Supporting information

Iterative multifunctionalization of unactivated C-H bonds in piperidines by way of intramolecular Rh(II)-catalyzed aminations

Sylvestre Toumieux, Philippe Compain,* Olivier R. Martin

ICOA, (1) UMR 6005 CNRS, (2) Université d'Orléans, rue de Chartres, BP 6759, 45067 Orléans (France)

Table of contents (Experimental)

General
Preparation and data of 3c and 11d
Preparation and data of 12
Preparation and data of 16

General: Unless otherwise stated, all reactions requiring anhydrous conditions were carried out under Argon. Dichloromethane was distilled from calcium hydride. All reagent-grade chemicals were obtained from commercial suppliers and were used as received, unless otherwise stated. 1H NMR and 13C NMR spectra were recorded at 25°C on a 250 MHz or a 400 MHz spectrometer. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal standard. The proton and carbon signal assignments were determined from decoupling experiments, COSY spectra and HSQC spectra. J values are quoted in Hertz. Infrared spectra were recorded using sodium chloride windows. Analytical thin layer chromatography was performed using silica gel 60F 254 precoated plates. Flash chromatography was performed on silica gel 60 (230-400 mesh) with ethyl acetate (AcOEt) and petroleum ether (PE) as eluants unless indicated otherwise.
For the description of NMR spectra, the compounds have been numbered as follow:

\[
\begin{array}{cc}
\text{R} & \text{Ts} \\
5 & 6 \\
4 & 3 \\
2 & 1
\end{array}
\]

\[
\begin{array}{cc}
\text{R} & \text{Ts} \\
5 & 6 \\
4 & 3 \\
2 & 1
\end{array}
\]

\((2S^*,6R^*S^*)-6-[^2\text{H}]-2\text{-sulfamoyloxymethyl-1-(toluene-4-sulfonyl)-piperidine (3c).}\)

To a 0.1 M solution of \(2^7\) (37 mg, 0.106 mmol) in \(\text{CH}_2\text{Cl}_2\), were added at -78°C, triethylsilane-(\(d\)) (0.051 ml, 0.318 mmol, 3 equiv.) and BF\(_3\).OEt\(_2\) (0.034 ml, 0.106 mmol, 1 equiv.). The solution was stirred 5 h at this temperature. The reaction mixture was quenched with water, extracted with \(\text{CH}_2\text{Cl}_2\), dried over MgSO\(_4\) and concentrated under reduced pressure. Purification on silica gel (EP/AcOEt 6/4) gave 3c as a colourless oil (22 mg, 66 %, d.e. ~60%).

\(^1\text{H NMR (CDCl}_3, \text{400 MHz):} \delta 1.16 (\text{m, 1H}), 1.35-1.58 (\text{m, 3H}), 1.70 (\text{m, 2H}) (\text{2H}_3, \text{2H}_4, \text{2H}_5), 2.42 (\text{s, 3H, Me}), 3.08 (\text{m, 0.2H, H}_6^{\text{proR}}), 3.67 (\text{br s, 0.8H, H}_6^{\text{proS}}), 4.22 (\text{m, 1H, H}_2), 4.43 (\text{m, 2H, CH}_2\text{OSO}_2), 5.21 (\text{s, 2H, NH}_2), 7.31 (\text{d, 2H, J ~ 8.0 Hz, H}_\text{Ar}), 7.73 (\text{d, 2H, J ~ 8.0 Hz, H}_\text{Ar}).\)

\(^{13}\text{C NMR (CDCl}_3, \text{100 MHz):} \delta 18.8 (\text{C}_4), 21.7 (\text{CH}_3), 23.9 (\text{C}_5), 24.8 (\text{C}_3), 41.0 (\text{m, C}_6), 51.1 (\text{C}_2), 68.0 (\text{CH}_2\text{OSO}_2), 127.2 (\text{CH}_\text{Ar}), 130.0 (\text{CH}_\text{Ar}), 137.8 (\text{Cq}), 143.7 (\text{Cq}).\)

IR (neat) 3274, 1373, 1163 cm\(^{-1}\).

HRMS: Cald. for C\(_{13}\)H\(_{19}\)DN\(_2\)O\(_5\)NaS\(_2\) [M+Na]\(^+\): 372.07741; found 372.0779 (1 ppm).

\((4aS^*,8aR^*)-3\text{-Oxa-5-(toluene-4-sulfonyl)-1,4,4a,5,6,8a-hexahydro-2-thia-1,5-diaza-naphthalene-2,2-dioxide (11d).}\)

To a solution of \(10\) (500 mg, 1.337 mmol) in \(\text{CH}_2\text{Cl}_2\) (10 ml), were added at -78°C, triethylsilane (0.849 ml, 5.347 mmol, 4 equiv.) and SnCl\(_4\) (1M in \(\text{CH}_2\text{Cl}_2\), 0.935 ml, 0.935 mmol, 0.7 equiv.). The solution was stirred 4 h at this temperature and was quenched with saturated aqueous NaHCO\(_3\) at-78°C, warmed up to
RT, extracted with CH$_2$Cl$_2$, dried over MgSO$_4$ and concentrated under reduced pressure. Purification by filtration on a pad of silica gel (CH$_2$Cl$_2$/acetone 9/1) gave **11d** as a colourless oil (455 mg, 99%).

$^1$H NMR (Acetone-$d_6$, 400 MHz): $\delta$ 2.43 (s, 3H, Me), 3.73 (m, 1H, H$_{6A}$), 4.00 (br s, 1H, H$_3$), 4.11 (m, 1H, H$_{6B}$), 4.18 (ddd, 1H, $J \sim 1.2$ Hz, $J \sim 4.8$ Hz, $J \sim 11.2$ Hz, CH$_A$OSO$_2$), 4.57 (dt, 1H, $J \sim 2$ x 5.0 Hz, $J \sim 10$ Hz, H$_2$), 4.69 (t, 1H, $J \sim 11.2$ Hz, CH$_B$OSO$_2$), 5.86 (AB, 2H, H$_4$, H$_5$), 6.96 (d, 1H, $J \sim 5.2$ Hz, NH), 7.44 (d, 2H, $J \sim 8.4$ Hz, H$_{Ar}$), 7.78 (d, 2H, $J \sim 8.0$ Hz, H$_{Ar}$).

$^{13}$C NMR (Acetone-$d_6$, 100 MHz): $\delta$ 21.4 (Me), 41.4 (C$_6$), 46.1 (C$_2$), 51.7 (C$_3$), 68.1 (CH$_2$OSO$_2$), 124.7 (C$_4$ or C$_5$), 126.0 (C$_4$ or C$_5$), 127.8 (CH$_{Ar}$), 131.0 (CH$_{Ar}$), 137.8 (Cq), 145.1(Cq).

IR (neat) 3296, 1355, 1215, 1163 cm$^{-1}$.

HRMS: Calcd. for C$_{13}$H$_{16}$N$_2$O$_5$NaS$_2$ [M+Na]$^+$: 367.03984; found 367.0394 (1 ppm).

**(4aS*,8aR*)-1-Acetyl-5-(toluene-4-sulfonyl)-1,4,4a,5,6,8a-hexahydro-3-oxa-2-thia-1,5-diaza-naphthalene-2,2-dioxide (12).**

To a solution of **11d** (250 mg, 0.726 mmol) in CH$_2$Cl$_2$ (4 ml), were added at -20°C acetic anhydride (0.271 ml, 3.637 mmol, 5 equiv.), DMAP (8.9 mg, 0.073 mmol, 0.1 equiv.) and t-BuOK (18 mg, 0.800 mmol, 1.1 equiv.). The solution was stirred 1h at this temperature and was quenched with water (10 ml), extracted with CH$_2$Cl$_2$, dried over MgSO$_4$ and concentrated under reduced pressure. Purification by filtration on a pad of silica gel (CH$_2$Cl$_2$/acetone 9/1) gave **12** as colourless oil (275 mg, 98%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.45 (s, 3H, Me), 2.50 (s, 3H, COMe), 3.68 (dxm, 1H, $J \sim 18.4$ Hz, H$_{6A}$), 4.11 (dxm, 1H, $J \sim 18.4$ Hz, H$_{6B}$), 4.51 (m, 2H, CH$_2$OSO$_2$), 4.66 (q, 1H, $J \sim 6.8$ Hz, H$_2$), 5.47 (m, 1H, H$_3$), 5.63 (dd, 1H, $J \sim 1.2$ Hz, $J \sim 10.4$ Hz, H$_4$), 5.83 (m, 1H, H$_5$), 7.35 (d, 2H, $J \sim 8.0$ Hz, H$_{Ar}$), 7.70 (d, 2H, $J \sim 8.0$ Hz, H$_{Ar}$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 21.7 (Me), 25.0 (COMe), 40.4 (C$_6$), 46.6 (C$_2$), 50.5 (C$_3$), 70.0 (CH$_2$OSO$_2$), 124.0 (C$_5$), 125.5 (C$_4$), 127.1 (CH$_{Ar}$), 130.4 (CH$_{Ar}$), 135.8 (Cq), 144.8 (Cq), 168.3 (C=O).

MS-IS m/z 409.0 [M+Na]$^+$, 387.0 [M+H]$^+$
(2S*,3R*,6R*S*)-2-Acetoxymethyl-6-allyl-3-tert-butyloxycarbonylamino-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine (16).

To a solution of diastereoisomers 15 (55 mg, 0.113 mmol) in dry DMF (2 ml) was added potassium acetate (28.1 mg, 226 mmol, 2 equiv.). The solution was stirred at 40°C during 15 h. The mixture was allowed to cool down to RT, aqueous HCl 1N (1 ml) and Et₂O (2 ml) were then added and the mixture was stirred for 0.5 h. The solution was extracted with Et₂O, washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification on silica gel (AE/EP 2/8) gave 16 as a colourless oil (48 mg, 91%, d. e. 70%).

¹H NMR (Acetone- d₆, 400 MHz, major isomer): δ 1.43 (s, 9H, t-Bu), 1.99 (s, 3H, Me), 2.26-2.50 (m, 4H, Me, CH-CH=CH₂), 2.65 (m, 1H, CH-CH=CH₂), 3.80-4.01 (m, 2H, H₃, CH₂OAc), 4.22-4.38 (m, 2H, H₆, CH₂OAc), 4.74 (m, 1H, H₂), 5.11 (m, 2H, CH₂-CH=CH₂), 5.55 (m, 1H, H₅), 5.79 (m, 1H, H₄), 5.93 (m, 1H, CH₂-CH=CH₂), 6.31 (br s, 1H, NH), 7.41 (m, 2H, H₄), 7.81 (m, 2H, H₅).

¹³C NMR (Acetone- d₆, 62.5 MHz): δ 20.9 (Me), 21.4 (Me), 28.6 (t-Bu), 42.7 (CH₂-CH=CH₂), 46.8 (C₃), 51.7 (C₂), 53.3 (C₆), 62.2 (CH₂OAc), 79.4 (t-Bu), 118.1 (CH₂-CH=CH₂), 126.1 (C₄ or C₅), 127.9 (CH₄ + C₄ or C₅), 130.7 (CH₃), 135.7 (CH₃ + CH₂-CH=CH₂), 139.0 (Cq), 144.3 (Cq), 156.0 (C=O), 170.8 (C=O).

IR (neat) 3373, 1742, 1710, 1367, 1164 cm⁻¹.

HRMS: Calcd. for C₂₃H₃₂N₂O₆NaS [M+Na]⁺: 487.18788; found 487.1881 (0 ppm).