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STEREODIVERGENT AND STEREOSELECTIVE SYNTHESIS OF *cis*- AND *trans*-4-SUBSTITUTED PROLINOLS

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Abstract – Stereoselective synthesis of 4-substituted prolinol derivatives has been developed. Thus, Suzuki–Miyaura cross-coupling of vinyl triflate provided the common synthetic intermediates toward the stereodivergent synthesis of *cis*- and *trans*-4-substituted prolinols. These two kinds of target compounds were obtained by diastereoselective hydrogenation of the coupling products with Pd/C and Crabtree catalyst, respectively. In addition, the obtained 4-substituted prolinol was transformed to the corresponding proline derivative via oxidation in one step.

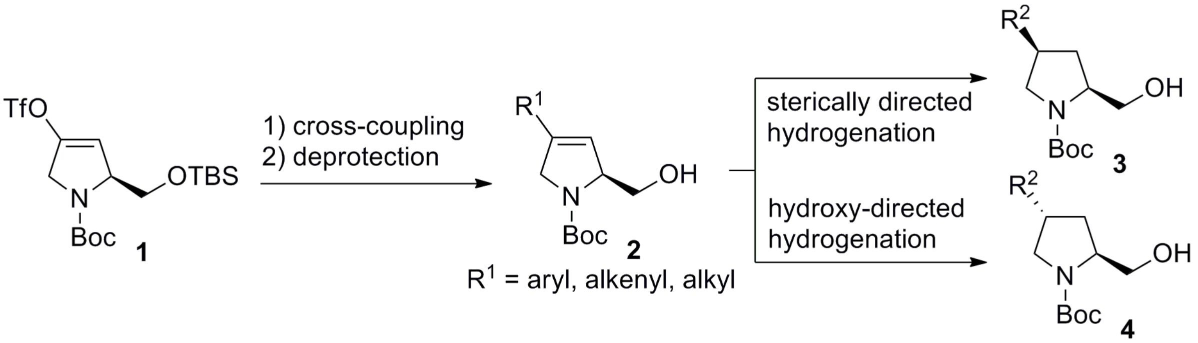
INTRODUCTION

Prolinol derivatives, which possess the pyrrolidine moiety as a structural feature, are valuable compounds in organic synthesis and medicinal chemistry. Thus, Hayashi–Jørgensen catalyst, diarylprolinol silyl ether, is one of the most useful asymmetric organocatalysts.[1] The substituted prolinols have been utilized as versatile synthetic intermediates toward the synthesis of natural products[2] and other biologically active compounds.[3] Moreover, the substituted prolinol is a central structural character of a wide range of drug candidates such as anti-virus agents,[4a] sphingosine-1-phosphate agonists,[4b,c] CCR3 receptor antagonists,[5a] poly(ADP-ribose)polymerase inhibitors,[5b] and sphingosine kinase antagonists.[5c]

To date, several examples of the stereodivergent synthesis[6,7] of *cis*- and *trans*-4-substituted prolinol derivatives from the common synthetic intermediates have been reported. Goodman synthesized *cis*- and *trans*-4-substituted prolinols by Wittig olefination of pyrrolidinone and subsequent diastereoselective hydrogenation, respectively.[8] Hanessian and co-workers carried out addition of 4-octyl-1-bromobenzene to pyrrolidinone with *n*-BuLi to provide alcohol, which was transformed to unsaturated pyrrolidine with Burgess reagent. This arylated alkene was hydrogenated to yield *cis*- and *trans*-4-substituted prolinols, respectively and diastereoselectively.[4c,9] In this full account, we report our recent efforts on the stereodivergent synthesis of *cis*- and *trans*-4-substituted prolinols by utilizing the combination of Suzuki–Miyaura cross-coupling[10] and diastereoselective hydrogenation. To the best of our knowledge, this is the first report on the stereodivergent synthesis of *cis*- and *trans*-4-substituted prolinols by using Suzuki–Miyaura cross-coupling[10] and subsequent diastereoselective hydrogenation wherein cross-coupling products possess alkenyl and alkyl substituents.

RESULTS AND DISCUSSION

Our synthetic plan is outlined in Scheme 1. Suzuki–Miyaura cross-coupling[10] of vinyl triflate **1** with organoboron compounds followed by deprotection would afford unsaturated pyrrolidines **2**, wherein the R^1 groups are broadly used as aryl, alkenyl, and alkyl substituents.[11] Hydrogenation of **2** with Pd/C would produce *cis*-4-prolinols **3** due to the steric factors. On the other hand, the hydroxy-directed hydrogenation of **2** with Crabtree catalyst, $[Ir(cod)(PCy_3)(py)]PF_6$,[12] would yield *trans*-4-prolinols **4**.[13]

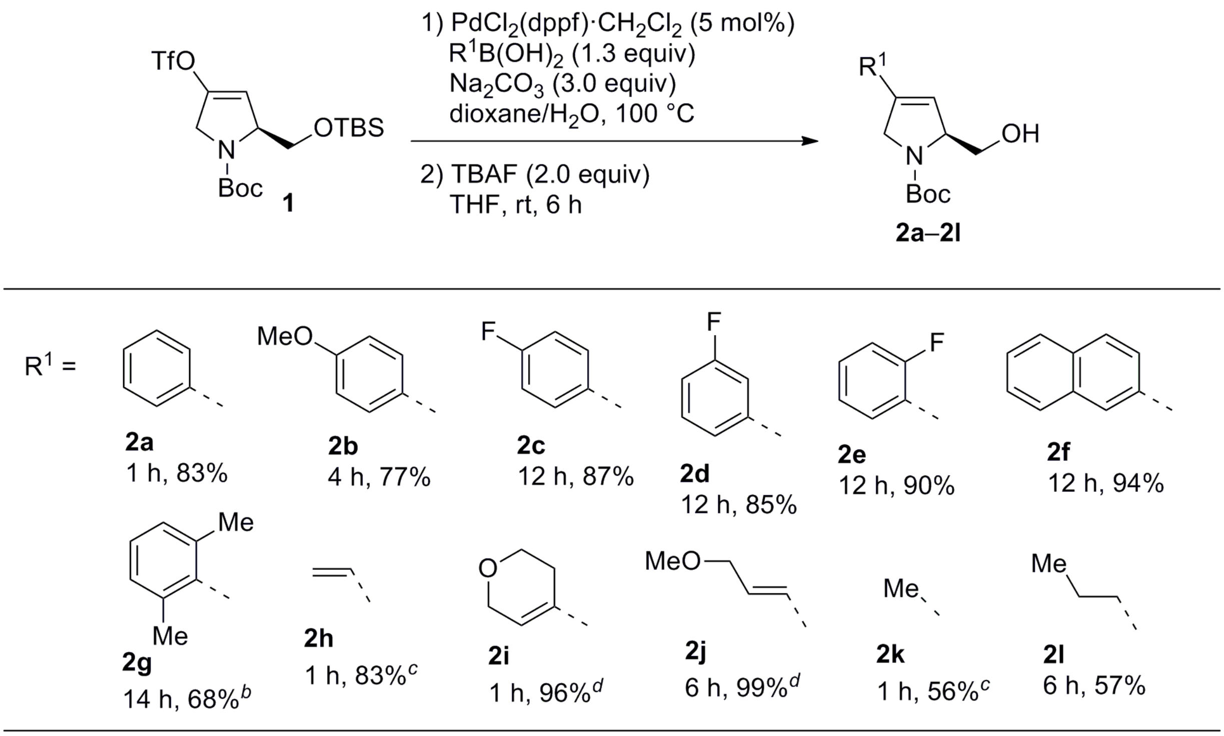


Scheme 1. Synthetic plan of *cis*- and *trans*-4-substituted prolinols **3** and **4**

We first investigated Suzuki–Miyaura cross-coupling[10] of the vinyl triflate **1**[14] with boronic acids. Treatment of **1** with phenylboronic acid in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2/Na_2CO_3$ provided the desired cross-coupling product (Table 1). Subsequently, the *tert*-butyldimethylsilyl (TBS) protecting group was removed with tetrabutylammonium fluoride (TBAF) to afford alcohol **2a** in 83% yield in two steps. When we used 4-methoxy and 2-/3-/4-fluorophenylboronic acids, and 2-naphthylboronic acid as coupling partners of **1**, the corresponding arylated products **2b**–**2f** were produced in 77% to 94% yields in two steps, respectively. In the case of synthesis of 2,6-dimethylphenyl compound **2g**, Suzuki–Miyaura cross-coupling[10] with $PdCl_2(dppf)\cdot CH_2Cl_2$ did not proceed. Further examination revealed that the use of

$PdCl_2(PCy_3)_2 \cdot CH_2Cl_2$ as a catalyst in the cross-coupling was effective and **2g** was obtained in 68% yield in two steps. In addition to the arylated compounds, alkenyl substituted products **2h**–**2j** were also synthesized by using the corresponding boroxine and boronic acid pinacol esters in Suzuki–Miyaura cross-coupling[10] in 83% to 99% yields. Methyl and propyl substituted products **2k** and **2l** were obtained in moderate chemical yields, respectively.

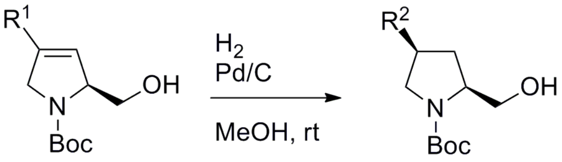
Table 1. Synthesis of common intermediates **2** for *cis*- and *trans*-4-substituted prolinols[a]



[a] Isolated yields in two steps. Reaction times in the first step are given in the Table. [b] $PdCl_2(PCy_3) \cdot CH_2Cl_2$ was used in place of $PdCl_2(dppf) \cdot CH_2Cl_2$. [c] Boroxines were used in place of the corresponding boronic acids. [d] Boronic acid pinacol esters were used.

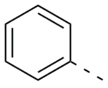
To obtain *cis*-4-substituted prolinols, stereoselectively, we next tried the sterically directed hydrogenation of **2**. Treatment of the alkene **2a** with Pd/C under H_2 atmosphere gave *cis*-4-phenylprolinol **3a** in 95% yield as a single diastereomer, as judged by its ^1H NMR spectrum (Table 2).[15] The methoxy and fluoro substituents on the aromatic rings did not affect the reactions including the facial selectivity (**3b**–**3e**). The use of naphthyl compound **2f** as a substrate provided hydrogenated compound **3f** in 89% yield. The reaction of **2g** with Pd/C did not proceed at all, therefore, $Pd(OH)_2$/C was used as an alternative catalyst and **3g** was obtained in 95% yield. The diene **2h** was hydrogenated to give *cis*-4-ethylprolinol **3h**[16] as a sole product in 94% yield. Hydrogenation of the dienes **2i** and **2j** produced *cis*- and *trans*-prolinols in diastereomeric ratios of 68:32 and 59:41, respectively. The alkylated alkenes **2k** and **2l** underwent hydrogenation to afford 4-methylprolinol **3k**[8] and 4-propylprolinol **3l**, respectively.

Table 2. Synthesis of *cis*-4-substituted prolinols **3**[a]

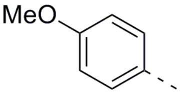


2a–**2l** → **3a**–**3l**

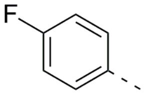
R² =



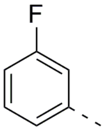
3a
10 h, 95%



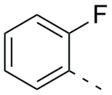
3b
10 h, 93%



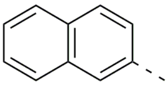
3c
10 h, 97%



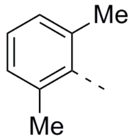
3d
10 h, 89%



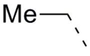
3e
14 h, 83%



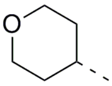
3f
10 h, 89%



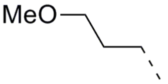
3g
10 h, 95%[b]



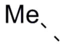
3h
10 h, 94%



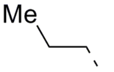
3i, 5 h, 89%
(dr = 68:32)[c]



3j, 10 h, 72%
(dr = 59:41)[c]



3k
14 h, 77%

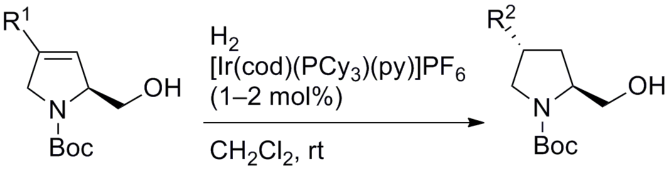


3l, 6 h, 84%
(dr = 43:57)[c]

[a] Isolated yield. [b] $Pd(OH)_2/C$ was used in place of Pd/C. [c] Diastereomeric ratio of *cis*- and *trans*-products.

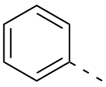
Our efforts to synthesize a variety of *trans*-4-substituted prolinols by the hydroxy-directed hydrogenation are summarized in Table 3.

Table 3. Synthesis of *trans*-4-substituted prolinols **4**[a]

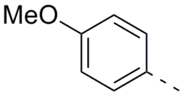


2a–**2l** → **4a**–**4l**

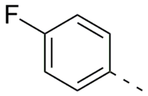
R² =



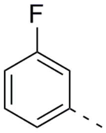
4a
14 h, 85%



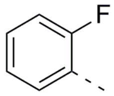
4b
12 h, 91%



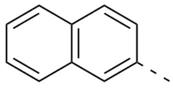
4c
10 h, 83%



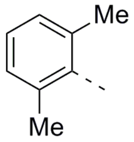
4d, N.D.[b]



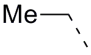
4e
10 h, 79%



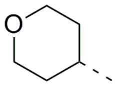
4f
10 h, 93%



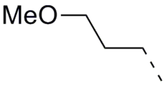
4g, N.D.[b]



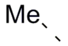
4h
12 h, 63%



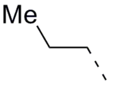
4i, 12 h, 79%
(dr = 78:22)[c]



4j, 12 h, 79%
(dr = 74:26)[c]



4k
12 h, 89%

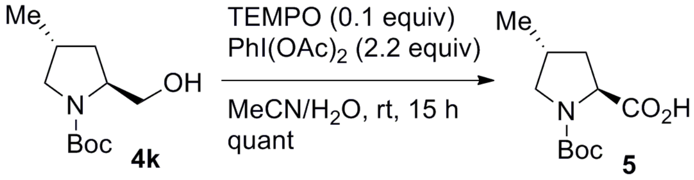


4l
10 h, 79%

[a] Isolated yield. [b] Not determined. Starting materials were recovered. [c] Diastereomeric ratio of *trans*- and *cis*-products.

Hydrogenation of the alkenes **2a**–**2c**, **2e**, and **2f** in the presence of Crabtree catalyst, $[Ir(cod)(PCy_3)(py)]PF_6$,[12] proceeded smoothly and stereoselectively to afford the corresponding *trans*-products **4a**[15]–**4c**, **4e**, and **4f** in 79% to 93% yields. The starting materials were recovered in the case of **2d** and **2g**.[17] The alkenyl and alkyl substituted alkenes **2h**–**2l** were hydrogenated to provide saturated prolinols **4h**–**4l**, respectively and stereoselectively.[18]

Having succeeded in the stereodivergent synthesis of *cis*- and *trans*-4-substituted prolinols, we next carried out one-step conversion of the *trans*-4-methylprolinol **4k** to the corresponding proline. Thus, treatment of **4k** with 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO)/$PhI(OAc)_2$ in $MeCN/H_2O$[19] produced *trans*-4-methylproline **5**,[8] quantitatively (Scheme 2).



Scheme 2. One-step oxidation of prolinol **4k** to proline **5**

In conclusion, 4-substituted prolinols have been stereoselectively synthesized in a stereodivergent fashion. First, vinyl triflate was converted to hydrogenation precursors, bearing aryl, alkenyl, and alkyl substituents, by Suzuki–Miyaura cross-coupling and deprotection. Various kinds of *cis*- and *trans*-4-substituted prolinols were produced by hydrogenation with Pd/C and Crabtree catalyst, respectively. The Boc-protected-*trans*-4-methylprolinol was oxidized to the corresponding proline in one step. Application of the methodology described herein to the synthesis of biologically active compounds will be reported in due course.

EXPERIMENTAL

IR spectra were recorded on PerkinElmer Spectrum One FT-IR Spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 UltraShield Plus. Chemical shifts in the NMR spectra are reported in ppm with reference to the internal residual solvent (^1H NMR, $CDCl_3$ 7.26 ppm; ^{13}C NMR, $CDCl_3$ 77.0 ppm). The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Coupling constants (J) are in hertz. High resolution mass spectra were recorded on LTQ Orbitrap Velos Pro mass spectrometer equipped with an ESI Lockspray source.

Synthesis of common intermediates 2a–2l for *cis*- and *trans*-4-substituted prolinols

A mixture of vinyl triflate **1** (0.3 M), boronic acid (1.3 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (5 mol%), and Na_2CO_3 (3.0 equiv) in dioxane/H_2O (3:1) was stirred at 100 °C. After vinyl triflate **1** was consumed, the mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl, and brine. The organic layer was dried over Na_2SO_4 and then concentrated. To a solution of the resulting crude material in THF (0.3 M) was added tetrabutylammonium fluoride (2.0 equiv) at room temperature. After the mixture was stirred at the same temperature for 6 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and then concentrated. The resulting crude material was purified by silica gel column chromatography to give **2**.

2a: IR 3394, 2974, 2930, 2863, 1672, 1636, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.64–3.70 (m, 1H), 3.83–3.88 (m, 1H), 4.44–4.50 (m, 1H), 4.53–4.57 (m, 1H), 4.66–4.68 (m, 1H), 4.89–4.92 (m, 1H), 5.98–6.07 (m, 1H), 7.29–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 54.3, 67.5, 68.6, 80.9, 120.1, 125.5, 128.7, 132.7, 138.4, 156.6; HRMS (ESI) calcd for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1600, found 276.1598.

2b: IR 3335, 2979, 2925, 2866, 1665, 1639, 1607, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.64 (dd, J = 11.2, 7.7 Hz, 1H), 3.82 (s, 3H), 3.82–3.86 (m, 1H), 4.41–4.46 (m, 1H), 4.49–4.53 (m, 1H), 4.65–4.70 (m, 1H), 4.87–4.91 (m, 1H), 5.83 (s, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 54.4, 55.3, 67.6, 68.6, 80.8, 114.0, 117.9, 126.8, 137.8, 159.8, 169.1, 198.8; HRMS (ESI) calcd for $C_{17}H_{24}NO_4$ $[M + H]^+$ 306.1705, found 306.1702.

2c: IR 3392, 2975, 2931, 2865, 1671, 1637, 1602, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.66 (dd, J = 11.2, 7.7 Hz, 1H), 3.84–3.86 (m, 1H), 4.42–4.55 (m, 2H), 4.63–4.65 (m, 1H), 4.89–4.91 (m, 1H), 5.92 (s, 1H), 7.02–7.08 (m, 2H), 7.34–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 54.3, 67.4, 68.6, 81.0, 115.7 (d, $J_{C,F}$ = 22.3 Hz), 119.9, 127.3 (d, $J_{C,F}$ = 7.7 Hz), 137.3, 161.5; HRMS (ESI) calcd for $C_{16}H_{21}FNO_3$ $[M + H]^+$ 294.1505, found 294.1504.

2d: IR 3360, 2977, 2931, 2865, 1670, 1636, 1613, 1583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.67 (dd, J = 11.8, 7.7 Hz, 1H), 3.84–3.87 (m, 1H), 4.42–4.47 (m, 1H), 4.51–4.55 (m, 1H), 4.88–4.92 (m, 1H), 6.02 (s, 1H), 6.98–7.08 (m, 2H), 7.14–7.16 (m, 1H), 7.30–7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 54.2, 67.3, 68.6, 81.0, 112.4 (d, $J_{C,F}$ = 22.2 Hz), 112.6, 115.3 (d, $J_{C,F}$ = 20.7 Hz), 121.3, 121.7, 130.2 (d, $J_{C,F}$ = 8.5 Hz), 156.8, 163.0 (d, $J_{C,F}$ = 244.3 Hz); HRMS (ESI) calcd for $C_{16}H_{21}FNO_3$ $[M + H]^+$ 294.1505, found 294.1503.

2e: IR 3413, 2975, 2930, 2869, 1672, 1631, 1497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.67 (dd, J = 11.3, 7.2 Hz, 1H), 3.85–3.90 (m, 1H), 4.48–4.77 (m, 3H), 4.91–4.94 (m, 1H), 6.18 (s, 1H), 7.07–7.16 (m, 2H), 7.24–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 55.0, 67.3, 68.7, 80.9, 116.1, 116.3 (d, $J_{C,F}$ = 22.2 Hz), 124.2, 125.0 (d, $J_{C,F}$ = 11.5 Hz), 128.1, 129.6, 129.7, 156.5; HRMS (ESI) calcd for $C_{16}H_{21}FNO_3$ $[M + H]^+$ 294.1505, found 294.1505.

2f: IR 3363, 3051, 2977, 2903, 2871, 2845, 1658, 1633, 1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 3.71 (dd, *J* = 12.3, 7.7 Hz, 1H), 3.87–3.92 (m, 1H), 4.58–4.82 (m, 3H), 4.94–4.98 (m, 1H), 6.11 (s, 1H), 7.55–7.61 (m, 2H), 7.80–7.82 (m, 3H), 7.95–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 54.3, 60.4, 68.8, 81.0, 120.8, 123.3, 124.6, 126.5, 126.6, 127.7, 128.2, 128.3, 128.6, 133.1, 137.1, 138.4; HRMS (ESI) calcd for $C_{20}H_{24}NO_3$ $[M + H]^+$ 326.1756, found 326.1754.

2g: IR 3396, 2974, 2922, 2861, 1697, 1677, 1652, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.25 (s, 3H), 2.25 (s, 3H), 3.71 (dd, *J* = 11.3, 7.2 Hz, 1H), 3.86–3.89 (m, 1H), 4.15–4.36 (m, 2H), 4.71–4.76 (m, 1H), 4.92–4.94 (m, 1H), 5.42 (s, 1H), 7.04 (d, *J* = 6.7 Hz, 2H), 7.12 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 28.4, 56.2, 67.6, 68.3, 80.8, 118.0, 123.9, 127.4, 127.7, 135.9, 139.4, 156.6; HRMS (ESI) calcd for $C_{18}H_{26}NO_3$ $[M + H]^+$ 304.1913, found 304.1909.

2h: IR 3393, 2976, 2933, 1672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 3.59 (dd, *J* = 11.3, 7.7 Hz, 1H), 3.77–3.79 (m, 1H), 4.17–4.26 (m, 1H), 4.26–4.30 (m, 1H), 4.62–4.66 (m, 1H), 4.77–4.81 (m, 1H), 5.12 (d, *J* = 18.0 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 5.56 (s, 1H), 6.44 (dd, *J* = 18.0, 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 52.8, 67.3, 68.1, 80.8, 116.9, 124.6, 130.3, 138.4, 156.6; HRMS (ESI) calcd for $C_{12}H_{20}NO_3$ $[M + H]^+$ 226.1443, found 226.1438.

2i: IR 3416, 2974, 2929, 2866, 1672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.30 (brs, 2H), 3.58 (dd, *J* = 10.8, 7.7 Hz, 1H), 3.76–3.80 (m, 1H), 3.84 (t, *J* = 5.4 Hz, 2H), 4.19–4.31 (m, 4H), 4.63 (d, *J* = 8.7 Hz, 1H), 4.81 (brs, 1H), 5.50–5.57 (m, 1H), 5.65 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 28.5, 53.3, 64.0, 65.3, 67.4, 68.3, 80.8, 119.5, 124.7, 128.5, 138.9, 156.6; HRMS (ESI) calcd for $C_{15}H_{24}NO_4$ $[M + H]^+$ 282.1705, found 282.1703.

2j: IR 3410, 2977, 2931, 2874, 1677, 1657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 3.36 (s, 3H), 3.55–3.60 (m, 1H), 3.74–3.80 (m, 1H), 3.99 (d, *J* = 5.7 Hz, 2H), 4.20–4.41 (m, 2H), 4.62 (dd, *J* = 8.7, 1.5, 1H), 4.78 (brs, 1H), 5.54 (s, 1H), 5.66 (dt, *J* = 16.2, 5.8 Hz, 1H), 6.33–6.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 58.2, 67.3, 68.1, 72.5, 75.0, 80.8, 124.3, 125.4, 129.2, 137.5, 156.5; HRMS (ESI) calcd for $C_{14}H_{24}NO_4$ $[M + H]^+$ 270.1705, found 270.1704.

2k: IR 3370, 2978, 2934, 1763, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.75 (s, 3H), 3.54 (dd, *J* = 11.3, 7.7 Hz, 1H), 3.71–3.75 (m, 1H), 3.94–4.07 (m, 2H), 4.69–4.71 (m, 2H), 5.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 28.5, 57.3, 67.6, 68.1, 80.5, 120.4, 136.5; HRMS (ESI) calcd for $C_{11}H_{20}NO_3$ $[M + H]^+$ 214.1443, found 214.1438.

2l: IR 3393, 2963, 2932, 2873, 1732, 1700, 1682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.44–1.52 (m, 11H), 2.03–2.07 (m, 2H), 3.53 (ddd, *J* = 11.3, 7.7, 1.5 Hz, 1H), 3.73 (ddd, *J* = 11.3, 9.4, 1.5 Hz, 1H), 3.95–4.22 (m, 2H), 4.68–4.75 (m, 1H), 5.21–5.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.6, 28.5, 30.8, 56.0, 67.8, 68.0, 80.5, 119.3, 141.0; HRMS (ESI) calcd for $C_{13}H_{24}NO_3$ $[M + H]^+$ 242.1756, found 242.1753.

Synthesis of *cis*-4-substituted prolinols 3a–3l

A mixture of alkene **2** (0.2 M) and Pd/C (0.2 w/w) in MeOH was stirred at room temperature under H_2 atmosphere. After alkene **2** was consumed, the mixture was filtered through a Celite pad and then concentrated. The resulting crude material was purified by silica gel column chromatography to give **3**.

3b: IR 3500, 2984, 2937, 2881, 1682, 1611, 1515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.57–1.65 (m, 1H), 2.34–2.40 (m, 1H), 3.16–3.24 (m, 2H), 3.64–3.77 (m, 3H), 3.80 (s, 3H), 3.94–3.98 (m, 1H), 4.06–4.11 (m, 1H), 6.86 (d, J = 6.8 Hz, 2H), 7.15 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 36.6, 41.8, 54.2, 55.3, 61.4, 67.7, 80.6, 114.0, 127.9, 128.0, 132.0, 158.6; HRMS (ESI) calcd for $C_{17}H_{26}NO_4$ [M + H]$^+$ 308.1862, found 308.1860.

3c: IR 3397, 2975, 2930, 2879, 1662, 1602, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.61–1.66 (m, 1H), 2.36–2.41 (m, 1H), 3.17–3.28 (m, 2H), 3.64–3.80 (m, 2H), 3.94–3.98 (m, 1H), 4.05–4.11 (m, 1H), 5.19 (brs, 1H), 6.99–7.03 (m, 2H), 7.17–7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 36.6, 41.9, 54.0, 61.4, 67.5, 80.7, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 128.5 (d, $J_{C,F}$ = 7.7 Hz), 135.7, 156.8, 161.8 (d, $J_{C,F}$ = 245.1 Hz); HRMS (ESI) calcd for $C_{16}H_{23}FNO_3$ [M + H]$^+$ 296.1662, found 296.1659.

3d: IR 3402, 2975, 2930, 2880, 1663, 1615, 1590, 1491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.60–1.65 (m, 1H), 2.38–2.43 (m, 1H), 3.20–3.30 (m, 2H), 3.64–3.78 (m, 2H), 3.98–4.11 (m, 2H), 6.92–7.02 (m, 3H), 7.28–7.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 36.3, 53.7, 61.4, 67.5, 80.8, 113.9 (d, $J_{C,F}$ = 16.2 Hz), 114.2 (d, $J_{C,F}$ = 17.6 Hz), 122.8, 130.1 (d, $J_{C,F}$ = 8.5 Hz), 163.0 (d, $J_{C,F}$ = 246.6 Hz); HRMS (ESI) calcd for $C_{16}H_{23}FNO_3$ [M + H]$^+$ 296.1662, found 296.1661.

3e: IR 3402, 2975, 2930, 2881, 1665, 1584, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 1.68–1.77 (m, 1H), 2.36–2.43 (m, 1H), 3.28 (t, J = 10.8 Hz, 1H), 3.45–3.54 (m, 1H), 3.65–3.70 (m, 1H), 3.73–3.81 (m, 1H), 3.96–4.12 (m, 2H), 5.22–5.24 (m, 1H), 7.01–7.06 (m, 1H), 7.09–7.13 (m, 1H), 7.21–7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 34.9, 36.2, 52.5, 61.1, 67.5, 80.7, 115.6 (d, $J_{C,F}$ = 22.3 Hz), 124.3, 127.9 (d, $J_{C,F}$ = 4.6 Hz), 128.5 (d, $J_{C,F}$ = 7.7 Hz), 161.2 (d, $J_{C,F}$ = 245.8 Hz); HRMS (ESI) calcd for $C_{16}H_{23}FNO_3$ [M + H]$^+$ 296.1662, found 296.1659.

3f: IR 3508, 2978, 2936, 2893, 1681, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.74–1.83 (m, 1H), 2.46–2.52 (m, 1H), 3.33–3.47 (m, 2H), 3.69–3.86 (m, 2H), 4.04–4.25 (m, 2H), 5.23–5.31 (m, 1H), 7.35–7.37 (m, 1H), 7.44–7.50 (m, 2H), 7.66 (s, 1H), 7.82–7.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 36.4, 42.7, 53.9, 61.5, 67.6, 80.7, 125.3, 125.6, 125.8, 126.3, 127.5, 127.6, 128.3, 132.5, 133.4, 137.5; HRMS (ESI) calcd for $C_{20}H_{26}NO_3$ [M + H]$^+$ 328.1913, found 328.1911.

3g: IR 3383, 2973, 2928, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.02–2.07 (m, 1H), 2.21–2.26 (m, 2H), 2.40 (s, 3H), 2.40 (s, 3H), 3.60–3.79 (m, 4H), 4.02–4.11 (m, 1H), 5.36–5.38 (m, 1H), 6.99–7.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 28.4, 33.3, 38.0, 51.0, 61.6, 67.5, 80.6, 126.7, 129.7, 135.3, 136.8; HRMS (ESI) calcd for $C_{18}H_{28}NO_3$ [M + H]$^+$ 306.2069, found 306.2055.

3i: IR 3433, 2968, 2931, 2858, 1671 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.31–1.42 (m, 3H), 1.47 (s, 9H), 1.52–1.98 (m, 5H), 2.85–2.90 (m, 0.68H), 2.98–3.02 (m, 0.32H), 3.32–3.39 (m, 2H), 3.50–3.73 (m, 3H), 3.91–3.98 (m, 2H), 4.09 (brs, 1H), 5.26 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.5, 31.3, 31.7, 31.8, 33.3, 38.9, 39.0, 43.1, 51.0, 59.7, 67.7, 67.9, 77.2, 80.5; HRMS (ESI) calcd for $C_{15}H_{28}NO_4$ [M + H]$^+$ 286.2018, found 286.2017.

3j: IR 3419, 2974, 2929, 2863, 1690, 1666 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.37–1.43 (m, 2H), 1.47 (s, 9H), 1.53–1.70 (m, 4H), 1.98–2.22 (m, 1H), 2.80 (t, J = 10.8 Hz, 0.59H), 2.98 (t, J = 9.5 Hz, 0.41H), 3.33 (s, 3H), 3.36 (t, J = 6.4 Hz, 2H), 3.48–3.73 (m, 3H), 3.90–3.98 (m, 0.59H), 4.05 (brs, 0.41H), 4.35 (brs, 0.41H), 5.30 (d, J = 8.7 Hz, 0.59H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.2, 28.5, 29.5, 29.9, 34.5, 35.6, 37.1, 37.3, 53.0, 53.3, 58.6, 59.6, 61.3, 67.9, 68.1, 72.6, 77.2, 80.3, 80.4, 157.2; HRMS (ESI) calcd for $C_{14}H_{28}NO_4$ [M + H]$^+$ 274.2018, found 274.2017.

3l: IR 3420, 2957, 2927, 2871, 1692, 1666 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89–0.93 (m, 3H), 1.31–1.32 (m, 4H), 1.47 (s, 9H), 1.60–1.69 (m, 2H), 2.12–2.16 (m, 1H), 2.79 (t, J = 10.5 Hz, 0.43H), 2.96 (t, J = 9.5 Hz, 0.57H), 3.47–3.71 (m, 3H), 3.90–3.96 (m, 0.43H), 4.04 (brs, 0.57H), 4.38 (brs, 0.57H), 5.34 (d, J = 8.7 Hz, 0.43H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.2, 21.3, 28.5, 34.6, 35.5, 35.6, 37.0, 37.2, 53.0, 53.3, 59.7, 61.4, 68.0, 68.3, 80.3; HRMS (ESI) calcd for $C_{13}H_{26}NO_3$ [M + H]$^+$ 244.1913, found 244.1911.

Synthesis of *trans*-4-substituted prolinols 4a–4l

A mixture of alkene **2** (0.05 M) and [Ir(cod)(PCy$_3$)(py)]PF$_6$ (1–2 mol%) in CH_2Cl_2 was stirred at room temperature under H_2 atmosphere. After alkene **2** was consumed, the mixture was purified by silica gel column chromatography to give **4**.

4b: IR 3493, 2980, 2938, 2876, 1682, 1610, 1514 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.48 (s, 9H), 1.92–2.02 (m, 1H), 2.09–2.14 (m, 1H), 3.32–3.42 (m, 2H), 3.66–3.76 (m, 3H), 3.80 (s, 3H), 4.15–4.27 (m, 2H), 6.86 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.5, 35.9, 41.6, 54.1, 55.3, 59.8, 67.9, 80.5, 114.0, 127.9, 154.6, 158.5; HRMS (ESI) calcd for $C_{17}H_{26}NO_4$ [M + H]$^+$ 308.1862, found 308.1858.

4c: IR 3418, 2981, 2941, 2879, 1676, 1600, 1512 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.48 (s, 9H), 2.02–2.04 (m, 1H), 2.08–2.15 (m, 1H), 3.33–3.44 (m, 2H), 3.70–3.80 (m, 3H), 4.16–4.26 (m, 2H), 6.98–7.03 (m, 2H), 7.16–7.19 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.5, 35.9, 41.6, 53.9, 59.7, 67.8, 80.6, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 128.4 (d, $J_{C,F}$ = 7.7 Hz), 136.8, 156.9, 161.7 (d, $J_{C,F}$ = 245.1 Hz); HRMS (ESI) calcd for $C_{16}H_{23}FNO_3$ [M + H]$^+$ 296.1662, found 296.1659.

4e: IR 3412, 2975, 2932, 2878, 1666, 1584, 1492 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.48 (s, 9H), 2.00–2.04 (m, 1H), 2.19–2.27 (m, 1H), 3.44–3.50 (m, 1H), 3.68–3.81 (m, 4H), 4.18–4.27 (m, 2H), 7.02–7.06 (m, 1H), 7.09–7.13 (m, 1H), 7.18–7.24 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 28.4, 34.3, 35.7, 52.5, 59.5, 67.7, 80.6, 115.6 (d, $J_{C,F}$ = 23.1 Hz), 124.3, 127.5 (d, $J_{C,F}$ = 3.9 Hz), 128.4 (d, $J_{C,F}$ = 7.7 Hz), 156.9, 161.0 (d, $J_{C,F}$ = 245.8 Hz); HRMS (ESI) calcd for $C_{16}H_{23}FNO_3$ $[M + H]^+$ 296.1662, found 296.1657.

4f: IR 3497, 2976, 2940, 2881, 1682, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.04–2.10 (m, 1H), 2.25–2.33 (m, 1H), 3.51–3.62 (m, 2H), 3.72–3.79 (m, 2H), 3.84–3.88 (m, 1H), 4.25–4.29 (m, 2H), 7.34–7.36 (m, 1H), 7.43–7.50 (m, 2H), 7.65 (s, 1H), 7.77–7.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 35.8, 42.5, 53.8, 56.9, 59.9, 67.9, 80.6, 125.3, 125.4, 125.7, 126.3, 127.6, 128.4, 132.5, 133.4, 138.5; HRMS (ESI) calcd for $C_{20}H_{26}NO_3$ $[M + H]^+$ 328.1913, found 328.1910.

4i: IR 3420, 2928, 2847, 1686, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31–1.42 (m, 3H), 1.47 (s, 9H), 1.52–1.98 (m, 5H), 2.85–2.90 (m, 0.22H), 2.98–3.02 (m, 0.78H), 3.32–3.39 (m, 2H), 3.50–3.73 (m, 3H), 3.95–3.98 (m, 2H), 4.09 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 31.3, 31.7, 31.8, 33.3, 38.9, 39.0, 43.1, 51.0, 59.7, 67.7, 67.9, 77.2, 80.3, 80.5; HRMS (ESI) calcd for $C_{15}H_{28}NO_4$ $[M + H]^+$ 286.2018, found 286.2018.

4j: IR 3420, 2974, 2928, 2862, 1691, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37–1.43 (m, 2H), 1.47 (s, 9H), 1.54–1.70 (m, 4H), 1.98–2.22 (m, 1H), 2.81 (t, J = 10.5 Hz, 0.26H), 2.98 (t, J = 9.5 Hz, 0.74H), 3.33 (s, 3H), 3.37 (t, J = 6.2 Hz, 2H), 3.48–3.73 (m, 3H), 3.90–3.98 (m, 0.26H), 4.05 (brs, 0.74H), 4.35 (brs, 0.74H), 5.30 (d, J = 8.7 Hz, 0.26H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 28.5, 29.5, 29.9, 34.6, 35.6, 37.1, 37.3, 53.0, 53.3, 58.6, 59.6, 61.4, 67.9, 68.1, 72.6, 77.3, 80.3, 80.4, 157.2; HRMS (ESI) calcd for $C_{14}H_{28}NO_4$ $[M + H]^+$ 274.2018, found 274.2017.

4l: IR 3421, 2957, 2928, 2871, 1693, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.93 (m, 3H), 1.31–1.32 (m, 4H), 1.47 (s, 9H), 1.63–1.69 (m, 2H), 2.16 (brs, 1H), 2.96 (t, J = 9.5 Hz, 1H), 3.49 (dd, J = 10.5, 7.5 Hz, 1H), 3.61 (t, J = 4.6 Hz, 2H), 4.04 (brs, 1H), 4.38 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.3, 28.5, 34.6, 35.5, 37.0, 53.0, 59.7, 68.3, 80.2, 167.4; HRMS (ESI) calcd for $C_{13}H_{26}NO_3$ $[M + H]^+$ 244.1913, found 244.1912.

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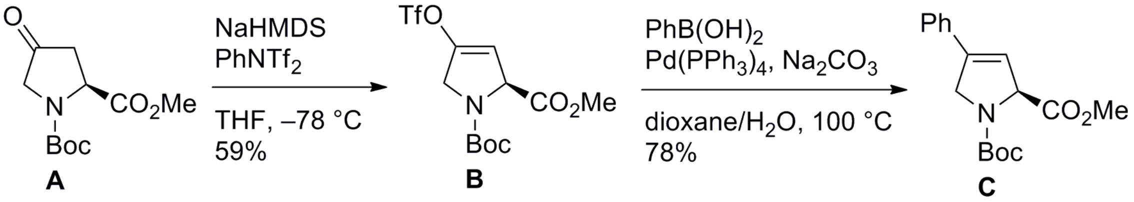

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