Tetrahedron 67 (2011) 1501–1505

Contents lists available at ScienceDirect

Tetrahedron

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

Pd(II)-catalyzed oxidative cyclization reaction for the preparation of 2-substituted 1,2,3,4-tetrahydroquinolines with halide functionality

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ARTICLE INFO

Article history:
Received 12 October 2010
Received in revised form 2 December 2010
Accepted 7 December 2010
Available online 10 December 2010

Keywords:
Oxidative cyclization reaction
Pd(II)
2-Substituted 1,2,3,4-tetrahydroquinolines
Olefinic tosylamides
Halide functionality

ABSTRACT

The first Pd(II)-catalyzed oxidative cyclization reaction was developed for preparation of 2-substituted 1,2,3,4-tetrahydroquinolines from olefinic tosylamides. Under the optimized conditions, up to 86% yield was obtained. This reaction provides direct and easy access to 2-substituted 1,2,3,4-tetrahydroquinolines with halide functionality.

1. Introduction

In recent years, considerable efforts have been prompted toward the synthesis of the 1,2,3,4-tetrahydroquinoline derivatives for their broad range of biological activities,[1] such as antibacteric[2] and fungicide.[3] Furthermore their inhibiting or antagonist properties toward specific enzymes or receptors involved in human diseases make them promising compounds in antidepressive[4] and antidiabetes[5] therapies. Besides pharmaceutical applications, they are also useful as pesticides,[6] antioxidants,[7] various types of dyes,[8] and charge-transporting agents for electrophotographic photoconductors in modern recording technologies.[9] Among these derivatives, 2-substituted 1,2,3,4-tetrahydroquinoline is the most important compound.[10] For example, oxamniquine with skeleton of 2-substituted 1,2,3,4-tetrahydroquinoline has been commonly used in therapeutics against *Schistosoma mansoni*.[11] Recently, some of these compounds have been used in finding selective estrogen receptor modulators[12] and inhibitors of the cholesteryl ester transfer protein.[13]

Many syntheses of 2-substituted 1,2,3,4-tetrahydroquinolines have been reported.[10] Pd(II)-catalyzed oxidative cyclization reaction is a powerful tool to construct nitrogen-containing heterocycles under mild conditions.[14] A landmark for this reaction was laid by Hegedus and co-workers, who obtained five-membered nitrogen-containing heterocycles with catalytic amounts of $PdCl_2(MeCN)_2$ or $PdCl_2$.[15] However, the formation of six-membered rings is difficult under the same conditions with this reaction.[15d] The approach was afterward improved by other groups for the preparation of six-membered dihydroquinolines and quinolines.[16] Recently, 3-substituted 1,2,3,4-tetrahydroquinolines were prepared with Pd(II)-catalyzed oxidative cyclization reaction in very low yields and five-membered dihydroindoles were afforded as predominant products.[17] However, the preparation of 2-substituted 1,2,3,4-tetrahydroquinolines with this reaction has not been reported so far.

Recently, we have been interested in the Pd(II)-catalyzed asymmetric oxidative cyclization reactions for the preparation of chiral five-membered dihydrobenzofurans[18] and dihydroindoles.[19] Here we report the first Pd(II)-catalyzed oxidative cyclization reaction for the preparation of 2-substituted 1,2,3,4-tetrahydroquinolines with halide functionality from olefinic tosylamides.

2. Results and discussion

As mentioned above, the 3-substituted tetrahydroquinolines had been obtained in very low yields from olefinic tosylamides with a 2-propenyl side chain.[17] So if we started from olefinic amides **1** with a 3-butenyl side chain, we anticipated that 2-substituted tetrahydroquinolines **2** may be afforded in high yields because the formation of six-membered ring (Scheme 1, path a) is generally much easier than seven-membered ring (Scheme 1, path b). Then we prepared a series of *p*-toluenesulfonamides to probe this reaction, because *p*-toluenesulfonamides could be synthesized with

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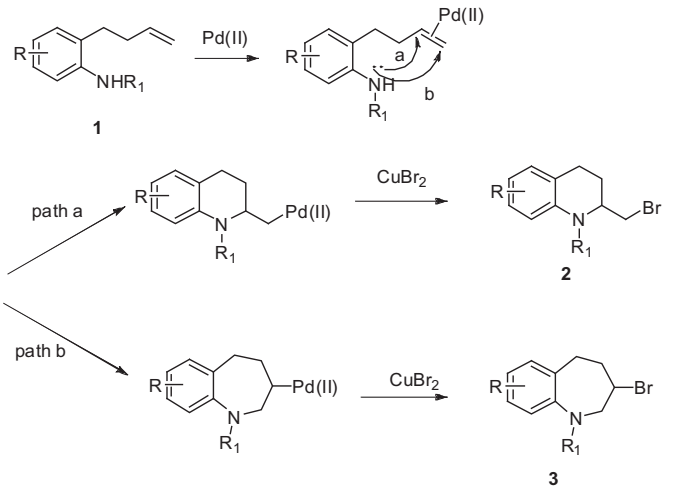
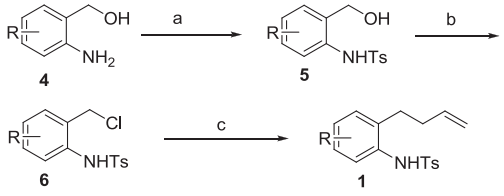
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.12.017



Scheme1. Pd(II)-catalyzed oxidative cyclization reactions.

ease from primary amines as stable crystalline solids (Scheme 2). Thus, to a solution of 2-aminobenzylalcohol **4** in dichloromethane was added 1.3 equiv of pyridine and 1.2 equiv of 4-methylbenzene-1-sulfonyl chloride, and then the reaction mixture was refluxed for 12 h. After purification, intermediate **5** was obtained. Next, 1.5 equiv of $SOCl_2$ was added slowly to the solution of **5** in dichloromethane at 0 °C and the mixture was refluxed for 12 h. After the solvent was removed in vacuo, the residue **6** was dissolved in THF, which was slowly added to a THF solution of 3.0 equiv of 3-propenyl Grignard reagent. After the mixture was stirred for 12 h, the substrates **1** were afforded with up to 89% yield from **5**.



a: R=H; **b**: R=4-CH_3; **c**: R=6-CH_3;
d: R=4-Cl; **e**: R=6-Cl; **f**: R=4-OCH_3.

Scheme 2. Reagents and conditions: (a) TsCl, pyridine, CH_2Cl_2, reflux; (b) $SOCl_2$, CH_2Cl_2, reflux; (c) 3-propenyl Grignard reagent, THF, rt.

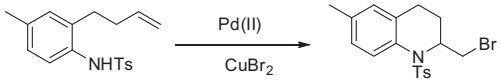
Then substrate **1b** was used in the Pd(II)-catalyzed oxidative cyclization reaction at first (Table 1). As expected, we were pleased to find that treatment of substrate **1b** with 20 mol % $Pd(OCOCF_3)_2$, K_2CO_3 (2 equiv), and $CuBr_2$ (3 equiv) in THF at 25 °C for 3 days afforded **2b** in 86% yield (entry 1), and seven-membered ring byproduct **3** was not detected. When we replaced $CuBr_2$ with $CuCl_2$, only trace product was detected.

The source of the Pd(II) profoundly affected the reaction (Table 1). It was shown that $Pd(OCOCF_3)_2$ and $Pd(OAc)_2$ were superior to $PdCl_2(MeCN)_2$ and $PdCl_2$ based on the yields (entries 1–4). Considering the price and performance, we chose inexpensive Pd $(OAc)_2$ as the catalyst.

The quantity of the $Pd(OAc)_2$ was also examined (Table 1 , entries 2, 5–9). It was shown that when the quantity of the $Pd(OAc)_2$ was decreased from 0.2 equiv to 0.05 equiv, the catalytic activities decreased sharply and the yields decreased from 85% to 34%. However, when we increased the quantity of the $Pd(OAc)_2$ from 0.2 equiv to 0.3 equiv and even to 0.4 equiv, the yields did not increase obviously.

Then, the effect of temperature on reaction was examined (Table 2). When the reaction temperature was increased from room

Table 1
The effect of Pd(II) source on the Pd(II)-catalyzed oxidative cyclization reaction[a]

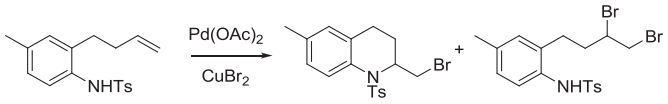


1b 2b

Entry	Pd(II)	Quantity	Time (days)	Yield[b] (%)
1	$Pd(OCOCF_3)_2$	0.2	3	86
2	$Pd(OAc)_2$	0.2	3	85
3	$PdCl_2(MeCN)_2$	0.2	3	33
4	$PdCl_2$	0.2	3	71
5	$Pd(OAc)_2$	0.05	3	34
6	$Pd(OAc)_2$	0.1	3	53
7	$Pd(OAc)_2$	0.15	3	69
8	$Pd(OAc)_2$	0.3	3	89
9	$Pd(OAc)_2$	0.4	3	89

[a] All reactions were catalyzed by Pd(II) in the presence of K_2CO_3 (2 equiv) and $CuBr_2$ (3 equiv) in THF at 25 °C.
[b] NMR yield (internal standard=ethyl acetate).

Table 2
Condition optimization for the Pd(II)-catalyzed oxidative cyclization reaction[a]



1b 2b 7b

Entry	Temp (°C)	Solvent	Additive	Time (days)	Yield[b] (%)
1	25	THF	K_2CO_3	3	85
2	45	THF	K_2CO_3	1	66
3	Reflux	THF	K_2CO_3	1	39
4	0	THF	K_2CO_3	3	Trace
5	25	THF	KOAc[c]	3	83
6	25	THF	PhCOOH[c]	3	80
7	25	THF	No additive	3	80
8	25	THF	NEt_3[c]	3	Trace
9	25	THF	Pyridine[c]	3	Trace
10	25	DMF	K_2CO_3	3	80
11	25	MeOH	K_2CO_3	3	61
12	25	MeCN	K_2CO_3	3	38

[a] All reactions were catalyzed by 20% $Pd(OAc)_2$ in the presence of additive (2 equiv) and $CuBr_2$ (3 equiv).
[b] NMR yield (internal standard=ethyl acetate).
[c] Additive (4 equiv).

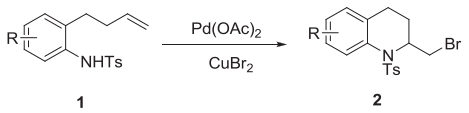
temperature to 45 °C, the yield decreased from 85% to 66%. When the reaction temperature was further increased to reflux, the yield decreased to 39% and a series of byproducts were produced (entries 1–3). However, when the temperature was decreased to 0 °C, only trace product was afforded and unreacted substrate was recovered in good yield (entry 4).

It was reported that acid and base had some effect on the Pd(II)-catalyzed oxidative cyclization reaction.[16b] Therefore, some acids and bases were selected to examine this reaction (Table 2, entries 5–9). It was shown that when using KOAc, PhCOOH or no additive, the catalytic activities as well as the yields of the reaction decreased comparing with that using K_2CO_3 (entries 1, 5–7). But when using triethylamine or pyridine, only trace products were afforded (entries 8 and 9).

The effect of solvents on the Pd(II)-catalyzed oxidative cyclization reaction was examined (Table 2, entries 1, 10–12). Compared with THF, DMF was also an efficient solvent (entry 10). When the reaction was carried out in methanol, the reaction could afford 61% yield (entry 11). However, when the reaction was carried out in MeCN, only 38% yield was obtained and a byproduct **7b** was detected in 45% yield (entry 12). Toluene, dichloromethane, diethyl ether, and ethyl acetate were also examined and only trace products were obtained.

With the optimized reaction conditions in hand, we applied this methodology to a series of olefinic tosylamides mentioned above to generalize the scope of the reaction (Table 3). It was observed that excellent yields were afforded for 4-substituted substrates in THF, regardless of electron-rich and electron-poor substrates, and **1d** with a 4-Cl group afforded the highest yield of 86% (entries 1, 2, 4, and 6). The substrate **1e** with a 6-Cl group could also afford high yield of 75% in THF (entry 5). However only 27% yield was afforded for substrate **1c** with a 6-CH_3 group in THF (entry 3). Fortunately, when this reaction was carried out in DMF, the substrate **1c** could afford up to 86% yield (entry 9). **1a**, **1b**, **1d**, and **1e** also afforded high yields in DMF (entries 7, 8, 10, and 11). It was interesting that the substrate **1f** with a 4-OCH_3 group afforded in 77% yield in THF (entry 6), however only 26% yield was given in DMF (entry 12).

Table 3
Different substrates[a]



1 2

Entry	Substrate	Solvent	Yield[b] (%)
1	**1a** (R=H)	THF	84
2	**1b** (R=4-CH_3)	THF	85
3	**1c** (R=6-CH_3)	THF	27
4	**1d** (R=4-Cl)	THF	86
5	**1e** (R=6-Cl)	THF	75
6	**1f** (R=4-OCH_3)	THF	77
7	**1a** (R=H)	DMF	75
8	**1b** (R=4-CH_3)	DMF	80
9	**1c** (R=6-CH_3)	DMF	86
10	**1d** (R=4-Cl)	DMF	83
11	**1e** (R=6-Cl)	DMF	76
12	**1f** (R=4-OCH_3)	DMF	26

[a] All reactions were catalyzed by 20% $Pd(OAc)_2$ in the presence of K_2CO_3 (2 equiv) and $CuBr_2$ (3 equiv) at 25 °C for 3 days.
[b] NMR yield (internal standard=ethyl acetate).

3. Conclusion

In summary, we have demonstrated the first Pd(II)-catalyzed oxidative cyclization reaction for the preparation of 2-substituted 1,2,3,4-tetrahydroquinolines from olefinic tosylamides. The reaction result is dependent on the Pd(II) source, reaction temperature, solvent, and the substituent of substrates. This method provides a direct access to 2-substituted 1,2,3,4-tetrahydroquinolines with halide functionality with up to 86% yield.

4. Experimental section

4.1. General

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen. DMF, MeCN, methanol, THF, ethyl acetate, Et_2O, dichloromethane, and toluene were dried according to published procedures. The commercially available reagents were used without further purification. TLC was run on 2 cm×5 cm silica plate. Column chromatography was run on silica gel (100–200 mesh). ^1H NMR (400 MHz) spectra and ^{13}C NMR (100 MHz) spectra were obtained on a Varian MERCURY plus-400 spectrometer. HRMS was performed on a Micromass LCT TM at the Instrumental Analysis Center of Shanghai Jiao Tong University.

4.2. Procedures and analytical data

*4.2.1. Preparation of the intermediates **5**.*

*4.2.1.1. N-(2-Hydroxymethyl-phenyl)-4-methyl-benzenesulfonamide (**5a**).* The 2-aminobenzylalcohol **4a** (12.3 g, 0.10 mol) was dissolved in 60 mL dichloromethane, and pyridine (10 mL, 0.13 mol) was added to the solution. Then 4-methylbenzene-1-sulfonyl chloride (22.9 g, 0.12 mol) was added and the solution was refluxed for 12 h. The solution was allowed to cool to room temperature and washed with dilute hydrochloric acid (50 mL, 1 mol/L), brine (3×50 mL) and dried over Na_2SO_4. After removal of the solvent, the residue was crystallized from CH_2Cl_2/toluene to give the intermediate **5a** (24.4 g, 88% yield). Characterization data of the compound agree with reference:[16b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.65 (d, J=8 Hz, 2H), 7.42–7.40 (m, 1H), 7.28–7.24 (m, 1H), 7.12–7.06 (m, 2H), 7.22 (d, J=8 Hz, 2H), 4.39 (s, 2H), 2.37 (s, 3H), 2.08 (s, 1H).

*4.2.1.2. N-(2-Hydroxymethyl-4-methyl-phenyl)-4-methyl-benzenesulfonamide (**5b**).* Compound **5b** was prepared from **4b** by a similar procedure with **5a** (25.3 g, 87% yield). Characterization data of the compound agree with reference:[16b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 3H), 7.26–7.19 (m, 3H), 7.04 (d, J=8 Hz, 1H), 6.93 (s, 1H), 4.33 (d, J=4 Hz, 2H), 2.39 (s, 3H), 2.27 (s, 3H), 2.05 (t, J=8 Hz, 1H).

*4.2.1.3. N-(2-Hydroxymethyl-6-methyl-phenyl)-4-methyl-benzenesulfonamide (**5c**).* Compound **5c** was prepared from **4c** by a similar procedure with **5a** (24.8 g, 85% yield). Characterization data of the compound agree with reference:[16b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=8 Hz, 2H), 7.28–7.10 (m, 5H), 6.69(s, 1H), 4.40 (d, J=6 Hz, 2H), 2.42 (s, 4H), 1.97 (s, 3H).

*4.2.1.4. N-(4-Chloro-2-hydroxymethyl-phenyl)-4-methyl-benzenesulfonamide (**5d**).* Compound **5d** was prepared from **4d** by a similar procedure with **5a** (25.9 g, 83% yield). Characterization data of the compound agree with reference:[16b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.63 (d, J=8 Hz, 2H), 7.38 (d, J=8 Hz, 1H), 7.27–7.20 (m, 3H), 7.09 (d, J=6 Hz, 1H), 4.34 (d, J=6 Hz, 2H), 2.40 (s, 3H), 2.08 (t, J=6 Hz, 1H).

*4.2.1.5. N-(6-Chloro-2-hydroxymethyl-phenyl)-4-methyl-benzenesulfonamide (**5e**).* Compound **5e** was prepared from **4e** by a similar procedure with **5a** (24.0 g, 77% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.44 (m, 3H), 7.28–7.16 (m, 4H), 6.44(s, 1H), 4.86 (d, J=8 Hz, 2H), 3.14 (t, J=8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 142.7, 135.9, 132.3, 130.8, 130.2, 129.8, 129.2, 129.1, 127.8, 62.1, 21.9; HRMS calcd for $C_{14}H_{14}ClNO_3S$ 311.0383, found 311.0386.

*4.2.1.6. N-(2-Hydroxymethyl-4-methoxyl-phenyl)-4-methyl-benzenesulfonamide (**5f**).* Compound **5f** was prepared from **4f** by a similar procedure with **5a** (28.0 g, 91% yield). Characterization data of the compound agree with reference:[20] ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J=8 Hz, 2H), 7.24–7.18 (m, 3H), 7.13 (d, J=8 Hz, 1H), 6.77–6.71 (m, 2H), 4.31 (d, J=4 Hz, 2H), 3.77 (s, 3H), 2.40 (s, 3H), 2.22 (t, J=8 Hz, 1H).

*4.2.2. Preparation of the substrates **1**.*

*4.2.2.1. N-(2-But-3-enyl-phenyl)-4-methyl-benzenesulfonamide (**1a**).* The intermediate **5a** (2.8 g, 0.010 mol) was dissolved in 20 mL dichloromethane. To this solution, $SOCl_2$ (1.1 mL, 0.015 mol) was added slowly at 0 °C and the reaction mixture was refluxed for 12 h. After the solvent was removed in vacuo, the residue **6a** was dissolved in 15 mL THF. Then the solution was slowly added to the THF solution of 3-propenyl Grignard reagent (30 mL, 1 mol/L, 0.030 mol). After the mixture was stirred for 12 h, it was quenched by the addition of cool water. The mixture was extracted with Et_2O (3×50 mL) and the combined organic layers were washed with brine (3×50 mL) and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to

afford the substrates **1a** (2.1 g, 70% yield). R_f=0.27 (10:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J=8 Hz, 2H), 7.33–7.29 (m, 1H), 7.21 (d, J=8 Hz, 2H), 7.15–7.09 (m, 3H), 6.33 (s, 1H), 5.78–5.66 (m, 1H), 4.99–4.91 (m, 2H), 2.43–2.37 (m, 5H), 2.16–2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 137.4, 136.9, 135.4, 134.2, 130.0, 129.8, 127.4, 127.2, 126.6, 125.0, 116.0, 34.0, 30.3, 21.7; HRMS calcd for $C_{17}H_{19}NO_2S$, 301.1136, found 301.1138.

*4.2.2.2. N-(2-But-3-enyl-4-methyl-phenyl)-4-methyl-benzenesulfonamide (**1b**).* Compound **1b** was prepared from **5b** by a similar procedure with **1a** (2.3 g, 73% yield). R_f=0.27 (10:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J=8 Hz, 2H), 7.22 (d, J=8 Hz, 2H), 7.13 (d, J=8 Hz, 1H), 6.95–6.91 (m, 2H), 6.20 (s, 1H), 5.77–5.66 (m, 1H), 4.99–4.92 (m, 2H), 2.41–2.34 (m, 5H), 2.28 (s, 3H), 2.14–2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 137.6, 137.0, 136.7, 136.1, 131.3, 130.7, 129.8, 127.8, 127.4, 125.8, 115.9, 34.3, 30.4, 21.7, 21.2; HRMS calcd for $C_{18}H_{21}NO_2S$, 315.1293, found 315.1294.

*4.2.2.3. N-(2-But-3-enyl-6-methyl-phenyl)-4-methyl-benzenesulfonamide (**1c**).* Compound **1c** was prepared from **5c** by a similar procedure with **1a** (1.8 g, 57% yield). R_f=0.29 (10:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J=8 Hz, 2H), 7.24 (d, J=8 Hz, 2H), 7.16–7.11 (m, 1H), 7.06–7.01 (m, 2H), 5.95 (s, 1H), 5.75–5.64 (m, 1H), 4.95–4.92 (m, 1H), 4.92–4.88 (m, 1H), 2.50–2.44 (m, 2H), 2.42 (s, 3H), 2.21–2.14 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 141.5, 138.2, 138.0, 137.9, 132.3, 129.8, 129.1, 128.2, 127.7, 127.4, 115.4, 34.6, 30.9, 21.8, 19.2; HRMS calcd for $C_{18}H_{21}NO_2S$, 315.1293, found 315.1298.

*4.2.2.4. N-(2-But-3-enyl-4-chloro-phenyl)-4-methyl-benzenesulfonamide (**1d**).* Compound **1d** was prepared from **5d** by a similar procedure with **1a** (2.9 g, 86% yield). R_f=0.24 (10:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J=8 Hz, 2H), 7.27–7.22 (m, 3H), 7.14–7.08 (m, 2H), 6.24 (s, 1H), 5.74–5.63 (m, 1H), 5.01–4.92 (m, 2H), 2.40 (s, 3H), 2.38–2.33 (m, 2H), 2.15–2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 137.8, 137.0, 136.6, 132.8, 132.1, 130.0, 129.9, 127.4, 127.2, 126.6, 116.2, 33.8, 30.2, 21.8; HRMS calcd for $C_{17}H_{18}ClNO_2S$, 335.0747, found 335.0745.

*4.2.2.5. N-(2-But-3-enyl-6-chloro-phenyl)-4-methyl-benzenesulfonamide (**1e**).* Compound **1e** was prepared from **5e** by a similar procedure with **1a** (3.0 g, 89% yield). R_f=0.19 (30:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J=8 Hz, 2H), 7.25–7.19 (m, 3H), 7.17–7.12 (m, 1H), 7.11–7.08 (m, 1H), 6.19 (s, 1H), 5.88–5.76 (m, 1H), 5.04–4.93 (m, 2H), 3.08–3.03 (m, 2H), 2.41 (s, 3H), 2.39–2.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 144.1, 137.9, 136.9, 133.1, 131.3, 129.6, 129.2, 128.7, 127.8, 127.4, 115.4, 34.5, 31.8, 21.8; HRMS calcd for $C_{17}H_{18}ClNO_2S$, 335.0747, found 335.0765.

*4.2.2.6. N-(2-But-3-enyl-4-methoxyl-phenyl)-4-methyl-benzenesulfonamide (**1f**).* The **1f** was prepared from **5f** by a similar procedure with **1a** (2.9 g, 87% yield). R_f=0.15 (10:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J=8 Hz, 2H), 7.25–7.21 (m, 2H), 7.11–7.06 (m, 1H), 6.68–6.64 (m, 2H), 6.04 (s, 1H), 5.76–5.65 (m, 1H), 4.99–4.91 (m, 2H), 3.77 (s, 3H), 2.41–2.34 (m, 5H), 2.15–2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 143.8, 139.5, 137.6, 137.0, 130.0, 128.6, 127.5, 126.6, 115.8, 115.3, 112.0, 55.5, 34.1, 30.5, 21.7; HRMS calcd for $C_{18}H_{21}NO_3S$, 331.1242, found 331.1240.

4.2.3. General procedure for Pd(II)-catalyzed oxidative cyclization reaction. Procedure a: 0.10 mmol of the substrates **1**, 0.20 mmol of potassium carbonate, and 0.30 mmol of copper bromide were suspended in 5 mL THF and the reaction mixture was stirred for 1 h at 0 °C. Then 0.02 mmol of palladium acetate was added and the mixture was stirred for 3 days at 25 °C. The mixture was filtered through SiO_2 and washed with Et_2O (3×10 mL). After removal of the solvent, the residue was purified by flash column chromatography to afford the products **2**.

Procedure b: 0.10 mmol of the substrates **1**, 0.20 mmol of potassium carbonate, and 0.30 mmol of copper bromide were suspended in 5 mL DMF and the reaction mixture was stirred for 1 h at 0 °C. Then 0.02 mmol of palladium acetate was added and the mixture was stirred for 3 days at 25 °C. The mixture was diluted with water (10 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (3×5 mL) and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to afford the products **2**.

*4.2.3.1. 2-Bromethyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline (**2a**).* Yield 84% (procedure a); R_f=0.24 (50:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J=8 Hz, 1H), 7.32 (d, J=8 Hz, 2H), 7.27–7.22 (m, 1H), 7.17–7.10 (m, 3H), 6.96 (d, J=8 Hz, 1H), 4.40–4.31 (m, 1H), 3.75–3.71 (m, 1H), 3.40–3.34 (m, 1H), 2.37 (s, 3H), 2.32–2.24 (m, 1H), 2.22–2.12 (m, 1H), 1.62–1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 135.6, 135.3, 134.9, 129.7, 128.1, 127.7, 127.3, 127.2, 126.5, 57.0, 36.5, 28.9, 25.2, 21.8; HRMS calcd for $C_{17}H_{18}BrNO_2S$, 379.0242, found 379.0237.

*4.2.3.2. 2-Bromethyl-6-methyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline (**2b**).* Yield 85% (procedure a); R_f=0.17 (30:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=8 Hz, 1H), 7.33 (d, J=8 Hz, 2H), 7.17 (d, J=8 Hz, 2H), 7.07–7.03 (m, 1H), 6.77 (s, 1H), 4.36–4.28 (m, 1H), 3.75–3.71 (m, 1H), 3.38–3.32 (m, 1H), 2.38 (s, 3H), 2.30 (s, 3H), 2.26–2.19 (m, 1H), 2.18–2.10 (m, 1H), 1.59–1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 136.3, 135.6, 134.7, 132.7, 129.7, 128.4, 128.0, 127.9, 127.3, 56.9, 36.6, 29.0, 25.1, 21.8, 21.2; HRMS calcd for $C_{18}H_{20}BrNO_2S$ 393.0398, found 393.0392.

*4.2.3.3. 2-Bromethyl-8-methyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline (**2c**).* Yield 86% (procedure b); R_f=0.24 (50:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J=8 Hz, 2H), 7.26–7.15 (m, 3H), 7.10 (t, J=8 Hz, 1H), 6.80 (d, J=8 Hz, 1H), 4.40–4.31 (m, 1H), 3.69–3.63 (m, 1H), 3.36–3.29 (m, 1H), 2.53 (s, 3H), 2.42 (s, 3H), 2.30–2.22 (m, 1H), 2.10–2.03 (m, 1H), 1.34–1.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 139.6, 139.2, 136.0, 134.4, 130.2, 129.8, 127.9, 127.3, 124.9, 57.5, 37.3, 31.0, 26.4, 21.8, 19.8; HRMS calcd for $C_{18}H_{20}BrNO_2S$ 393.0398, found 393.0379.

*4.2.3.4. 2-Bromethyl-6-chloro-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline (**2d**).* Yield 86% (procedure a); R_f=0.24 (50:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8 Hz, 1H), 7.35 (d, J=8 Hz, 2H), 7.24–7.17 (m, 3H), 6.97–6.95 (m, 1H), 4.39–4.31 (m, 1H), 3.72–3.67 (m, 1H), 3.41–3.35 (m, 1H), 2.39 (s, 3H), 2.30–2.22 (m, 1H), 2.17–2.08 (m, 1H), 1.64–1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 136.4, 135.3, 134.1, 131.9, 129.9, 129.3, 127.7, 127.5, 127.3, 56.8, 36.3, 28.5, 25.0, 21.8; HRMS calcd for $C_{17}H_{17}BrClNO_2S$, 412.9852, found 412.9850.

*4.2.3.5. 2-Bromethyl-8-chloro-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline (**2e**).* Yield 76% (procedure b); R_f=0.17 (30:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J=8 Hz, 2H), 7.37 (d, J=8 Hz, 1H), 7.27 (d, J=8 Hz, 2H), 7.14 (t, J=8 Hz, 1H), 6.96 (d, J=8 Hz, 1H), 4.42–4.32 (m, 1H), 3.59–3.53 (m, 1H), 3.20–3.13 (m, 1H), 2.45–2.36 (m, 4H), 2.26–2.20 (m, 1H), 1.70–1.60 (m, 1H), 1.41–1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 141.6, 136.1, 135.1, 133.4, 130.0, 129.4, 128.4, 128.2, 126.0, 57.1, 36.5, 31.1, 26.7, 21.8; HRMS calcd for $C_{17}H_{17}BrClNO_2S$, 412.9852, found 412.9823.

*4.2.3.6. 2-Bromethyl-6-methoxyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline (**2f**).* Yield 77% (procedure a); R_f=0.17 (30:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J=8 Hz, 1H), 7.31 (d, J=8 Hz, 2H), 7.16 (d, J=8 Hz, 2H), 6.81–6.76 (m, 1H), 6.51–6.48 (m, 1H), 4.33–4.25 (m, 1H), 3.78 (s, 3H), 3.74–3.69 (m, 1H), 3.38–3.32 (m, 1H), 2.38 (s, 3H), 2.24–2.12 (m, 2H), 1.54–1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 143.9, 136.8, 135.4, 129.7, 129.5, 128.1, 127.3, 113.0, 112.2, 56.9, 55.6, 36.7, 29.2, 25.6, 21.8; HRMS calcd for $C_{18}H_{20}BrNO_3S$, 409.0347, found 409.0352.

*4.2.3.7. N-(2-But-3,4-dibromo-4-methyl-phenyl)-4-methyl-benzenesulfonamide (**7b**).* Yield 45%; R_f=0.15 (50:1 petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J=8 Hz, 2H), 7.23 (d, J=8 Hz, 2H), 7.12 (d, J=8 Hz, 1H), 6.97–6.94 (m, 2H), 6.30 (s, 1H), 4.10–4.02 (m, 1H), 3.83–3.78 (m, 1H), 3.59–3.53 (m, 1H), 2.60–2.52 (m, 1H), 2.50–2.43 (m, 1H), 2.40 (s, 3H), 2.28 (s, 3H), 2.26–2.17 (m, 1H), 1.89–1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 137.1, 136.8, 135.0, 131.5, 130.7, 129.8, 128.3, 127.5, 126.2, 52.2, 36.7, 36.0, 28.0, 21.8, 21.2; HRMS calcd for $C_{18}H_{21}Br_2NO_2S$, 472.9660, found 472.9662.

Acknowledgements

This work was supported by the National Nature Science Foundation of China (No. 20772081), Science and Technology Commission of Shanghai Municipality (No. 09JC1407800), and Nippon Chemical Industrial Co., Ltd. We thank Professor T. Imamoto and Dr. M. Sugiya for the helpful discussion and Instrumental Analysis Center of Shanghai Jiao Tong University for HRMS analysis.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.017.

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