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N-Heterocyclic carbene ligands bearing poly(ethylene glycol) chains: effect of the chain length on palladium-catalyzed coupling reactions employing aryl chlorides

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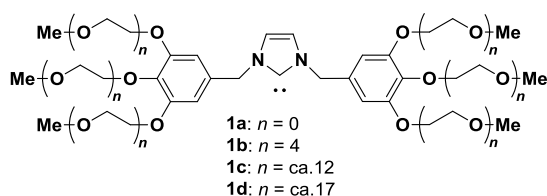
Tetsuaki Fujihara,* Takahiro Yoshikawa, Motoi Satou, Hidetoshi Ohta, Jun Terao, and Yasushi Tsuji*

N-Heterocyclic carbenes bearing poly(ethylene glycol) chains of different length have been designed and employed as a ligand in palladium-catalyzed coupling reactions. The catalyst system having longer chains was found to be highly efficient for Suzuki-Miyaura coupling and borylation reactions employing aryl chlorides under mild reaction conditions.

For homogeneous catalysts, ligands play important roles to realize high catalytic activity and selectivity.¹ To date, ligand modification within close proximity of a metal center (within a few angstroms) is beneficial to develop active and selective reactions. In contrast, the functionalization at periphery of ligands expands catalytic environment and adds unique ability to catalysis.² Actually, we have developed a wide range of ligands bearing steric bulk apart from coordination sites.³

For constructing such a distinctive catalytic environment, N-heterocyclic carbene (NHC) ligands⁴ are more suitable than phosphines^{3b,c,d,g,j,k} and nitrogen-ligands,^{3i,l} since they tend to stick to metal centers. Furthermore, polyether substituents such as poly(ethylene glycol) (EG) chains^{5,6} on the NHC ligands may add unique function to transition metal catalysts.

In the present study, the NHC ligands (**1a–d**) bearing EG chains of different length (i.e., $n = 0, 4, \text{ca.}12$, and $\text{ca.}17$)



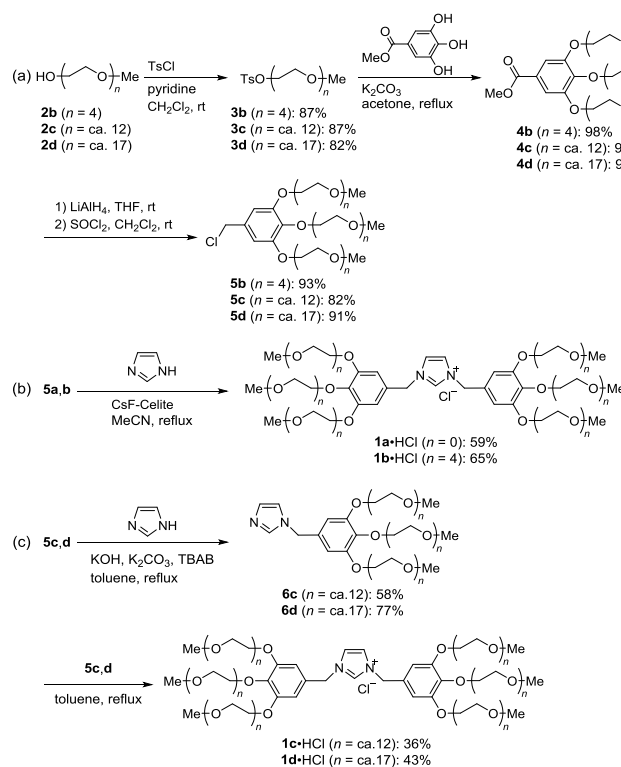
Scheme 1. N-heterocyclic carbene ligands bearing ethylene glycol (EG) chains.

Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan. E-mail: ytsuji@scl.kyoto-u.ac.jp; tfuji@scl.kyoto-u.ac.jp, FAX: +81-75-383-2514

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(Scheme 1) are prepared, and effect of the chain length is examined in palladium-catalyzed coupling reactions employing aryl chlorides.

A series of benzyl chlorides (**5b–d**) bearing different EG chain length were prepared from commercially available **2b–d** as shown in Scheme 2a, in which **2c** ($n = \text{ca.}12$) and **2d** ($n = \text{ca.}17$) have narrow molecular weight distributions. The NHC ligand precursors (**1a**·HCl^{3e} and **1b**·HCl^{3e}) were obtained by the reaction of imidazole with 2 equiv of the corresponding benzyl chlorides (**5a** and **5b**) (Scheme 2b). On the other hand, **1c**·HCl and **1d**·HCl bearing longer EG chains ($n = \text{ca.}12$ and $\text{ca.}17$) were synthesized in the stepwise manner via the mono-benzylation products (**6c** and **6d**) (Scheme 2c).



Scheme 2. Synthesis of imidazolium salts (**1a–d**·HCl) bearing EG chains.

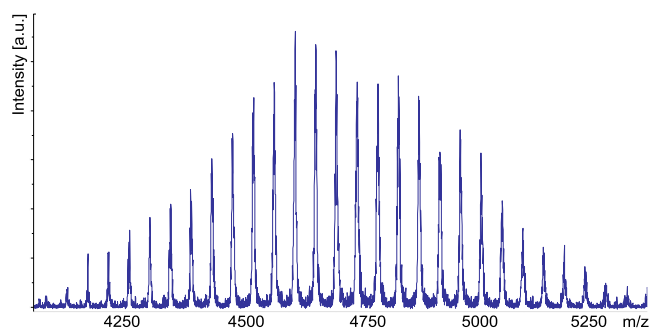


Fig. 1. MALDI-TOF-MS spectrum of **1d**·HCl (Matrix: Dithranol)

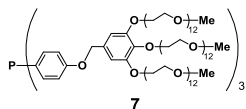
These imidazolium salts (**1a–d**·HCl) were characterized by ^1H NMR, ^{13}C NMR and MALDI-TOF MS analyses.⁸ The MALDI-TOF MS spectrum of **1d**·HCl is shown in Fig. 1.

With $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)_2]$, **1a–d**·HCl, and KHMDS as a catalyst, the coupling reaction of 4-chlorotoluene with phenylboronic acid was carried out in THF at 45 °C with K_3PO_4 as a base (Table 1). Employing **1a** ($n = 0$) and **1b** ($n = 4$) as the ligand ($1/\text{Pd} = 1.1$), 4-phenyltoluene was obtained as a coupling product in only trace and 22% yields, respectively (entries 1 and 2). In contrast, a catalyst with **1c** ($n = \text{ca. } 12$) afforded the product in much higher yield of 63% (entry 3). Finally, the catalyst system employing the ligand having longer chains (**1d**; $n = \text{ca. } 17$) gave the coupling product in 91% yield (entry 4). From this reaction mixture, the product was isolated in 89% yield. Thus, the catalytic activity increased with increasing the chain length of

Table 1. Effect of ligands on the palladium-catalyzed Suzuki-Miyaura Coupling of 4-chlorotoluene with phenylboronic acid.^a

Entry	Ligand system	Yield (%) ^b
1	1a ·HCl	trace
2	1b ·HCl	22
3	1c ·HCl	63
4	1d ·HCl	91 (89) ^c
5	1d ·HCl ^d	trace
6	IMes HCl	trace
7	IPr HCl	trace
8	7 ^e	26
9	1a ·HCl + 8 ^f	trace
10	1a ·HCl + 4d ^g	trace

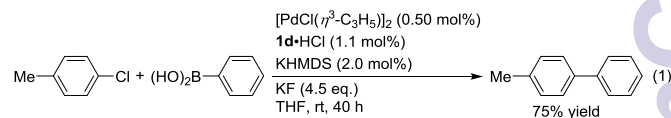
^a 4-Chlorotoluene (1.0 mmol), phenylboronic acid (3.0 mmol), $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)_2]$ (0.0050 mmol, 0.50 mol%), **1a–d**·HCl (0.011 mmol, $1/\text{Pd} = 1.1$), KHMDS (potassium hexamethyldisilazide, 0.020 mmol), K_3PO_4 (3.5 mmol) in THF (1.0 mL) at 45 °C for 15 h. ^b GC yields determined by the internal standard method. ^c Isolated yield. ^d Conditions ($1/\text{Pd} = 2.2$; **1d**·HCl (0.022 mmol) and KHMDS (0.030 mmol) were used. ^e A mixture of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)_2]$ (0.0050 mmol, 0.50 mol%) and **7** (0.011 mmol, 1.1 mol%) was used. ^f $\text{MeO}(\text{CH}_2\text{CH}_2\text{O})_{17}\text{Me}$ (**8**) (0.066 mmol) was added. ^g **4d** (0.022 mmol) was added.



EG ($n = 0$ to 17, entries 1–4). As the base, KF and CsF in place of K_3PO_4 also afforded the product in 87% and 85% yield, respectively, under otherwise the same reaction conditions as in entry 4. Notably, the NHC/Pd ratio affected the activity considerably and a use of more NHC ligand (NHC/Pd = 2.2) decreased the yield to trace (entry 5). With conventional NHC ligand such as IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), conversions of 4-chlorotoluene were quite low under the reaction conditions (entries 6 and 7). A phosphine ligand bearing the same EG chain moiety with $n = \text{ca. } 12$ (**7**)^{4b} was not so effective under the present reaction conditions (entry 8). Interestingly, the efficiency of the NHC ligand (**1d**) is affected considerably by the nature of solvents. In THF, the catalytic system with **1d** afforded the product in high yield (entry 4). However, in place of THF in entry 4, 1,4-dioxane, toluene, DMF, and 2-propanol provided the product in 5%, 8%, 11%, and 30% yields, respectively, while they were often used in the Suzuki-Miyaura coupling reaction. In water, the product was afforded in 3% yield under otherwise the same reaction conditions as entry 4.

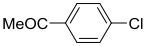
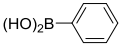
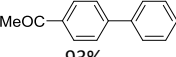
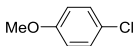
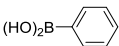
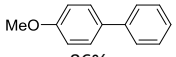
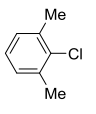

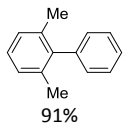

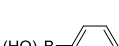
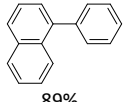

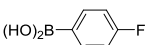
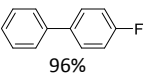

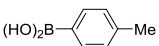
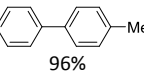
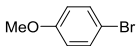
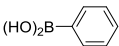
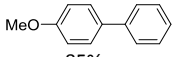
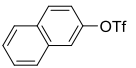
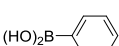
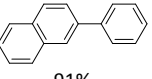
To gain insight into the effect of EG chain, some control experiments were carried out. A simple mixture of $\text{MeO}(\text{CH}_2\text{CH}_2\text{O})_{17}\text{Me}$ (**8**) and **1a**·HCl in place of **1d**·HCl only afforded a trace amount of product (entry 9). Furthermore, a mixture of **1a**·HCl and **4d** (Scheme 2a) were not effective at all, either (entry 10). Hence, these results clearly indicate that the EG chains must be connected onto the NHC core in order to cause the high catalytic activity.

The effectiveness of **1d**·HCl as the ligand precursor was further confirmed employing various aryl chlorides and arylboronic acids under the optimum reaction conditions (Table 2). Aryl chlorides having electron-withdrawing and donating substituents were smoothly converted to the corresponding biaryls in high yields (entries 1 and 2). Even in the more sterically demanding coupling reaction, the product was obtained in 91% yield (entry 3). 1-Phenylnaphthalene was obtained from 1-chloronaphthalene in 89% yield (entry 4). 4-Fluoro- and 4-methylphenylboronic acids afforded the corresponding products in high yields (entries 5 and 6). More reactive aryl bromide and triflate also smoothly gave the corresponding products (entries 7 and 8). Sterically hindered arylboronic acids such as 2,6-xylylboronic acid could not be used in the reaction. Gratifyingly, the present catalyst system affords the product even at room temperature employing KF as the base as shown in eqn. (1).



The ligand precursor **1d**·HCl is also efficient in the borylation⁹ of aryl chlorides with bis(pinacolato)diboron. The

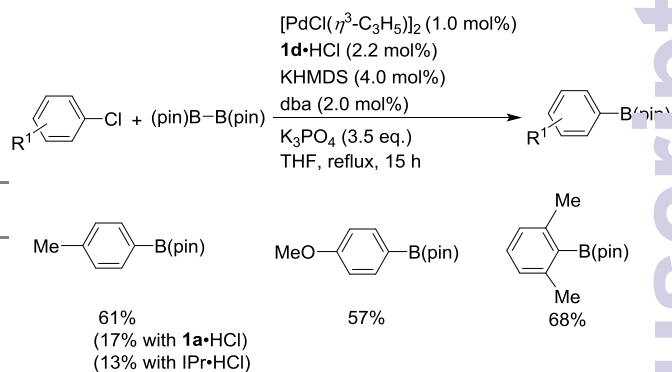
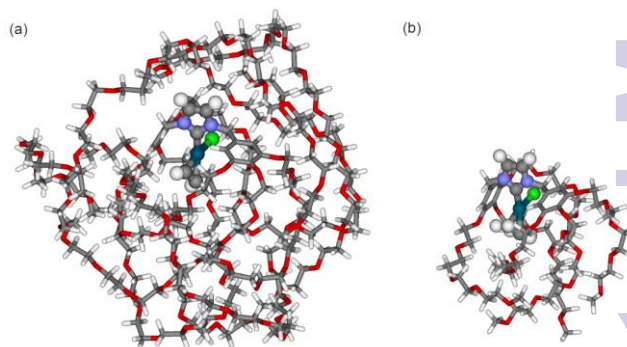
Table 2. The reaction of various substrates under the optimum conditions.^a

Entry	Aryl halide	Arylboronic acid	Product/ Yield ^b
1			 93%
2 ^c			 86%
3			 91%
4			 89%
5			 96%
6			 96%
7			 85%
8			 91%

^a Aryl chloride (1.0 mmol), arylboronic acid (3.0 mmol), [PdCl(η^3 -C₃H₅)₂] (0.0050 mmol, 0.50 mol%), **1d**-HCl (0.011 mmol, 1.1 mol%), KHMDS (0.020 mmol), K₃PO₄ (3.5 mmol) in THF (1.0 mL) at 45 °C for 15 h. ^b Isolated yields. ^c Phenylboronic acid (4.0 mmol) and K₃PO₄ (4.5 mmol) were used.

reaction of 4-chlorotoluene in the presence of a catalytic amount of [PdCl(η^3 -C₃H₅)₂] and dibenzylideneacetone (dba) as an additive afforded the corresponding arylboronate in 61% isolated yield (Scheme 3). Under the reaction conditions, other ligand precursors such as **1a**-HCl and IPr-HCl were much less effective to provide the product in 17% and 13% yields, respectively. 4-Chloroanisole and 2-chloro-1,3-dimethylbenzene also afforded the corresponding borylated products in good isolated yields. Under the reaction conditions, a trace amount of biaryls was detected by the reaction of the aryl chlorides with the resulting arylboronates. Although we tried other coupling reactions such as Sonogashira coupling and Hiyama coupling employing an aryl chloride as the substrate and **1d** as the ligand, the desired products were not obtained at all.⁸

With **1b-d**/Pd = 1, [PdCl(η^3 -C₃H₅)₂](**1b-d**) must be generated from [PdCl(η^3 -C₃H₅)₂] and **1b-d** in the catalytic

**Scheme 3.** Palladium-catalyzed borylation of aryl chlorides employing bis(pinacolato)diboron. Isolated yields of the products were given. The figures in parentheses show GC yields. dba = dibenzylideneacetone**Fig. 2.** Optimized structures of [PdCl(η^3 -C₃H₅)(**1**)] calculated by ONIOM (B3LYP/LANL2DZ-UFF). (a) [PdCl(η^3 -C₃H₅)(**1d**)] and (b) [PdCl(η^3 -C₃H₅)(**1b**)]. The core parts other than EG chains are shown with the bowl and stick model.

solution.¹⁰ Thus, structures of [PdCl(η^3 -C₃H₅)(**1b-d**)] were optimized by ONIOM¹¹ (B3LYP/LANL2DZ-UFF) calculation. Fig. 2 shows the structures of [PdCl(η^3 -C₃H₅)(**1b**)] and [PdCl(η^3 -C₃H₅)(**1d**)], in which the Pd center is wrapped up in the folded long EG chain. As a result, [PdCl(η^3 -C₃H₅)(**1d**)] has the particular large shape as shown in Fig. 2a: the calculated Connolly solvent-excluded volumes¹² of the optimized [PdCl(η^3 -C₃H₅)(**1d**)] is 5903 Å³, while those of [PdCl(η^3 -C₃H₅)(**1c**)] and [PdCl(η^3 -C₃H₅)(**1b**)] are 4289 Å³ and 1711 Å³, respectively. The high efficiency of the Pd catalyst with **1d** as the ligand would be attributed to the unique structure with Pd catalyst center wrapped in the flexible long EG chains, which successfully stabilizes the highly active Pd species bearing only the one NHC ligand.

In summary, *N*-heterocyclic carbene ligands bearing poly(ethylene glycol) chains of different length were designed, synthesized, and employed in catalytic reactions. In the palladium-catalyzed Suzuki-Miyaura coupling and borylation reactions of aryl chlorides, **1d** having longer ethylene glycol chains (*n* = ca.17) was found to be highly efficient ligand.

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