Synthesis X. Zhang et al. Special Topic

Synthesis of Substituted Piperidines via Cationic Palladium(II)-Catalyzed Reductive Coupling of *N*-Tosyl-Tethered Alkynones

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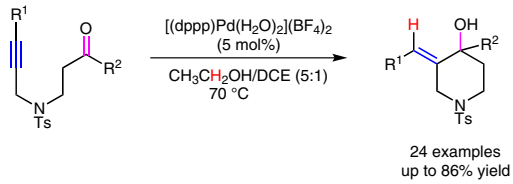

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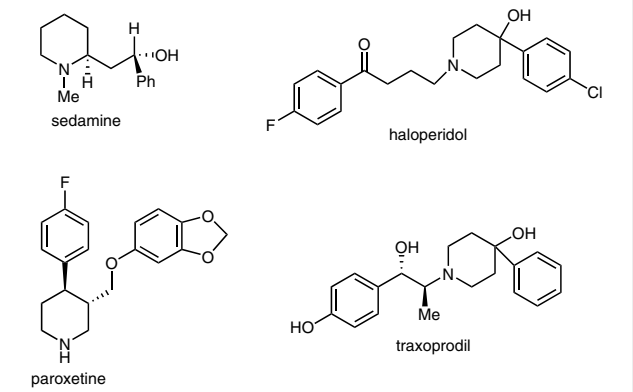
Abstract A cationic palladium(II) complex catalyzed reductive coupling of *N*-tosyl-tethered alkynones for the synthesis of functionalized piperidines was successfully developed. This reaction was initiated by hydropalladation of the alkyne and quenched by addition to the intramolecular carbonyl group. The substituent on the alkyne is key to the reaction.

Key words addition reaction, hydropalladation, palladium(II)-catalyzed, piperidine, reductive coupling

Saturated heterocycles are essential substructures in a large variety of natural and synthetic bioactive compounds. Piperidines are of particular interest due to their presence in a myriad of natural products exhibiting significant biological and pharmacological activity (Scheme 1).[1] In addition, they are also important starting materials for constructing other complex heterocycles.[2] As a result, considerable efforts have been devoted toward the development of efficient methods for the synthesis of this class of six-membered nitrogen-containing compounds.[3] Among the developing methods to prepare piperidines, the metal-catalyzed heterocyclization of amino derivatives has emerged as a powerful and efficient strategy that is particularly interesting in terms of both atom-economy and readily available precursors.[4]

Palladium-catalyzed coupling reactions have become a powerful tool in organic synthesis due to their utility in affecting a broad range of very useful organic transformations under relatively mild reaction conditions.[5] There are numerous applications of palladium catalysis in the preparation of heterocycles with good regio- and stereoselective control and toleration for a wide variety of functional groups.[6] Among many approaches to heterocycles catalyzed by palladium, few examples are available to produce piperidines.[7]

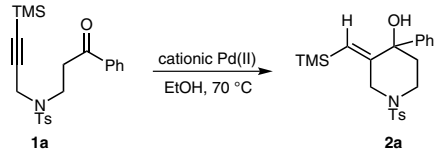
Our group has been focused on palladium(II)-catalyzed reactions for several years. Recently, we developed the reductive cyclization of alkynones for the synthesis of pyrrolidine or hydroquinoline derivatives by using ethanol as a hydrogen source.[8] These reactions were initiated by the hydropalladation of alkynes and quenched by addition to the intramolecular carbonyl groups. The use of cationic palladium complexes is the key for the success of the process. Although there are many examples of intermolecular reductive coupling of alkynes and carbonyl compounds, the intramolecular version is rare and using palladium(II) as the catalyst has not been previously reported in the literature.[9] As an extension of our studies on this chemistry, we decided to employ the intramolecular reductive cyclization of alkynones to synthesize functionalized piperidines. Herein, we report the results of this study.



Scheme 1 Selected bioactive piperidine derivatives

In our previous work, it was found when *N*-tosyl-tethered alkynone **1a** reacted in ethanol as the solvent under the catalysis of a cationic palladium complex, a reductive coupling occurred to give piperidine **2a**.[8a] Therefore, substrate **1a** was chosen as the model compound to test the reaction conditions. First, the influence of the catalyst was investigated: $[(dppp)Pd(H_2O)_2](BF_4)_2$ gave the best yield of **2a** of all of the tested cationic palladium complexes (Table 1, entries 1–4) when EtOH was used as the solvent and hydrogen source at 70 °C. The in situ prepared cationic palladium gave lower yields (Table 1, entries 5 and 6). Substrate **1a** was poorly soluble in ethanol, but upon addition of DCE substrate **1a** dissolved completely. We tested the reaction in different ratios of EtOH and DCE and found that 5:1 gave the best result (Table 1, entries 7–10). Increasing or decreasing the concentration of the reactant lowered the yield (Table 1, entries 11 and 12). Addition of water also inhibited the coupling (Table 1, entry 13). Without EtOH, no reaction occurred (Table 1, entries 14 and 15). Using *i*-PrOH as the hydrogen source gave only a low yield of the product (Table 1, entry 16). When the temperature was lowered to 50 °C or raised to 90 °C, the yield of the product was reduced (Table 1, entries 17 and 18). The stereochemistry of the exocyclic double bond in **2a** was assigned as *E*, as confirmed by single-crystal X-ray crystallography.[10]

Table 1 Optimization of Reaction Conditions[a]



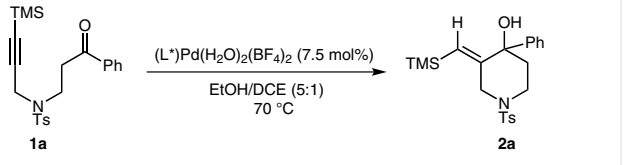
1a **2a**

Entry	Catalyst	Solvent (mL)		Yield[b] (%)
		EtOH	DCE	
1	$[(dppp)Pd(H_2O)_2](BF_4)_2$	1	0	47
2	$[(dppb)Pd(H_2O)_2](BF_4)_2$	1	0	–[c]
3	$[(dppp)Pd(H_2O)_2](OTf)_2$	1	0	27
4	$[(dppe)Pd(H_2O)_2](OTf)_2$	1	0	7
5	$(dppp)PdCl_2 + AgBF_4$	1	0	–[c]
6	$[(MeCN)_4Pd](BF_4)_2 + dppp$	1	0	15
7	$[(dppp)Pd(H_2O)_2](BF_4)_2$	1	0.2	78 (75)[d]
8	$[(dppp)Pd(H_2O)_2](BF_4)_2$	0.9	0.3	63
9	$[(dppp)Pd(H_2O)_2](BF_4)_2$	0.8	0.4	59
10	$[(dppp)Pd(H_2O)_2](BF_4)_2$	0.6	0.6	59
11	$[(dppp)Pd(H_2O)_2](BF_4)_2$	0.5	0.1	35
12	$[(dppp)Pd(H_2O)_2](BF_4)_2$	2	0.4	58
13[e]	$[(dppp)Pd(H_2O)_2](BF_4)_2$	1	0.2	24
14	$[(dppp)Pd(H_2O)_2](BF_4)_2$	0	1	–[c]
15[e]	$[(dppp)Pd(H_2O)_2](BF_4)_2$	0	1	–[c]
16[f]	$[(dppp)Pd(H_2O)_2](BF_4)_2$	0	0.2	15
17[g]	$[(dppp)Pd(H_2O)_2](BF_4)_2$	1	0.2	37
18[h]	$[(dppp)Pd(H_2O)_2](BF_4)_2$	1	0.2	62

[a] Reaction conditions: **1a** (0.1 mmol), Pd catalyst (0.0075 mmol), solvent, 70 °C, stirring, 5–8 h, unless otherwise noted.
[b] ^1H NMR yield.
[c] No reaction.
[d] Isolated yield in parentheses.
[e] H_2O (0.2 mL) was added.
[f] *i*-PrOH (1.0 mL) was added to replace EtOH.
[g] The reaction was carried out at 50 °C.
[h] The reaction was carried out at 90 °C.

With the optimized reaction conditions in hand (Table 1, entry 7), the substrate scope was examined and the results are shown in Table 2. First, the effect of substituents on the carbonyl group (R^2) was investigated. When R^2 was an aryl group bearing a fluoro, chloro, trifluoromethyl, or methyl substituent, the reactions proceeded smoothly to give the corresponding products in moderate yields (Table 2, entries 1, 2, 4 and 5). However, when R^2 was a bromo-substituted aryl group, only a very low yield was obtained (Table 2, entry 3). Substrate bearing a 1-naphthyl or 2-thienyl ketone can also give the corresponding piperidines **2g** and **2h** successfully (Table 2, entries 6 and 7). Then the aryl group was changed to an alkyl group and the results showed that substrates with linear alkyl groups reacted well to form the products in moderate yields. However, sterically hindered alkyl groups, such as Cy or *t*-Bu, totally prevented the reaction (Table 2, entries 8–13). For the substituent on the alkyne (R^1), only medium-sized groups such as TBS (*tert*-butyldimethylsilyl), TES (triethylsilyl), and *t*-Bu give good results comparable to TMS; linear or more bulky groups inhibited the reaction (Table 2, entries 14–21). The reason for this cannot be explained at present. When the tethered group in the substrate was changed to NBn or $C(CO_2Et)_2$, no reaction occurred at all (Table 2, entries 22 and 23).

Next, we used two cationic palladium complexes which contained (*S*,*S*)-bdpp or (*R*)-binap as the chiral ligand to explore the asymmetric version of this reductive cyclization preliminarily. However, the result is very poor (Scheme 2).



1a **2a**

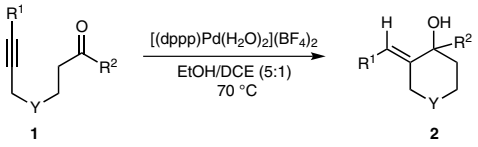
Scheme 2 Preliminarily studies for asymmetric cyclization of **1a**

Similar to our previous work,[8] deuterium-labeling experiments were conducted subsequently to examine the reaction mechanism. The use of CH_3CH_2OD as the hydrogen source and cosolvent afforded **2a** in 68% yield with no deuterium incorporation into the product (Scheme 3, eq 1). On

the other hand, the reaction using CH_3CD_2OH provided **2a** with deuterium (93%) at the vinyl position in 58% yield (Scheme 3, eq 2).

Based on above results and our previous work,[8] a possible mechanism was proposed as shown in Scheme 4. First, the Pd–hydroxyl complex **A**, generated from the cationic palladium catalyst, reacts with EtOH to give Pd–ethoxide complex **B**. Subsequently, β-hydride elimination of **B** produces Pd–H complex **C**, which is inserted by the alkyne to yield intermediate **D**. Addition of the carbon–palladium bond to the intramolecular carbonyl group in the intermediate **D** offers **E**. Finally, protonolysis of **E** generates the product.

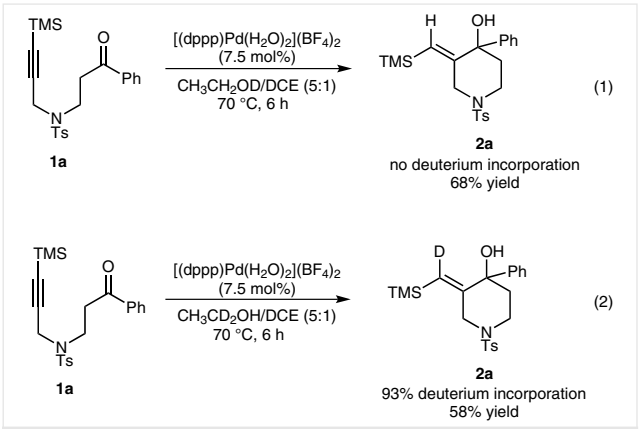
Table 2 Substrate Scope[a]



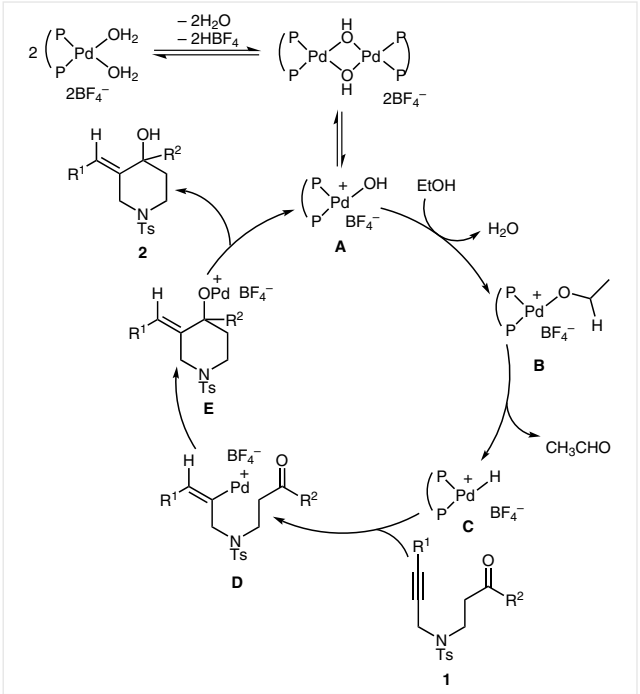
1 2

Entry	Y	R^1	R^2	Product	Yield[b] (%)
1	NTs	TMS	4-FC_6H_4 (**1b**)	**2b**	58
2	NTs	TMS	4-ClC_6H_4 (**1c**)	**2c**	54
3	NTs	TMS	4-BrC_6H_4 (**1d**)	**2d**	16
4	NTs	TMS	4-$F_3CC_6H_4$ (**1e**)	**2e**	79
5	NTs	TMS	4-MeC_6H_4 (**1f**)	**2f**	49
6	NTs	TMS	1-naphthyl (**1g**)	**2g**	69
7	NTs	TMS	2-thienyl (**1h**)	**2h**	31
8	NTs	TMS	Et (**1i**)	**2i**	76
9	NTs	TMS	*n*-Pr (**1j**)	**2j**	58
10	NTs	TMS	$(CH_2)_4Me$ (**1k**)	**2k**	56
11	NTs	TMS	Bn (**1l**)	**2l**	75
12	NTs	TMS	Cy (**1m**)	**2m**	–[d]
13	NTs	TMS	*t*-Bu (**1n**)	**2n**	–[d]
14	NTs	TBS	Ph (**1o**)	**2o**	86
15	NTs	TES	Ph (**1p**)	**2p**	74
16	NTs	TIPS	Ph (**1q**)	**2q**	–[d]
17	NTs	Ph	Ph (**1r**)	**2r**	–[d]
18	NTs	Bu	Ph (**1s**)	**2s**	–[d]
19	NTs	*t*-Bu	Ph (**1t**)	**2t**	85[c]
20	NTs	Me	Ph (**1u**)	**2u**	–[e]
21	NTs	H	Ph (**1v**)	**2v**	–[d]
22	NBn	TMS	Ph (**1w**)	**2w**	–[d]
23	$C(CO_2Et)_2$	TMS	Ph (**1x**)	**2x**	–[d]

[a] Reaction conditions: substrate **1** (0.1 mmol), $[(dppp)Pd(H_2O)_2](BF_4)_2$ (0.0075 mmol), EtOH (1 mL)/DCE (0.2 mL), 70 °C, stirring.
[b] Isolated yield.
[c] The reaction was carried out at r.t.
[d] No reaction.
[e] The reaction was complicated and the products were not determined.



Scheme 3 Deuterium-labeling experiments



Scheme 4 Possible mechanism for the cyclization reaction

In summary, a reductive coupling reaction of *N*-tosyl-tethered alkynones catalyzed by a cationic palladium(II) complex was developed. The substituent on the alkyne (R^1 in substrate **1**) is the key for the reaction. This process provides a convenient method for the synthesis of substituted piperidines. Further study will be focused on asymmetric version and application of the reaction.

All reactions were performed with freshly distilled and dried solvents. All solvents were distilled using standard procedures. Unless otherwise noted, reagents were obtained from commercial sources

and used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ using a 400 MHz spectrometer. HRMS were carried out on a mass spectrometer with a TOF analyzer (ESI, EI). Infrared spectra were recorded on a FT-IR spectrophotometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. For column chromatography, silica gel of 200–300 mesh size was used.

Substrate **1a** is a known compound which was prepared according to the reported procedure[8a] and other substrates **1b–x** were synthesized by a similar method. For preparations of **1b–x**, see the Supporting Information.

Piperidines 2a–x; General Procedure

The solution of $[(dppp)Pd(H_2O)_2](BF_4)_2$ (5.6 mg, 7.5 mol%) and alkynone **1** (0.1 mmol) in EtOH (1.0 mL) and DCE (0.2 mL) was stirred at 70 °C until completion (TLC monitoring). After cooling the mixture to r.t., the solvents were removed under vacuum, and the residue was purified by flash column chromatography (EtOAc/petroleum ether 1:5) to obtain the product **2**.

(*E*)-4-Phenyl-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2a)

White solid; yield: 31 mg (75%); mp 135.6–136.4 °C.

IR (KBr): 3507, 2958, 2929, 2866, 1490, 1335, 1159, 854, 756, 661 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.4 Hz, 2 H), 7.35–7.28 (m, 7 H), 5.47 (s, 1 H), 3.90 (d, *J* = 12.8 Hz, 1 H), 3.79 (d, *J* = 12.8 Hz, 1 H), 3.30–3.19 (m, 2 H), 2.49–2.43 (m, 4 H), 1.93–1.87 (m, 1 H), 1.77 (s, 1 H), 0.17 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 143.7, 143.0, 133.4, 129.9, 129.0, 128.5, 127.9, 127.8, 126.4, 76.3, 48.7, 43.2, 38.7, 21.7, 0.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{30}NO_3SSi$: 417.1710; found: 417.1710.

(*E*)-4-(4-Fluorophenyl)-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2b)

Pale yellow oil; yield: 25 mg (58%).

IR (KBr): 3480, 2956, 1708, 1622, 1599, 1508, 1462, 1407, 1351, 1306, 1250, 1227, 1163, 1090, 1037, 986, 929, 839, 815, 751, 664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.35–7.25 (m, 4 H), 7.00 (t, *J* = 8.7 Hz, 2 H), 5.43 (s, 1 H), 3.90 (d, *J* = 12.8 Hz, 1 H), 3.74 (d, *J* = 12.8 Hz, 1 H), 3.33–3.23 (m, 1 H), 3.22–3.12 (m, 1 H), 2.43 (s, 3 H), 2.41–2.35 (m, 1 H), 1.92–1.87 (m, 1 H), 1.80 (s, 1 H), 0.16 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 143.7, 133.1, 129.7, 129.1, 128.1, 128.0, 127.7, 115.2, 115.0, 75.8, 48.4, 42.9, 38.7, 21.5, –0.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}FNO_3SSi$: 434.1616; found: 434.1612.

(*E*)-4-(4-Chlorophenyl)-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2c)

White solid; yield: 24 mg (54%); mp 124.4–125.2 °C.

IR (KBr): 3465, 2953, 1626, 1597, 1489, 1460, 1400, 1348, 1331, 1305, 1249, 1219, 1158, 1092, 1071, 1043, 991, 947, 856, 838, 811, 748, 666 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 2 H), 7.37–7.27 (m, 6 H), 5.41 (s, 1 H), 3.98 (d, *J* = 12.4 Hz, 1 H), 3.72 (d, *J* = 12.8 Hz, 1 H), 3.42–3.30 (m, 1 H), 3.26–3.06 (m, 1 H), 2.45 (s, 3 H), 2.42–2.36 (m, 1 H), 1.92–1.86 (m, 1 H), 1.75 (s, 1 H), 0.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 143.7, 141.6, 133.4, 133.1, 129.7, 129.5, 128.4, 127.8, 127.7, 75.9, 48.3, 42.8, 38.7, 21.5, –0.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}ClNO_3SSi$: 450.1320; found: 450.1318.

(*E*)-4-(4-Bromophenyl)-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2d)

White solid; yield: 8 mg (16%); mp 141.8–143.9 °C.

IR (KBr): 3467, 2951, 1686, 1630, 1598, 1587, 1486, 1460, 1377, 1348, 1329, 1307, 1250, 1162, 1093, 1072, 932, 866, 838, 811, 666, 548 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.2 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.39 (s, 1 H), 3.97 (d, *J* = 12.8 Hz, 1 H), 3.69 (d, *J* = 12.8 Hz, 1 H), 3.36–3.33 (m, 1 H), 3.17–3.11 (m, 1 H), 2.44 (s, 3 H), 2.39–2.33 (m, 1 H), 1.90–1.85 (m, 1 H), 1.70 (s, 1 H), 0.16 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7, 143.7, 142.2, 133.1, 131.3, 129.7, 129.5, 128.1, 127.7, 121.6, 76.0, 48.3, 42.8, 38.6, 21.5, –0.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}BrNO_3SSi$: 494.0815; found: 494.0805.

(*E*)-1-Tosyl-4-[4-(trifluoromethyl)phenyl]-3-[(trimethylsilyl)methylene]piperidin-4-ol (2e)

White solid; yield: 38 mg (79%); mp 147.4–149.5 °C.

IR (KBr): 3472, 2951, 1632, 1618, 1599, 1460, 1408, 1382, 1332, 1308, 1296, 1252, 1223, 1163, 1120, 1071, 1039, 931, 859, 838, 666, 549 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.2 Hz, 2 H), 7.58 (d, *J* = 8.3 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 5.31 (s, 1 H), 4.09 (d, *J* = 12.8 Hz, 1 H), 3.64 (d, *J* = 13.2 Hz, 1 H), 3.46–3.41 (m, 1 H), 3.13–3.07 (m, 1 H), 2.44 (s, 3 H), 2.41–2.33 (m, 1 H), 1.91–1.85 (m, 2 H), 0.15 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 147.4, 143.8, 133.1, 130.0, 129.8, 127.7, 126.8, 125.1, 76.1, 48.2, 42.6, 38.8, 21.5, –0.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{29}F_3NO_3SSi$: 484.1584; found: 484.1603.

(*E*)-4-(*p*-Tolyl)-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2f)

White solid; yield: 21 mg (49%); mp 160.5–162.0 °C.

IR (KBr): 3507, 2957, 1597, 1509, 1492, 1461, 1348, 1334, 1303, 1250, 1221, 1184, 1163, 1118, 1091, 1073, 1039, 987, 972, 934, 865, 816, 751, 662, 547 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.13 (d, *J* = 8.1 Hz, 2 H), 5.51 (s, 1 H), 3.83 (d, *J* = 2.8 Hz, 2 H), 3.24 (t, *J* = 5.2 Hz, 2 H), 2.46–2.43 (m, 4 H), 2.33 (s, 3 H), 1.91–1.87 (m, 1 H), 1.74 (s, 1 H), 0.17 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 143.8, 140.0, 137.6, 133.6, 129.9, 129.3, 128.8, 127.9, 126.4, 76.2, 48.8, 43.3, 38.7, 21.7, 21.2, 0.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{32}NO_3SSi$: 430.1867; Found: 430.1865.

(*E*)-4-(Naphthalen-1-yl)-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2g)

White solid; yield: 32 mg (69%); mp 162.8–163.2 °C.

IR (neat): 3481, 2953, 1598, 1500, 1459, 1344, 1159, 856, 748, 662 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.79 (m, 4 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.51–7.48 (m, 2 H), 7.36–7.31 (m, 3 H), 5.47 (s, 1 H), 4.03 (d, *J* = 12.8 Hz, 1 H), 3.77 (d, *J* = 12.4 Hz, 1 H), 3.43–3.78 (m, 1 H), 3.28–3.19 (m, 1 H), 2.59–2.52 (m 1 H), 2.43 (s, 3 H), 1.98–1.92 (m, 1 H), 1.85 (s, 1 H), 0.17 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 143.8, 140.8, 133.4, 133.2, 132.8, 129.9, 129.7, 128.3, 128.0, 127.9, 127.6, 126.4, 126.36, 125.0, 124.9, 76.5, 48.6, 43.1, 38.7, 21.7, 0.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{32}NO_3SSi$: 466.1867; found: 466.1865.

(*E*)-4-(Thiophen-2-yl)-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2h)

White solid; yield: 13 mg (31%); mp 49.8–50.4 °C.

IR (neat): 3474, 2953, 2857, 1623, 1597, 1345, 1159, 837, 661 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 4.8 Hz, 1 H), 6.94 (t, *J* = 4.4 Hz, 1 H), 6.87–6.86 (m, 1 H), 5.89 (s, 1 H), 4.10 (d, *J* = 12.4 Hz, 1 H), 3.52–3.48 (m, 2 H), 3.01–2.95 (m, 1 H), 2.47–2.42 (m, 4 H), 2.13–2.04 (m, 2 H), 0.21 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 148.0, 143.7, 133.5, 129.9, 127.8, 127.5, 127.3, 125.8, 125.3, 74.2, 48.7, 43.6, 39.8, 21.6, 0.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{28}NO_3S_2Si$: 422.1274; found: 422.1275.

(*E*)-4-Ethyl-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2i)

White solid; yield: 28 mg (76%); mp 61.6–63.5 °C.

IR (KBr): 3515, 2954, 2897, 2854, 1625, 1598, 1495, 1464, 1350, 1305, 1263, 1250, 1167, 1120, 1092, 1050, 974, 883, 840, 751, 664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 5.71 (s, 1 H), 4.13 (dd, *J* = 12.8, 1.6 Hz, 1 H), 3.51–3.45 (m, 1 H), 3.18 (d, *J* = 12.8 Hz, 1 H), 2.84–2.77 (m, 1 H), 2.44 (s, 3 H), 1.82–1.73 (m, 2 H), 1.59–1.40 (m, 2 H), 1.25 (s, 1 H), 0.75 (t, *J* = 7.6 Hz, 3 H), 0.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 143.8, 133.1, 129.9, 127.9, 124.8, 73.6, 48.7, 43.7, 38.1, 29.5, 21.7, 7.3, 0.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{29}NNaO_3SSi$: 390.1530; found: 390.1538.

(*E*)-4-Propyl-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2j)

White solid; yield: 22 mg (58%); mp 108.7–110.9 °C.

IR (KBr): 3463, 2955, 2927, 2852, 1711, 1620, 1598, 1370, 1345, 1250, 1218, 1166, 1088, 980, 881, 758, 665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 5.71 (s, 1 H), 4.10 (d, *J* = 12.4 Hz, 1 H), 3.49–3.44 (m, 1 H), 3.22 (d, *J* = 12.4 Hz, 1 H), 2.87–2.80 (m, 1 H), 2.44 (s, 3 H), 1.83–1.70 (m, 2 H),1.50–1.37 (m, 3 H), 1.31–1.23 (m, 1 H), 1.17–1.11 (m, 1 H), 0.85 (t, *J* = 7.2 Hz, 3 H), 0.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 143.6, 133.1, 129.7, 127.7, 124.3, 73.4, 48.5, 43.6, 39.1, 38.3, 21.5, 16.1, 14.3, 0.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{32}NO_3SSi$: 382.1867; found: 382.1871.

(*E*)-4-Pentyl-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2k)

Yellow oil; yield: 23 mg (56%).

IR (KBr): 3514, 2954, 2932, 2858, 1622, 1598, 1466, 1349, 1305, 1249, 1164, 1090, 999, 957, 909, 856, 815, 729, 663 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 5.70 (s, 1 H), 4.10 (d, *J* = 12.4 Hz, 1 H), 3.48–3.43 (m, 1 H), 3.24 (d, *J* = 12.8 Hz, 1 H), 2.87–2.81 (m, 1 H), 2.44 (s, 3 H), 1.80–1.73 (m, 2 H), 1.49–1.41 (m, 2 H), 1.38 (s, 1 H), 1.25–1.20 (m, 6 H), 0.83 (t, *J* = 7.2 Hz, 3 H), 0.18 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 143.6, 133.1, 129.7, 127.7, 124.3, 73.4, 48.5, 43.5, 38.2, 36.8, 32.0, 22.5, 22.4, 21.5, 14.0, 0.0.

HRMS (ESI): *m*/*z* [M + H]$^+$calcd for $C_{21}H_{36}NO_3SSi$: 410.2180; found: 410.2181.

(*E*)-4-Benzyl-1-tosyl-3-[(trimethylsilyl)methylene]piperidin-4-ol (2l)

White solid; yield: 32 mg (75%); mp 116.5–117.7 °C.

IR (KBr): 3495, 2954, 2928, 2856, 1615, 1598, 1495, 1456, 1389, 1338, 1306, 1248, 1186, 1162, 1119, 1090, 1004, 987, 958, 936, 849, 815, 749, 662 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.24–7.20 (m, 3 H), 7.02 (d, *J* = 6.8 Hz, 2 H), 5.50 (s, 1 H), 4.15 (d, *J* = 12.8 Hz, 1 H), 3.44 (d, *J* = 12.8 Hz, 2 H), 2.96 (d, *J* = 12.8 Hz, 1 H), 2.88 (d, *J* = 13.6 Hz, 1 H), 2.70 (d, *J* = 13.2 Hz, 1 H), 2.43 (s, 3 H), 1.84–1.78 (m, 1 H), 1.73–1.66 (m, 1 H), 1.54 (s, 1 H), 0.13 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 143.7, 135.7, 133.1, 130.5, 129.8, 128.1, 127.8, 126.9, 125.6, 73.0, 48.7, 43.4, 37.6, 21.6, –0.09.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{32}NO_3SSi$: 430.1867; found: 430.1876.

(*E*)-3-[(*tert*-Butyldimethylsilyl)methylene]-4-phenyl-1-tosylpiperidin-4-ol (2o)

White solid; yield: 39 mg (86%); mp 161.8–164.2 °C.

IR (KBr): 3503, 2956, 2926, 2855, 1615, 1598, 1494, 1470, 1445, 1423, 1363, 1351, 1337, 1304, 1253, 1217, 1166, 1119, 1094, 1038, 983, 928, 828, 760, 702, 667 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.30 (m, 7 H), 5.45 (s, 1 H), 3.91 (d, *J* = 12.4 Hz, 1 H), 3.73 (d, *J* = 12.8 Hz, 1 H), 3.34–3.29 (m, 1 H), 3.20–3.14 (m, 1 H), 2.51–2.44 (m, 1 H), 2.43 (s, 3 H), 1.95–1.89 (m, 1 H), 1.76 (s, 1 H), 0.84 (s, 9 H), 0.20 (s, 3 H), 0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 143.6, 143.0, 133.0, 129.7, 128.2, 127.7, 127.6, 126.6, 126.2, 76.3, 48.6, 43.0, 38.5, 26.3, 21.5, 16.9, –4.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{36}NO_3SSi$: 458.2180; found: 458.2199.

(*E*)-4-Phenyl-1-tosyl-3-[(triethylsilyl)methylene]piperidin-4-ol (2p)

White solid; yield: 34 mg (74%); mp 110.1–111.2 °C.

IR (KBr): 3500, 2948, 2928, 2868, 1618, 1597, 1492, 1456, 1444, 1417, 1298, 1216, 1183, 1118, 1094, 1070, 1018, 983, 928, 877, 815, 758, 700, 667 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 2 H), 7.32–7.24 (m, 7 H), 5.42 (s, 1 H), 3.79 (d, *J* = 12.4 Hz, 1 H), 3.73 (d, *J* = 12.8 Hz, 1 H), 3.26–3.15 (m, 2 H), 2.48–2.41 (m, 4 H), 1.94–1.88 (m, 1 H), 1.74 (s, 1 H), 0.91 (t, *J* = 8.0 Hz, 9 H), 0.64 (q, *J* = 7.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 143.6, 142.9, 133.0, 129.7, 128.3, 127.8, 127.6, 126.2, 125.8, 76.3, 48.9, 43.1, 38.6, 21.5, 7.6, 4.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{36}NO_3SSi$: 458.2180; found: 458.2167.

(*E*)-3-(2,2-Dimethylpropylidene)-4-phenyl-1-tosylpiperidin-4-ol (2t)

White solid; yield: 34 mg (85%); mp 131.2–132.0 °C.

IR (KBr): 3504, 2960, 1597, 1492, 1468, 1446, 1366, 1337, 1307, 1270, 1214, 1166, 1092, 1042, 1018, 981, 938, 756, 666 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 2 H), 7.37–7.26 (m, 7 H), 5.33 (s, 1 H), 4.19 (d, *J* = 12.8 Hz, 1 H), 3.75 (d, *J* = 13.2 Hz, 1 H), 3.35–3.30 (m, 1 H), 3.18–3.12 (m, 1 H), 2.48–2.41 (m, 4 H), 1.90–1.85 (m, 1 H), 1.63 (s, 1 H), 1.12 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 143.5, 140.2, 135.4, 133.3, 129.7, 128.2, 127.7, 127.4, 126.3, 75.6, 44.2, 42.8, 38.9, 32.1, 31.2, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{30}NO_3S$: 400.1941; found: 400.1957.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588803.

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(10) CCDC 1534327 (**2a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.