Copper-catalyzed direct coupling of benzoxazin-2-ones with indoles for the synthesis of diverse 3-indolylbenzoxazin-2-ones: access to natural cephalandole A†

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A novel and facile copper-catalyzed direct coupling for the synthesis of diverse and functionalized 3-indolyl benzoxazin-2-ones from benzoxazin-2-ones and indoles has been developed. This new methodology offers an easy and rapid approach to a variety of 3-indolylbenz[b][1,4]oxazin-2-ones in high yield. As an application of this protocol, a gram-scale synthesis of naturally occurring cephalandole A has also been accomplished.

Introduction

Benzoxazines and benzoxazin-2-ones are important heterocyclic compounds found in natural products and biologically active molecules (Fig. 1).1,2 These compounds possess a wide range of pharmaceutical properties such as antihypertensive,3 anti-fungal,4 antimycobacterial,5 anti-inflammatory,6 bacterial histidine protein kinase inhibitory,7 and D2 receptor antagonist activities.8 In addition, compound 1 exhibits a potent effect of pyruvate kinase activators for the treatment of hereditary non-spherocytic hemolytic anemia and sickle cell anemia9 and compound 2 is useful for the treatment of lung cancer.10 Naturally occurring alkaloid, cephalandole A was originally isolated from Taiwanese orchid Cephalanceopsis gracilis11 and its structure was later revised into 3 by organic structure determination using atomic resolution scanning probe microscopy.12 Moreover, molecules bearing these skeletons have been also used as valuable building blocks for the synthesis of pharmaceuticals and photoactive materials.13,14

Owing to the importance of benzoxazin-2-ones, several methods for their synthesis have been reported.15,16 The general methods for benzoxazin-2-ones include the domino reaction of o-aminophenol with b-nitroacrylates,17 cleavage of resin-bound pseudooxazolones with 2-aminophenols,18 and TFA-catalyzed tandem reaction of benzoxazoles with 2-oxo-2-arylacetic acids.19 In addition, enantioselective hydrogenation of benzoxazinones and enantioselective addition of indoles to ketimines to give chiral dihydrobenzoxazinones have been accomplished.20,21

Although several methodologies for the synthesis of benzoxazin-2-ones and dihydrobenzoxazinones have been developed, there are no reports on the direct coupling of benzoxazin-2-ones with indoles for the construction of 3-indolylbenzoxazin-2-ones so far. Recently, an iron-catalyzed oxidative sp3 carbon–hydrogen bond functionalization of dihydrobenzoxazin-2-ones with indoles for the synthesis of 3-indolyl dihydrobenzoxazin-2-ones has been described (Scheme 1a).22 As a part of continuing efforts to develop new synthetic protocols for nitrogen heterocycles,23 we herein report the copper-catalyzed direct coupling of benzoxazin-2-ones with indoles for the formation of diverse 3-indolyl benzoxazin-2-ones in air (Scheme 1b).

Results and discussion

Our initial study commenced with the model reaction between benzoxazin-2-one 4a and N-methylindole 5a for the optimization of reaction condition (Table 1). Various metals were
examined as catalysts under several solvents in air. When using 10 mol% of CoCl₂, ZnCl₂ and NiCl₂ at 80 ℃ for 24 h in dichloroethane, product 6a was isolated in 32, 40, and 41% yields, respectively (entries 1–3, Table 1). Encouraged by these results, we screened other catalysts for the reaction. With 10 mol% of FeCl₃ and CuCl₂, the yield of 6a increased to 80 and 89% respectively (entries 4–5). However, additional attempt using other copper catalysts such as CuF₂, Cu(OAc)₂, and Cu(OTf)₂, failed to further increase the yield (entries 6–8).

Results of solvent screening showed that tetrahydrofuranylene (THF) was the best solvent (94%) among the solvents such as dioxane (87%), ethanol (66%), and water (60%) (entries 9–12). Changes in the loading of CuCl₂ to 5 mol%, 2 mol%, and 13 mol% did not improve the yield of 6a (entries 13–15). In addition, the effect of temperature was next studied. It was found out that decreasing or increasing temperature decreased the yield of 6a (entries 16 and 17). The structure of 6a was determined by spectroscopic analysis. The ¹H NMR spectrum of 6a showed a characteristic singlet singlet for indolyl C₂ proton at δ 8.60 ppm and N-methyl moiety at δ 3.85 ppm.

With the optimized reaction condition in hand, we further investigated the substrates scope employing different indoles 5b–5m (Table 2). Reaction of 4a with indoles 5b–5d bearing N-ethyl, N-benzyl, and N-phenyl moieties provided the desired products 6b–6d in 91, 67, and 72% yield, respectively. Treatment of 4a with N-arylated indoles 5e–5g having electron-donating or electron-withdrawing groups on the N-aryl ring, such as 4-Me, 4-OMe, and 4-Cl afforded the corresponding products 6e–6g in 76%, 70%, and 77% yield, respectively. Indoles 5h–5l bearing electron-donating or electron-withdrawing groups on the benzene ring were successful to afford the desired products. For example, reaction with N-methylindoles 5h–5i bearing electron-donating groups like methyl at 5- and 6-position on the aryl ring provided 6h (72%) and 6i (70%), respectively. The reaction of N-methylindolines 5j–5l bearing electron-withdrawing groups (5-F, 6-Cl, and 5-CO₂Me) afforded products 6j–6l in 66, 61, and 78% yield, respectively.

To demonstrate the versatility of this coupling reaction, further reactions between various substituted benzoxazin-2-ones 4b–4g and several N-substituted indoles 5a, 5b, 5d, and 5g were examined (Table 3). The reactions of 4b–4e bearing electron-donating groups such as 6-methyl, 7-methyl, 6-tert-butyl, and 6-phenyl with N-substituted indoles 5a, 5b, 5d, or 5g provided products 7a–7g in the range of 60–88% yield. The

**Table 1: Optimization of reaction condition for the synthesis of 6a**

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<tr>
<th>Entry</th>
<th>Catalyst</th>
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<th>Temp (℃)</th>
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a Reaction conditions: 4a (0.5 mmol), 5a (0.5 mmol), and catalyst (10 or 5 mol%) in solvent (3.0 mL) under air. b Yield of the isolated product 6a after column chromatography.
reactions of 4f and 4g bearing electron-withdrawing groups of 6-F and 6-Cl with 5a afforded the products 7h and 7i in 82% and 93% yield, respectively.

The utility of this new methodology for the gram-scale synthesis of naturally occurring cephalandole A (3) was next demonstrated (Scheme 2). Upon treatment of 4a with indole 5m at 60 °C for 12 h in THF, 3 was obtained in 75% yield. This one-pot protocol has several advantages such as higher yield, fewer steps, and lower cost. The synthesized compound was confirmed to be natural product 3 by comparison of its spectroscopic data with those previously reported.22

To elucidate the mechanism of this coupling reaction, we performed a control experiment (Scheme 3). The reaction between 4a with 5a in the absence of CuCl2 in THF at room temperature for 30 h provided compound 8 in 93% yield. Further reaction of 8 in the presence of 10 mol% of CuCl2 in THF at 60 °C for 1 h furnished 6a in 96% yield. These results suggest that compound 8 might be the intermediate in the coupling reaction.

Based on the above experiment, the mechanism for the formation of 6a is proposed as shown in Scheme 4. First, CuCl2
catalyst binds to 4a gives complex 4a', which subsequently undergoes nucleophilic attack by 5a to give 9. Deprotonation and protonation of 9 would afford intermediate 8, which undergoes air oxidation to give 6a.24

Conclusions

In summary, a novel and efficient copper-catalyzed direct coupling of benzoxazin-2-ones with indoles for the synthesis of diverse and functionalized 3-indolylbenzoxazin-2-ones has been developed. This methodology provides a rapid synthetic route to natural cephalandole A and its derivatives. The proposed protocol has a wide substrate scope for both benzoxazin-2-ones and indoles.

Experimental

Imino cyclic esters were synthesized in the laboratory according to known procedure.25 All indoles were prepared by either N-alkylation or N-arylation according to known method.26 Solvents were used without further purification. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points are uncorrected and were determined on Fisher-Johns Melting Point Apparatus. 1H NMR and 13C NMR spectra were recorded on a Varian VNS (600 and 150 MHz, respectively) spectrometer in CDCl3 using δ = 7.24 and 77 ppm as solvent chemical shift. Chemical shifts (δ) are expressed in units of ppm and coupling constants (J) values are given in Hz. Multiplicities are abbreviated as follows; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet and td = triplet of doublet. FT-IR (neat) spectra were recorded on ATR (PerkinElmer Spectrum 2) and HRMS was obtained on JEOL JMS-700 spectrometer at Korean Basic Science Institute.

General procedure for synthesis of 3-indolylbenzoxazin-2-ones

To the solution of imino cyclic esters (0.5 mmol) and indoles (0.5 mmol) in THF (3.0 mL), CuCl2 (7 mg, 10 mol%) was added at room temperature and heated at 60 °C for 3–24 h. Upon completion of reaction as indicated by thin layer chromatography, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography (hexane/ethyl acetate = 20:1) to afford the desired compounds.

3-(1-Ethyl-1H-indol-3-yl)-2H-benzo[1,4]oxazin-2-one (6b). Prepared from 4a (74 mg, 0.5 mmol) and N-ethylindole 5b (72 mg, 0.5 mmol) according to general procedure in 6 h as a yellow solid (132 mg, 91%); mp 180–182 °C; 1H NMR (600 MHz, CDCl3) δ 8.90–8.86 (m, 1H), 8.69 (s, 1H), 7.85 (dd, J = 7.8, 1.8 Hz, 1H), 7.41–7.33 (m, 5H), 7.29–7.27 (m, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.55 (t, J = 7.2 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 152.76, 147.39, 145.03, 136.50, 135.60, 132.45, 128.51, 128.22, 127.26, 125.31, 123.68, 123.32, 122.15, 115.95, 110.62, 109.74, 41.78, 15.25; ATR-IR (neat) 2973, 1725, 1528, 1386, 737 cm–1; HRMS (EI) m/z (M+) calcd for C18H14N2O2: 290.1055; found: 290.1053.

3-(1-Benzyl-1H-indol-3-yl)-2H-benzo[1,4]oxazin-2-one (6c). Prepared from 4a (74 mg, 0.5 mmol) and N-benzylindole 5c (104 mg, 0.5 mmol) according to general procedure in 6 h as a yellow solid (111 mg, 67%); mp 160–162 °C; 1H NMR (600 MHz, CDCl3) δ 8.90 (d, J = 7.8 Hz, 1H), 8.75 (s, 1H), 8.77 (dd, J = 7.8, 1.2 Hz, 1H), 7.41–7.25 (m, 9H), 7.17 (d, J = 7.2 Hz, 2H), 5.41 (s, 2H); 13C NMR (150 MHz, CDCl3) δ 152.70, 147.44, 145.09, 136.95, 136.68, 136.17, 132.89, 128.94, 128.74, 128.31, 128.02, 127.30, 126.80, 123.63, 123.61, 122.34, 116.01, 111.07, 110.34, 50.90; ATR-IR (neat) 2920, 1701, 1534, 1285, 739 cm–1; HRMS (EI) m/z (M+) calcd for C23H19N2O2: 352.1212; found: 352.1214.

3-(1-Phenyl-1H-indol-3-yl)-2H-benzo[1,4]oxazin-2-one (6d). Prepared from 4a (74 mg, 0.5 mmol) and N-phenylindole 5d (96 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (121 mg, 72%); mp 169–171 °C; 1H NMR (600 MHz, CDCl3) δ 8.95 (d, J = 8.4 Hz, 1H), 8.87 (s, 1H), 7.89 (dd, J = 7.8, 1.2 Hz, 1H), 7.58–7.53 (m, 5H), 7.43–7.27 (m, 1H), 7.41–7.36 (m, 3H), 7.34–7.29 (m, 2H); 13C NMR (150 MHz, CDCl3) δ 152.56, 147.38, 145.14, 138.57, 136.86, 135.87, 132.29, 129.76, 129.00, 128.43, 127.75, 127.43, 125.38, 124.91, 123.98, 123.70, 122.76, 116.03, 112.37, 110.92; ATR-IR (neat) 3056, 1734, 1531, 736 cm–1; HRMS (EI) m/z (M+) calcd for C23H19N2O2: 338.1055; found: 338.1052.

3-(1-(p-Tolyl)-1H-indol-3-yl)-2H-benzo[1,4]oxazin-2-one (6e). Prepared from 4a (74 mg, 0.5 mmol) and 1-(p-tolyl)-1H-indole 5e (104 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (133 mg, 76%); mp 175–177 °C; 1H NMR (600 MHz, CDCl3) δ 8.94 (d, J = 7.8 Hz, 1H), 8.84 (s, 1H), 7.89 (dd, J = 7.8, 1.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.36 (m, 7H), 2.45 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 152.60, 147.43, 145.15, 137.78, 137.04, 136.03, 132.35, 130.30, 128.91, 128.41, 127.37, 125.37, 124.80, 123.88, 123.65, 122.66, 116.03, 112.14, 110.97, 21.14; ATR-IR (neat) 3050, 1734, 1530, 1244, 1078, 741 cm–1; HRMS (EI) m/z (M+) calcd for C23H19N2O2: 352.1212; found: 352.1212.

3-(1-(4-Methoxyphenyl)-1H-indol-3-yl)-2H-benzo[1,4]oxazin-2-one (6f). Prepared from 4a (74 mg, 0.5 mmol) and 1-(4-methoxyphenyl)-1H-indole 5f (111 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (128 mg, 70%); mp 148–150 °C; 1H NMR (600 MHz, CDCl3) δ 8.94 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 7.89 (dd, J = 7.8, 1.8 Hz, 1H), 7.47–7.44 (m, 7H), 7.41–7.36 (m, 3H), 7.33–7.29 (m, 2H), 7.06 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 159.12, 152.61, 147.43,
methyl-1H-indole 5k (83 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (95 mg, 61%); mp 241–243 °C; 1H NMR (600 MHz, CDCl3) δ 8.76 (d, J = 8.4 Hz, 1H), 8.59 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.41–7.32 (m, 3H), 7.30–7.27 (m, 1H), 7.24 (s, 1H), 3.84 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 152.59, 147.09, 145.10, 137.93, 135.71, 132.22, 129.44, 128.95, 128.31, 125.53, 125.43, 124.52, 122.68, 116.04, 110.62, 109.82, 33.59; ATR-IR (neat) 1728, 1528, 1452, 918, 746 cm⁻¹; HRMS (EI) m/z (M⁺) calcd for C24H18ClN2O5: 374.0790; found: 374.0787.

Methyl 1-ethyl-1H-indol-3-yl-2H-benzo[b][1,4]oxazin-2-one (7b). Prepared from 7-methyl-1H-indol-3-yl-2H-benzo[b][1,4]oxazin-2-one 4c (81 mg, 0.5 mmol) and N-methylindole 5a (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (133 mg, 88%); mp 184–186 °C; 1H NMR (600 MHz, CDCl3) δ 8.90–8.86 (m, 1H), 8.66 (s, 1H), 7.64 (s, 1H), 7.40–7.37 (m, 1H), 7.34–7.31 (m, 2H), 7.18–7.14 (m, 2H), 4.23 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.54 (t, J = 7.2 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 152.91, 147.26, 142.95, 134.41, 135.05, 132.10, 129.44, 128.13, 127.25, 127.30, 123.20, 122.03, 115.47, 110.66, 109.66, 41.70, 20.86, 15.22; ATR-IR (neat) 1725, 1528, 1370, 1055, 744 cm⁻¹; HRMS (EI) m/z (M⁺) calcd for C19H16N4O2: 304.1212; found: 304.1216.

7-Methyl-3-(1-methyl-1H-indol-3-yl)-2H-benzo[b][1,4]oxazin-2-one (7c). Prepared from 7-methyl-2H-benzo[b][1,4]oxazin-2-one 4c (81 mg, 0.5 mmol) and N-methylindole 5a (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (122 mg, 84%); mp 216–218 °C; 1H NMR (600 MHz, CDCl3) δ 8.85–8.82 (m, 1H), 8.55 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.36–7.31 (m, 3H), 7.16–7.13 (m, 1H), 7.05 (s, 1H), 3.83 (s, 3H), 2.43 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 152.85, 146.36, 144.86, 139.53, 137.34, 136.64, 130.29, 127.80, 126.98, 126.37, 123.47, 123.25, 121.99, 116.03, 110.48, 109.51, 33.39, 21.54; ATR-IR
2.45 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 7.42 (dd, 112.40, 110.82, 21.60; ATR-IR (neat) 3051, 1738, 1514, 1228, 127.62, 127.43, 126.47, 124.86, 123.84, 123.67, 122.59, 116.12, 114.00, 110.82, 21.60; ATR-IR (neat) 3051, 1738, 1514, 1228, 736 cm−1; HRMS (EI) m/z (M+) calefd for C23H16N2O2: 352.1212; found: 352.1214.

6-(tert-Butyl)-3-(1-methyl-1H-indol-3-yl)-2H-benzo[b][1,4]oxazin-2-one (7e). Prepared from 6-(tert-butyl)-2H-benzo[b][1,4]oxazin-2-one 4d (101 mg, 0.5 mmol) and 1H-benzimidazoles 5a (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (352 mg, 87%); mp 140–142 °C; 1H NMR (600 MHz, CDCl3) δ 8.93 (d, J = 7.8 Hz, 1H), 8.88 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.57–7.52 (m, 5H), 7.44–7.41 (m, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.31 (td, J = 7.8, 1.2, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 2.45 (s, 3H); 13C NMR (150 MHz, CDCl3) δ 152.72, 146.36, 145.00, 140.08, 138.64, 136.77, 135.38, 130.22, 129.72, 128.02, 127.62, 127.43, 126.47, 124.86, 123.84, 123.67, 122.59, 116.12, 114.00, 110.82, 21.60; ATR-IR (neat) 3051, 1738, 1514, 1228, 736 cm−1; HRMS (EI) m/z (M+) calefd for C23H16N2O2: 352.1212; found: 352.1214.

6-Chloro-3-(1-methyl-1H-indol-3-yl)-2H-benzo[b][1,4]oxazin-2-one (7f). Prepared from 6-chloro-2H-benzo[b][1,4]oxazin-2-one 4g (91 mg, 0.5 mmol) and N-methylindole 5a (65 mg, 0.5 mmol) according to general procedure in 12 h as a yellow solid (137 mg, 78%); mp 236–238 °C; 1H NMR (600 MHz, CDCl3) δ 8.96 (d, J = 7.8 Hz, 1H), 8.80 (s, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.53–7.45 (m, 6H), 7.40 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 1.42 (s, 9H); 13C NMR (150 MHz, CDCl3) δ 152.96, 148.63, 147.15, 142.78, 137.37, 137.00, 131.77, 127.01, 126.13, 124.75, 123.54, 123.33, 122.10, 115.29, 110.51, 109.57, 34.64, 33.43, 31.45; ATR-IR (neat) 2952, 1727, 1526, 1369, 1074, 741 cm−1; HRMS (EI) m/z (M+) calefd for C23H16N2O2: 332.1525; found: 332.1527.

Gram-scale synthesis of cephalandole A

The solution of 2H-benzo[b][1,4]oxazin-2-one 4a (1.0 gram, 6.80 mmol) and indole 5m (0.81 gram, 6.80 mmol) in THF (15 mL), CuCl2 (48 mg, 10 mol%) was added at room temperature and heated at 60 °C for 12 h. Upon completion of reaction as indicated by thin layer chromatography, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography (hexane/ethyl acetate = 5:1) to afford cephalandole A (3, 1.337 gram, 75%); mp 237–239 °C; 1H NMR (600 MHz, acetone-d6) δ 11.07 (s, 1H), 8.89 (dd, J = 6.6, 4.8 Hz, 1H), 8.82 (dd, J = 3.0, 1.0 Hz, 1H), 7.89 (dd, J = 7.8, 1.2 Hz, 1H), 7.59–7.55 (m, 1H), 7.49 (td, J = 7.8, 1.8 Hz, 1H), 7.43 (td, J = 7.8, 1.8 Hz, 1H), 7.35 (dd, J = 7.8, 1.2 Hz, 1H), 7.30–7.26 (m, 2H); 13C NMR (150 MHz, acetone-d6) δ 152.95, 149.01, 146.19, 137.82, 134.53, 133.17, 129.53, 128.83, 127.32, 126.07, 124.13, 124.05, 122.43, 116.71, 112.72, 112.33; ATR-IR (neat) 3285, 1715, 1602, 1530, 1429 cm−1; HRMS (EI) m/z (M+) calefd for C17H18N2O2: 290.0725; found: 290.0724.

Control experiments

The solution of 4a (147 mg, 1.0 mmol) and N-methylindole 5a (130 mg, 1.0 mmol) in THF (3.0 mL) was stirred at room temperature 30 h. Upon completion of reaction as indicated by thin layer chromatography, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography (hexane/ethyl acetate = 5:1) to afford 8 as a solid (258 mg, 93%); mp 170–172 °C; 1H NMR (600 MHz, CDCl3) δ 7.67 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.26–7.23 (m, 1H), 7.16–7.13 (m, 1H), 7.07 (d, J =...
7.8, 1.2 Hz, 1H), 7.00 (td, J = 7.8, 1.2 Hz, 1H), 6.98 (s, 1H), 6.87 (td, J = 7.8, 1.2 Hz, 1H), 6.76 (dd, J = 7.8, 1.2 Hz, 1H), 5.33 (s, 1H), 3.70 (s, 4H). ¹³C NMR (150 MHz, CDCl₃) δ 165.15, 141.31, 137.10, 132.83, 127.74, 125.99, 124.99, 122.42, 120.36, 119.99, 119.24, 116.89, 115.04, 109.69, 109.63, 52.56, 32.89; ATR-IR (neat) 3346, 1735, 1529, 1119, 737 cm⁻¹; HRMS (EI) m/z (M⁺) calcd for C₁₇H₁₄N₂O₂: 278.1055; found: 278.1058.

To the solution of 8 (139 mg, 0.5 mmol) in THF (3.0 mL), CuCl₂ (7 mg, 10 mol%) was added at room temperature and was puriﬁed by column chromatography (hexane/ethyl acetate = 20 : 1) to afford 6a as a solid (132 mg, 96%).

Conflicts of interest
There are no conﬂicts to declare.

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Notes and references


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