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Kumada–Tamao–Corriu Coupling Using *N*-Heterocyclic Carbene Ligands Bearing Pyridyl and Ethylenedioxyl Moieties

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Carbene ligands bearing a pyridyl group and an ethylenedioxyl moiety were developed, and utilized as efficient ligands for the nickel-catalyzed Kumada–Tamao–Corriu coupling. A wide variety of aryl chlorides could be used for the cross-coupling reaction with aryl Grignard reagents to afford the corresponding products in high yields in short time.

Since the synthesis by Arduengo and co-workers in 1991,[1] *N*-heterocyclic carbenes (NHCs) have received considerable attentions because of their unique characters as ligands[2] and organocatalysts.[3]

The most commonly used NHC ligands are imidazolium derivatives bearing sterically hindered arenes, such as IPr, SIPr, and SIMes (Figure 1). While the steric hindrance should decrease the catalytic activity, the bulkiness prevents the aggregation of catalysts, which as a whole leads to the high activity of NHC catalysts.[2h] If the aggregation of a less hindered NHC catalyst can be suppressed by another method, the catalyst would be more efficient than the existing catalysts. We assumed that the introduction of coordinating groups, which coordinate to the metal center of the catalyst, would suppress the aggregation.

We considered the introduction of two different coordinating groups. One of them strongly coordinates to the metal center of the catalyst, which suppresses the aggregation of the catalyst, and the other weakly coordinates to the metal center, which would act as a liberal coordination site. Thus, appropriate stability and high activity of the complex would be expected.

According to our hypothesis, we designed novel NHC ligands bearing a 2-pyridyl group[4] and an ethylenedioxy moiety[5] as coordinating groups, and found that they were efficient ligands for the Ni-catalyzed Kumada–Tamao–Corriu coupling.[6]

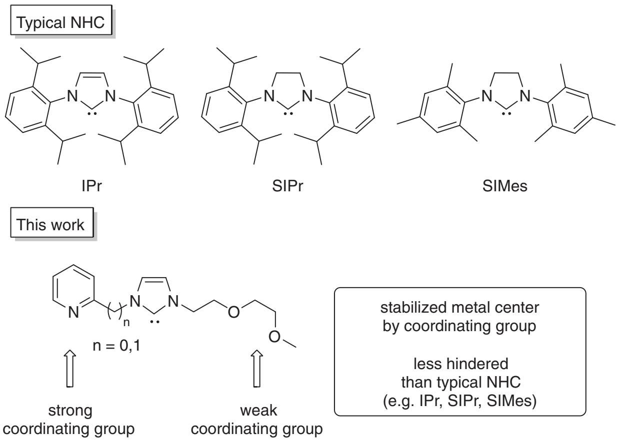
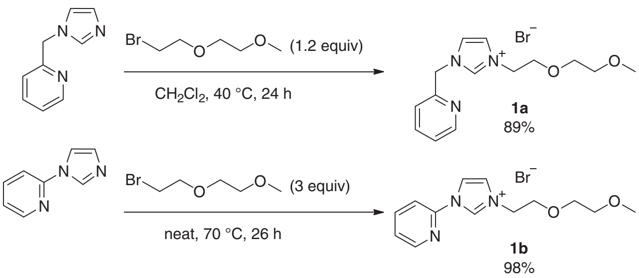


Figure 1. Typical and novel designed *N*-heterocyclic carbenes.

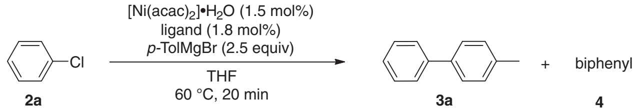
Carbene precursor **1a**, bearing a 2-pyridylmethyl group, was readily prepared from the reaction of 2-pyridylmethyl-1-imidazole with 1-bromo-2-(2-methoxyethoxy)ethane in high yield (Scheme 1).[7] Precursor **1b**, which has a pyridyl group, was also obtained in a similar manner.

Thus obtained carbene precursors **1a** and **1b** were applied to the nickel-catalyzed coupling reaction between chlorobenzene and *p*-tolyl Grignard reagent (Table 1). In the presence of a catalytic amount of $[Ni(acac)_2]\cdot H_2O$ (1.5 mol %) and **1a** (1.8 mol %), the cross-coupling of chlorobenzene (**2a**) and *p*-tolylmagnesium bromide (2.5 equiv) proceeded smoothly and terminated in 20 min to afford 4-methylbiphenyl (**3a**) in 94% yield (Entry 1). Using **1b**, **3a** was obtained in 84% yield (Entry 2). To compare the efficiency of the ligands, we next applied typical NHC ligands (IPr, SIPr, and SIMes) to the reaction (Entries 3–5). In each case, the reaction was slower than that with **1a** or **1b**, and the yields of **3a** were quite low (18–24%) and 60–69% of chlorobenzene (**2a**) was recovered. Using 1,1′-



Scheme 1. Synthesis of ligand precursors **1a** and **1b**.

Table 1. Ni-Catalyzed cross-coupling between chlorobenzene (**2a**) and *p*-tolylmagnesium bromide with several ligands[a]



Entry	Ligand	**3a**/%	**4**/%	Recov. **2a**/%
1	**1a**	94	6	0
2	**1b**	84	6	0
3	IPr•HCl	24	2	60
4	SIPr•HCl	22	3	60
5	SIMes•HCl	18	2	69
6	dppf	49	6	39
7	**1c**	41	4	46
8	**1d**	69	4	22
9	**1e**	68	15	7
10	**1f**	78	4	17

[a] GC yield.

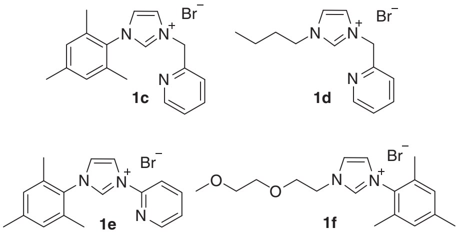
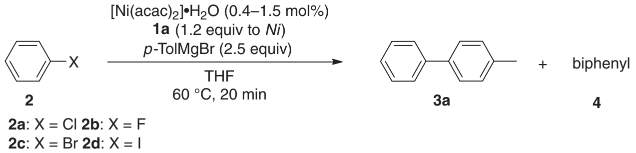


Figure 2. Other ligand precursors used in this work.

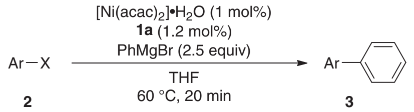
Table 2. $[Ni(acac)_2]\cdot H_2O$/**1a**-catalyzed Kumada–Tamao–Corriu coupling of halobenzenes and *p*-tolylmagnesium bromide[a]

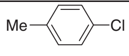
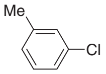
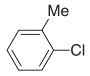
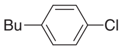
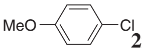
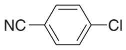
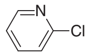
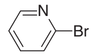
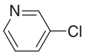


Entry	2	$[Ni(acac)_2]\cdot H_2O$ /mol %	3a /%	4 /%	Recov. 2a /%
1	**2a**	1.5	94	6	0
2	**2a**	1.0	92	5	0
3	**2a**	0.8	88	7	0
4	**2a**	0.4	31 (93)[b]	1 (6)[b]	62 (0)[b]
5	**2b**	1.0	0 (75)[c]	0.2 (10)[c]	99 (0)[c]
6	**2c**	1.0	61	7	0
7	**2d**	1.0	70 (77)[d]	3 (3)[d]	0 (0)[d]

[a]GC yield. [b]Reaction time was extended to 60 min. [c]Reaction time was extended to 12 h. [d]Performed at 0 °C.

Table 3. $[Ni(acac)_2]\cdot H_2O$/**1a**-catalyzed Kumada–Tamao–Corriu coupling of several haloarenes[a]



Entry	2	3	Yield/%	Recov. 2/%
1	 **2e**	**3a**	86	0
2	 **2f**	**3f**	91	0
3	 **2g**	**3g**	86	0
4	 **2h**	**3h**	80	0
5	 **2i**	**3i**	77	0
6	 **2j**	**3j**	81	0
7	 **2k**	**3k**	42 (53)[b]	26 (27)[b]
8	 **2l**	**3l**	71 (78)[c]	0 (0)[c]
9	 **2m**	**3m**	64	0

[a]GC yield. [b]Performed at 80 °C. [c]Performed at 40 °C.

bis(diphenylphosphano)ferrocene (dppf), which has been known to be an efficient ligand for the Kumada–Tamao–Corriu coupling, 49% yield of **3a** was afforded under similar conditions (Entry 6). To clarify the role of 2-pyridyl and ethylenedioxy groups, we next carried out the Ni-catalyzed coupling with carbene ligand precursors **1c**–**1f** shown in Figure 2, which have one pyridyl moiety or ethylenedioxy group. Using imidazolium salt **1c** or **1d**, which possesses a 2-pyridylmethyl group, coupling product **3a** was obtained in 41% and 69% yields, respectively (Entries 7 and 8). With 1-mesityl-3-pyridylimidazolium salt (**1e**), **3a** was obtained in moderate yield (68%, Entry 9). **1f** bearing an ethylenedioxy moiety, which would have relatively weak coordination ability, showed better catalytic activity to afford **3a** in 78% (Entry 10). These results suggest that both a pyridyl group and an ethylenedioxy moiety, which could coordinate to the nickel metal center, may suppress the aggregation and make the complexes active. The ethylenedioxy moiety seems to be more easily liberated, and hence the reaction using **1f** might be slightly faster than others, although further investigation is necessary to understand the role of the coordination moieties.

We next optimized the conditions of the $[Ni(acac)_2]\cdot H_2O$/**1a**-catalyzed coupling reactions, and several halobenzenes were applied under the conditions (Table 2). As mentioned above, coupling product **3a** was obtained in 94% yield from chlorobenzene with 1.5 mol % of $[Ni(acac)_2]\cdot H_2O$ (Entry 1). Reducing the amount of nickel source to 0.8–1.0 mol %, **3a** was obtained in similar yields (Entries 2 and 3). Using 0.4 mol % of $[Ni(acac)_2]\cdot H_2O$, **3a** was obtained in only 31% yield in 20 min, but the reaction was finished within 1 h to afford coupling product **3a** in 93% yield (Entry 4). These results suggest that a highly active and relatively stable species was generated in situ from $[Ni(acac)_2]\cdot H_2O$ and **1a**. We next applied other halobenzenes to the reaction. Even fluorobenzene can be used under these conditions. The reaction was slower than that with chlorobenzene but was finished within 12 h to afford **3a** in 75% yield (Entry 5). Bromobenzene and iodobenzene could also be used for the reaction to afford **3a** in 61% and 77% yields, respectively (Entries 6 and 7).

To study the scope of the reaction, we next conducted $[Ni(acac)_2]\cdot H_2O$/**1a**-catalyzed coupling of several haloarenes (Table 3). First, chloroarenes bearing electron-donating groups were carried out. The coupling reaction of *o*-, *m*-, and *p*-chlorotoluene (**2e**–**2g**) proceeded smoothly and corresponding coupling adducts **3e**–**3g** were obtained in respective yields of 86%, 91%, and 86% (Entries 1–3). In the case of *p*-butylchlorobenzene (**2h**) and *p*-chloromethoxybenzene (**2i**), the corresponding coupling products were also obtained in good yields (Entries 4 and 5). We next carried out the coupling reaction of **2j**, possessing an electron-withdrawing cyano group, and found that desired product **3j** was obtained in good yield (81%, Entry 6). The coupling reactions of 2- and 3-halopyridines also proceeded under similar conditions, and corresponding coupling products **3k**, **3l**, and **3m** were obtained in moderate to good yields (Entries 7–9). In the Kumada–Tamao–Corriu coupling of halopyridines, the use of typical NHC such as IPr gave better results.[6n] It is probably because steric hindered NHC ligands would suppress the coordination of a halopyridine to the metal center and prevent the deactivation of the catalyst.

In conclusion, we synthesized novel NHC carbene ligand precursors **1a** and **1b**, bearing a pyridyl group and an ethylenedioxy moiety, and found that they were efficient for the Ni-catalyzed Kumada–Tamao–Corriu coupling. Further scope of the ligands is under investigation.

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