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A highly efficient catalytic system for cross-coupling of aryl chlorides and bromides with malononitrile anion by palladium carbene complexes†

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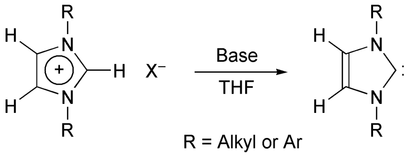
Six imidazolium chlorides (1–6) as precursors of 1,3-diaryl substituted N-heterocyclic carbene ligands were synthesized and evaluated in palladium-catalyzed cross-coupling reactions of aryl chlorides and bromides with malononitrile in the presence of NaH. Among them, 1,3-bis(2,4,6-triethylphenyl)imidazolium chloride (5) and 1,3-bis(2,4,6-triisopropylphenyl)imidazolium chloride (6) are novel. The catalytic system combining Pd(0) with imidazolium salts 4, 5 and 6 with bulky aryl groups in pyridine is found to be superior over others and afforded α-arylmalononitriles in high yields when employing a wide variety of substrates.

Palladium-catalyzed cross-coupling reactions of aryl halides or halide equivalents with various nucleophiles have been shown to be highly effective and practical approaches for the formation of C–C bonds.[1] There has been much interest recently in the application of N-heterocyclic carbenes as ligands (Scheme 1) in organic synthesis and coordination chemistry.[2] N-Heterocyclic carbene complexes have been successfully used in a wide range of catalytic reactions.[2,3] Obviously, because of their stability and ease of preparation, imidazolium salts, as precursors to form N-heterocyclic carbenes are especially suitable and economic for high throughput approaches.

It is known that arylmalononitriles as well as α-aryl-β-cyanoacetates are important intermediates in the preparation of useful organic compounds like bioactive materials,[4] heterocyclic compounds[5] and organic conducting materials.[6] However, under basic conditions the reactions of aryl halides with active methylene compounds are difficult and give no condensation products. Suzuki *et al.*[7] and Miura *et al.*[8] reported a synthetic route to arylmalononitriles by catalytic coupling of aryl iodides with malononitrile anion in the presence of copper(I) iodide, respectively. Uno *et al.*[9] reported another synthetic preparation of arylmalononitriles by $Pd(PPh_3)_2Cl_2$ from aryl iodides. In addition, Yamanaka *et al.*[10] reported $Pd(PPh_3)_4$ catalysed coupling of bromobenzene and N-heteroaryl bromides with malononitrile anion in moderate yields. Recently Cristau *et al.* reported the arylation of iodobenzene with malononitrile anion catalyzed by 20 mol% of nickel(0) complexes in 70% yield.[11] Evidently, the use of aryl chlorides or aryl bromides as substrates has proved difficult but would economically benefit a number of industrial processes.

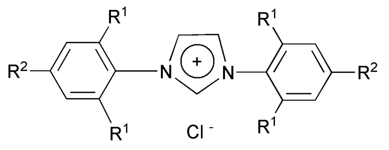
We wish here to report the palladium-catalyzed C–C coupling of normally less active aryl halides with malononitrile in the presence of sodium hydride using a catalytic system of Pd(0) and bulky nucleophilic carbenes as ligands, generated *in situ* from the imidazolium salts. To explore the effect of substituent groups of the carbene ligands on the catalytic C–C bond formation processes, six imidazolium salts with different substituents have been prepared (Scheme 2). Among them, 1,3-bis(2,4,6-triethylphenyl)imidazolium chloride (**5**) and 1,3-bis(2,4,6-triisopropylphenyl)imidazolium chloride (**6**) are novel. We wondered if the catalytic arylation could be performed with the help of palladium complexes bearing the N-heterocyclic carbene ligands in a suitable solvent.



Scheme 1 Preparation of *N*-heterocyclic carbenes from imidazolium salts.

As part of an effort to develop high-throughput synthetic methods for α-arylmalononitriles by palladium-catalyzed cross-coupling with a number of precursors of the carbene ligands (Scheme 2), we found that the bulky substituted N-heterocyclic carbene ligands could effectively promote the reactions of the palladium-catalyzed coupling of bromobenzene with malononitrile when the reaction is performed in pyridine (Scheme 3 and Table 1). The imidazolium salts **4** and **5** showed excellent catalytic activity in a high yield of 91% (Table 1, entries 6 and 7), and the imidazolium salt **6** (entry 8) also showed high yield of 78%. For others only moderate yields of phenylmalononitrile (entries 2–4) were obtained. In the absence of imidazolium salts, the product was not detected in the reaction (entries 1 and 9).

As to the catalytic coupling of chlorobenzene, the activity of the catalytic system was somewhat lower than that for bromobenzene. By increasing the moles of palladium(0) complex and imidazolium salt as well as moderately extending the reaction time, the satisfactory results for the coupling were also obtained in yields of 70–75% for imidazolium salts **4, 5** and **6** (Table 1, entries 14–16). As shown in Table 1, the activity of the imidazolium chlorides in the palladium-catalyzed coupling of bromobenzene and chlorobenzene was in the following order: **4** ≈ **5** > **6** ≫ **3** > **2** > **1**. In addition, our work has showed that the palladium N-heterocyclic carbene complex could smoothly realize cross-coupling of aryl iodides with malononitrile in tetrahydrofuran as solvent and gave arylmalonontriles in satisfactory yields.[12] But under similar

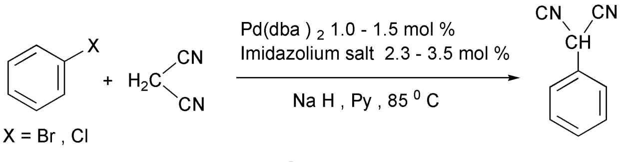


1 : $R^1 = H$, $R^2 = CH_3$; **2** : $R^1 = CH_3$, $R^2 = H$

3 : $R^1 = CH(CH_3)_2$, $R^2 = H$; **4** : $R^1 = R^2 = CH_3$

5 : $R^1 = R^2 = CH_2CH_3$; **6** : $R^1 = R^2 = CH(CH_3)_2$

Scheme 2 Imidazolium salts used.



Scheme 3

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b302890a/

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Table 1 Cross-coupling of bromobenzene and chlorobenzene with malononitrile using Pd(dba)$_2$ and imidazolium salts (**1–6**) in pyridine

Entry	X	Imidazolium salt	Time/h	Isolated yields (%)
1	Br	None	12	0
2	Br	**1**	10	26
3	Br	**2**	10	30
4	Br	**3**	10	35
5[a]	Br	**4**	12	45
6	Br	**4**	10	91
7	Br	**5**	10	91
8	Br	**6**	10	78
9	Cl	None	16	0
10	Cl	**1**	14	Trace
11	Cl	**2**	14	3
12	Cl	**3**	14	4
13[a]	Cl	**4**	16	15
14	Cl	**4**	14	75
15	Cl	**5**	14	73
16	Cl	**6**	14	70

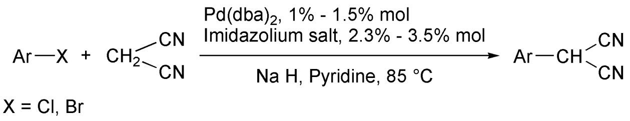
[a] Refluxed in THF as solvent.

reaction conditions, the coupling only gave 45% yield for bromobenzene, and 15% for chlorobenzene, respectively (Table 1, entry 5 and 13). Obviously, pyridine, as solvent, is not only high efficient, but also has high recovery (> 90%) after distillation. Therefore, the high activity of this catalytic system presumably results from the combination of strong electron-donating ability with steric demands of the N-heterocyclic carbene ligands as well as the effect of the solvents.

The coupling results of a number of aryl bromides and aryl chlorides (Scheme 4) with malononitrile anion using the bulky substituted imidazolium salts (**4, 5** and **6**) and Pd(0) as catalytic systems are listed in Table 2. It can be seen from Table 2 that the imidazolium chlorides **4** and **5** have similar high activity. Because of its steric effects, the activity of the imidazolium chloride **6** is a little bit lower.

As seen from Table 2, the bromine atom in the aryl bromides could be smoothly substituted by a malononitrile group with high efficiency, and the corresponding coupling products were obtained in good yields of 64–94% (entries 1–17). For the methoxybromobenzene substrates, when the methoxy group is in the *ortho*-position, good coupling yields of 85–91% are obtained (entries 7–9), while in the *para*-position the yields decrease to 60–65% (entries 10–12). Generally, with imidazolium salts **4, 5** and **6**, most aryl bromides have high reaction rates and higher coupling yields.

However when using aryl chlorides instead of aryl bromides under the above conditions, the reaction became somewhat difficult. When the amounts of Pd(dba)$_2$ and imidazolium salts are increased up to 50% with appropriate reaction time, the coupling with aryl chlorides could be performed with good results. For most aryl chlorides, the catalytic cross-coupling can also proceed under these conditions; all substrates gave yields from 45% to 94% (Table 2, entries 18–29). The 4′-biphenyl chloride as substrate showed high activity and gave yields of 90% and 94% for imidazolium salts **4** and **5** (entries 28 and 29), respectively. The steric and electronic effects of the substituent groups on the aromatic rings were also observed in this case. The electron-donating group, methoxy, in 2-methoxyphenyl chlorides led to a sharp decrease in the yields (entries 22 and 23). Generally, the electron-withdrawing groups on aryl chloride rings could promote the activity of the coupling (entries 26 and 27).



Scheme 4

Table 2 Cross-coupling of halides with malononitrile catalyzed by the catalytic system of Pd(dba)$_2$–imidazolium salts in pyridine

Entry	Ar	X	Imidazolium salt	Time/h	Yield (%)
1	2-Me–C_6H_4	Br	**4**	10	91
2	2-Me–C_6H_4	Br	**5**	10	91
3	2-Me–C_6H_4	Br	**6**	10	88
4	4-Me–C_6H_4	Br	**4**	10	94
5	4-Me–C_6H_4	Br	**5**	10	92
6	4-Me–C_6H_4	Br	**6**	10	90
7	2-MeO–C_6H_4	Br	**4**	10	85
8	2-MeO–C_6H_4	Br	**5**	10	91
9	2-MeO–C_6H_4	Br	**6**	10	90
10	4-MeO–C_6H_4	Br	**4**	14	65
11	4-MeO–C_6H_4	Br	**5**	14	64
12	4-MeO–C_6H_4	Br	**6**	14	60
13	4-F–C_6H_4	Br	**4**	12	75
14	4-F–C_6H_4	Br	**5**	12	75
15	4-F–C_6H_4	Br	**6**	12	70
16	1-Naphthyl	Br	**4**	10	85
17	1-Naphthyl	Br	**5**	10	94
18	2-Me–C_6H_4	Cl	**4**	16	51
19	2-Me–C_6H_4	Cl	**5**	16	50
20	4-Me–C_6H_4	Cl	**4**	14	73
21	4-Me–C_6H_4	Cl	**5**	14	71
22	2-MeO–C_6H_4	Cl	**4**	14	45
23	2-MeO–C_6H_4	Cl	**5**	14	45
24	1-Naphthyl	Cl	**4**	14	85
25	1-Naphthyl	Cl	**5**	14	86
26	4-F_3C–C_6H_4	Cl	**4**	14	77
27	4-F_3C–C_6H_4–	Cl	**5**	14	70
28	4-Ph–C_6H_4	Cl	**4**	14	90
29	4-Ph–C_6H_4	Cl	**5**	14	94

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