Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 64 (2008) 248–254
www.elsevier.com/locate/tet

Intramolecular palladium-catalyzed cyclization of alkenylboronate prepared from hydroboration of terminal acetylene and its application to the stereoselective synthesis of (*E*)-doxepin

Cuihua Xue, Shi-Hao Kung, Jian-Zhung Wu, Fen-Tair Luo*

Institute of Chemistry, Academia Sinica, Nankang, Taipei 11529, Taiwan, ROC

Received 26 July 2007; received in revised form 12 September 2007; accepted 14 September 2007
Available online 22 October 2007

Abstract

The hydroboration of 2-[(2-ethynylphenyl)methoxy]-1-iodobenzene with bis(pinacolato)diboron in the presence of palladium catalyst and followed by consecutive oxidative addition, cis-cyclocarbopalladation, and cis-β-elimination could give highly stereoselective exocyclic alkenylboronate ester. The following cross-coupling of the exocyclic alkenylboronate ester with 2-bromo-*N*,*N*-dimethylacetamide in the presence of palladium catalyst and followed by LAH reduction gives (*E*)-doxepin in fair yields.

1. Introduction

Palladium-catalyzed reactions have steadily increased in importance in the last decade. They are among the most versatile processes for forming carbon–carbon bonds. A vast range of such methods are known, which usually feature a high tolerance of many functional groups as well as a high regio- and stereoselectivities.[1] In order to improve the efficiency in increasing complexity and selectivity in product formation of such reactions, many papers have reported the design of multiple transformations in consecutive or cascade or domino types of reactions in a one pot without isolating any of the intermediates.[1,2] Thus, the domino processes are becoming more popular nowadays. Recently, we have reported a facile Suzuki-type cross-coupling reaction of alkenylborane with 2-bromo-*N*,*N*-dimethylacetamide as a convenient way for the synthesis of (*E*)-β,γ-unsaturated amides.[3] We also reported previously that the alkenylpalladium(II) intermediate generated by intramolecular cyclic carbopalladation of alkynes can be further cross-coupled with trapping reagents to recycle the Pd(0) catalyst and give stereodefined exocyclic carbon–carbon double bond.[4] With this in mind, we envisioned that a substrate of 2-[(2-ethynylphenyl)methoxy]-1-iodobenzene **1** would undergo oxidative addition and intramolecular cyclocarbopalladation,[4,5] then the incipient exocyclic alkenylpalladium intermediate may undergo cross-coupling reaction with 2-bromo-*N*,*N*-dimethylacetamide, and if successful this methodology might allow us stereoselective access to the domino-type synthesis of (*Z*)-β,γ-unsaturated amide. However, we failed to get any detectable amount of the desired products under various reaction conditions; instead, a mixture of unidentified products was obtained as judged by their crude ^{1}H NMR spectral analysis. We then turned our attention to the trapping of the expected alkenylpalladium intermediate with bis(pinacolato)diboron as similarly reported by Miyaura.[6] To the best of our knowledge, the challenging seven-membered ring formation through the palladium-catalyzed cyclocarbopalladation is still very rare.[5a,b,d,7] Herein, we report the novel domino-type reaction of hydroboration and the following intramolecular cyclic carbopalladation by using aryl iodide with terminal acetylene **1** and bis(pinacolato)diboron in the presence of palladium catalyst and the identification of the corresponding stereoselective alkenylboronates by their

* Corresponding author.
E-mail address: luoft@chem.sinica.edu.tw (F.-T. Luo).

0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.085

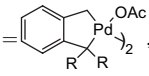
HRMS, 2D-COSY, NOESY, HMQC, and HMBC spectral analyses, as well as the application to the stereoselective synthesis of (*E*)-doxepin[8] as an antidepressant drug.[9]

2. Results and discussion

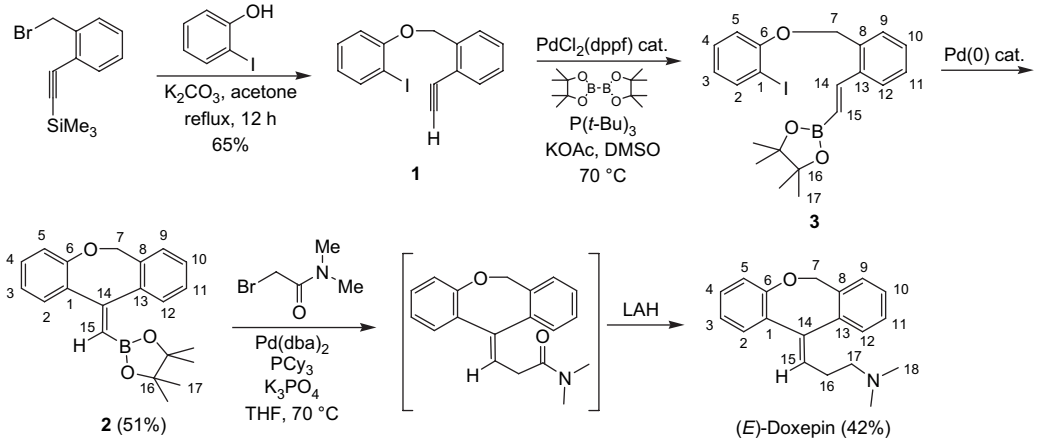
The results of the consecutive Pd-catalyzed hydroboration and intramolecular cyclic carbopalladation of **1** by using bis-(pinacolato)diboron are summarized in Scheme 1 and Table 1. Initially, in order to test the trapping ability of bis(pinacolato)diboron for the attempted cyclized exocyclic alkenylpalladium intermediate obtained from the oxidative addition and the following intramolecular carbopalladation of **1**, prepared from 2-iodobenzyl alcohol via Sonogashira reaction [trimethylsilylacetylene, CuI, $PdCl_2(PPh_3)_2$], bromination (PBr_3), and Williamson ether synthesis (2-iodophenol, potassium carbonate)[10] (Scheme 1), compound **1** was treated with bis(pinacolato)diboron (1.1 equiv) in the presence of $PdCl_2$(dppf) (5 mol %) and potassium acetate (3 equiv) in DMSO at 80 °C for 4 h.[6] The reaction temperature was finally optimized at 70 °C. Either lower or higher than 70 °C will give lower yields of the isolated products. Interestingly, in contrast to our original prediction of obtaining the exocyclic (*Z*)-alkenylboronate ester, we found that only exocyclic (*E*)-alkenylboronate ester **2** in 12% yield along with 25% yield of uncyclized hydroboration product **3** and unidentified polymerized products were obtained (entry 1, Table 1). The yield of uncyclized hydroboration product **3** can reach up to 70% if the reaction is quenched after half an hour. This result indicated that **3** was the reaction intermediate for the formation of **2**. Attempts to use K_3PO_4, K_2CO_3, $Ba(OH)_2$, NEt_3, $^iPrNEt_2$, CsF,[11] KF,[11] or Cs_2CO_3 as the base did not provide any improvement in the yields. Adding either cuprous halides or Cu_2O[12] did not improve the yields. No reaction was observed and the starting material **1** was isolated almost completely when the reaction was run in the absence of palladium catalyst (entry 2, Table 1). The structures of **2** and **3** were confirmed according to their ^1H, ^{13}C NMR, as well as their 2D-COSY, NOESY, HMQC, HMBC, NMR, HRMS, and EI-GC–MS (at 25 eV) spectral analysis

Table 1
Effects of Pd catalysts and ligands in the formation of **2** from **1**[a]

Entry	Pd catalyst	Ligand	Isolated yield of **2**[b] (%)
1	$PdCl_2$(dppf)	—	12[c]
2	—	—	0
3	Palladacycle[d]	—	10
4	$Pd(OAc)_2$	—	<5
5	$Pd(PPh_3)_4$	—	<5
6	$PdCl_2(PPh_3)_2$	—	<5
7	$Pd(dba)_2$	—	<5
8	$PdCl_2$(dppf)	P(*t*-Bu)$_3$	51
9	Palladacycle	P(*t*-Bu)$_3$	42
10	$Pd(OAc)_2$	P(*t*-Bu)$_3$	16
11	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	29
12	$PdCl_2(PPh_3)_2$	P(*t*-Bu)$_3$	23
13	$Pd(dba)_2$	P(*t*-Bu)$_3$	32
14	$PdCl_2$(dppf)	PPh_3	24
15	$PdCl_2$(dppf)	P(*o*-tol)$_3$	37
16	$PdCl_2$(dppf)	PCy_3	41

[a] The reaction was run with KOAc and bis(pinacolato)diboron in DMSO at 70 °C.
[b] The major byproducts were unidentified polymers.
[c] Compound **3** was isolated in 25% yield.
[d] Palladacycle =  , R=*o*-tolyl.

(Tables 2 and 3). The stereochemistry of the hydroboration of the terminal acetylene to form the carbon–carbon double bond in **3** was proved by its ^1H NMR spectral analysis (the coupling constant between the two vinylic protons H-14 and H-15 is 18 Hz). It is also interesting to observe that there are cross-peaks between H-12 and H-15, and between H-7 and H-5, H-9, H-14, H-15, H-17 in 2D NOESY spectrum of **3**. Calculations from molecular modeling (Spartan'04) showed that the distances between H-7 and H-5, H-9, H-14, H-15, and H-17 in **3** are 2.246 Å, 3.440 Å, 2.789 Å, 2.938 Å, and 2.715 Å, respectively (Molecular Mechanics//MMFF). The molecular ion of **3** in the EI-GC–MS spectrum can be observed at 25 eV. Electron voltages at 70, 30, and 20 or lower than 20 do not show a detectable amount of molecular ion in the EI-GC–MS spectrum. The stereochemistry of the exocyclic double bond in **2** was proved by its 2D NOESY NMR spectral analysis (there is a cross-peak



Scheme 1. Synthesis of (*E*)-alkenylboronates and (*E*)-doxepin and the corresponding number for the carbon atoms in **2**, **3**, and (*E*)-doxepin.

Table 2
^{1}H and ^{13}C NMR spectral data, HMBC, NOESY, and COSY correlations for **3**

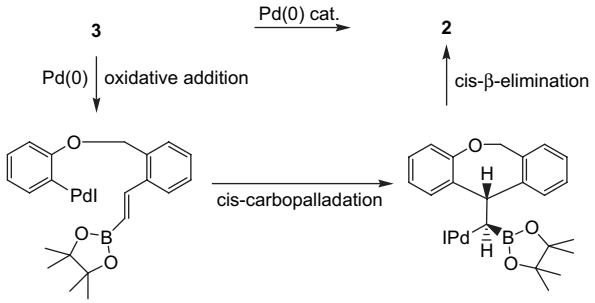
Position	H (ppm)	C (ppm)	HMBC correlation (H→C)	NOESY (H→H)	COSY (H→H)
1	—	86.86			
2	7.79 (d)	139.51	C-4, C-13		H-3
3	6.73 (t)	122.87	C-5, C-1	H-4	H-2, H-4
4	7.28 (t)	129.35	C-2, C-13	H-3, H-5	H-3, H-5
5	6.90 (d)	113.13	C-3, C-1	H-7, H-4	H-4
6	—	134.01			
7	5.28 (s)	68.77	C-9, C-6, C-8, C-13	H-5, H-9, H-14, H-15, H-17	
8	—	136.04			
9	7.61 (d)	127.89	C-10, C-6	H-7, H-10	H-10
10	7.3–7.4 (m)	128.08		H-9	H-9, H-11
11	7.3–7.4 (m)	128.76		H-12	H-10, H-12
12	7.61 (d)	126.28	C-11	H-11, H-15	H-11
13	—	157.34			
14	7.65 (d)	145.64	C-12, C-8	H-7	H-15
15	6.13 (d)	120.00	C-14, C-8	H-12	H-14
16	—	83.41			
17	1.31 (s)	24.80	C-16		

between H-2 and H-15). It is also interesting to observe that there are cross-peaks between H-7 and H-5, H-9, H-15, H-17 in the 2D NOESY spectrum of **2**. Calculations from molecular modeling (Spartan'04) showed that the distances between H-7 and H-5, H-9, H-15, and H-17 in **2** are 4.270 Å, 2.413 Å, 3.800 Å, and 3.263 Å, respectively (Molecular Mechanics// MMFF). This result showed that the highly stereoselective formation of **2** plausibly took place through the oxidative addition, cis-cyclocarbopalladation, and cis-β-elimination of **3** in the presence of palladium catalyst (Scheme 2). These results indicated that the coupling product initially went through the hydroboration of terminal acetylene and followed by the intramolecular cyclocarbopalladation. In other words, under these reaction conditions, the oxidative addition of **1** is slower than the hydroboration of **1** in the presence of palladium catalyst.

We then tried to study the above reaction by using different palladium catalysts or in the presence of ligands as commonly reported in the literature.[11,13] Changing the palladium catalyst from $PdCl_2$(dppf), to palladacycle, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or $Pd(dba)_2$, while used potassium acetate as the base and DMSO as the solvent did not greatly improve the yields (entries 3–7, Table 1). The major byproducts were the unidentified polymers. However, we found that the addition of the sterically hindered chelating phosphine ligand, P(*t*-Bu)$_3$, furnished good yield in the above reactions to afford up to 51% yield of the desired product by using $PdCl_2$(dppf) as the catalyst (entries 8–13, Table 1). Thus, $PdCl_2$(dppf) seems to be superior to other palladium catalysts in the above reactions. Furthermore, using other ligands such as PPh_3, P(*o*-tol)$_3$, or PCy_3 produced somewhat lower yields than when using $PdCl_2$(dppf) as the catalyst (entries 14–16, Table 1). It was noted that attempts to run the hydroboration by the use of pinacolboronate and $Rh(PPh_3)_3Cl$, $Rh(CO)CPPh_3)_2Cl$, or $NiCpPPh_3Cl$ as the catalyst as described by Srebnik[14] to run the hydroboration of **1** were failed. The hydroboration for

Table 3
^{1}H and ^{13}C NMR spectral data, HMBC, NOESY, and COSY correlations for **2**

Position	H (ppm)	C (ppm)	HMBC correlation (H→C)	NOESY (H→H)	COSY (H→H)
1	—	124.18			
2	7.01 (d)	132.62	C-15, C-4	H-3, H-15	H-3
3	6.77 (t)	120.05	C-5, C-1	H-4, H-2	H-2, H-4
4	7.00 (t)	128.88	C-2		H-3, H-5
5	6.79 (d)	120.45	C-3		H-4
6	—	154.80			
7	5.35 (s)	70.41	C-9, C-6, C-13	H-5, H-9, H-15, H-17	
8	—	141.61			
9	7.44 (d)	130.74	C-11, C-13	H-7	H-10
10	7.22 (t)	127.09			H-9, H-11
11	7.30 (t)	128.32			H-10, H-12
12	7.28 (d)	129.25			H-11
13	—	134.22			
14	—	181.51			
15	7.50 (s)	145.39	C-2, C-6, C-13	H-2, H-17	
16	—	83.95			
17	1.33 (s)	24.80	C-16	H-7, H-12, H-15	



Scheme 2. The plausible reaction pathway for the formation of **2** from **3**.

ortho-substituted phenylacetylene as **1** by using bis(pinacolato)diboron and copper reagent (CuCl/KOAc/PBu_3 or CuCl/KOAc/LiCl) reported by Miyaura was also failed to give any detectable amount of the desired product.[15] Thus, as to our best knowledge, this is the first example to the success of the hydroboration for *ortho*-substituted phenylacetylene by using bis(pinacolato)diboron in the presence of palladium catalyst.

The synthesis of (*E*)-doxepin is shown in Scheme 1. Thus, treatment of **2** with 2-bromo-*N*,*N*-dimethylacetamide[16] in the presence of a catalytic amount of tricyclohexylphosphine, $Pd(dba)_2$, and K_3PO_4 in THF at 70 °C could give β,γ-unsaturated amide.[3] The β,γ-unsaturated amide seemed to be very unstable at room temperature. The following LAH reduction of the β,γ-unsaturated amide in THF could give (*E*)-doxepin in 42% total yield. The structure of (*E*)-doxepin was proved by its GC–MS, ^1H, and ^{13}C NMR, as well as by its low temperature ^1H NMR (Fig. 1) and 2D NOESY spectral analysis (Table 4). Since the signals for two protons at C-7 in (*E*)-doxepin were broad singlets at δ 4.72 ppm and 5.50 ppm by the ring flexibility[17] of the tricyclic compound at room temperature they became two doublets in the ^1H NMR spectrum at 0 °C and became well separated at 223 K or lower temperature (Fig. 1). It is interesting to note that while (*E*)-doxepin shows ring flexibility in its seven-membered ring at room temperature, compound **2** with a seven-membered ring in the structure and with two protons at C-7 appearing at δ 5.35 ppm as a singlet did not show ring flexibility at room temperature. The detailed mechanism for the hydroboration of the terminal acetylene in **1** by using bis(pinacolato)diboron in the presence of palladium catalyst and tri(*tert*-butyl)phosphine in DMSO to give **3** is still under investigation in our laboratory.

3. Conclusion

In conclusion, we have succeeded in the synthesis of (*E*)-doxepin via the hydroboration of **1** with bis(pinacolato)diboron in the presence of palladium catalyst. The following consecutive oxidative addition, cis-cyclocarbopalladation, and cis-β-elimination in the presence of palladium catalyst could give highly stereoselective exocyclic alkenylboronate

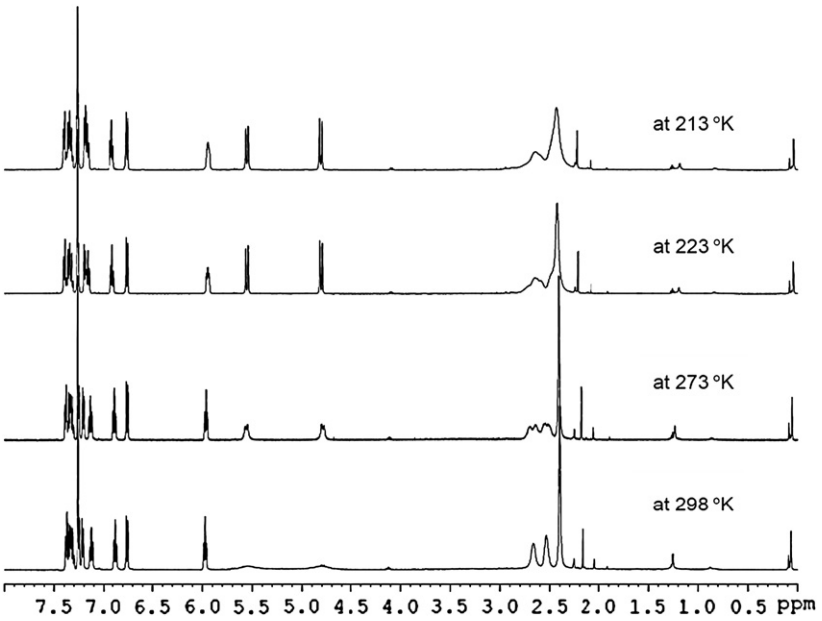


Figure 1. The ^1H NMR spectra of (*E*)-doxepin at various temperatures.

Table 4
^{1}H and ^{13}C NMR spectral data, HMBC, NOESY, and COSY correlations for (*E*)-doxepin

Position	H (ppm)	C (ppm)	HMBC correlation (H→C)	NOESY (H→H)	COSY (H→H)
1	—	127.20			
2	7.20 (d)	130.27	C-4, C-6	H-3, H-15	H-3
3	6.85 (t)	121.23	C-1	H-2, H-4, H-5	H-2, H-4
4	7.10 (t)	129.39	C-2, C-6	H-2, H-3, H-5	H-3, H-5
5	6.73 (d)	119.39		H-3, H-4	H-4
6	—	155.29			
7	4.72 (br s), 5.50 (br s)	70.24			
8	—	141.26			
9	7.33 (t)	128.85	C-8, C-11		H-10
10	7.28 (t)	128.18			H-9, H-11
11	7.31 (d)	128.46			H-10, H-12
12	7.24 (d)	127.90	C-11	H-16, H-17	H-11
13	—	134.43			
14	—	141.04			
15	5.97 (t)	128.30	C-1, C-14	H-2, H-16, H-17	H-16
16	2.40 (m)	26.96		H-12, H-15, H-17, H-18	H-15, H-17
17	2.50 (m)	58.82		H-12, H-15, H-18	H-16
18		44.75		H-16, H-17	

ester **2**. The following sequential cross-coupling of **2** with 2-bromo-*N*,*N*-dimethylacetamide in the presence of palladium catalyst and the LAH reduction of the β,γ-unsaturated amide intermediate could give (*E*)-doxepin in fair yields.

4. Experimental section

4.1. General experimental

All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran (THF) was treated with dried NaH first and then distilled over sodium/benzophenone ketyl whenever needed. All organic extracts were dried over anhydrous magnesium sulfate. TLC was done on aluminum sheets with precoated silica gel 60 F_{254} (40×80 mm) from Merck. Purification by column chromatography was carried out with neutral silica gel 60 (70–230 mesh ASTM). The purity of each compound was judged to be >95% by ^{1}H NMR or ^{13}C NMR spectral analyses. Melting points were taken on a MEL-TEMP capillary tube apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on 300 MHz, 400 MHz, or 500 MHz instrument using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards. HRMS spectra were collected on an Autospec orthogonal acceleration time-of-flight mass spectrometer with a resolution of 6000 (5% valley definition), and fitted with a magnet bypass flight tube. MALDI-MS spectra were collected on spectrometer equipped with a nitrogen laser (337 nm) and operated in the delayed extraction reflector mode. EIMS spectra were determined on a Shimadzu QP-1000 spectrometer or Fisons MD800 GC/MS, Focus GC/DSQ, or VG 70-250S spectrometer.

4.1.1. 2-[(Trimethylsilyl)ethynyl]benzyl alcohol[18]

To a solution of 2-iodobenzyl alcohol (4.68 g, 20 mmol), $PdCl_2(PPh_3)_2$ (0.42 g, 0.6 mmol), CuI (0.11 g, 0.6 mmol), and benzene (15 mL) under nitrogen atmosphere was added dropwise trimethylsilylacetylene (3.0 mL, 22 mmol) at room temperature. The color of the solution would turn from pale yellow to dark brown when trimethylsilylacetylene was added in excess. The mixture was stirred for another half an hour at room temperature. The volatile material was removed by rotavap and to the residue was added water (25 mL). The aqueous layer was extracted with ethyl acetate (30 mL×3) and the combined organic layer was dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate=5:1) to afford 2-[(trimethylsilyl)ethynyl]benzyl alcohol (3.88 g, 19 mmol) as an brown oil in 95% yield: ^{1}H NMR ($CDCl_3$, TMS) δ 0.27 (s, 9H), 4.82 (s, 2H), 7.24 (t, *J*=7 Hz, 1H), 7.33 (t, *J*=7 Hz, 1H), 7.41 (d, *J*=7 Hz, 1H), 7.46 (d, *J*=7 Hz, 1H) ppm.

4.1.2. 2-[(Trimethylsilyl)ethynyl]benzyl bromide[18d]

To a solution of 2-[(trimethylsilyl)ethynyl]benzyl alcohol (1.84 g, 9 mmol), pyridine (1.0 mL, 12.4 mmol), and chloroform (10 mL) under nitrogen atmosphere was added dropwise PBr_3 (1.0 mL, 10 mmol) at 0 °C and the resulting mixture was warmed to room temperature with stirring for 12 h. The volatile material was removed by rotavap and to the residue was added water (15 mL). The aqueous layer was extracted with ethyl acetate (20 mL×3) and the combined organic layer was dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/ethyl acetate=20:1) to afford the title compound (1.68 g, 6.3 mmol) as an orange oil in 70% yield: ^{1}H NMR ($CDCl_3$, TMS) δ 0.29 (s, 9H), 4.66 (s, 2H), 7.29 (dt, *J*=7.5, 1.5 Hz, 1H), 7.34 (dt, *J*=7.5, 1.5 Hz, 1H), 7.45 (dd, *J*=7.5, 1.5 Hz, 1H), 7.51 (dd, *J*=7.5, 1.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ −0.17, 31.75, 100.71, 101.90, 123.01, 128.30, 128.94, 129.58, 132.62, 139.66 ppm; MS *m/z* 268, 266 (M^+), 251, 187, 171, 129; HRMS calcd for $C_{12}H_{15}BrSi$ 266.0126, found 266.0131.

4.1.3. 2-{[2-(3,3-Dimethyl-3-silabut-1-ynyl)-phenyl]methoxy}-1-iodobenzene

^{1}H NMR ($CDCl_3$, TMS) δ 0.25 (s, 9H), 5.29 (s, 2H), 6.67 (t, J=7.5 Hz, 1H), 6.83 (d, J=8 Hz, 1H), 7.22 (t, J=8 Hz, 1H), 7.25 (t, J=8 Hz, 1H), 7.34 (t, J=7.5 Hz, 1H), 7.47 (d, J=7.5 Hz, 1H), 7.67 (d, J=7.5 Hz, 1H), 7.77 (d, J=7.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 0.22, 69.08, 86.83, 100.37, 102.35, 112.61, 121.11, 122.95, 127.19, 127.60, 129.16, 129.65, 132.27, 138.85, 139.73, 157.28 ppm; MS *m/z* 406 (M^+), 264, 249, 219, 187, 159; HRMS calcd for $C_{18}H_{19}OISi$ 406.0250, found 406.0248.

*4.1.4. 2-[(2-Ethynylphenyl)methoxy]-1-iodobenzene (**1**)*

To a solution of 2-iodophenol (1.10 g, 5 mmol), K_2CO_3 (0.81 g, 5.9 mmol) in acetone (10 mL) under nitrogen atmosphere was added dropwise a solution of 2-[(trimethylsilyl)-ethynyl]benzyl bromide[18] (1.20 g, 4.5 mmol) in 5 mL of acetone at room temperature and the resulting mixture was refluxed with stirring for another 12 h. The volatile material was removed by rotavap and the residue was recrystallized via methanol to afford the title compound (1.09 g, 3.3 mmol) as a white solid in 65% yield: mp 58–60 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 3.39 (s, 1H), 5.36 (s, 2H), 6.74 (t, J=7 Hz, 1H), 6.90 (d, J=7 Hz, 1H), 7.30 (t, J=7 Hz, 2H), 7.43 (t, J=7 Hz, 1H), 7.54 (d, J=7 Hz, 1H), 7.80 (d, J=7 Hz, 1H), 7.83 (d, J=7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 68.75, 80.79, 82.66, 86.60, 112.64, 119.60, 122.83, 126.94, 127.39, 129.27, 129.44, 132.53, 138.90, 139.52, 156.98 ppm; MS *m/z* 334 (M^+), 207, 115; HRMS calcd for $C_{15}H_{11}OI$ 333.9855, found 333.9853. Anal. Calcd for $C_{15}H_{11}OI$: C, 53.92; H, 3.32. Found: C, 53.85; H, 3.37.

*4.1.5. 2-({2-[(1E)-2-(4,4,5,5-Tetramethyl(1,3,2-dioxaborolan-2-yl))vinyl]phenyl}methoxy)-1-iodobenzene (**3**)*

To a pre-heated solution of bis(pinacolato)diboron (1.02 g, 4 mmol) and potassium acetate (0.39 g, 5 mmol) in DMSO (20 mL) under nitrogen atmosphere in 100 mL of two-necked round-bottomed flask at 70 °C was dropwise added a solution of $PdCl_2$(dppf) (dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II)) (22 mg, 0.03 mmol) and P(*t*-Bu)$_3$ (12 mg, 0.06 mmol) in 10 mL of DMSO and followed by the addition of a solution of 2-[(2-ethynylphenyl)methoxy]-1-iodobenzene **1** (0.67 g, 2 mmol) in 7 mL of DMSO and keep stirring for another half an hour at 70 °C. The above reaction mixture was dropwise added into a stirring solution of ethyl acetate (100 mL) and water (100 mL) at 0 °C. After stirring for another 10 min, the organic layer was separated, drying over magnesium sulfate, filtrated, and concentrated at lower pressure. The residue was purified by column chromatography (hexane/ethyl acetate=50:1) to afford the title compound (0.65 g, 1.4 mmol) as a pale yellow solid in 70% yield: mp 47–49 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.31 (s, 12H), 5.28 (s, 2H), 6.13 (d, J=18 Hz, 1H), 6.73 (t, J=8 Hz, 1H), 6.90 (d, J=8 Hz, 1H), 7.28 (t, J=8 Hz, 1H), 7.30–7.36 (m, 2H), 7.61 (d, J=8 Hz, 2H), 7.65 (d, J=18 Hz, 1H), 7.79 (d, J=8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 24.80, 68.77, 83.41, 86.86, 113.13, 120.00, 122.87, 126.28, 127.89, 128.08, 128.76, 129.35, 134.01, 136.04, 139.51, 145.64, 157.13 ppm; EI-GC–MS (25 eV) *m/z* 462 (M^+), 461, 447, 401, 327, 243, 207; HRMS calcd for $C_{21}H_{23}O_3BI$ 461.0785, found 461.0781.

*4.1.6. 2-(6H-Dibenzo[c,f]oxepan-11-ylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**)*

The procedure was similar to that for the preparation of **3** except stirring the reaction for another 3 h after dropwise adding all the chemicals at 70 °C. The above reaction mixture was quenched by dropwise adding water at 0 °C and followed by adding ethyl acetate. The organic layer was separated, drying over magnesium sulfate, filtrated, and concentrated at lower pressure. The residue was purified by column chromatography (hexane/ethyl acetate=30:1) to afford the title compound (0.34 g, 1.0 mmol) as a white solid in 51% yield: mp 43–45 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.33 (s, 12H), 5.35 (s, 2H), 6.77 (t, J=7 Hz, 1H), 6.79 (d, J=7 Hz, 1H), 7.00 (t, J=7 Hz, 1H), 7.01 (d, J=7 Hz, 1H), 7.22 (t, J=7 Hz, 1H), 7.28 (d, J=7 Hz, 1H), 7.30 (t, J=7 Hz, 1H), 7.44 (d, J=7 Hz, 1H), 7.50 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 24.80, 70.41, 83.95, 120.05, 120.45, 124.18, 127.09, 128.32, 128.88, 129.25, 130.74, 132.62, 134.22, 141.61, 145.39, 154.80, 181.51 ppm; EI-GC–MS (25 eV) *m/z* 334 (M^+), 234, 233, 215; HRMS calcd for $C_{21}H_{23}O_3B$ 334.1740, found 334.1742.

4.1.7. (E)-Doxepin

To a mixture of Pd(dba)$_2$ (29 mg, 0.05 mmol), PCy_3 (28 mg, 0.1 mmol), K_3PO_4 (1.28 g, 6 mmol) in 10 mL of dry THF was added 2-bromo-*N*,*N*-dimethylacetamide[16] (0.25 g, 1.5 mmol) at 70 °C. After stirring for 20 min, the alkenylboronate **2** (0.33 g, 1 mmol) in 5 mL of THF was added and the mixture was stirred for another 16 h at 70 °C. The mixture was quenched with water, extracted with EtOAc, and purified by flash column chromatography (hexane/EtOAc=2:1). After removing the volatile solvents and without further purification of the residue, the crude amide (0.23 g, 0.78 mmol), $LiAlH_4$ (0.11 g, 3 mmol), and THF (10 mL) were stirred for 48 h at room temperature. The mixture was treated with AcOEt (1 mL) and 10% NaOH (2 mL) and then extracted with ether (10 mL×3). The extraction layers were combined and dried over $MgSO_4$ and concentrated to give 0.12 g (42%) of (*E*)-doxepin as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 2.26 (s, 6H), 2.35–2.45 (m, 2H), 2.45–2.55 (m, 2H), 4.72 (br s, 1H), 5.50 (br s, 1H), 5.97 (t, J=7 Hz, 1H), 6.73 (d, J=7 Hz, 1H), 6.85 (t, J=7 Hz, 1H), 7.10 (t, J=7 Hz, 1H), 7.20 (d, J=7 Hz, 1H), 7.24 (d, J=7 Hz, 1H), 7.28 (t, J=7 Hz, 1H), 7.31 (t, J=7 Hz, 1H), 7.33 (d, J=7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 26.96, 44.75 (2C′s), 58.82, 70.24, 119.39, 121.23, 127.20, 127.90, 128.18, 128.30, 128.46, 128.85, 129.39, 130.27, 134.43, 141.04, 141.26, 155.29 ppm; EI-GC–MS *m/z* 279 (M^+), 277, 219, 202, 189, 178, 165, 152, 139, 128, 115, 58; FAB *m/z* 280 (M^++1); HRMS calcd for $C_{19}H_{22}ON$ 280.1701, found 280.1697.

Acknowledgements

The authors thank the National Science Council of ROC and Academia Sinica for their kind financial support. Thanks are given to Dr. Suching Lin of the NMR instrument center and Ms. Ping-Yu Lin of the MS instrument center in our institute for assistance in obtaining 1D and 2D NMR and MS spectra.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.085.

References and notes

1. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., de Meijere, A., Eds.; Wiley: New York, NY, 2002.
2. *Metal Catalyzed Cascade Reactions*; Muller, T. J. J., Ed.; Springer: Berlin, 2006.
3. Luo, F.-T.; Lu, T.-Y.; Xue, C. *Tetrahedron Lett.* **2003**, *44*, 7249.
4. Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4846.
5. (a) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454; (b) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135; (c) Grigg, R.; Sandano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton, P. M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803; (d) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959; (e) Frewell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525; (f) Tietze, L. F.; Kahle, K.; Raschke, T. *Chem.—Eur. J.* **2002**, *8*, 401; (g) Salem, B.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 845.
6. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
7. (a) Yu, H.; Richey, R. N.; Carson, M. W.; Coghlan, M. *J. Org. Lett.* **2006**, *8*, 1685; (b) Grigg, R.; Savic, V.; Sridharan, V.; Terrier, C. *Tetrahedron* **2002**, *58*, 8613.
8. Jalander, L.; Oksanen, L.; Tahtinen, J. *Synth. Commun.* **1989**, *19*, 3349.
9. Fulton-Kehoe, D.; Rossing, M. A.; Rutter, C.; Mandelson, M. T.; Weiss, N. S. *Br. J. Cancer* **2006**, *94*, 1071 and papers cited therein.
10. 2-{[2-(3,3-Dimethyl-3-silabut-1-ynyl)phenyl]methoxy}-1-iodobenzene with trimethylsilyl group attached at the acetylene group was isolated in 24% yield.
11. Littke, A. F.; Dai, C.; Fu, G. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
12. Liu, X.; Deng, M. *Chem. Commun.* **2002**, 622.
13. (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382; (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473; (c) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1366.
14. Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283.
15. Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47.
16. (a) Hand, E. S.; Johnson, S. C.; Baker, D. C. *J. Org. Chem.* **1997**, *62*, 1348; (b) Bartlett, P. A.; Carruthers, N. I.; Winter, B. M.; Long, K. P. *J. Org. Chem.* **1982**, *47*, 1284.
17. (a) Casarotto, M. G.; Craik, D. J. *J. Pharm. Sci.* **2001**, *90*, 713; (b) Casarotto, M. G.; Craik, D. J.; Munro, S. L. *Magn. Reson. Chem.* **1990**, *28*, 533; (c) Wyatt, D. K.; Roscher, N. M.; Grady, L. T. *Appl. Spectrosc.* **1986**, *40*, 538.
18. (a) Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877; (b) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251; (c) Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697; (d) Sashida, H.; Ohyanagi, K.; Minoura, M.; Akiba, K.-Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 606.