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Synthesis of 2,3-disubstituted benzofurans and indoles by π-Lewis acidic transition metal-catalyzed cyclization of *ortho*-alkynylphenyl *O*,*O*- and *N*,*O*-acetals

Itaru Nakamura,* Yuya Mizushima, Uichiro Yamagishi and Yoshinori Yamamoto

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

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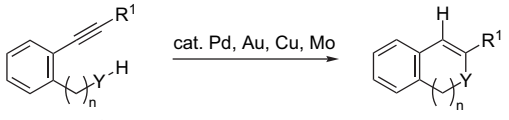
Dedicated to Professor Hisashi Yamamoto in honor of his receipt of the Tetrahedron Prize

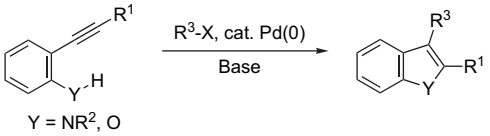
Abstract—The $PtCl_2$-catalyzed cyclization reaction of *ortho*-alkynylphenyl acetals **1** in the presence of COD (1,5-cyclooctadiene) produces 3-(α-alkoxyalkyl)benzofurans **2** in good to high yields. For example, the reaction of acetaldehyde ethyl 2-(1-octynyl)phenyl acetal (**1a**), acetaldehyde ethyl 2-(cyclohexylethynyl)phenyl acetal (**1c**), and acetaldehyde ethyl 2-(phenylethynyl)phenyl acetal (**1f**) in the presence of 2 mol % of platinum(II) chloride and 8 mol % of 1,5-cycloocatadiene in toluene at 30 °C gave the corresponding 2,3-disubstituted benzofurans **2a**, **2c**, and **2f** in 91, 94, and 88% yields, respectively. Moreover, the reaction of *N*-methoxymethyl-2-alkynylanilines **3** was catalyzed by $PdBr_2$, affording the corresponding 2,3-disubstituted indoles **4** in moderate yields. For example, the reaction of *N*-methoxymethyl-2-(1-pentynyl)-*N*-tosylaniline (**3a**) and *N*-methoxymethyl-2-(phenylethynyl)-*N*-tosylaniline (**3b**) in the presence of 10 mol % of $PdBr_2$ in toluene at 80 °C gave 3-methoxymethyl-2-propyl-1-tosylindole (**4a**) and 3-methoxymethyl-2-phenyl-1-tosylindole (**4b**) in 33 and 33% yields, respectively.

1. Introduction

Transition metal-catalyzed annulation of *ortho*-alkynylaryl amines and alcohols has been widely investigated as a synthetic method of the corresponding mono-substituted heterocycles (Eq. 1).[1] Furthermore, it is becoming popular that the 2,3-disubstituted indoles and benzofurans shown in Eq. 2 can be synthesized from *ortho*-alkynylanilines and phenols, through the external addition of organopalladium species to the triple bond (Eq. 2).[2] Recently, the intramolecular annulation accompanied with the migration of the functional group (E) on the heteroatom (Y) has been noted as a synthetic method for disubstituted heterocycles (Eq. 3).[3–6] This type of formal sequential addition of the two functional groups to the triple bond is important from synthetic point of view, since the structural framework of α,β-disubstituted indoles and benzofurans is often found in biologically active compounds.[7] Allyl,[3] propargyl,[4] acyl,[5] and methoxyphenylmethyl (MPM) groups[6] have been utilized as a migrating group. More recently, we disclosed that the $PtCl_2$-catalyzed cyclization reaction of *ortho*-alkynylphenyl acetals **1** in the presence of COD (1,5-cyclooctadiene) produces 3-(α-alkoxyalkyl)benzofurans **2** in good to high yields (Eq. 4).[8] This reaction proceeds through formal addition of a carbon–oxygen bond to triple bond, so-called carboalkoxylation.[9] Now, we report the detailed study of the platinum-catalyzed carboalkoxylation of the *O*,*O*-acetals **1**, together with the palladium-catalyzed cyclization of the *N*,*O*-acetal analogues **3**, which produces 2,3-disubstituted indoles **4** (Eq. 5).



(1)



(2)

Keywords: Platinum catalysts; Benzofuran; Acetal; Cyclization; Indole.
* Corresponding author. Tel.: +81 22 795 6754; fax: +81 22 795 6784; e-mail addresses: itaru-n@mail.tains.tohoku.ac.jp; yoshi@mail.tains.tohoku.ac.jp

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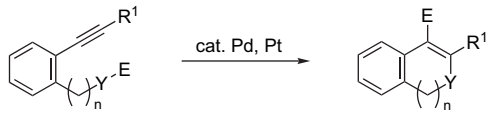
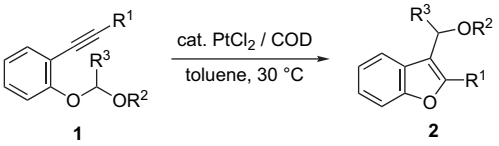
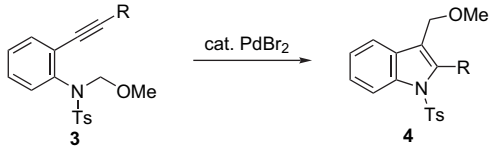


(3)

Y = NR^2, O
n = 0,1
E = allyl, propargyl, acyl, MPM



(4)



(5)

2. Results and discussion

The reaction of acetaldehyde *ortho*-(1-octynyl)phenyl ethyl acetal **1a** in the presence of 2 mol % of $PtCl_2$ and 8 mol % of COD in toluene proceeded at 30 °C, and 1 h later 3-(1-ethoxyethyl)-2-hexylbenzofuran **2a** was produced in 91% yield (Table 1, entry 1). The use of COD as an additive is very important for facilitating this migration as shown in Table 1. The reaction in the absence of COD gave **2a** in 24% yield (entry 2). The reaction using 1-hexene or cyclooctene, instead of COD, gave **2a** in a similar yield (entries 3 and 4), while the use of β-pinene, norbornadiene, or styrene resulted in lower yields (entries 5–7). Interestingly, $PtCl_2$(cod) did not promote the reaction at all (entry 8). Other transition metal complexes, such as $PtBr_2$, PtI_2, K_2PtCl_4, $PdCl_2$, $NiCl_2$, $Yb(OTf)_3$, $[RhCl(cod)]_2$, and $Pd(PPh_3)_4$, did not promote the reaction at all. The reaction of **1a** under the same reaction conditions using acetonitrile as solvent produced **2a** in 60% yield along with a small amount of unknown byproducts.

We applied the optimal conditions (2 mol % of $PtCl_2$ and 8 mol % of COD in toluene at 30 °C) to various substrates of **1**. The results are summarized in Table 2. The reaction of substrates bearing 4-chlorobutyl (**1b**) and cyclohexyl group (**1c**) at the alkynyl terminus proceeded very smoothly, while the reaction of **1d** having a *tert*-butyl group was sluggish (entries 2–4). The reaction of **1e**, which had an electron-rich aromatic group at R^1 position, gave the desired product in a high yield, while the reaction of **1g**, which had an electron-deficient aromatic group, proceeded slowly, producing **2g** in a moderate yield (entries 5–7). The reaction of substrates without any substituents at R^3 required higher catalyst loading. For example, the reaction of the MOM ethers (**1h** and **1i**) and the BOM ethers (**1j** and **1k**) proceeded smoothly using slightly higher amounts of platinum catalysts (entries 8–11); the reaction of **1h** using 2 mol % of $PtCl_2$ and 8 mol % of COD proceeded very slowly and it took 5 days, giving **2h** in 50% yield along with 50% yield of recovered **1h**. The reaction of TBS ether **1l** was promoted by the use of a stoichiometric amount of the platinum catalyst (entry 12).

Table 1. Carboalkoxylation of **1a** catalyzed by platinum–olefin system[a]

Entry	Pt	Olefin (mol %)	Yield of **2a**[b] (%)	Recovery of **1a**[b] (%)
1	$PtCl_2$	COD (8)	93 (91)[c]	—
2	$PtCl_2$	None	24	68
3	$PtCl_2$	1-Hexene (16)	90	Trace
4	$PtCl_2$	Cyclooctene (16)	84	16
5	$PtCl_2$	β-Pinene (16)	51	48
6	$PtCl_2$	Norbornadiene (8)	50	50
7	$PtCl_2$	Styrene (16)	40	60
8	$PtCl_2$(cod)	None	0	Quant.

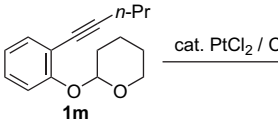
[a] The reaction of **1a** (0.3 mmol) was carried out in the presence of 2 mol % of $PtCl_2$ and olefin in toluene at 30 °C for 1 h.
[b] The yield was determined by ^1H NMR using 1,4-dioxane as an internal standard.
[c] Isolated yield in parenthesis.

Table 2. Platinum-catalyzed carboalkoxylation of *ortho*-alkynylphenyl *O*,*O*-acetals **1**[a]

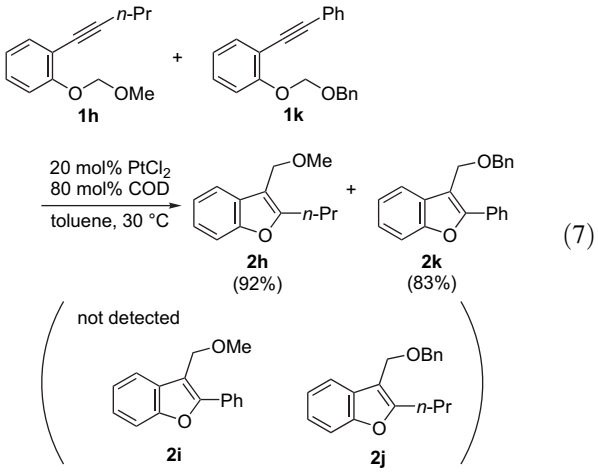
Entry	**1**	R^1	R^2	R^3	Time (h)	**2**	Yield[b] (%)
1	**1a**	*n*-Hex	Et	Me	1	**2a**	91
2	**1b**	$(CH_2)_4Cl$	Et	Me	1	**2b**	92
3	**1c**	Cyclohexyl	Et	Me	2.5	**2c**	94
4	**1d**	*t*-Bu	Et	Me	24	**2d**	Trace
5	**1e**	*p*-(MeO)C_6H_4	Et	Me	24	**2e**	90
6	**1f**	Ph	Et	Me	3	**2f**	88
7	**1g**	*p*-(CF_3)C_6H_4	Et	Me	4 days	**2g**	61
8[c]	**1h**	*n*-Pr	Me	H	22	**2h**	92
9[c]	**1i**	Ph	Me	H	24	**2i**	73
10[d]	**1j**	*n*-Pr	Bn	H	20	**2j**	94
11[d]	**1k**	Ph	Bn	H	48	**2k**	83
12[e]	**1l**	Ph	TBS	H	4 days	**2l**	61

[a] The reaction of **1** was carried out in the presence of 2 mol % of $PtCl_2$ and 8 mol % of COD in toluene at 30 °C.
[b] Isolated yield.
[c] 20 mol % of $PtCl_2$ and 80 mol % of COD were used.
[d] 10 mol % of $PtCl_2$ and 40 mol % of COD were used.
[e] 100 mol % of $PtCl_2$ and 80 mol % of COD were used.

We found that the reaction of the substrate **1m** having a THP group did not proceed under the standard reaction conditions; the substrate **1m** was quantitatively recovered (Eq. 6). This result indicates that the bulky THP group interfered the cyclization step even though the substrate had a substituent at R^3; it is unlikely that cleavage of the acetal carbon–oxygen bond occurs prior to cyclization. To find out if the reaction proceeds in an intramolecular or intermolecular fashion, we carried out a crossover experiment (Eq. 7). The reaction of a 1:1 mixture of **1h** and **1k** in the presence of 20 mol % of $PtCl_2$ and 80 mol % of COD afforded the products **2h** and **2k** deriving from **1h** and **1k**, respectively; the crossover products, such as **2i** and **2j**, were not detected by GC–MS and NMR. This result clearly indicates that the present reaction proceeds in an intramolecular manner.

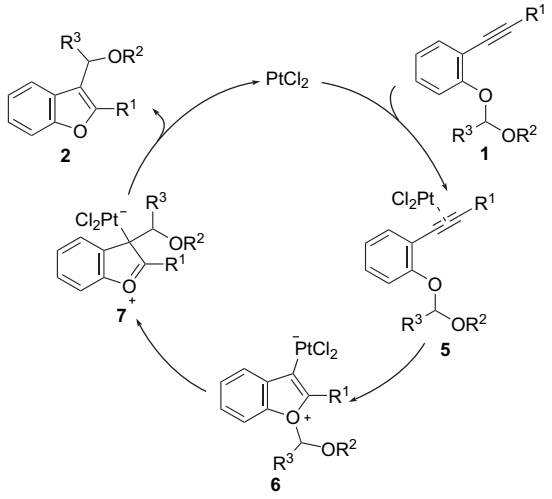


(6)



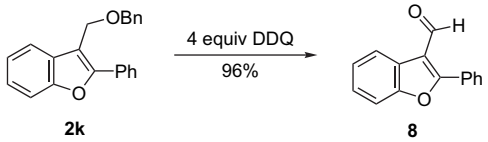
(7)

Based on these results, we propose the reaction mechanism for the platinum-catalyzed reaction of **1** as illustrated in Scheme 1. Platinum chloride coordinates to the triple bond of the substrate **1**. Nucleophilic attack of the oxygen atom of the phenyl acetal moiety of **5** would give the cyclized intermediate **6**. Migration of α-alkoxyalkyl group of **6** to the carbon atom bonded to platinum atom would produce the intermediate **7**. Elimination of platinum chloride from **7** gives the product **2**. COD probably works as an activating agent to disconnect Pt–Cl bonds of polymeric platinum chloride and to generate a reactive platinum catalyst.[10] However, since $PtCl_2$(cod) itself did not promote the present reaction at all, a real active species might be a platinum oligomer (Table 1, entry 8).

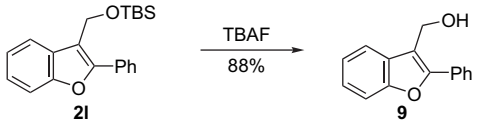


Scheme 1. Mechanism of the carboalkoxylation of **1**.

The benzyl ether **2k** was converted to 3-(2-phenylbenzofuran)carbaldehyde **8** by treatment with 4 equiv of DDQ. The reaction of the TBS ether **2l** with TBAF afforded the 3-(2-phenylbenzofuran)carbinol **9** in 88% yield (Eq. 9).

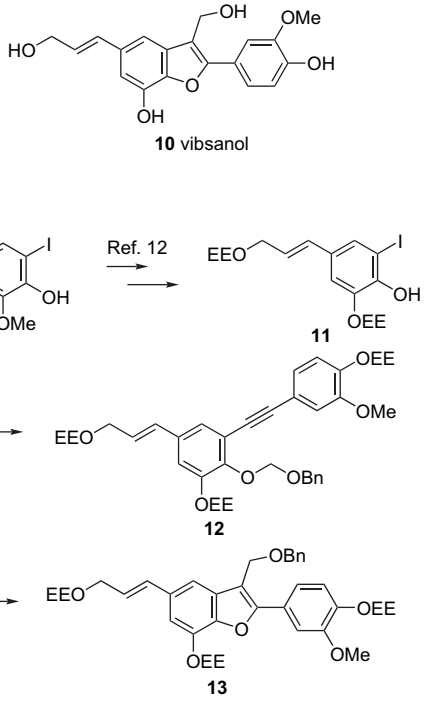


(8)



(9)

We applied the present reaction for the synthesis of vibsanol **10**, which was isolated from *Viburnum awabuki* (Scheme 2). It is well known that **10** works as an inhibitor for lipid peroxidation.[11,12] The precursor of carboalkoxylation, *ortho*-alkynylaryl benzyl acetal **12**, was synthesized from the *ortho*-iodophenol **11**, prepared from iodovaniline according to the reported procedures.[12] The carboalkoxylation of **12** proceeded smoothly, giving the desired vibsanol precursor **13** in 76% yield.[13]



Scheme 2. Synthesis of vibsanol precursor **13** via carboalkoxylation. (a) BOMCl, NaH, 0 °C, quantitative; (b) [4-(1-ethoxyethyl)-3-methoxyphenyl]acetylene, $Pd(PPh_3)_4$, CuI, Et_3N, THF, room temperature, 64%; (c) 20 mol % $PtCl_2$, 80 mol % COD, toluene, 30 °C, 76%.

It is interesting to know whether or not the present methodology for the *O*,*O*-acetals can be extended to the *N*,*O*-acetal analogues, since 2,3-disubstituted indoles can be synthesized through the carboamination of alkynes. The reaction of *N*-methoxymethyl-2-(1-pentynyl)-*N*-tosylaniline **3a** in the presence of 10 mol % of $PdBr_2$ in toluene at 80 °C gave 3-methoxymethyl-1-methyl-2-propylindole **4a** in 33% yield (Eq. 10). The use of $Pd(NO_3)_2$, instead of $PdBr_2$, afforded **4a** in 26% yield and other catalyst systems, such as $PtCl_2$–COD, $PtCl_2$, and $PdCl_2$ did not show the catalytic activity. The reaction of **3b** bearing a phenyl group at the alkynyl moiety gave the desired product **4b** in 33% yield. The structure of **4a** was unambiguously determined by X-ray crystallographic analysis as shown in Figure 1.[14] In contrast, the reaction of *N*-acetyl-*N*-methoxymethyl-2-(1-pentynyl)aniline **3c** proceeded through migration of the acetyl group, affording the 3-acetylindole **14** in

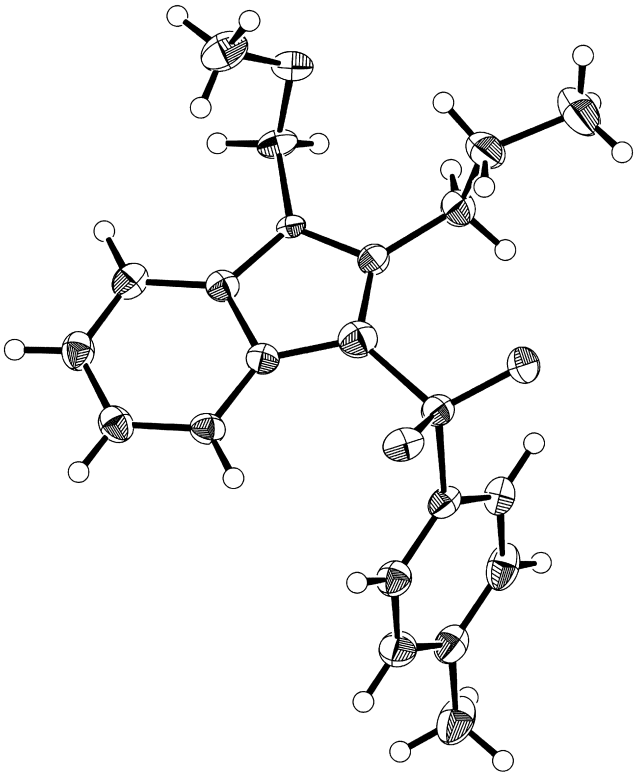
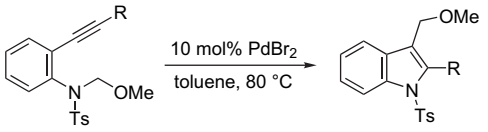


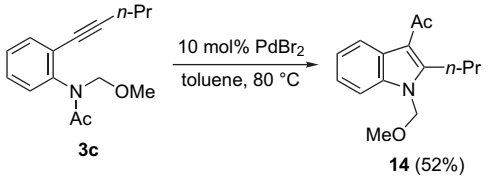
Figure 1. ORTEP drawing of **4a**.

52% yield (Eq. 11).[5] It is noteworthy that acetyl group is transferred more easily in comparison with methoxymethyl group.



3a (R = *n*-Pr) **4a** (R = *n*-Pr) 33%
3b (R = Ph) **4b** (R = Ph) 33%

(10)



(11)

3. Conclusions

We are in a position to synthesize 3-(α-alkoxyalkyl)-2-substituted benzofurans and indoles in an efficient and atom economic manner. The present result suggests that a cation stabilizing group E may undergo the transition metal-catalyzed intramolecular 1,3-transfer from the heteroatom to C-3 position of the heterocycles containing E (Eq. 3).

4. Experimental

4.1. General

Spectroscopic measurements were carried out by the use of following instruments: JEOL JNM AL 400 (^{1}H and ^{13}C NMR), JASCO FTIR-460 plus (FTIR), HITACHI M-2500s (HRMS). $PtCl_2$ was purchased from WAKO Co. Ltd. The starting materials **1** were prepared from 2-iodophenol through acetalization and Sonogashira coupling. Chromatography was performed using Kanto Chemical silica gel 60N (spherical, neutral, 100–210 μm) or Fuji Silysia silica gel BW-300 (200–400 mesh).

4.2. General procedure for platinum-catalyzed cyclization of 2-alkynylphenyl acetals

To $PtCl_2$ (1.6 mg, 0.006 mmol) and 1,5-cyclooctadiene (2.9 μL, 0.024 mmol) in toluene (0.5 ml) was added the acetal **1** (0.3 mmol) in toluene (0.7 ml) under Ar atmosphere in a pressure vial. After heating at 30 °C for 1–24 h, the reaction mixture was filtered through a short silica gel column using ethyl acetate as an eluant. Separation by silica gel column chromatography using hexane/EtOAc (30:1) as an eluant afforded the products **2**.

4.2.1. 3-(1-Ethoxyethyl)-2-hexylbenzofuran (2a). IR (neat) 3055, 2975–2860, 1622, 1370, 1101, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.16 (t, J=7.2 Hz, 3H), 1.26–1.40 (m, 6H), 1.58 (d, J=6.8 Hz, 3H), 1.72 (quint, J=7.3 Hz, 2H), 2.74 (td, J=7.3, 3.1 Hz, 2H), 3.30–3.41 (m, 2H), 4.66 (q, J=6.8 Hz, 1H), 7.15–7.22 (m, 2H), 7.39 (dd, J=7.4, 1.4 Hz, 1H), 7.71 (d, J=7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.08, 15.43, 22.42, 22.60, 26.60, 28.45, 29.02, 31.60, 63.58, 70.17, 110.59, 116.03, 120.38, 122.06, 123.09, 127.47, 154.01, 155.01. Anal. Calcd for $C_{18}H_{26}O_2$ (274.40): C, 78.79; H, 9.55. Found: C, 79.05; H, 9.73. HRMS (ESI) calcd for $C_{18}H_{26}O_2$ (M+Na)$^+$: m/z 297.1825. Found: m/z 297.1825.

4.2.2. 2-(4-Chlorobutyl)-3-(1-ethoxyethyl)benzofuran (2b). IR (neat) 3055, 2975–2867, 1622, 1455, 1370, 1089, 1012, 940, 849, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J=7.0 Hz, 3H), 1.58 (d, J=6.8 Hz, 3H), 1.81–1.93 (m, 4H), 2.75–2.85 (m, 2H), 3.33–3.40 (m, 2H), 3.56 (t, J=6.2 Hz, 2H), 4.66 (q, J=6.8 Hz, 1H), 7.17–7.25 (m, 2H), 7.39 (dd, J=7.0, 1.0 Hz, 1H), 7.71 (dd, J=7.0, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 22.4, 25.7, 25.8, 32.0, 44.5, 63.6, 70.1, 110.6, 116.5, 120.3, 122.1, 123.3, 127.3, 153.8, 153.9. Anal. Calcd for $C_{16}H_{21}ClO_2$ (280.79): C, 68.44; H, 7.54; Cl, 12.63. Found: C, 68.47; H, 7.67; Cl, 12.52. HRMS (ESI) calcd for $C_{16}H_{21}ClO_2$ (M+Na)$^+$: m/z 303.1122. Found: m/z 303.1123.

4.2.3. 2-Cyclohexyl-3-(1-ethoxyethyl)benzofuran (2c). IR (neat) 3087–2857, 1963, 1786, 1621, 1446, 943, 845, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J=7.2 Hz, 3H), 1.29–1.44 (m, 3H), 1.58 (d, J=6.4 Hz, 3H), 1.77–1.89 (m, 7H), 2.80–2.88 (m, 1H), 3.30–3.39 (m, 2H), 4.71 (q, J=6.4 Hz, 1H), 7.14–7.23 (m, 2H), 7.39 (dd, J=7.2, 1.2 Hz, 1H), 7.71 (d, J=6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 22.6, 25.8, 26.37, 26.38, 31.4,

31.7, 36.5, 63.5, 69.9, 110.6, 114.4, 120.4, 121.9, 122.9, 127.4, 153.8, 158.7. Anal. Calcd for $C_{18}H_{24}O_2$ (272.38): C, 79.37; H, 8.88. Found: C, 79.11; H, 8.91. HRMS (ESI) calcd for $C_{18}H_{24}O_2$ $(M+Na)^+$: *m/z* 295.1669. Found: *m/z* 295.1669.

4.2.4. 3-(1-Ethoxyethyl)-2-(4-methoxyphenyl)benzofuran (2e). IR (neat) 3226, 3049–2843, 2042, 1604, 1508, 1449, 1257, 1176–1087, 1026, 937, 833, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.0 Hz, 3H), 1.70 (d, J=6.4 Hz, 3H), 3.27–3.39 (m, 2H), 3.87 (s, 3H), 4.97 (q, J=6.4 Hz, 1H), 7.00–7.03 (m, 2H), 7.22 (ddd, J=7.4, 7.4, 1.1 Hz, 1H), 7.28 (ddd, J=8.0, 7.2, 1.6 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.64–7.68 (m, 2H), 7.87 (dd, J=7.8, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 22.0, 55.4, 63.7, 70.3, 110.9, 114.1, 116.7, 121.3, 122.4, 123.3, 123.9, 128.2, 129.1, 151.6, 153.9, 159.8. Anal. Calcd for $C_{19}H_{20}O_3$ (296.36): C, 77.00; H, 6.80. Found: C, 76.83; H, 6.87. HRMS (ESI) calcd for $C_{19}H_{20}O_3$ $(M+Na)^+$: *m/z* 319.1305. Found: *m/z* 319.1305.

4.2.5. 3-(1-Ethoxyethyl)-2-phenylbenzofuran (2f). IR (neat) 3057–2870, 1590, 1493, 1454, 1371, 1256, 1210, 1125–1062, 936, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.2 Hz, 3H), 1.72 (d, J=6.4 Hz, 3H), 3.28–3.39 (m, 2H), 5.01 (q, J=6.4 Hz, 1H), 7.24 (ddd, J=7.5, 7.5, 1.1 Hz, 1H), 7.30 (ddd, J=7.5, 7.5, 1.1 Hz, 1H), 7.37–7.41 (m, 1H), 7.46–7.51 (m, 3H), 7.72 (dd, J=8.6, 1.4 Hz, 1H), 7.91 (d, J=7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 22.0, 63.7, 70.2, 110.9, 118.1, 121.5, 122.4, 124.5, 127.6, 128.4, 128.5, 130.6, 151.3, 154.1. Anal. Calcd for $C_{18}H_{18}O_2$ (266.33): C, 81.17; H, 6.81. Found: C, 81.25; H, 6.94. HRMS (ESI) calcd for $C_{18}H_{18}O_2$ $(M+Na)^+$: *m/z* 289.1199. Found: *m/z* 289.1199.

4.2.6. 3-(1-Ethoxyethyl)-2-(4-trifluoromethylphenyl)-benzofuran (2g). IR (neat) 3059–2883, 1625, 1448, 1408, 1322, 1164–1070, 936, 847, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J=7.2 Hz, 3H), 1.72 (d, J=6.6 Hz, 3H), 3.30 (m, 2H), 5.02 (q, J=6.6 Hz, 1H), 7.25–7.29 (m, 1H), 7.35 (ddd, J=8.0, 7.2, 1.2 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 7.73–7.75 (m, 2H), 7.87–7.93 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ Anal. Calcd for $C_{19}H_{17}F_3O_2$ (334.33): C, 68.26; H, 5.13; F, 17.05. Found: C, 68.19; H, 5.17; F, 16.88. HRMS (ESI) calcd for $C_{19}H_{17}F_3O_2$ $(M+Na)^+$: *m/z* 357.1073. Found: *m/z* 357.1074.

4.2.7. 3-Methoxymethyl-2-propylbenzofuran (2h). IR (neat) 3056, 2962–2816, 1627, 1455, 1174, 1094, 910, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J=7.4 Hz, 3H), 1.77 (sext, J=7.4 Hz, 2H), 3.36 (s, 3H), 4.56 (s, 2H), 7.18–7.24 (m, 2H), 7.37–7.41 (m, 1H), 7.57–7.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.8, 28.5, 57.7, 64.6, 110.6, 111.6, 119.3, 122.4, 123.4, 128.8, 153.9, 157.0. Anal. Calcd for $C_{13}H_{16}O_2$ (204.26): C, 76.44; H, 7.90. Found: C, 76.16; H, 7.92. HRMS (ESI) calcd for $C_{13}H_{16}O_2$ $(M+Na)^+$: *m/z* 227.1043. Found: *m/z* 227.1044.

4.2.8. 3-Methoxymethyl-2-phenylbenzofuran (2i). IR (neat) 3061–2817, 1592, 1455, 1255, 1190, 1088, 949, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H), 4.74 (s, 2H), 7.25–7.33 (m, 2H), 7.41 (tt, J=7.2, 1.5 Hz, 1H), 7.47–7.53 (m, 3H), 7.69–7.71 (m, 1H), 7.83–7.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.9, 64.6, 111.0, 112.4, 119.6, 122.7, 124.4, 127.3, 128.57, 128.64, 129.8, 130.2, 153.8, 153.9. Anal. Calcd for $C_{16}H_{14}O_2$ (238.28): C, 80.65; H, 5.92. Found: C, 80.42; H, 6.18. HRMS (ESI) calcd for $C_{16}H_{14}O_2$ $(M+Na)^+$: *m/z* 261.0886. Found: *m/z* 261.0885.

4.2.9. 3-Benzyloxymethyl-2-propylbenzofuran (2j). IR (neat) 3087–2871, 1626, 1455, 1175, 1072, 1028, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J=7.6 Hz, 3H), 1.75 (sext, J=7.6 Hz, 2H), 2.73 (t, J=7.6 Hz, 2H), 4.55 (s, 2H), 4.64 (s, 2H), 7.21–7.24 (m, 2H), 7.28–7.33 (m, 1H), 7.34–7.36 (m, 4H), 7.41 (dd, J=6.4, 2.4 Hz, 1H), 7.57–7.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.8, 28.5, 62.1, 71.7, 110.6, 111.6, 119.4, 122.4, 123.4, 127.6, 127.8, 128.3, 128.9, 138.2, 153.9, 157.1. Anal. Calcd for $C_{19}H_{20}O_2$ (280.36): C, 81.40; H, 7.19. Found: C, 81.60; H, 7.15. HRMS (ESI) calcd for $C_{19}H_{20}O_2$ $(M+Na)^+$: *m/z* 303.1356. Found: *m/z* 303.1358.

4.2.10. 3-Benzyloxymethyl-2-phenylbenzofuran (2k). IR (neat) 3084–3033, 2925–2858, 1591, 1496, 1454, 1352, 1252, 1202, 1065, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (s, 2H), 4.82 (s, 2H), 7.23–7.41 (m, 8H), 7.43–7.47 (m, 2H), 7.51 (dd, J=8.2, 0.6 Hz, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.82–7.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 72.2, 111.1, 112.5, 119.8, 122.8, 124.5, 127.4, 127.7, 128.0, 128.4, 128.6, 128.7, 129.8, 130.3, 137.9, 153.9, 154.0. Anal. Calcd for $C_{22}H_{18}O_2$ (314.38): C, 84.05; H, 5.77. Found: C, 84.19; H, 6.00. HRMS (ESI) calcd for $C_{22}H_{18}O_2$ $(M+Na)^+$: *m/z* 337.1199. Found: *m/z* 337.1198.

4.2.11. *tert*-Butyldimethyl-(2-phenylbenzofuran-3-yl-methoxy)silane (2l). IR (neat) 3062–2854, 1876, 1757, 1594, 1455, 1362, 850, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 4.97 (s, 2H), 7.24–7.32 (m, 2H), 7.38–7.42 (m, 1H), 7.46–7.52 (m, 3H), 7.69 (d, J=7.9 Hz, 1H), 7.82 (d, J=7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 18.5, 26.0, 56.1, 111.1, 115.2, 120.0, 122.6, 124.3, 127.4, 128.5, 129.6, 130.5, 152.9, 153.9. Anal. Calcd for $C_{21}H_{26}O_2Si$ (338.52): C, 74.51; H, 7.74. Found: C, 74.59; H, 7.80. HRMS (ESI) calcd for $C_{21}H_{26}O_2Si$ $(M+Na)^+$: *m/z* 361.1594. Found: *m/z* 361.1596.

4.2.12. *ortho*-Alkynylphenyl benzyloxymethyl ether 12. (a) To a suspension of NaH (1.5 mmol, prewashed by hexane) in THF (2.5 ml) at 0 °C was added **9** (1.0 mmol) in THF (0.5 ml). After stirring for 1 h at 0 °C, to the resulting mixture at 0 °C was added benzyl chloromethyl ether (4 mmol). After stirring at room temperature for 5 h, the reaction mixture was quenched with Et_3N (0.2 ml). The mixture was diluted by ether and washed with water. The organic layer was washed with brine and dried over Na_2SO_4. Purification by silica gel column chromatography using hexane/ethyl acetate (2:1) gave BOM ether quantitatively. IR (neat) 2977–2934, 1737, 1572, 1509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13–1.24 (m, 6H), 1.36 (d, J=5.6 Hz, 3H), 1.48 (d, J=5.2 Hz, 3H), 3.50–3.54 (m, 2H), 3.65–3.75 (m, 2H), 4.15 (dd, J=4.8, 6.0 Hz, 1H),

4.24 (m, 1H), 4.79 (q, J=5.2 Hz, 1H), 4.96 (s, 2H), 5.40 (s, 2H), 5.36 (q, J=5.6 Hz), 6.18 (m, 1H), 6.46 (d, J=15.6 Hz), 7.11 (s, 1H), 7.28–7.39 (m, 5H), 7.48 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 15.4, 19.9, 20.3, 60.7, 61.8, 71.9, 77.2, 92.7, 96.7, 99.2, 100.8, 116.5, 126.9, 127.7, 127.9, 128.3, 129.6, 130.5, 135.0, 146.8, 149.1. HRMS (ESI) calcd $C_{25}H_{33}IO_6$ (M+Na)$^+$: m/z 579.1214. Found: m/z 579.1216.

(b) To a mixture of $Pd(PPh_3)_4$ (0.1 mmol), CuI (0.2 mmol), and Et_3N (3 mmol) in THF (2.5 ml) were added the BOM ether (1 mmol) and 4-(1-ethoxyethyl)-3-methoxyphenylacetylene (1.3 mmol) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was diluted with ether. The ethereal solution was washed with a saturated NH_4Cl aqueous solution and water, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate (5:1) as an eluant to give **12** in 64% yield. IR (neat) 2977–2934, 2210, 1737, 1572, 1509 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07–1.15 (m, 9H), 1.28 (d, J=5.2 Hz, 3H), 1.42–1.43 (m, 6H), 3.43–3.49 (m, 4H), 3.50–3.57 (m, 2H), 3.59–3.74 (m, 2H), 3.59 (s, 3H), 4.72 (q, J=5.2 Hz, 1H), 4.91 (s, 2H), 5.29–5.34 (m, 2H), 5.33 (s, 2H), 6.17 (m, 1H), 6.44 (d, J=16.0 Hz, 1H), 6.91–6.96 (m, 3H), 7.06 (s, 1H), 7.14–7.25 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.15, 15.24, 15.4, 19.9, 20.3, 20.4, 55.8, 60.6, 61.7, 62.0, 65.5, 71.0, 84.8, 93.4, 96.4, 99.1, 100.8, 101.0, 114.9, 116.7, 117.1, 118.6, 118.7, 124.6, 124.8, 126.4, 127.5, 127.9, 128.2, 130.5, 133.0, 137.5, 146.4, 147.6, 149.6, 150.3. HRMS (ESI) calcd for $C_{38}H_{48}O_9$ (M+Na)$^+$: m/z 671.3191. Found: m/z 671.3188.

4.2.13. Vibsanol precursor 13. To a mixture of $PtCl_2$ (20 mol %) and 1,5-cyclooctadiene (80 mol %) in toluene (0.5 ml) was added **12** in toluene (0.3 ml) at room temperature. After stirring at 30 °C for 1 h, the reaction mixture was filtered through a short silica gel column using ethyl acetate as an eluant. Purification by silica gel column chromatography using hexane/EtOAc (2:1) as an eluant afforded **13** in 76% yield. IR (neat) 2977–2934, 2247, 1737, 1596, 1509, 1466 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.27 (m, 9H), 1.39 (d, J=5.2 Hz, 3H), 1.55 (d, J=5.2 Hz, 3H), 1.61 (d, J=4.8 Hz, 3H), 3.55–3.71 (m, 4H), 3.86 (s, 3H), 3.87–4.01 (m, 2H), 4.65 (s, 2H), 4.77 (s, 2H), 4.83 (q, J=5.6 Hz, 1H), 5.44 (q, J=5.2 Hz, 1H), 5.64 (q, J=5.6 Hz, 1H), 6.28 (m, 1H), 6.67 (d, J=16.0 Hz, 1H), 7.09 (d, J=1.6 Hz, 1H), 7.14–7.45 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 15.3, 15.4, 20.0, 20.3, 20.9, 55.9, 60.6, 62.0, 62.1, 62.8, 65.9, 72.1, 99.1, 101.0, 101.7, 111.2, 111.7, 112.0, 112.3, 118.8, 120.3, 124.6, 125.2, 127.7, 127.9, 128.3, 132.2, 133.0, 137.9, 141.6, 144.1, 146.6, 150.7, 154.9. HRMS (ESI) calcd for $C_{38}H_{48}O_9$ (M+Na)$^+$: m/z 671.3191. Found: m/z 671.3187.

4.3. General procedure for palladium-catalyzed cyclization of *N*,*O*-acetals 3

To $PdBr_2$ (0.03 mmol) in toluene (0.5 ml) was added the *N*,*O*-acetal **3** (0.3 mmol) in toluene (0.7 ml) under Ar atmosphere in a pressure vial. After heating at 80 °C for 18 h, the reaction mixture was filtered through a short silica gel column using ethyl acetate as an eluant. Separation by silica gel column chromatography using hexane/EtOAc (30:1) as an eluant afforded the products **4**.

4.3.1. 3-Methoxymethyl-2-propyl-1-tosylindole (4a). IR (neat) 2961–2854, 1519, 1458, 1300, 1260, 1113 cm^{-1}. ^{1}H NMR (399.65 MHz, $CDCl_3$) δ 2.32 (3H, s), 3.12 (3H, s) 5.19 (2H, s), 7.10 (2H, d, J=8.0 Hz), 7.33–7.38 (4H, m), 7.46–7.57 (6H, m), 8.32–8.35 (1H, m). ^{13}C NMR (149.40 MHz, $CDCl_3$) δ 21.4, 56.1, 74.8, 110.8, 115.5, 120.9, 123.1, 124.1, 125.1, 126.6, 127.6, 127.8, 127.9, 128.5, 129.2, 129.9, 131.2, 135.6, 140.8, 143.0, 144.1. HRMS (ESI) calcd $C_{20}H_{23}NO_3S$ (M+Na)$^+$: m/z 380.1296. Found: m/z 380.1291.

4.3.2. 3-Methoxymethyl-2-phenyl-1-tosylindole (4b). IR (neat) 3055–2824, 1733, 1456, 1379, 1321, 1143, 1077 cm^{-1}. ^{1}H NMR (399.65 MHz, $CDCl_3$) δ 1.07 (3H, t, J=7.6 Hz), 1.62–1.71 (2H, m), 2.35 (3H, s), 3.17–3.21 (2H, m), 3.28 (3H, s), 5.44 (2H, s), 7.10–7.21 (4H, m), 7.33–7.37 (1H, m), 7.79 (2H, d, J=8.4 Hz), 7.99–8.03 (1H, m). ^{13}C NMR (100.40 MHz, $CDCl_3$) δ 14.4, 21.5, 23.9, 26.8, 56.3, 74.1, 110.0, 112.8, 120.1, 122.3, 122.6, 125.0, 126.2, 129.4, 136.2, 141.2, 143.1, 146.3. HRMS (ESI) calcd $C_{23}H_{21}NO_3S$ (M+Na)$^+$: m/z 414.1140. Found: m/z 414.1134.

4.3.3. 3-Acetyl-1-methoxymethyl-2-propylindole (14). IR (neat) 2964–2828, 1632, 1510, 1459, 1122, 1104 cm^{-1}. ^{1}H NMR (270.05 MHz, $CDCl_3$) δ 1.04 (3H, t, J=7.6 Hz), 1.68 (2H, m), 2.70 (3H, s), 3.20 (2H, m), 3.30 (3H, s), 5.50 (2H, s), 7.24–7.34 (2H, m), 7.46–7.52 (1H, m), 7.94–8.00 (1H, s). ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 14.3, 23.1, 27.8, 31.8, 73.6, 110.1, 114.9, 120.8, 122.3, 122.5, 126.4, 136.7, 149.4, 194.7. HRMS (ESI) calcd $C_{15}H_{19}NO_2$ (M+Na)$^+$: m/z 268.1313. Found: m/z 268.1308.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.039.

References and notes

1. For a review: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2258 and references therein.
2. For a review: (a) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671; (b) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613; (c) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, *14*, 2115.
3. For cyclization of allylic amines: (a) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001; (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280; Palladium(0)-catalyzed *endo*-cyclization of allylic ethers: (c) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741; (d) Monterio, N.; Balme, G. *Synlett* **1998**, 746; For $PtCl_2$-catalyzed *exo*-cyclization of allylic ethers: (e) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785; (f) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863.

4. Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101.
5. Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546.
6. Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024.
7. For a recent report: (a) Gfesser, G. A.; Faghih, R.; Bennani, Y. L.; Curtis, M. P.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2559; (b) Locuson, C. W., II; Suzuki, H.; Rettie, A. E.; Jones, J. P. *J. Med. Chem.* **2004**, *47*, 6768; (c) Abele, E.; Abele, R.; Dzenitis, O.; Lukevics, E. *Chem. Heterocycl. Comp.* **2003**, *39*, 3.
8. (a) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. Fürstner's group independently reported the same reaction using $PtCl_2$ as a catalyst under CO atmosphere. See, Ref. 6.
9. (a) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328; (b) Nakamura, I.; Kamada, M.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2903; (c) Nakamura, I.; Bajracharya, G. B.; Yamamoto, Y. *Chem. Lett.* **2005**, *34*, 174; (d) Dube, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062.
10. (a) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423; (b) Pujanauski, B. G.; Prasad, B. A. B.; Sarpong, R. *J. Am. Chem. Soc.* **2006**, *128*, 6786.
11. Fukuyama, Y.; Nakahara, M.; Minami, H.; Kodama, M. *Chem. Pharm. Bull.* **1996**, *44*, 1418.
12. (a) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 4211; (b) Sakai, A.; Aoyama, T.; Shioiri, T. *Heterocycles* **2000**, *52*, 643.
13. Our preliminary attempts to deprotect the BOM group of **13** failed.
14. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-629327. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).