Site-Selective Cross-Coupling of Dichlorinated Benzo-Fused Nitrogen-Heterocycles with Grignard Reagents

Hideyuki KONISHI, Tatsuya ITOH, and Kei MANABE*

School of Pharmaceutical Sciences, University of Shizuoka; 52–1 Yada, Suruga-ku, Shizuoka 422–8526, Japan.
Received May 11, 2010; accepted June 8, 2010; published online June 10, 2010

Site-selective cross-coupling of dihaloarenes constitutes a useful method for synthesis of multi-substituted arenes. In this paper, we report the site-selective cross-coupling of dichlorinated benzo-fused nitrogen-heterocycles having two chloro groups on the benzene ring. These dichlorinated heterocycles reacted with Grignard reagents in the presence of $PdCl_2(PCy_3)_2$ at the positions *ortho* to the nitrogen-based substituents with high selectivities. A mechanism in which interaction between Lewis acidic Mg and Cl of the *ortho* position facilitates C–Cl bond cleavage is proposed.

Key words catalysis; cross-coupling; palladium; site-selective; Grignard reagent; heterocycle

Site-selective cross-coupling of dihaloarenes constitutes a useful method for synthesis of multi-substituted arenes.[1—3] For dihalobenzenes having two substituents of the same halogen atom, however, site-selective cross-coupling involving selective conversion of one of the halogen atoms to another group still remains unestablished. Therefore, developing a new method of such cross-coupling is an important issue for synthesis of multi-substituted benzenes.

Recently, we developed a new site-selective cross-coupling in which chloro groups at a position *ortho* to a directing group such as OH, NH_2, CH_2OH, NHAc, or NHBoc reacted with Grignard reagents in the presence of a catalyst based on Pd and PCy_3 with high site-selectivities (Chart 1).[4—6] This reaction system has several unique features: (1) although electron-donating groups typically retard the oxidative addition step in cross-coupling reactions, the presence of electron-donating groups such as OH and NH_2 is essential in the reactions for acceleration at the *ortho*-position; (2) substrates with protic substituents react faster than those with a non-protic substituent such as a methoxy group; (3) this type of high *ortho*-selectivity was not observed in Suzuki–Miyaura coupling with boronic acids.

To expand the utility of this catalytic system, we planned to apply it to benzo-fused heterocycles such as indole, indoline, and tetrahydroquinoline, which are frameworks ubiquitous in natural products and pharmaceuticals.[7—11] There are some examples of site-selective cross-coupling of dibrominated or dichlorinated benzo-fused heterocycles.[1,2] For substrates having two halo groups on the benzene ring, however, no examples of highly selective cross-coupling have been reported. Therefore, development of site-selective cross-coupling of these benzo-fused heterocycles should be valuable. In addition, these benzo-fused heterocycles have a feature distinct from *N*-unsubstituted anilines that we previously used as substrates: rotation of the C_{ipso}–N bonds is restricted for the benzo-fused heterocycles, while that of the anilines is not. We were interested in effects of the restricted conformation on site-selectivity. Herein we report the site-selective cross-coupling of dichlorinated benzo-fused nitrogen-heterocycles having two chloro groups on the benzene ring. The substrates reacted with Grignard reagents in the presence of $PdCl_2(PCy_3)_2$ at the positions *ortho* to the nitrogen-based substituents with high selectivities.

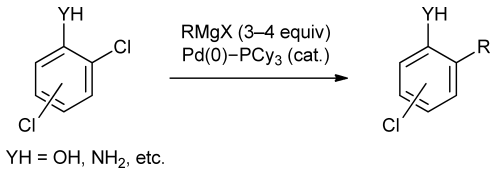
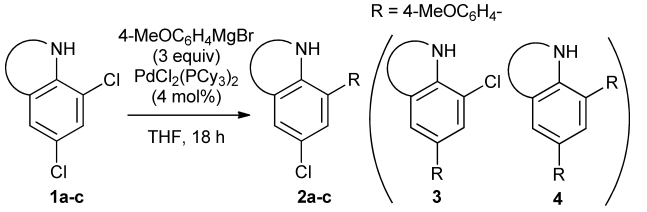
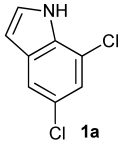
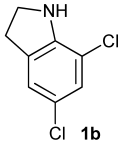
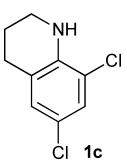


Chart 1. Previous *ortho*-Selective Cross-Coupling

Substrates **1a**—**c**, which were easily prepared according to literature procedures,[12—15] were subjected to cross-coupling with 4-methoxyphenylmagnesium bromide in the presence of $PdCl_2(PCy_3)_2$ at 50—70 °C. We were pleased to find that highly site-selective reactions occurred to give products **2a**—**c** (Table 1). Although the yields of **2a** and **2b** were modest

Table 1. Site-Selective Cross-Coupling of Dichlorinated Benzo-Fused Nitrogen-Heterocycles



Entry	Substrate **1**	Temperature (°C)	Yield (%) of **2**
1	 **1a**	70	60 (**2a**)
2	 **1b**	50	41 (**2b**)
3	 **1c**	70	87 (**2c**)

* To whom correspondence should be addressed. e-mail: manabe@u-shizuoka-ken.ac.jp

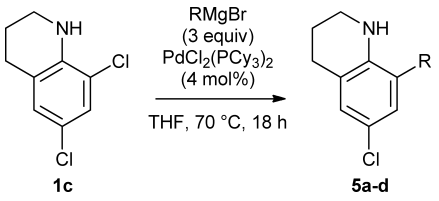
(entries 1, 2), neither isomers **3** nor doubly cross-coupled products **4** were obtained in any cases. In all cases, the homo-coupling product of the Grignard reagent was observed as the major by-product.

We next carried out reactions of **1c** with various Grignard reagents. As shown in Table 2, the reactions proceeded to give the products with high site-selectivities. Not only aryl Grignard reagents but also heteroaryl and alkenyl Grignard reagents worked well. In all cases, the para Cl group of **1c** did not react. When *n*-octylmagnesium bromide was used, the desired cross-coupled product was obtained only in a very small amount, and instead, a reduced compound in which the *ortho*-chloro group was converted to hydrogen was obtained.

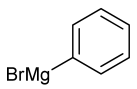
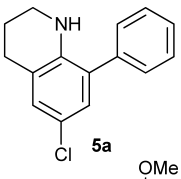
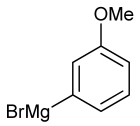
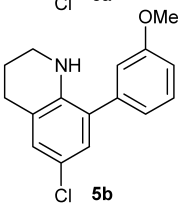
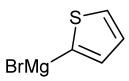
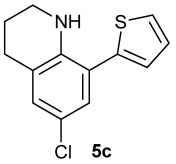
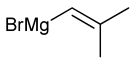
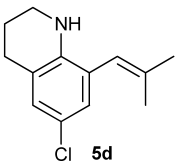
The preference of the reaction at the *ortho*-position was also observed in a competitive reaction between two substrates. Thus, 7-chloroindole (**6**) preferentially reacted over 5-chloroindole (**7**) as shown in Eq. 1.

For substrates **1a**—**c**, the proton on the nitrogen atom must be deprotonated with a Grignard reagent under the reaction conditions to generate the corresponding Mg amides. We assume that formation of the Mg amides is important for acceleration of the reactions at the position *ortho* to the Mg amido groups. To support this assumption, *N*-methylated compound **10**, which cannot generate a Mg amide, was used as a substrate. As shown in Eq. 2, no cross-coupled products were obtained (homo-coupling of the Grignard reagent was observed). This result suggests that the formation of the Mg amides is the key for the acceleration at the *ortho*-positions in the cross-coupling of these benzo-fused nitrogen-heterocycles.

Table 2. Site-Selective Cross-Coupling of **1c** with Various Grignard Reagents

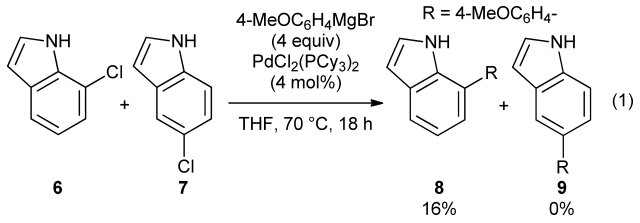


1c **5a-d**

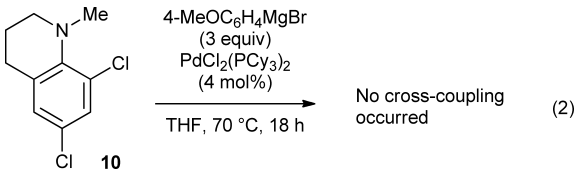
Entry	RMgBr	Product **5**	Yield (%)
1		 **5a**	78
2		 **5b**	76
3		 **5c**	77
4		 **5d**	53

We conducted a preliminary study using density functional theory (DFT) calculations (B3LYP/6-31G*) on Mg amides **11a**—**c** derived from **1a**—**c** (Fig. 2). One molecule of dimethyl ether, which is a simplified surrogate of THF, was included as a solvent coordinated to Mg. In the structures of **11a**—**c**, the *ortho*-C–Cl bonds were found to be significantly longer than the *para*-C–Cl bonds; the differences between the *ortho*- and *para*-C–Cl bond lengths are 0.028 Å, 0.028 Å, and 0.038 Å for **11a**—**c**, respectively. In the structures of the parent compounds (**1a**—**c**), the differences between the *ortho*- and *para*-C–Cl bond lengths are less than 0.008 Å. The elongation of the *ortho*-C–Cl bonds of Mg amides **11a**—**c** is likely to result from an interaction between Cl and the Lewis acidic Mg. This interaction should activate the *ortho*-C–Cl bond for the oxidative addition step.

Although rotation of the C_{ipso}–N bond is restricted for the benzo-fused heterocycles compared with anilines, high site-selectivity was still observed as in the cases of the aniline substrates. This suggests that the conformations shown in the calculated structures are plausible as the transition states.



6 **7** **8** 16% **9** 0%



10

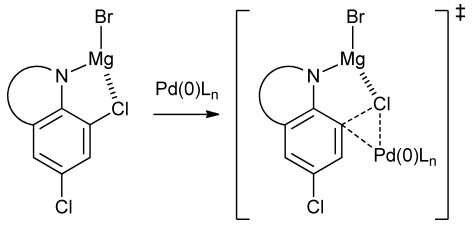


Fig. 1. Proposed Mechanism of Activation of *ortho*-C–Cl Bond

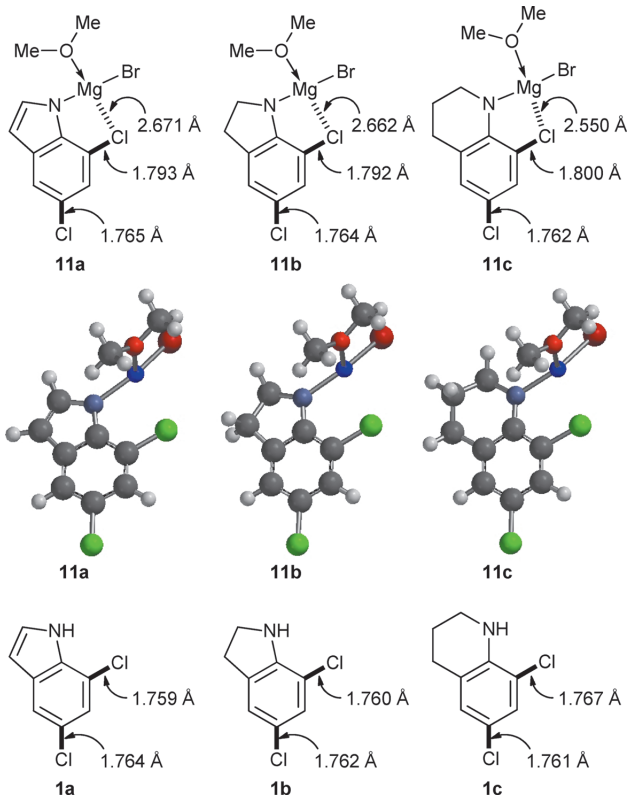


Fig. 2. Selected Bond Lengths in **11a**—**c** and **1a**—**c** Calculated Using a DFT Method (B3LYP/6-31G*)

The results shown in this paper strongly support the mechanism that the Mg–Cl interaction is the key for the acceleration of the cross-coupling at the position *ortho* to the nitrogen-based substituents, while further studies including those on transition states of the oxidative addition are necessary to clarify the precise mechanism for the site-selectivity.[19—24]

In summary, we found that nitrogen-heterocycles fused with a dichlorobenzene ring underwent site-selective cross-coupling with Grignard reagents in the presence of a Pd catalyst. The reactions occurred at the position *ortho* to the nitrogen-based substituents with high selectivities. Experimental and computational studies suggest that Mg–Cl interaction plays an important role in the acceleration of the cross-coupling at the *ortho*-position. This work should expand the utility of site-selective cross-coupling and shed light on the mechanism of the reaction.

Experimental

General All reactions were performed in oven dried or flame dried glassware under argon atmosphere. Reactions were monitored by TLC on Merck silica gel 60 F254 plates visualized by UV lump at 254 nm. Column chromatography was performed on MERCK Silica Gel 60 and preparative TLC was performed on Merck silica gel 60 F254 0.5 mm plates. NMR spectra were measured on a JEOL ECA-500 NMR spectrometer at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra, and for ^{1}H-NMR, tetramethylsilane (TMS) (δ=0) in $CDCl_3$ served as an internal standard. For ^{13}C-NMR, $CDCl_3$ (δ=77.00) served as an internal standard. Infrared spectra were measured on a SHIMADZU IR Prestige-21 spectrometer (ATR). High resolution-mass spectra (HR-MS) were measured on a BRUKER DALTONICS micrOTOF (electrospray ionization (ESI)). Melting point was measured using a YAZAWA MICRO MELTING POINT BY-1.

Materials Tetrahydrofuran (THF) was distilled from Na/benzophenone and used immediately. $PdCl_2(PCy_3)_2$, all Grignard reagents, 7-chloroindole (**6**) and 5-chloroindole (**7**) were purchased from Aldrich and used as received. Compounds **1a**,[12,13] **1b**,[14] and **1c**[15] were prepared according to previously reported procedures.

***N*-Methyl-6,8-dichloro-1,2,3,4-tetrahydroquinoline (10)** *N*-Methyl-1,2,3,4-tetrahydroquinoline was obtained by methylation of 1,2,3,4-tetrahydroquinoline in the presence of formaldehyde and sodium cyanoborohydride in 75% yield.[24] To a solution of *N*-methyl-1,2,3,4-tetrahydroquinoline (180 mg, 1.22 mmol) in CH_2Cl_2 (30 ml) was added *N*-chlorosuccinimide (360 mg, 2.69 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h then at 40 °C for 42 h. The reaction mixture was diluted with CH_2Cl_2, successively washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. After filtration, all volatiles were evaporated and the crude mixture was purified by column chromatography (hexane : Et_2O=10 : 1) to give **10** as a yellow oil (215 mg, 82%). ^{1}H-NMR ($CDCl_3$) δ: 1.83—1.85 (2H, m), 2.77 (2H, t, J=6.5 Hz), 2.87 (3H, s), 3.12—3.17 (2H, m), 6.95 (1H, s), 7.18 (1H, d, J=2.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 16.9, 27.8, 42.7, 51.8, 122.1, 126.2, 127.8, 127.9, 132.2, 144.6. IR (ATR): 2938, 2862, 1686, 1466, 1449, 1416, 1161, 905, 808 cm^{-1}. HR-MS (ESI): Calcd for $C_{10}H_{12}Cl_2N$ $(M+H)^+$ 216.0341, Found 216.0329.

Representative Experimental Procedure for Site-Selective Cross-Coupling (Table 1, Entry 1) To a solution of **1a** (81.0 mg, 0.500 mmol) and $PdCl_2(PCy_3)_2$ (4 mol%) in THF (0.25 M) was slowly added a 0.5 M solution of 4-methoxyphenylmagnesium bromide in THF (3.00 ml, 1.50 mmol, 3 eq) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 70 °C for 18 h. The reaction was quenched by a saturated NH_4Cl aqueous solution. After AcOEt was added, the layers were separated, and the aqueous layer was extracted with AcOEt. Combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After filtration, all volatiles were evaporated and the crude mixture was purified by preparative TLC (hexane : AcOEt=5 : 1) to give **2a** (78.0 mg, 0.303 mmol, 61%) as a white solid. Note: in case that a biphenyl-type by-product which was obtained through homocoupling of the Grignard reagent was contaminated after preparative TLC separation, yields of the products were determined by ^{1}H-NMR analysis, and analytically pure compounds were obtained by further purification using preparative TLC. The structures of regioisomers were determined through conversion of the products to the corresponding dechlorinated compound (Pd/C, HCOONa) whose structures could be determined by NMR.

5-Chloro-7-(4-methoxyphenyl)indole (2a) White solid. mp 142—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s), 6.54—6.55 (1H, m), 7.05 (2H, d, J=8.5 Hz), 7.15 (1H, d, J=1.2 Hz), 7.23 (1H, t, J=2.9 Hz), 7.53 (2H, d, J=8.5 Hz), 7.57 (1H, d, J=1.2 Hz), 8.38 (1H, br). ^{13}C-NMR ($CDCl_3$) δ: 55.4, 102.8, 114.7, 118.7, 121.7, 125.5, 125.8, 126.4, 129.1, 129.2, 130.3, 132.3, 159.4. IR (ATR): 3326, 1611, 1516, 1502, 1463, 1238, 1175, 722 cm^{-1}. HR-MS (ESI, negative mode): Calcd for $C_{15}H_{11}ClNO$ $(M-H)^-$ 256.0535, Found 256.0502.

5-Chloro-7-(4-methoxyphenyl)indoline (2b) The reaction was performed with **1b** (94.0 mg, 0.500 mmol) at 50 °C. Purification by preparative TLC (hexane : AcOEt=1 : 1) afforded **2b** (54.0 mg, 0.208 mmol, 41%) as a yellow-white solid. mp 118—122 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.06 (2H, t, J=8.2 Hz), 3.53 (2H, t, J=8.2 Hz), 3.84 (3H, s), 3.98 (1H, br), 6.96 (2H, d, J=8.5 Hz), 7.02—7.02 (2H, m), 7.44 (2H, d, J=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 30.0, 47.6, 55.3, 114.2, 123.2, 123.4, 123.5, 126.6, 129.0, 130.7, 131.4, 147.7, 158.8. IR (ATR): 3377, 2924, 1609, 1510, 1460, 1236, 1173 cm^{-1}. HR-MS (ESI): Calcd for $C_{15}H_{15}ClNO$ $(M+H)^+$ 260.0837, Found 260.0804.

6-Chloro-8-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (2c) The reaction was performed with **1c** (68.0 mg, 0.336 mmol). Purification by preparative TLC (hexane : AcOEt=7 : 1) afforded **2c** (80.0 mg, 0.293 mmol, 87%) as a yellow-white solid. mp 117—120 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.91—1.93 (2H, m), 2.80 (2H, t, J=6.2 Hz), 3.23 (2H, t, J=6.2 Hz), 3.85 (3H, s), 4.02 (1H, br), 6.87 (1H, s), 6.91 (1H, d, J=1.1 Hz), 6.97 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 27.3, 41.8, 55.3, 114.3, 120.6, 122.7, 127.5, 127.7, 128.0, 130.3, 130.5, 140.5, 159.0. IR (ATR): 3401, 2835, 1609, 1513, 1493, 1238, 1177 cm^{-1}. HR-MS (ESI): Calcd for $C_{16}H_{16}ClNO$ $(M)^+$ 273.0915, Found 273.0909.

6-Chloro-8-phenyl-1,2,3,4-tetrahydroquinoline (5a) The reaction was performed with **1c** (89.6 mg, 0.443 mmol) and a 1 M solution of phenylmagnesium bromide in THF (1.33 ml, 1.33 mmol). Purification by preparative TLC (hexane : AcOEt=7 : 1) afforded **5a** (86.3 mg, 0.344 mmol, 78%) as a yellow-white solid. mp 101—104 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.90—1.95 (2H, m), 2.80 (2H, t, J=6.5 Hz), 3.23 (2H, t, J=6.5 Hz), 4.03 (1H, br), 6.89 (1H, d, J=2.3 Hz), 6.93 (1H, d, J=2.3 Hz), 7.33—7.45 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 27.4, 41.8, 120.7, 122.8, 127.4, 127.4, 127.7, 128.2, 128.9, 129.2, 138.3, 140.3. IR (ATR): 3420, 2926, 1487, 1420, 1356, 1261, 1072 cm^{-1}. HR-MS (ESI): Calcd for $C_{15}H_{14}ClN$ $(M)^+$ 243.0809, Found

243.0838.

6-Chloro-8-(3-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (5b) The reaction was performed with **1c** (57.6 mg, 0.285 mmol) and a 1 M solution of 3-methoxyphenylmagnesium bromide in THF (0.855 ml, 0.855 mmol). Purification by preparative TLC (hexane : AcOEt=9 : 1, developed twice) afforded **5b** (59.6 mg, 0.218 mmol, 76%) as a yellow-white solid. mp 88—92 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.91—1.95 (2H, m), 2.80 (2H, t, J=6.5 Hz), 3.24 (2H, t, J=5.7 Hz), 3.84 (3H, s), 4.09 (1H, br), 6.88—6.93 (4H, m), 6.96 (1H, d, J=7.9 Hz), 7.34 (1H, t, J=7.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 27.4, 41.8, 55.3, 113.1, 114.6, 120.5, 121.4, 122.7, 127.3, 127.4, 128.2, 130.0, 139.7, 140.2, 160.0. IR (ATR): 3406, 2930, 1585, 1485, 1462, 1356, 1290, 1227, 1034, 864, 781, 702 cm^{-1}. HR-MS (ESI): Calcd for $C_{16}H_{16}ClNO$ $(M)^+$ 273.0915, Found 273.0913.

6-Chloro-8-(2-thienyl)-1,2,3,4-tetrahydroquinoline (5c) The reaction was performed with **1c** (59.0 mg, 0.292 mmol) and a 1 M solution of 2-thienylmagnesium bromide in THF (0.876 mg, 0.876 mmol). Purification by preparative TLC (hexane : AcOEt=5 : 1) afforded **5c** (55.6 mg, 0.223 mmol, 77%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.91—1.96 (2H, m), 2.79 (2H, t, J=6.2 Hz), 3.29 (2H, t, J=6.2 Hz), 4.46 (1H, br), 6.93 (1H, d, J=2.3 Hz), 7.04 (1H, d, J=2.3 Hz), 7.10—7.11 (1H, m), 7.13—7.14 (1H, m), 7.35 (1H, dd, J=5.1, 1.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 27.4, 41.8, 119.7, 120.4, 123.0, 125.6, 126.3, 127.5, 128.2, 128.8, 139.6, 141.0. IR (ATR): 3418, 2928, 2837, 1489, 1439, 1425, 1354, 1287, 1190, 851 cm^{-1}. HR-MS (ESI): Calcd for $C_{13}H_{12}ClNS$ $(M)^+$ 249.0373, Found 249.0381.

6-Chloro-8-(2-methylprop-1-en-1-yl)-1,2,3,4-tetrahydroquinoline (5d) The reaction was performed with **1c** (55.0 mg, 0.272 mmol) and a 0.5 M solution of 2-methylpropen-1-ylmagnesium bromide in THF (1.63 ml, 0.816 mmol). Purification by preparative TLC (hexane : AcOEt=7 : 1) afforded **5d** (31.7 mg, 0.143 mmol, 53%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (3H, d, J=1.1 Hz), 1.90 (3H, d, J=1.1 Hz), 1.91—1.94 (2H, m), 2.75 (2H, t, J=6.5 Hz), 3.32 (2H, t, J=6.5 Hz), 3.83 (1H, br), 5.88 (1H, s), 6.78 (1H, d, J=2.3 Hz), 6.82 (1H, d, J=2.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.4, 21.7, 26.0, 27.2, 41.9, 119.8, 120.1, 122.2, 124.4, 127.0, 127.1, 138.4, 140.8. IR (ATR): 3426, 2928, 2853, 1489, 1447, 1352, 1292, 1179, 1070, 880, 866 cm^{-1}. HR-MS (ESI): Calcd for $C_{13}H_{16}ClN$ $(M)^+$ 221.0966, Found 221.0975.

Experimental Procedure for a Competitive Reaction of Compounds 6 and 7 To a solution of 7-chloroindole (**6**) (71.0 mg, 0.468 mmol), 5-chloroindole (**7**) (71.0 mg, 0.468 mmol) and $PdCl_2(PCy_3)_2$ (17.3 mg, 0.0234 mmol, 5 mol%) in THF (0.125 M) was slowly added 4-methoxyphenylmagnesium bromide (0.5 M in THF, 3.74 ml, 1.87 mmol, 4 eq) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 70 °C for 18 h. The reaction was quenched with a saturated NH_4Cl aqueous solution. After AcOEt was added, the layers were separated, and the aqueous layer was extracted with AcOEt. Combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After filtration, all volatiles were evaporated, and the crude mixture was analyzed by ^{1}H-NMR spectra with comparison to literature data[25] to obtain yields of products **8** and **9**.

Computational Analysis All the molecular calculations were performed with Spartan '04.[26] Geometry optimizations in the gas phase were carried out with the B3LYP/6-31G(d) DFT method.[27,28]

Acknowledgment We thank Takeda Science Foundation for financial support.

References

1) Schröter S., Stock C., Bach T., *Tetrahedron*, **61**, 2245—2267 (2005).
2) Fairlamb I. J. S., *Chem. Soc. Rev.*, **36**, 1036—1045 (2007).
3) Wang J.-R., Manabe K., *Synthesis*, 1405—1427 (2009).
4) Ishikawa S., Manabe K., *Org. Lett.*, **9**, 5593—5595 (2007).
5) Manabe K., Ishikawa S., *Synthesis*, 2645—2649 (2008).
6) Ishikawa S., Manabe K., *Synthesis*, 3180—3182 (2008).
7) Sundberg R. J., "Comprehensive Heterocyclic Chemistry II," Vol. 2, ed. by Katritzky A. R., Ress C. W., Scriven E. F. V., Bird C. W., Pergamon Press, Oxford, 1996, pp. 119—206.
8) Gribble G. W., "Comprehensive Heterocyclic Chemistry II," Vol. 2, ed. by Katritzky A. R., Ress C. W., Scriven E. F. V., Bird C. W., Pergamon Press, Oxford, 1996, pp. 207—258.
9) Kawasaki T., Higuchi K., *Nat. Prod. Rep.*, **22**, 761—793 (2005).
10) Somei M., Yamada F., *Nat. Prod. Rep.*, **22**, 73—103 (2005).
11) Katritzky A. R., Rachwal S., Rachwal B., *Tetrahedron*, **52**, 15031—15070 (1996).
12) Bartoli G., Palmieri G., *Tetrahedron Lett.*, **30**, 2129—2132 (1989).
13) Teng X., Degterev A., Jagtap P., Xing X., Choi S., Denu R., Yuan J., Cuny G. D., *Bioorg. Med. Chem. Lett.*, **15**, 5039—5044 (2005).
14) Nomura S., Yamamoto Y., WO 2006080577 (2006) [PCT Int. Appl.].
15) Su D.-S., Anthony N. J., Lim J. J., Tinney E., Williams T. M., WO 2007146230 A2 (2007) [PCT Int. Appl.].
16) Activation of C–X bonds by coordination to Mg has been reported. See: Terao J., Ikumi A., Kuniyasu H., Kambe N., *J. Am. Chem. Soc.*, **125**, 5646—5647 (2003).
17) Yoshikai N., Mashima H., Nakamura E., *J. Am. Chem. Soc.*, **127**, 17978—17979 (2005).
18) Saeki T., Takashima Y., Tamao K., *Synlett*, 1771—1774 (2005).
19) Fairlamb I. J. S., O'Brien C. T., Linb Z., Lam K. C., *Org. Biomol. Chem.*, **4**, 1213—1216 (2006).
20) Handy S. T., Zhang Y., *Chem. Commun.*, 299—301 (2006).
21) Legault C. Y., Garcia Y., Merlic C. A., Houk K. N., *J. Am. Chem. Soc.*, **129**, 12664—12665 (2007).
22) Garcia Y., Schoenebeck F., Legault C. Y., Merlic C. A., Houk K. N., *J. Am. Chem. Soc.*, **131**, 6632—6639 (2009).
23) Schaub T., Fischer P., Steffen A., Braun T., Radius U., Mix A., *J. Am. Chem. Soc.*, **130**, 9304—9317 (2008).
24) Shaffer C. L., Morton M. D., Hanzlik R. P., *J. Am. Chem. Soc.*, **123**, 8502—8508 (2001).
25) Prieto M., Zurita E., Rosa E., Munoz L., Williams L. P., Giralt E., *J. Org. Chem.*, **69**, 6812—6820 (2004).
26) Kong J., White C. A., Krylov A. I., Sherrill C. D., Adamson R. D., Furlani T. R., Lee M. S., Lee A. M., Gwaltney S. R., Adams T. R., Ochsenfeld C., Gilbert A. T. B., Kedziora G. S., Rassolov V. A., Maurice D. R., Nair N., Shao Y., Besley N. A., Maslen P. E., Dombroski J. P., Daschel H., Zhang W., Korambath P. P., Baker J., Byrd E. F. C., Van Voorhis T., Oumi M., Hirata S., Hsu C.-P., Ishikawa N., Florian J., Warshel A., Johnson B. G., Gill P. M. W., Head-Gordon M., Pople J. A., *J. Computational Chem.*, **21**, 1532—1548 (2000).
27) Kohn W., Becke A. D., Parr R. G., *J. Phys. Chem.*, **100**, 12974—12980 (1996).
28) Becke A. D., *J. Chem. Phys.*, **98**, 5648—5652 (1993).