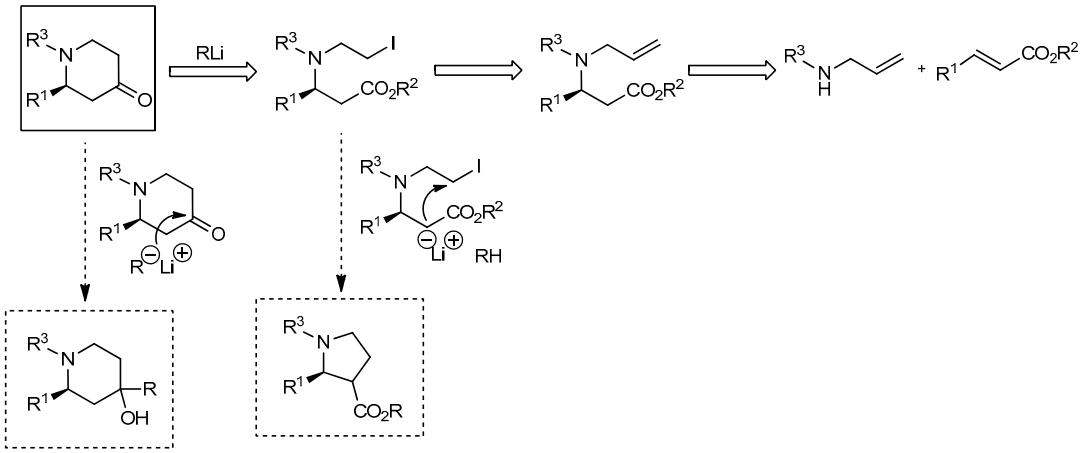
2 Experimental

2.1 General experimental section

All manipulations were carried out in chemical fume hood. All reagents were purchased from Sigma-Aldrich, Alfa Aser Chemicals and SCRC unless otherwise noted. Solvents were distilled under nitrogen from sodium and benzophenone (THF, DMF, toluene, diethyl ether) and calcium hydride (DCM, Acetonitrile, DMF and DMSO). All ^{1}H and ^{13}C NMR data were recorded at ambient temperature in $CDCl_3$ (^{1}H 500 MHz, C 125 MHz) unless indicated otherwise. Chemical shifts were reported in parts per million as



Scheme 1 (a) Formation of cyclopentanone and cyclohexanone via carbanion attacking ester group intramolecularly; (b) Total synthesis of Allopumiliotoxin 267A using carbanion attacking ester group as key ring-formation step.



Scheme 2 Retrosynthetic analysis of chiral 2-substituted-4-piperidone based on our hypothesis.

follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant. Optical rotations were recorded at 589 nm, and were reported as [α]D (concentration in grams/100 mL solvent). High-resolution mass spectrum was performed on SHIMADZU LCMS-IT-TOF machine.

2.2 Synthesis of (3*S*)-3-[[(1*R*)-1-phenylethyl]-2-propen-1-ylamino]-4-methylpentanoic acid methyl ester (compound 2)

(*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine (240 mg, 1.5 mmol) was dissolved in THF (10 mL) and cooled to –78°C. *n*-BuLi (0.75 mL, 1.6 M in hexane) was slowly dropped into the reaction system under stirring. After *n*-BuLi was added, stirring continued for 45min at –78°C before *trans*-β-substituted-α,β-unsaturated methyl ester (1 mmol) dissolved in THF was added. The reaction was completed after another 40 min and quenched with saturated NH_4Cl aqueous solution. After the reaction mixture was extracted with diethyl ether three times, the combined organic phase was washed, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluted with EtOAc/hexane.

Compound **2**: yield 75%. $[\alpha]_D^{26}$ –51.4 (c 1.45, CHCl3); ^{1}H NMR (CDCl3) δ 7.32–7.18 (m, 5H), 5.91–5.80 (m, 1H), 5.20 (dd, 1H, *J* = 17.6, 1.6 Hz), 5.07 (dd, 1H, *J* = 10.0, 1.2 Hz), 3.91 (q, 1H, *J* = 6.8 Hz), 3.58 (s, 3H), 3.22–3.15 (m, 1H), 3.11–3.00 (m, 2H), 2.14–1.98 (m, 2H), 1.73–1.60 (m, 1H), 1.39 (d, 3H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 6.8 Hz), 0.80, 3H, *J* = 6.4 Hz); ^{13}C NMR (CDCl3) δ 173.8, 143.7, 139.1, 127.9, 127.8, 126.7, 115.3, 59.6, 58.7, 51.3, 49.6, 34.8, 32.7, 20.9, 20.8, 19.7; HR-ESI-MS *m*/*z* Calcd for $C_{18}H_{28}NO_2$ (M + H^+) 290.2120, Found 290.2120.

Compound **2a** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-propen-1-ylamino]-butanoic acid methyl ester): yield 85%. $[\alpha]_D^{26}$ –14.2 (c 1.85, CHCl3); ^{1}H NMR (CDCl3) δ 7.36–7.20 (m, 5H), 5.90–5.77 (m, 1H), 5.14 (dd, 1H, *J* = 17.1, 1.8 Hz), 5.03 (dd, 1H, *J* = 10.3, 1.8 Hz), 3.95 (q, 1H, *J* = 7.2 Hz), 3.56 (s, 3H), 3.47 (q, 1H, *J* = 7.2 Hz), 3.16 (d, 2H, *J* = 6.3 Hz), 2.40 (dd, 1H, *J* = 14.1, 7.2 Hz), 2.17 (dd, 1H, *J* = 14.4, 7.5 Hz), 1.37 (d, 3H, *J* = 6.9 Hz), 1.05 (d, 3H, *J* = 6.6 Hz);

Compound **2b** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-propen-1-ylamino]-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-hexa noic acid methyl ester): yield 100%. $[\alpha]_D^{26}$ –11.9 (*c* 1.75, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 7.33–7.18 (m, 5H), 5.90–5.79 (m, 1H), 5.17 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.05 (dd, 1H, *J* = 10.0, 1.2 Hz), 3.94 (q, 1H, *J* = 6.8 Hz), 3.60–3.52 (m, 2H), 3.55 (s, 3H), 3.31–3.19 (m, 2H), 3.12–3.04 (m, 1H), 2.19–2.05 (m, 2H), 1.73–1.63 (m, 1H), 1.57–1.24 (m, 3H), 1.38 (d, 3H, *J* = 6.8 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.2, 144.3, 139.0, 128.0, 127.6, 126.7, 115.5, 63.1, 58.0, 54.7, 51.3, 48.6, 37.0, 30.3, 29.2, 25.9, 20.2, 18.3, –5.3; HR-ESI-MS *m*/*z* Calcd for $C_{24}H_{42}NO_3Si$ (M + H^+) 420.2934, Found 420.2945.

Compound **2c** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-propen-1-ylamino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-butanoic acid methyl ester): yield 91%. $[\alpha]_D^{28}$ –18.8 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35–7.17 (m, 5H), 5.86–5.75 (m, 1H), 5.11 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.03 (dd, 1H, *J* = 10.0, 1.6 Hz), 4.05 (q, 1H, *J* = 6.8 Hz), 3.72–3.65 (m, 1H), 3.60 (s, 3H), 3.59–3.51 (m, 2H), 3.31–3.14 (m, 2H), 2.46–2.23 (m, 2H), 1.39 (d, 3H, *J* = 6.8 Hz), 0.88 (s, 9H), 0.02 (d, 6H, *J* = 3.6 Hz); ^{13}C NMR ($CDCl_3$) δ 173.1, 144.8, 138.8, 128.0, 127.4, 126.5, 115.6, 64.3, 57.2, 55.8, 51.3, 49.6, 35.0, 25.8. 19.4, 18.2. –5.6; HR-ESI-MS *m*/*z* Calcd for $C_{22}H_{38}NO_3Si$ (M + H^+) 392.2621, Found 392.2628.

Compound **2d** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-propen-1-ylamino]-benzenepropanoic acid methyl ester): yield 90%. $[\alpha]_D^{26}$ –3.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.42–7.19 (m, 10H), 5.85–5.74 (m, 1H), 5.15 (dd, 1H, *J* = 17.6, 1.6 Hz), 5.06 (dd, 1H, *J* = 10.0, 1.6 Hz), 4.51 (t, 1H, *J* = 8.8 Hz), 4.05 (q, 1H, *J* = 6.0 Hz), 3.55 (s, 3H), 3.24–3.11 (m, 2H), 2.93–2.61 (m, 2H), 1.15 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 144.7, 141.3, 138.6, 128.2, 127.9, 127.8, 127.3, 127.1, 126.5, 115.8, 58.6, 56.0, 51.4, 49.6, 37.8, 16.3; HR-ESI-MS *m*/*z* Calcd for $C_{21}H_{26}NO_2$ (M + H^+) 324.1964, Found 324.1964.

Compound **2e** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-propen-1-ylamino]-benzenepentanoic acid methyl ester): yield 94%. $[\alpha]_D^{25}$ –12.6 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34–7.14 (m, 10H), 5.95–5.84 (m, 1H), 5.22 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.10 (dd, 1H, *J* = 10.0, 1.6 Hz), 3.96 (q, 1H, *J* = 6.8 Hz), 3.56 (s, 3H), 3.40–3.23 (m, 1H), 3.16–3.08 (m, 1H), 2.90–2.80 (m, 1H), 2.56–2.47 (m, 1H), 2.21–2.09 (m, 2H), 1.80–1.69 (m, 1H), 1.66–1.55 (m, 1H), 1.39 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 173.1, 144.0, 142.5, 138.9, 128.3, 128.2, 128.0, 127.6, 126.7, 125.6, 115.5, 58.2, 54.5, 51.3, 48.6, 36.6, 35.2, 33.3, 20.2; HR-ESI-MS *m*/*z* Calcd for $C_{23}H_{30}NO_2$ (M + H^+) 352.2277, Found 352.2263.

Compound **2f** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-propen-1-ylamino]-4-methylbenzenepropanoic acid methyl ester): yield 95%. $[\alpha]_D^{27}$ –0.04 (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40–7.10 (m, 9H), 5.85–5.73 (m, 1H), 5.14 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.05 (dd, 1H, *J* = 10.4, 1.6 Hz), 4.47 (t, 1H, *J* = 7.6 Hz), 4.05 (q, 1H, *J* = 6.8 Hz), 3.55 (s, 3H), 3.23–3.10 (m, 2H), 2.91–2.83 (m, 1H), 2.67–2.60 (m, 1H), 2.34 (s, 3H), 1.15 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.5, 145.0, 138.9, 138.4, 136.8, 129.1, 128.1, 127.9, 127.6, 126.6, 115.9, 58.6, 56.2, 51.5, 49.8, 38.2, 21.2, 16.6; HR-ESI-MS *m*/*z* Calcd for $C_{22}H_{28}NO_2$ (M + H^+) 338.2120, Found 338.2129.

2.3 Synthesis of (3*S*)-3-[[(1*R*)-1-phenylethyl]-2-hydroxyethylamino]-4-methylpentanoic acid methyl ester (compound 3)

Compound **2** (1 mmol) was dissolved in *t*-BuOH/THF/H_2O (4 mL/4 mL/4 mL) followed by addition of catalytic amount of OsO_4 and NMO (3 mmol). The mixture was stirred at

room temperature. Once the reaction was completed evidenced by TLC, saturated Na_2SO_3 and saturated Na_2CO_3 aqueous solution were both added to quench the reaction. After stirring at room temperature for another 10 min, the reaction mixture was extracted with ethyl acetate three times. The combined organic phase was washed, dried and concentrated at reduced pressure. The residue was directly dissolved in THF/H_2O (3 mL/3 mL) and $NaIO_4$ (1.2 mmol) was added at room temperature. When TLC monitoring showed the reaction was completed, the reaction temperature was lowered to 0 °C and $NaBH_4$ (2 mmol) was added. After half an hour, water was added to quench the reaction at 0 °C. The reaction mixture was extracted with DCM three times and combined organic phase was washed, dried and concentrated at reduced pressure. The residue was purified by silica gel flash column chromatography eluted with EtOAc/hexane.

Compound **3**: yield 95%. $[\alpha]_D^{27}$ –55.6 (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32–7.18 (m, 5H), 3.94 (q, 1H, *J* = 6.8 Hz), 3.59–3.41 (m, 2H), 3.53 (s, 3H), 3.15–3.08 (m, 1H), 2.95–2.80 (br, 1H), 2.77–2.72 (m, 2H), 2.19–2.01 (m, 2H), 1.85–1.75 (m, 1H), 1.42 (d, 3H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 6.8 Hz), 0.83 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 174.0, 143.7, 128.3, 128.0, 127.2, 60.1, 59.9, 58.2, 51.6, 48.3, 35.4, 31.9, 21.6, 20.0, 19.6; HR-ESI-MS *m/z* Calcd for $C_{17}H_{28}NO_3$ (M + H^+) 294.2069, Found 294.2051.

Compound **3a** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-hydroxyethylamino]-butanoic acid methyl ester): yield 95%. $[\alpha]_D^{26}$ –66.4 (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39–7.18 (m, 5H), 3.95 (q, 1H, *J* = 6.8 Hz), 3.65–3.57 (m, 1H), 3.52–3.40 (m, 2H), 3.38 (s, 9H), 2.82–2.65 (m, 2H), 2.33 (dd, 1H, *J* = 13.2, 9.2 Hz), 2.11 (dd, 1H, *J* = 14.0, 4.8 Hz), 1.39 (d, 3H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 143.9, 128.1, 127.7, 126.7, 59.6, 57.1, 51.5, 49.5, 46.9, 40.7, 17.7, 16.1; HR-ESI-MS *m/z* Calcd for $C_{15}H_{24}NO_3$ (M + H^+) 266.1756, Found 266.1752.

Compound **3b** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-hydroxyethylamino]-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-hexanoic acid methyl ester): yield 73%. $[\alpha]_D^{24}$ –39.6 (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35–7.18 (m, 5H), 3.95 (q, 1H, *J* = 6.8 Hz), 3.63–3.54 (m, 3H), 3.54–3.46 (m, 1H), 3.39 (s, 3H), 3.30–3.14 (m, 2H), 2.81–2.71 (m, 2H), 2.21–2.15 (m, 2H), 1.76–1.70 (m, 1H), 1.69–1.44 (m, 3H), 1.40 (d, 3H, *J* = 6.8 Hz), 1.36–1.23 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.2, 143.7, 128.1, 127.9, 126.9, 62.7, 59.8, 57.2, 54.7, 51.6, 47.4, 38.0, 30.6, 28.7, 25.9, 18.3, 17.0, –5.3; HR-ESI-MS *m/z* Calcd for $C_{23}H_{42}NO_4Si$ (M + H^+) 424.2883, Found 424.2902.

Compound **3c** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-hydroxyethylamino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-butanoic acid methyl ester): yield 91%. $[\alpha]_D^{28}$ –21.7 (*c* 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34–7.19 (m, 5H), 4.01 (q, 1H, *J* = 6.4 Hz), 3.68–3.40 (m, 5H), 3.51 (s, 3H), 2.86–2.70 (m, 2H), 2.25–2.14 (m, 2H), 1.42 (d, 3H, *J* = 6.4 Hz), 0.90 (s, 9H), 0.04 (d, 6H, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 173.1, 143.8, 128.2, 127.6, 126.9, 63.6, 60.0, 57.5, 55.8, 51.6, 47.4, 34.2, 25.8, 18.8, 18.1, –5.5, –5.6; HR-ESI-MS *m/z* Calcd for $C_{21}H_{38}NO_4Si$ (M + H^+) 396.2570, Found 396.2574.

Compound **3d** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-hydroxyethylamino]-benzenepropanoic acid methyl ester): yield 94%. $[\alpha]_D^{26}$ –13.1 (*c* 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40–7.17 (m, 10H), 4.52 (dd, 1H, *J* = 8.0, 7.2 Hz), 4.08 (t, 1H, *J* = 6.8 Hz), 3.58 (s, 3H), 3.57–3.37 (m, 2H), 2.99–2.91 (m, 1H), 2.86–2.78 (m, 1H), 2.75–2.55 (m, 3H), 1.11 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.7, 144.3, 140.4, 128.5, 128.2, 127.8, 127.5, 127.4, 126.9, 59.8, 58.2, 56.3, 51.7, 47.8, 37.2, 16.5; HR-ESI-MS *m/z* Calcd for $C_{20}H_{26}NO_3$ (M + H^+) 328.1913, Found 328.1916.

Compound **3e** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-hydroxyethylamino]-benzenepentanoic acid methyl ester): yield 90%. $[\alpha]_D^{25}$ –48.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34–7.14 (m, 10H), 3.94 (q, 1H, *J* = 6.8 Hz), 3.63–3.48 (m, 2H), 3.39 (s, 3H), 3.36–3.20 (m, 2H), 2.82–2.70 (m, 2H), 2.69–2.57 (m, 2H), 2.32–2.16 (m, 2H), 1.91–1.81 (m, 1H), 1.78–1.68 (br, 1H), 1.67–1.56 (m, 1H), 1.32 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 173.0, 143.3, 141.4, 128.4, 128.0, 127.8, 126.8, 125.9, 59.7, 57.3, 53.8, 51.5, 47.3, 37.7, 34.6, 33.5, 16.7; HR-ESI-MS *m/z* Calcd for $C_{22}H_{30}NO_3$ (M + H^+) 356.2226, Found 356.2241.

Compound **3f** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-hydroxyethylamino]-4-methylbenzenepropanoic acid methyl ester): yield 98%. $[\alpha]_D^{27}$ –12.2 (*c* 1.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40–7.13 (m, 9H), 4.49 (t, 1H, *J* = 7.8 Hz), 4.06 (q, 1H, *J* = 6.8 Hz), 3.57 (s, 3H), 3.55–3.48 (m, 1H), 3.43–3.35 (m, 1H), 2.97–2.89 (m, 1H), 2.85–2.77 (m, 1H), 2.74–2.62 (m, 3H), 2.34 (s, 3H), 1.13 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.9, 144.6, 137.6, 137.3, 129.3, 128.4, 127.9, 127.6, 127.0, 60.1, 58.2, 56.6, 51.8, 48.0, 37.5, 21.2, 16.8; HR-ESI-MS *m/z* Calcd for $C_{21}H_{28}NO_3$ (M + H^+) 342.2069, Found 342.2082.

2.4 Synthesis of (3*S*)-3-[[(1*R*)-1-phenylethyl]-2-iodoethylamino]-4-methylpentanoic acid methyl ester (compound 4)

Compound **3** (1 mmol) along with PPh3 (1.5 mmol) and imidazole (2 mmol) was dissolved in ether/CH_3CN (9 mL/3 mL) under Ar atmosphere. I_2 (1.5 mmol) was quickly added to this mixture at 0 °C. After stirring for 1 h, the reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution and extracted with ethyl acetate three times. The combined organic phase was washed, dried and concentrated at reduced pressure to yield white solid. The white solid was loaded onto a column filled with silica gel followed by elution with EtOAc/hexane (1/20). Elution was collected and concentrated again at reduced pressure to give desired products.

Compound **4**: yield 90%. ^{1}H NMR ($CDCl_3$) δ 7.34–7.19 (m, 5H), 3.87 (q, 1H, *J* = 6.8 Hz), 3.61 (s, 3H), 3.03–2.80 (m, 5H), 2.35–2.10 (m, 2H), 1.75–1.60 (m, 1H), 1.41 (d, 3H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 6.6 Hz), 0.81 (d, 3H, *J* = 6.6

Hz).

Compound **4a** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-iodoethylamino]-butanoic acid methyl ester): yield 81%. ^{1}H NMR ($CDCl_3$) δ 7.34–7.19 (m, 5H), 3.86 (q, 1H, J = 6.6 Hz), 3.60 (s, 3H), 3.53–3.39 (m, 1H), 2.99–2.76 (m, 4H), 2.45–2.17 (m, 2H), 1.38 (d, 3H, J = 6.6 Hz), 1.05 (d, 3H, J = 6.6 Hz).

Compound **4b** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-iodoethylamino]-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-hexanoic acid methyl ester): yield 89%. ^{1}H NMR ($CDCl_3$) δ 7.34–7.19 (m, 5H), 3.86 (q, 1H, J = 6.6 Hz), 3.59 (s, 3H), 3.64–3.48 (m, 2H), 3.26–3.14 (m, 1H), 3.02–2.82 (m, 4H), 2.28–2.18 (m, 2H), 1.73–1.11 (m, 4H), 1.39 (d, 3H, J = 6.6 Hz), 0.90 (s, 9H), 0.04 (s, 6H).

Compound **4c** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-iodoethylamino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-butanoic acid methyl ester): yield 90%. ^{1}H NMR ($CDCl_3$) δ 7.33–7.16 (m, 5H), 3.95 (q, 1H, J = 6.9 Hz), 3.60 (s, 3H), 3.67–3.38 (m, 3H), 3.04–2.80 (m, 4H), 2.52–2.23 (m, 2H), 1.37 (d, 3H, J = 6.9 Hz), 0.86 (s, 9H), 0.01 (d, 6H, J = 4.8 Hz).

Compound **4d** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-iodoethylamino]-benzenepropanoic acid methyl ester): yield 88%. ^{1}H NMR ($CDCl_3$) δ 7.38–7.20 (m, 10H), 4.45 (t, 1H, J = 8.1 Hz), 3.94 (t, 1H, J = 6.9 Hz), 3.57 (s, 3H), 3.03–2.62 (m, 6H), 1.26 (d, 3H, J = 6.9 Hz).

Compound **4e** ((3*R*)-3-[[(1*R*)-1-phenylethyl]-2-iodoethylamino]-benzenepentanoic acid methyl ester): yield 91%. ^{1}H NMR ($CDCl_3$) δ 7.37–7.12 (m, 10H), 3.89 (q, 1H, J = 6.6 Hz), 3.60 (s, 3H), 3.41–3.24 (m, 1H), 3.09–2.72 (m, 5H), 2.61–2.47 (m, 1H), 2.26 (d, 2H, J = 6.3 Hz), 1.81–1.58 (m, 2H), 1.40 (d, 3H, J = 6.6 Hz).

Compound **4f** ((3*S*)-3-[[(1*R*)-1-phenylethyl]-2-iodoethylamino]-4-methylbenzenepropanoic acid methyl ester): yield 91%. ^{1}H NMR ($CDCl_3$) δ 7.36–7.10 (m, 9H), 4.42 (t, 1H, J = 7.2 Hz), 3.93 (q, 1H, J = 6.9 Hz), 3.57 (s, 3H), 3.02–2.61 (m, 6H), 2.34 (s, 3H), 1.25 (d, 3H, J = 6.9 Hz).

2.5 Synthesis of (2*S*)-2-isopropyl-1-[(1*R*)-1-phenylethyl]-4-piperidone (compound 5)

Compound **4** (1 mmol) was dissolved in dry THF (20 mL) under Ar atmosphere and cooled to –78°C. *n*-BuLi (0.63 mL, 1.6 M in hexane) was dropped into the reaction mixture at same temperature. After 30 min, saturated $NaHCO_3$ aqueous solution was added to quench the reaction. The mixture was extracted with diethyl ether three times and combined organic phase was washed, dried and concentrated at reduced pressure. The residue was purified by silica gel flash column chromatography eluted with EtOAc/hexane.

Compound **5**: yield 50%. $[\alpha]_D^{26}$ +21.3 (*c* 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.47–7.21 (m, 5H), 4.20 (q, 1H, J = 6.8 Hz), 3.05–2.89 (m, 2H), 2.69–2.63 (m, 1H), 2.55–2.47 (m, 1H), 2.40–2.27 (m, 2H), 2.25–2.16 (m, 1H), 1.98–1.86 (m, 1H), 1.37 (d, 3H, J = 6.8 Hz), 0.89 (d, 3H, J = 6.8 Hz), 0.86 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 210.9, 145.0, 128.6, 127.3, 126.8, 63.6, 56.1, 43.1, 39.9, 39.7, 28.7, 19.7, 17.7, 16.3; HR-ESI-MS *m/z* Calcd for $C_{16}H_{24}NO$ ($M + H^+$) 246.1858, Found 246.1865.

Compound **5a** ((2*R*)-2-methyl-1-[(1*R*)-1-phenylethyl]-4-piperidone): yield 53%. $[\alpha]_D^{26}$ +3.5 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.47–7.22 (m, 5H), 4.00 (q, 1H, J = 6.4 Hz), 3.42–3.32 (m, 1H), 2.79–2.59 (m, 3H), 2.37–2.14 (m, 3H), 1.33 (d, 3H, J = 7.2 Hz), 1.13 (d, 3H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 210.5, 145.1, 128.3, 127.2, 126.8, 57.6, 52.4, 48.7, 43.8, 41.2, 16.3, 16.2; HR-ESI-MS *m/z* Calcd for $C_{14}H_{20}NO$ ($M + H^+$) 218.1545, Found 218.1534.

Compound **5b** ((2*R*)-2-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-1-[(1*R*)-1-phenylethyl]-4-piperidone): yield 42%. $[\alpha]_D^{24}$ +14.5 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.43–7.19 (m, 5H), 4.01 (q, 1H, J = 6.6 Hz), 3.61–3.41 (m, 2H), 3.22–3.13 (m, 1H), 2.99–2.80 (m, 2H), 2.68–2.59 (m, 1H), 2.44–2.32 (m, 1H), 2.26–2.10 (m, 2H), 1.70–1.38 (m, 4H), 1.34 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.03 (d, 6H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 210.3, 145.5, 128.4, 127.2, 127.0, 62.8, 57.8, 56.8, 44.4, 43.4, 40.1, 28.9, 26.6, 25.9, 18.7, 18.2, –5.3; HR-ESI-MS *m/z* Calcd for $C_{22}H_{38}NO_2Si$ ($M + H^+$) 376.2672, Found 376.2682.

Compound **5c** ((2*S*)-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-[(1*R*)-1-phenylethyl]-4-piperidone): yield 67%. $[\alpha]_D^{28}$ +12.1 (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.42–7.20 (m, 5H), 4.10 (q, 1H, J = 6.8 Hz), 3.69 (d, 2H, J = 4.6 Hz), 3.36–3.30 (m, 1H), 2.95–2.79 (m, 2H), 2.59–2.52 (m, 1H), 2.45–2.38 (m, 1H), 2.37–2.28 (m, 1H), 2.24–2.15 (m, 1H), 1.37 (d, 3H, J = 6.8 Hz), 0.88 (s, 9H), 0.03 (d, 6H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 210.1, 145.5, 128.4, 127.2, 127.0, 64.1, 58.8, 57.7, 44.0, 43.0, 40.5, 26.0, 25.9, 18.3, 17.9; HR-ESI-MS *m/z* Calcd for $C_{20}H_{34}NO_2Si$ ($M + H^+$) 348.2359, Found 348.2360.

Compound **5d** ((2*S*)-2-phenyl-1-[(1*R*)-1-phenylethyl]-4-piperidone): yield 32%. $[\alpha]_D^{26}$ +23.9 (*c* 1.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.54–7.22 (m, 10H), 3.97 (q, 1H, J = 6.4 Hz), 3.93 (dd, 1H, J = 10.4, 4.0 Hz), 2.95–2.88 (m, 1H), 2.78–2.69 (m, 1H), 2.66–2.49 (m, 3H), 2.36–2.29 (m, 1H), 1.24 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 209.0, 143.8, 142.1, 129.0, 128.1, 127.8, 127.4, 127.3, 126.7, 64.7, 54.8, 50.2, 44.0, 41.9, 9.4; HR-ESI-MS *m/z* Calcd for $C_{19}H_{22}NO$ ($M + H^+$) 280.1701, Found 280.1700.

Compound **5e** ((2*R*)-2-(2-phenylethyl)-1-[(1*R*)-1-phenylethyl]-4-piperidone): yield 45%. $[\alpha]_D^{28}$ +14.1 (*c* 1.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45–7.11 (m, 10H), 4.00 (q, 1H, J = 6.4 Hz), 3.33–3.25 (m, 1H), 3.08–2.99 (m, 1H), 2.96–2.87 (m, 1H), 2.77–2.69 (m, 1H), 2.62 (t, 2H, J = 8.0 Hz), 2.50–2.40 (m, 1H), 2.36–2.28 (m, 1H), 2.22–2.14 (m, 1H), 1.90–1.79 (m, 1H), 1.74–1.61 (m, 1H), 1.33 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 210.3, 145.5, 141.8, 128.5, 128.4, 128.3, 127.1, 127.0, 125.9, 58.3, 56.6, 44.1, 43.5, 40.0, 32.1, 32.0, 19.6; HR-ESI-MS *m/z* Calcd for $C_{21}H_{26}NO$ ($M + H^+$) 308.2014, Found 308.2046.

Compound **5f** ((2*S*)-2-(4-methylphenyl)-1-[(1*R*)-1-phenylethyl]-4-piperidone): yield 20%. $[\alpha]_D^{24}$ +24.3 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.50–7.17 (m, 9H), 3.96 (q, 1H, *J* = 6.4 Hz), 3.87 (dd, 1H, *J* = 10.0, 3.6 Hz), 2.93–2.86 (m, 1H), 2.76–2.68 (m, 1H), 2.62–2.49 (m, 3H), 2.34 (s, 3H), 2.33–2.26 (m, 1H), 1.22 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ204.8, 139.5, 134.8, 133.2, 125.3, 123.7, 123.0, 122.9, 122.3, 60.1, 50.3, 46.0, 39.7, 37.6, 16.8, 4.9; HR-ESI-MS *m/z* Calcd for $C_{20}H_{24}NO$ ($M + H^+$) 294.1858, Found 294.1862.

2.6 Synthesis of some non-chiral 3-substituted-4-piperidones

Compound **9**, **11** were synthesized according to previous report [29] and compound **17**, **18** were gifts from lab colleagues. Compound **6**, **7**, **8**, **10**, **12**, **16** were synthesized via above methods. Procedures of synthesis of compound **13**, **14**, **15** were described in supporting information.

Compound **10** (2-methyl-3-[(2-iodoethyl)(phenylmethyl) amino]-propanoic acid methyl ester): yield 82%. ^1H NMR ($CDCl_3$) δ 7.37–7.20 (m, 5H), 3.70–3.54 (AB, 2H, J_{AB} = 13.8 Hz), 3.68 (s, 3H), 3.15–3.00 (m, 2H), 2.88–2.61 (m, 4H), 2.54–2.44 (m, 1H), 1.12 (d, 3H, *J* = 7.2 Hz).

Compound **6** (3-Methyl-1-(phenylmethyl)-4-piperidone): yield 70%. ^1H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5H), 3.60 (s, 2H), 3.13–3.04 (m, 2H), 2.70–2.54 (m, 2H), 2.46–2.30 (m, 2H), 2.18–2.03 (m, 1H), 0.99 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 211.1, 138.2, 128.9, 128.4, 127.3, 61.8, 60.7, 53.8, 44.3, 40.9, 12.0; HR-ESI-MS *m/z* Calcd for $C_{13}H_{18}NO$ ($M + H^+$) 204.1379, Found 204.1367.

Compound **12** (2,2-dimethyl-3-[(2-iodoethyl)(phenylmethyl)amino]-propanoic acid methyl ester): yield 83%. ^1H NMR ($CDCl_3$) δ 7.38–7.21 (m, 5H), 3.66 (s, 2H), 3.65 (s, 3H), 3.08–2.78 (m, 4H), 2.77 (s, 2H), 1.17 (s, 6H).

Compound **7** (3,3-dimethyl-1-(phenylmethyl)-4-piperidone): yield 77%. ^1H NMR ($CDCl_3$) δ 7.45–7.23 (m, 5H), 3.56 (s, 2H), 2.72 (t, 2H, *J* = 6.0 Hz), 2.51 (t, 2H, *J* = 6.0 Hz), 2.40 (s, 2H), 1.13 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 214.0, 138.6, 128.6, 128.3, 127.1, 65.5, 62.0, 54.0, 53.4, 45.7, 38.4, 23.6; HR-ESI-MS *m/z* Calcd for $C_{14}H_{20}NO$ ($M + H^+$) 218.1545, Found 218.1536.

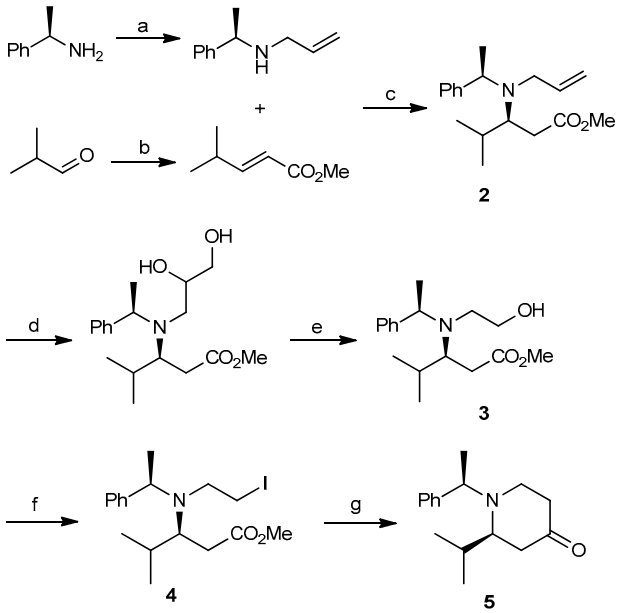
Compound **16** (2-methyl-2-(phenylmethoxy)-3-[(2-iodo ethyl)(phenylmethyl)amino]-butanoic acid methyl ester): yield 86%. ^1H NMR ($CDCl_3$) δ 7.42–7.18 (m, 10H), 4.60–4.46 (AB, 2H, J_{AB} = 10.8 Hz), 3.88–3.66 (AB, 2H, J_{AB} = 13.8 Hz), 3.73 (s, 3H), 3.11–2.85 (m, 6H), 1.50 (s, 3H).

Compound **8** (3-methyl-3-(phenylmethoxy)-1-(phenylmethyl)-4-piperidone): yield 85%. ^1H NMR ($CDCl_3$) δ 7.43–7.24 (m, 10H), 4.59–4.48 (AB, 2H, J_{AB} = 10.8 Hz), 3.66 (s, 2H), 2.94–2.56 (AB, 2H, J_{AB} = 12.0 Hz), 2.83–2.72 (m, 3H), 2.54–2.44 (m, 1H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 209.9, 138.8, 138.1, 128.8, 128.4, 128.3, 127.4, 127.3, 80.4, 65.9, 63.3, 61.5, 53.5, 39.0, 19.5; HR-ESI-MS *m/z* Calcd for $C_{20}H_{24}NO_2$ ($M + H^+$) 310.1807, Found 310.1798.

3 Results and discussion

3.1 Novel synthetic access to (2*S*)-2-isopropyl-1-[(1*R*)-1-phenylethyl]-4-piperidone

According to the proposed retrosythetic analysis, we started our experiment with the highly diastereoselective conjugate addition of homochiral lithium amides to *trans*-β-substituted-α,β-unsaturated esters developed by Davis [28]. Because of the commercial availability of isobutyraldehyde and (*R*)-α-methylbenzylamines, we easily synthesized (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine and corresponding *trans*-β-isopropyl methyl ester. These two compounds underwent highly diastereoselective conjugate addition, affording compound **2** while the minor diasteroisomeric product can be discarded through silica gel flash column chromatography. Consecutive dihydroxylation reaction catalyzed by OsO_4, oxidation and cleavage of diol by $NaIO_4$ and reduction of aldehyde by $NaBH_4$ converts compound **2** to compound **3**. After the hydroxyl group was replaced by iodine via PPh_3/imidazole/I_2 reaction system with satisfied yield, compound **4** was in hand. We first exploited previous condition [25] for the ring-formation reaction with compound **4** and successfully obtained the desired product compound **5** with 50% yield and 81% conversion (Scheme 3). In summary, (2*S*)-2-isopropyl-1-[(1*R*)-1-phenylethyl]-4-piperidone was synthesized with three steps and 42% overall yield starting from compound **2**. However, the low yield of the ring-formation reaction compromised the whole efficiency of this novel



Scheme 3 Synthesis of compound **5.** (a) Allyl bromide, *n*-BuLi, THF, –50°C to r.t., 74%; (b) $Ph_3P{=}CCO_2Me$, DCM, r.t., 85%; (c) *n*-BuLi, THF, –78°C, 75%; (d) OsO4, THF/H_2O, r.t., quant; (e) $NaIO_4$, $NaBH_4$, MeOH, 95%; (f) PPh_3, imidazole, I_2, ether/CH_3CN, 90%; g) *n*-BuLi, THF, –78°C, 50% (conv 81%). The yield of the ring-formation step was calculated based on consumed substrate.

route, which urges us to further explore the cyclization condition.

3.2 Optimization of the cyclization condition

With compound **4** in hand, we tested different conditions for the key ring-formation reaction (Table 1). Solvents always play decisive roles in organic reactions, so we first screened several kinds of solvents. When diethyl ether and hexane were used as solvents, no products was detected and compound **4** was recovered (entry 2, 4). DME gave trace product and yield of compound **5** can only be raised up to 17% even 2.5 equiv *n*-BuLi was added (entry 3). The attempt of using mixed solvent (hexane/THF = 1:1) also failed (entry 5). These results showed that THF was most suitable for this ring-formation reaction.

Since ester functions as an electrophilic group in this reaction which may play a pivotal role in outcome, we next screened three kinds of esters: methyl ester, ethyl ester and *t*-butyl ester (entry 6, 7, 8). We can find that ethyl ester substrate gave little lower yield than methyl ester substrate while *t*-Butyl ester substrate failed in this reaction with complicated results, indicating that methyl ester was better than the other two counterparts.

Schakel [26] and Sakamoto [30] reported *t*-BuLi and MesLi were good lithium-iodine exchange reagents as well, which guided us to test these two lithium reagents. The theoretical amount of *t*-BuLi used in this reaction was 2 equiv. However, when 2equiv *t*-BuLi was used, the yield was only 40%. With the decreased amount of *t*-BuLi used, the yield increased to 65%. On the contrary, the conversion ratio decreased from 75% to 44% (entry 9, 10, 11). Moreover, employment of MesLi gave a major side product due to the prevalence of deprotonation at the α-position of ester (entry 12).

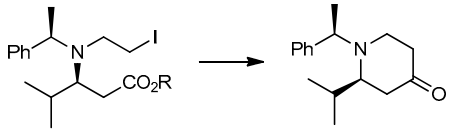
We also performed this reaction at lower temperature (–100°C) according to previous reports[25, 26]. To our disappointment, lower temperature did not show any advantage because both yield and conversion ratio were similar compared to –78°C (entry 13). From another point of view, liquid nitrogen was more dangerous in manipulation than dry ice in lab.

After screening of various solvents, reagents, substrates and temperatures and based on the above observations, we make sure that this ring-formation reaction should be best performed in THF at –78°C using 1eq *n*-BuLi as reagent and methyl ester as substrate.

3.3 Synthesis of a diversity of chiral 2-aryl/alkyl-4-piperidones and non-chiral 3-substituted-4-piperidones

Next we prepared a series of *trans*-β-aryl/alkyl-α,β-unsaturated methyl esters (Figure 2) and set to synthesize a diversity of chiral 2-aryl/alkyl-4-piperidone (Scheme 4) as well as some non-chiral 3-substituted-4-piperidones (Scheme 5) via this novel route we developed. From the results below (Table 2), we can see that compounds **4a–4f** can be prepared smoothly with good yield after 3 steps starting from various methyl esters. For the key ring-formation step, 2-aryl substrates showed lower yield (entry

Table 1 Screening of conditions for key ring-formation reaction, including substrates, solvents, reagents and temperature



4 **5**

Entry	R	Solvent	Reagent	Equiv	Temperature	Yield [a] % (conv %)
1	Me	THF	*n*-BuLi	1.3	–78°C	50 (81)
2	Me	DEE	*n*-BuLi	1.3	–78°C	NR
3	Me	DME	*n*-BuLi	2.5	–78°C	17 (90)
4	Me	hexane	*n*-BuLi	1.9	–78°C	NR
5	Me	hexane/THF (1:1)	*n*-BuLi	1.8	–78°C	30 (100)
6	Me	THF	*n*-BuLi	1.3	–78°C	50 (81)
7	Et	THF	*n*-BuLi	1.3	–78°C	40 (83)
8	*t*-Bu	THF	*n*-BuLi	1.3	–78°C	complex
9	Me	THF	*t*-BuLi	1	–78°C	65 (44)
10	Me	THF	*t*-BuLi	1.5	–78°C	50 (50)
11	Me	THF	*t*-BuLi	2	–78°C	40 (75)
12	Me	THF	MesLi	1.3	–78°C	side product [b]
13	Me	THF	*n*-BuLi	1.3	–100°C	47 (70)

a) The yield was calculated based on consumed substrate. b) The major product was formed due to the prevailing deprotonation followed by SN reaction.

Table 2 Results of this novel synthetic access to chiral 2-aryl/alkyl-4-piperidones and non-chiral 3-substituted-4-piperidones

Entry	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)	Product	Yield [a] (%) (conv %)
1	**2a**	85	**3a**	95	**4a**	81	**5a**	53 (67)
2	**2b**	100	**3b**	73	**4b**	89	**5b**	42 (92)
3	**2c**	91	**3c**	91	**4c**	90	**5c**	67 (80)
4	**2d**	90	**3d**	94	**4d**	88	**5d**	32 (87)
5	**2e**	94	**3e**	90	**4e**	91	**5e**	45 (80)
6	**2f**	95	**3f**	98	**4f**	91	**5f**	20 (80)
7			**9**		**10**	82	**6**	70 (84)
8			**11**		**12**	83	**7**	77 (70)
9			**15**		**16**	82	**8**	85 (99)

a) Yield was calculated based on consumed substrates.

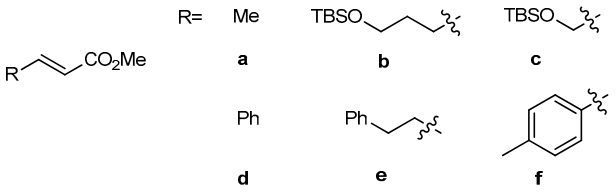
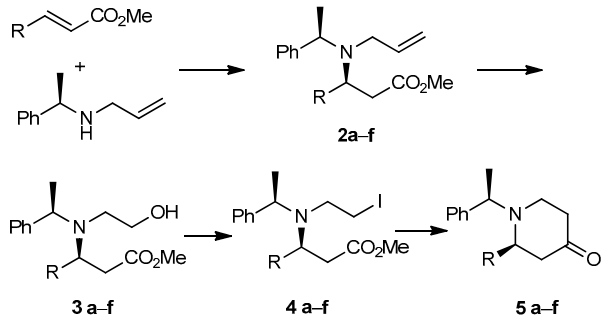
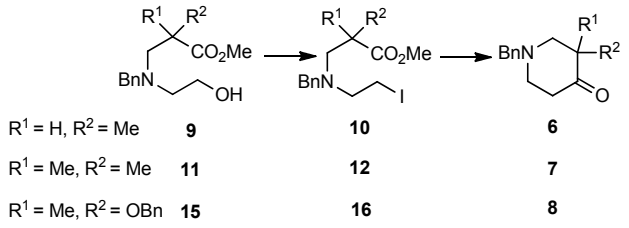


Figure 2 A variety of *trans*-β-aryl/alkyl-α,β-unsaturated methyl esters were prepared.



Scheme 4 Synthesis of various chiral 2-aryl/alkyl-4-piperidones using above method.



Scheme 5 Synthesis of some non-chiral 3-substituted-4-piperidones using similar method.

4, 6), possibly attributed to the severe side interaction between lithium reagent and the bezene ring. Generally 2-alkyl substrates afforded higher yield and compound **4c** gave the highest yield (65%, entry 3). Structure analysis inspired us that the steric effect at the 2-position may to a certain extent impede the side reactions. When the α-position of ester in the substrate was substituted by methyl, dimethyl and methyl/phenylmethoxy respectively, the yield of ring-formation reaction can be enhanced to 70%, 77% and 85% (entry 7, 8, 9) due to the more steric effect and less incidence of deprotonation. This great achievement clearly demonstrated that side reactions of this ring-formation reaction could be significantly abolished by increased steric effect adjacent to the ester group and excellent yield could be anticipated.

4 Conclusions

In summary, we reported here a novel, concise and versatile access to a diversity of chiral 2-aryl/alkyl-4-piperidones that can be further converted to chiral piperidine structures occurring in many nature products and drug molecules. The establishment of chirality at 2-position was dependent on the highly diastereoselective conjugate addition of homochiral lithium amides to *trans*-β-substituted-α,β-unsaturated methyl esters. The ring-formation reaction relies on the competitive intramolecular attack of carbanion to ester. This method complemented current methods to chiral 2-substituted-4-piperidone in that it can give chiral 2-aryl and 2-alkyl-4-piperidones simultaneously. Because the severe side reaction caused by lithium reagents attacking unanticipated reactive sites in the substrate, only modest yield were obtained in the final ring-formation reaction. However, increasing the steric effect adjacent to the ester group led to satisfied yield of the ring-formation reaction and remarkably enhanced the overall efficiency of this new route, showing the great potential of its application in the synthesis of chiral piperidine structure in the near future.

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1 O'Hagan D. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat Prod Rep*, 2000, 17(5): 435–446

2 Liu Q-F, Wang J-D, Wang X-J, Liu C-X, Zhang J, Pang Y-W, Yu C, Xiang W-S. Two new piperidine alkaloids from *Streptomyces* sp.

Neau-z4. *J Asian Nat Prod Res*, 2013, 15(3): 221–224
3 Radha Krishna P, Reddy BK. Total synthesis of the 2,6-disubstituted piperidine alkaloid (–)-andrachcinidine. *Tetrahedron: Asymm*, 2013, 758–763
4 Murty M, Ram KR, Yadav J. $BiCl_3$ promoted aza-prins type cyclization: a rapid and efficient synthesis of 2,4-disubstituted piperidines. *Tetrahedron Lett*, 2008, 49(7): 1141–1145
5 Howard N, Abell C, Blakemore W, Chessari G, Congreve M, Howard S, Jhoti H, Murray CW, Seavers LC, van Montfort RL. Application of fragment screening and fragment linking to the discovery of novel thrombin inhibitors. *J Med Chem*, 2006, 49(4): 1346–1355
6 Wright JL, Gregory TF, Kesten SR, Boxer PA, Serpa KA, Meltzer LT, Wise LD, Espitia SA, Konkoy CS, Whittemore ER. Subtype-selective *N*-methyl-D-aspartate receptor antagonists: synthesis and biological evaluation of 1-(heteroarylalkynyl)-4-benzylpiperidines. *J Med Chem*, 2000, 43(18): 3408–3419
7 Hutchison AJ, Williams M, Angst C, De Jesus R, Blanchard L, Jackson RH, Wilusz EJ, Murphy DE, Bernard PS. 4-(Phosphonoalkyl)- and 4-(phosphonoalkenyl)-2-piperidinecarboxylic acids: synthesis, activity at *N*-methyl-D-aspartic acid receptors and anticonvulsant activity. *J Med Chem*, 1989, 32(9): 2171–2178
8 Lamarre D, Croteau G, Wardrop E, Bourgon L, Thibeault D, Clouette C, Vaillancourt M, Cohen E, Pargellis C, Yoakim C. Antiviral properties of palinavir, a potent inhibitor of the human immunodeficiency virus type 1 protease. *Ant Agents Chemoth*, 1997, 41(5): 965–971
9 Shintani R, Tokunaga N, Doi H, Hayashi T. A new entry of nucleophiles in rhodium-catalyzed asymmetric 1,4-addition reactions: addition of organozinc reagents for the synthesis of 2-aryl-4-piperidones. *J Am Chem Soc*, 2004, 126(20): 6240–6241
10 Xu Q, Zhang R, Zhang T, Shi M. Asymmetric 1,4-addition of arylboronic acids to 2,3-dihydro-4-pyridones catalyzed by axially chiral NHC-Pd (II) complexes. *J Org Chem*, 2010, 75(11): 3935–3937
11 Thaler T, Guo L-N, Steib AK, Raducan M, Karaghiosoff K, Mayer P, Knochel P. Sulfoxide-alkene hybrids: a new class of chiral ligands for the Hayashi–Miyaura reaction. *Org Lett*, 2011, 13(12): 3182–3185
12 Jagt RB, de Vries JG, Feringa BL, Minnaard AJ. Enantioselective synthesis of 2-aryl-4-piperidones via rhodium/phosphoramidite-catalyzed conjugate addition of arylboroxines. *Org Lett*, 2005, 7(12): 2433–2435
13 Zhang X, Chen J, Han F, Cun L, Liao J. Rhodium-catalyzed enantioselective conjugate addition of sodium tetraarylborates to 2,3-dihydro-4-pyridones and 4-quinolones by using (*R,R*)-1,2-bis(*tert*-butylsulfinyl) benzene as a ligand. *Eur J Org Chem*, 2011, 2011(8): 1443–1446
14 Gini F, Hessen B, Feringa BL, Minnaard AJ. Enantioselective palladium-catalysed conjugate addition of arylsiloxanes. *Chem Commun*, 2007, (7): 710–712
15 Nakao Y, Chen J, Imanaka H, Hiyama T, Ichikawa Y, Duan W-L, Shintani R, Hayashi T. Organo [2-(hydroxymethyl) phenyl] dimethylsilanes as mild and reproducible agents for rhodium-catalyzed 1,4-addition reactions. *J Am Chem Soc*, 2007, 129(29): 9137–9143
16 Šebesta R, Pizzuti MG, Boersma AJ, Minnaard AJ, Feringa BL. Catalytic enantioselective conjugate addition of dialkylzinc reagents to *N*-substituted-2,3-dehydro-4-piperidones. *Chem Commun*, 2005, (13): 1711–1713
17 Endo K, Ogawa M, Shibata T. Multinuclear catalyst for copper-catalyzed asymmetric conjugate addition of organozinc reagents. *Angew Chemie Int Ed*, 2010, 49(13): 2410–2413
18 Pizzuti MG, Minnaard AJ, Feringa BL. Catalytic asymmetric synthesis of the alkaloid (+)-myrtine. *Org Biomol Chem*, 2008, 6(19): 3464–3466
19 Muller D, Alexakis A. Copper-catalyzed asymmetric 1,4-addition of alkenyl alanes to *N*-substituted-2-3-dehydro-4-piperidones. *Org Lett*, 2012, 14(7): 1842–1845
20 Hattori K, Yamamoto H. Asymmetric aza-diels-alder reaction mediated by chiral boron reagent. *J Org Chem*, 1992, 57(12): 3264–3265
21 Mancheño OG, Arrayás RG, Carretero JC. Chiral copper complexes of phosphino sulfenyl ferrocenes as efficient catalysts for enantioselective formal aza Diels-Alder reactions of *N*-sulfonyl imines. *J Am Chem Soc*, 2004, 126(2): 456–457
22 Josephsohn NS, Snapper ML, Hoveyda AH. Efficient and practical ag-catalyzed cycloadditions between arylimines and the danishefsky diene. *J Am Chem Soc*, 2003, 125(14): 4018–4019
23 Yao S, Johannsen M, Hazell RG, Jørgensen KA. Catalytic enantioselective aza Diels-Alder reactions of imino dienophiles. *Angew Chem Int Ed*, 1998, 37(22): 3121–3124
24 Kobayashi S, Komiyama S, Ishitani H. The first enantioselective aza-Diels-Alder reactions of imino dienophiles on use of a chiral zirconium catalyst. *Angew Chem Int Ed*, 1998, 37(7): 979–981
25 Cooke MP, Houpis IN. Metal-halogen exchange-initiated cyclization of iodo carbonyl compounds. *Tetrahedron Lett*, 1985, 26(41): 4987–4990
26 Van der Does T, Klumpp G, Schakel M. Spiro ketone synthesis via lithium-iodine exchange of α-(ω-iodoalkyl) esters. *Tetrahedron Lett*, 1986, 27(4): 519–520
27 Wang B, Zhong Z, Lin G-Q. Efficient construction of stereodefined α-alkylidene aza-cycloketones via β-amino-alkenyllithium: straightforward and protection-free synthesis of allopumiliotoxin 267A. *Org Lett*, 2009, 11(9): 2011–2014
28 Davies SG, Smith AD, Price PD. The conjugate addition of enantiomerically pure lithium amides as homochiral ammonia equivalents: scope, limitations and synthetic applications. *Tetrahedron: Asymm*, 2005, 16(17): 2833–2891
29 Wang B. Stereoselective total synthesis of sphingofungine and synthetic studies toward mycestericine and pumiliotoxin-a alkaloids. *Dissertation for the Doctoral Degree*. Shanghai: Shanghai Institute of Organic Chemistry, 2002
30 Kondo Y, Asai M, Miura T, Uchiyama M, Sakamoto T. Mesityllithium as a reagent for chemoselective halogen-lithium exchange reaction. *Org Lett*, 2001, 3(1): 13–15