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Ni- AND Cu-CATALYZED COUPLING REACTIONS UISING 2-(4,5-DIHYDRO-1*H*-IMIDAZO-2-YL)PHENOL AS A VERSATILE PHOSPHINE-FREE LIGAND

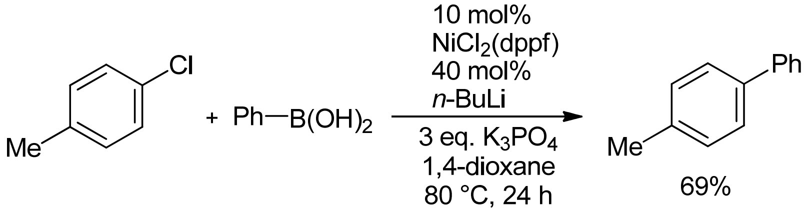
Satoshi Haneda, Kazuhiko Sudo, and Masahiko Hayashi*

Department of Chemistry, Graduate School of Science, Kobe University, Nada, Kobe 657-8501, Japan *E-mail: mhayashi@kobe-u.ac.jp

Abstract – We have disclosed 2-(4,5-dihydro-1*H*-imidazo-2-yl)phenol (**1**) worked efficiently as a ligand in Ni-catalyzed Suzuki-Miyaura coupling reactions and Cu-catalyzed *N*-cyclopropylation of indoles using cyclopropylboronic acid.

INTRODUCTION

In 1995, Percec and his co-workers first reported Ni-catalyzed Suzuki-Miyaura coupling of aryl mesylates with arylboronic acid using 10 mol% of $NiCl_2$(dppf) (dppf = 1,1’-bis(diphenylphosphino)ferrocene) in the presence of K_3PO_4 in dioxane at 100 °C. They used Zn to generate Ni(0) *in situ* from $NiCl_2$(dppf).[1] In 1996, Miyaura *et al.* reported the use of 4 eq. of *n*-BuLi instead of Zn as a reducing reagent (eq. 1).[2]



(1)

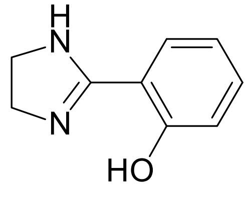
Indolese revealed the Suzuki-Miyaura coupling of aryl chlorides with arylboronic acids proceeded using $NiCl_2$(dppf) in the presence of K_3PO_4 in dioxane without any reducing reagents in 1997.[3] Miyaura also, reported the system of $NiCl_2(PPh_3)_2/2PPh_3/K_3PO_4.n\text{-}H_2O$/toluene in Suzuki—Miyaura coupling.[4-6]

As for phosphine-free ligand, Leadbeater first reported nitrogen based Ni-catalyzed coupling reactions using $NiCl_2(NEt)_3$ and $NiCl_2$(bpy) complexes as a catalyst.[7] We also reported nitrogen-based, especially, including imidazole or imidazoline ligand—$PdCl_2$ catalyzed Mizoroki-Heck and Suzuki-Miyaura coupling reactions.[8]

This paper is dedicated to Prof. Dr. Albert Padwa on the occasion of his 75th birthday.

Here we report the utility of 2-(4,5-dihydro-1*H*-imidazo-2-yl)phenol **1** as a useful ligand in Ni- and Cu-catalyzed coupling reaction using boronic acid as a coupling partner.

RESULTS AND DISCUSSION



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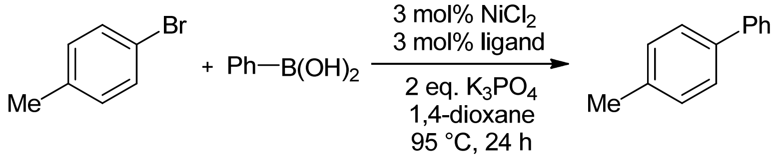
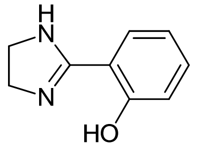
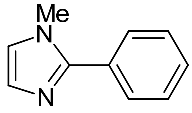
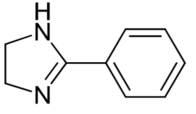
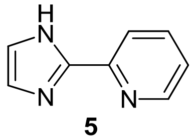
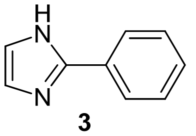
We first examined the reaction of Ni-catalyzed reaction of 4-methylbromobenzene with phenylboronic acid. The nature of the ligand is summarized in Table 1. Only ligand **1** exhibited the high performance to give the coupling product in high yield (72% and 92% by the use of $NiCl_2$ and $Ni(cod)_2$ as a catalyst precursor, respectively). In Mizoroki-Heck reaction, other ligand or catalyst, for example, ligand **5**—$PdCl_2$ complex showed high catalytic activity,[8a] however, in the present Ni-catalyzed reaction, catalytic activity of ligand **5**—$PdCl_2$ complex was proved to be quite low. After screening of the metal source, ligand, solvent, base, and reaction temperature, we optimized the reaction condition as follows: 3 mol% of $NiCl_2$ in the presence of 3 mol% of ligand, in the presence of 2 eq. of K_3PO_4 as a base in dioxane at 95 °C for 24 h. The reaction of 2-bromonaphthalene with phenylboronic acid gave the coupling product in 49% yield (eq. 2). In this case, $Ni(OAc)_2•4H_2O$ exhibited higher reactivity than $NiCl_2$ and $Ni(cod)_2$ as a Ni source.

Table 1. Reaction of 4-methylbromobenzene with phenylboronic acid[a]



Entry	Ligand	Yield/%	Entry	Ligand	Yield/%
1	 **1**	72 92^b	4	 **4**	25
2	 **2**	23^c	5	 **5**	21
3	 **3**	27^c	6	none	30

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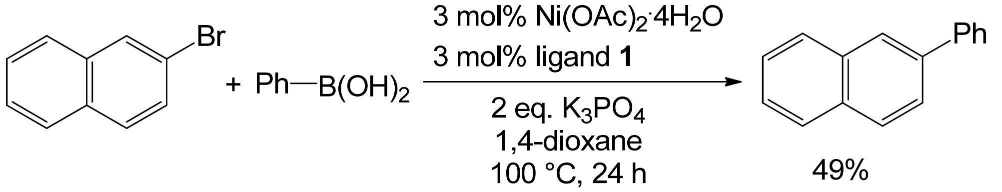
[a] All reactions were carried out in dioxane at 95 °C for 24 h using 3 mol% of $NiCl_2$ and 3 mol% of ligand in the presence of 2 eq. K_3PO_4 unless otherwise noted. [b] $Ni(cod)_2$ was used instead of $NiCl_2$. [c] ligand; 6 mol%.



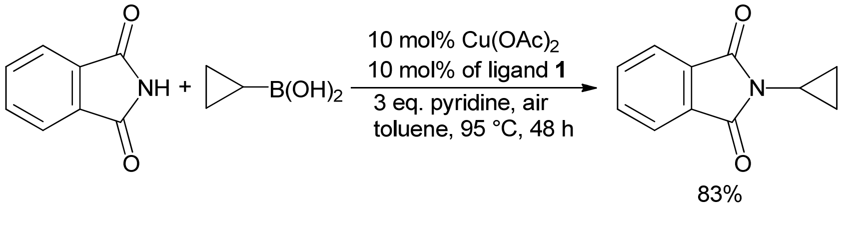
(2)

Then we examined Cu-catalyzed *N*-cyclopropylation of indoles using ligand **1**. The direct introduction of cyclopropyl group is one of the important problems for the synthesis pharmacuitical compounds such as Nevirapine, Ciprofloxacin and Sparfloxacin. To the best of our knowledge, there are two reports of *N*-cyclopropylation of indoles. In 2007, Gagnon and his co-workers reported the *N*-cyclopropylation of indoles using tricyclopropylbismus reagents promoted by 1.5 eq. $Cu(OAc)_2$ and 3 eq. pyridine to give the cyclopropylation products in 31—98% yield.[9] Tsuritani and his co-workers reported the use of cyclopropylboronic acid in the presence of 0.1 eq. or 1 eq. of $Cu(OAc)_2$, 3 eq. DMAP, 1 eq. NaHMDS. In both of catalytic and stoichiometric cases, the yields range from low to good or high, that is, <5—72% yield (0.1 eq.) and 15—93% yield (1 eq.), respectively.[10]

Based on the above reported background, we examined the utility of 2-(4,5-dihydro-1*H*-imidazo-2-yl)phenol **1** as a ligand in the reaction of substituted indoles and cyclopropylboronic acid catalyzed by $Cu(OAc)_2$. After screening of a variety of reaction factors such as Cu prepursors, solvent, base and temperature, we found the combination of $Cu(OAc)_2$, ligand **1**, toluene as a solvent, pyridine as a base 95 °C was the best choice. By using this system, cycloproplated product of indole was obtained in 41% yield. It should be mentioned that the ligand **1** also gave the best result in this reaction among the ligands we examined such as bipyridyl, and 9,10-phenanthroline. Then, we examined the reaction of substituted indoles with cyclopropylboronic acid. The indole having nitro group at 5 and 6 position gave the products in 62% and 63% yield, respectively.

As for the reaction mechanism, Tromp and his co-workers examined the reaction of Cu(II)-catalyzed arylation of imidazoles and phenylboronic acid using multiple and time-resolved spectroscopic techniques such as EDXFAFS, UV-vis, EPR, and NMR.[11] Based on their proposed mechanism, we adopted disproportionation mechanism as shown in Scheme 1. Cu-alkoxide will form the dimeric species of Cu(II), which disproportionationated Cu(I) and Cu(III), then, the latter will catalyze the cyclopropanation of indole with cyclopropylboronic acid. The resulting Cu(I) will be oxidized to Cu(III) by O_2.

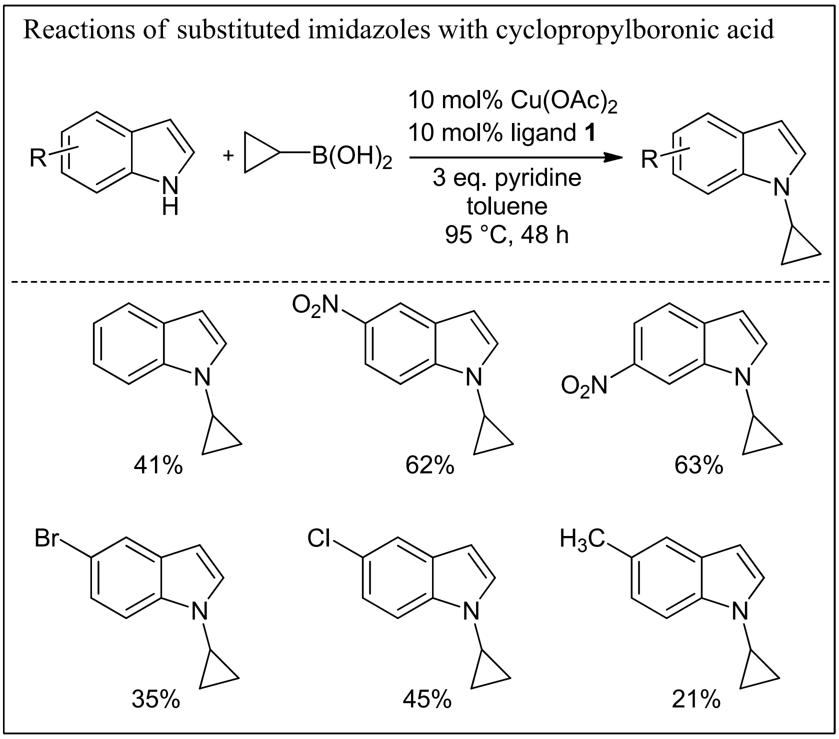
Phthalimide is more reactive than indole. Under the reaction condition, that is, 10 mol% of $Cu(OAc)_2$ and 10 mol% of ligand **1** in the presence of 3 equiv. of pyridine in toluene afforded the cyclopropyl product in 83% yield (eq. 3).

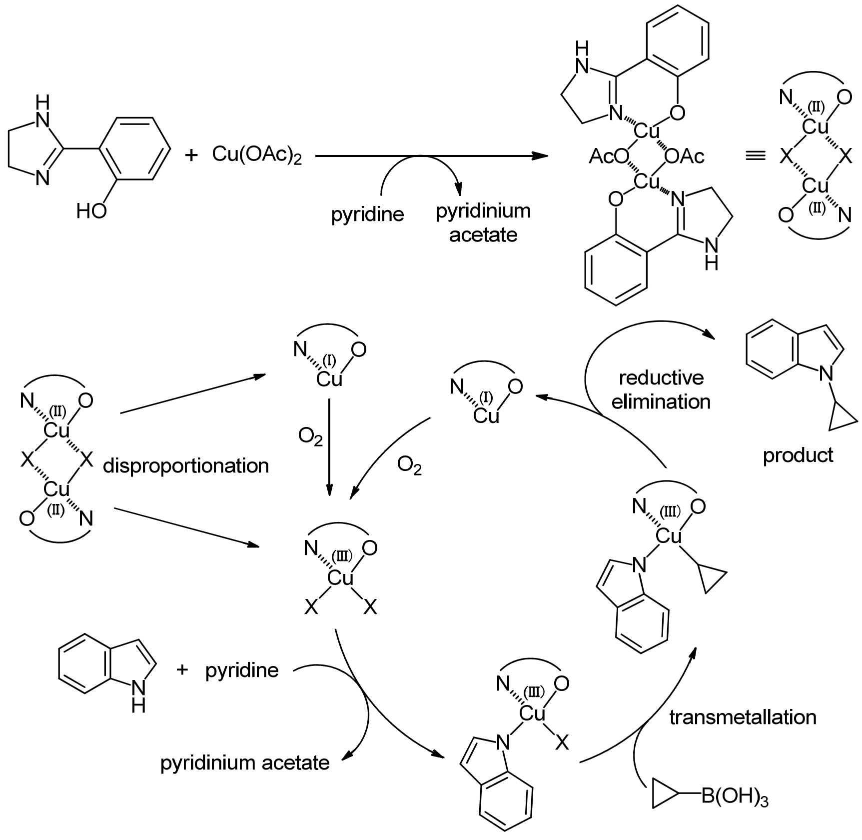


(3)

CONCLUSION

We have revealed that 2-(4,5-dihydro-1*H*-imidazo-2-yl)phenol worked efficiently in Ni-catalyzed Suzuki-Miyaura reaction and Cu-catalyzed *N*-cyclopropylation of indoles using cyclopropylboronic acid.





Scheme 1. Proposed mechanism of Cu-catalyzed *N*-cyclopropylation of indoles

EXPERIMENTAL

General: IR spectra were measured on a PERKIN ELMER FT-IR Spectrometer SPECTRUM 1000. ^{1}H and ^{13}C NMR spectra (400.0 and 100.6 MHz, respectively) were recorded on a JEOL JNM-LA 400 using Me_4Si as the internal standard in $CDCl_3$. Elemental analyses were performed with a Yanaco CHN Corder MT-5. Mass spectra were measured on a Thermo Quest LCQ DECA XP^{Plus}. Preparative column chromatography was carried out on Fuji Silysia BW-820MH or YMC∗GEL Silica (6nm I-40-63 um). Filtrations were carried out using nacalai tesque Celite®500 (grain size 1.5 μm) or nacalai tesque Hyflo Super-Cel® (grain size 7 μm). Thin-layer chromatography (TLC) was carried out on Merck 25 TLC aluminum Sheets silica gel 60 F_{254} (layer thickness 0.2 mm). As for Ni-catalyzed coupling product, the spectra of these compounds were consistent with the authentic sample of commercially available 4-phenyltoluene and 2-phenylnaphthalene.

1-Cyclopropylindole[10]

R_f = 0.80 (hexane:EtOAc =3:1). Pale yellow oil. IR (neat): ν_{max} (cm^{-1}); 1511, 1464, 1316, 1024, 742, 420. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.12—7.09 (m, 2H), 6.41 (d, 1H, *J* = 3.2 Hz), 3.3—3.4 (m, 1H), 1.2—1.0 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.14, 128.69, 127.96, 121.44, 120.81, 119.66, 110.25, 101.01, 26.86, 6.13.

1-Cyclopropyl-5-nitroindole[10]

R_f = 0.45 (hexane: EtOAc =3:1). Yellow oil. IR (KBr): ν_{max} (cm^{-1}); 3040, 1514, 1476, 1330, 1278, 1060, 1033, 888, 814, 745, 710, 422. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 2.4 Hz, 1H), 8.13 (dd, *J* = 2.4 Hz, 8.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 3.4 Hz, 1H), 6.35 (d, *J* = 3.4 Hz, 1H), 3.3—3.2 (m, 1H), 1.1—1.0 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 131.26, 118.09, 117.28, 110.12, 103.75, 27.36, 6.42.

1-Cyclopropyl-6-nitroindole

R_f = 0.63 (hexane: EtOAc =3:1). Yellow oil. IR (KBr): ν_{max} (cm^{-1}); 1587, 1511, 1493, 1467, 1326, 1283, 1055, 1027, 869, 824, 764, 731. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H), 3.5—3.4 (m, 1H), 1.2—1.0 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.80, 120.72, 115.33, 107.33, 102.13, 27.27, 6.38. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34,; H, 4.98; N, 13.85. Found: C, 65.03; H, 5.08; N, 13.48.

1-Cyclopropyl-5-bromoindole[12]

R_f = 0.76 (hexane: EtOAc =3:1). Organge oil. IR (neat): ν_{max} (cm^{-1}); 3092, 3011, 2923, 1506, 1467, 1382, 1277, 1231, 1027, 795. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 2.0 Hz, 1H), 8.10 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.27 (dd, *J* = 2.0 Hz, 8.8 Hz, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 3.4—3.3 (m, 1H), 1.1—1.2 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.05, 130.28, 129.09, 124.22, 123.16, 112.94, 111.63, 100.56, 26.91, 6.12.

1-Cyclopropyl-5-chloroindole[10]

R_f = 0.75 (hexane: EtOAc =3:1). Pale yellow liquid. IR (neat): ν_{max} (cm^{-1}); 3011, 1464, 1385, 1277, 1231, 1062, 1026, 907, 870, 796, 780, 755, 720, 438. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.2—7.1 (m, 2H), 6.35 (d, *J* = 3.2 Hz, 1H), 3.3—3.2 (m, 1H), 1.1—1.0 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.82, 129.62, 129.25, 125.36, 121.71, 120.12, 111.64, 100.66.

1-Cyclopropyl-5-methylindole[10]

R_f = 0.83 (hexane: EtOAc =3:1). Pale yellow liquid. IR (neat): ν_{max} (cm^{-1}); 3013, 1713, 1486, 1386, 1293, 1240, 1227, 1025, 871, 793, 761, 760. ^1H NMR (400 MHz, $CDCl_3$): δ 7.5—7.4 (m, 2H), 7.1—7.0 (m, 2H), 6.33 (d, *J* = 4.0 Hz, 1H), 3.3—3.2 (m, 1H), 2.45 (s, 3H), 1.1—1.0 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.84, 128.87, 128.00, 123.06, 120.50, 109.92, 100.47, 26.88, 21.36, 6.11.

N-Cyclopropylphthalimide[12]

R_f = 0.51 (hexane: EtOAc =3:1). White solid (mp 135—136 °C, lit.[12] 136 °C). IR (KBr): ν_{max} (cm^{-1}); 3025, 1765, 1713, 1700, 1610, 1401, 1140, 946, 720. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (m, 2H), 7.71 (m, 2H), 2.72 (m, 1H), 1.1—1.0 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.99, 131.81, 123.14, 20.94, 5.20.

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