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Original article

Efficient imidazolium salts for palladium-catalyzed Mizoroki–Heck and Suzuki–Miyaura cross-coupling reactions

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ABSTRACT

The system, $Pd(OAc)_2$/imidazolium salts (L_2), was found as an efficient catalyst in the Heck coupling reaction of olefins with aryl halides and Suzuki reactions of various aryl halides with aryl boronic acids under aerobic condition. This catalytic system demonstrates great tolerance to a wide range of groups on all substrates of aryl halides, alkenes and aryl boronic acids.

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1. Introduction

Palladium-catalyzed formation of the carbon–carbon bond has become an extremely powerful tool in modern organic chemistry [1–4]. Among them, the Suzuki–Miyaura and Mizoroki–Heck coupling reactions have emerged as two of the most important reactions, and in the last ten years have witnessed an exponential growth in the application of Pd-catalyzed Heck and Suzuki reactions in target-oriented organic synthesis [5–8].

N-Heterocyclic carbenes (NHCs) derived by deprotonation of imidazolium salts are often considered phosphine mimics and have consequently received a great deal of attention as alternatives to phosphine based ligands in Pd-catalyzed chemistry [9–11]. A combination of their powerful σ-donating and weak π-accepting characteristics make them the ligands of choice for many catalytic systems, thus leading to the preparation of organometallic catalysts of enormous utility in organic synthesis [12–14].

Therefore, herein, we report the use of easily prepared, oxygen, moisture, and thermally stable imidazolium salts (L_{1-4}) as ligands for Pd(II)-catalyzed Heck and Suzuki coupling reactions of aryl iodides, bromides, and chlorides (Scheme 1).

2. Experimental

2.1. Preparation of 4,5-dibromo-1,3-bis(2,4,6-trimethylphenyl) imidazolium chloride (L_4)

In a Schlenk flask under argon, to a THF suspension (20 mL) of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (1 g, 2.93 mmol), solid potassium *tert*-butoxide (0.35 g, 3.12 mmol) was added in a single portion. The mixture was stirred for 45 min at room temperature, and volatiles were removed under vacuum. After addition of THF (20 mL) and stirring for 5 min, the reaction mixture was filtered under argon, and carbon tetrabromide (2.42 g, 5.86 mmol) in THF (10 mL) was added dropwise to solution, over a period of *ca.* 30 min. The resulting brown solution was stirred for 4 h. Subsequent removal of volatiles in vacuo gave a dark brown residue that was extracted into toluene (10 mL) and then a solution of HCl in dioxane (4 mol/L) was added, and the resulting white precipitate was collected. Yield 351 mg (29%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.13 (s, 12H, *o*-CH_3), 2.39 (s, 6H, *p*-CH_3), 7.27 (s, 4H, Ar–H), 10.13 (s, 1H, HNCN); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 (s, 6H, *p*-CH_3), 2.54 (s, 12H, *o*-CH_3), 6.82 (s, 4H, Ar–H), 10.16 (s, 1H, HNCN); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.9, 20.7, 113.1, 129.3, 129.6, 135.1, 140.5, 141.7; Elemental analysis calcd. for $C_{21}H_{23}Br_2ClN_2$: C 50.58, H 4.65, N 5.62; found C 50.55, H 4.59, N 5.67; ESI-MS ($C_{21}H_{23}Br_2Cl_1N_2$) (*m*/*z*): 497.4 $[M]^+$.

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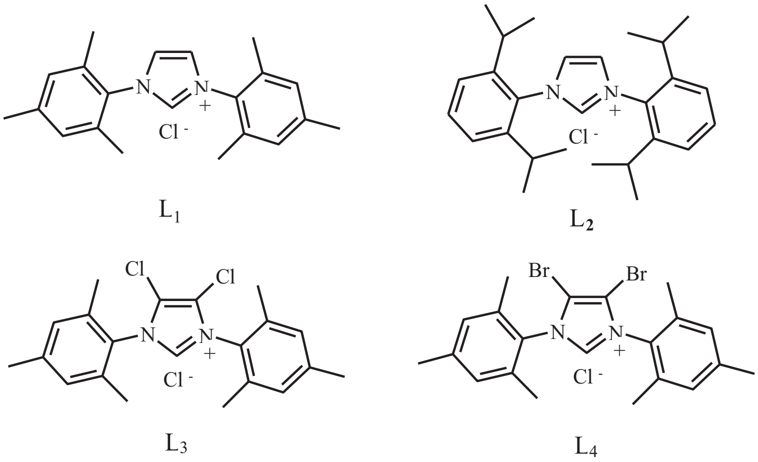


Scheme 1. The imidazolium salts (L_{1-4}) used as ligands for Pd(II)-catalyzed Heck and Suzuki coupling reactions.

2.2. General procedure for the Heck reactions

All Heck reactions were carried out in air. A mixture of aryl halide (1.0 mmol), olefins (1.2 mmol), K_2CO_3 (2 mmol), $Pd(OAc)_2$ (0.5 mol%), and imidazolium salt L_2 (1.0 mol%) in DMF (3 mL) was allowed to react in a sealed tube at 80 °C. The reaction mixtures was added to brine (15 mL) and extracted three times with diethyl ether (3 × 15 mL). The further purification of the product was achieved by flash chromatography on a silica gel column using hexane/ethyl acetate (5/1).

2.3. General procedure for the Suzuki reactions

All Suzuki reactions were carried out in air. A mixture of aryl halide (1.0 mmol), aryl boronic acid (1.2 mmol), KOH (2 mmol), $Pd(OAc)_2$ (0.5 mol%) and imidazolium salt L_2 (1.0 mol%) in mixture of H_2O/*i*-PrOH (3 mL) (1/1, v/v) was allowed to react in a sealed tube at 80 °C. The reaction mixtures was added to brine (15 mL) and extracted three times with diethyl ether (3 × 15 mL). The further purification of the product was achieved by flash chromatography on a silica gel column using hexane/ethyl acetate (5/1, v/v).

3. Results and discussion

The ligands (L_1–L_3) were prepared according to the literature [15,16]. The new imidazolium salt, 4,5-dibromo-1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (L_4), was readily prepared *via* a one-step synthesis. Deprotonation of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (L_1) with *t*-BuOK in THF following addition of CBr_4 and then a solution of HCl in dioxane affords the corresponding imidazolium salt L_4 as a white precipitate which can be isolated and stored in the air for several months. The L_4 was fully characterized by spectroscopy (^1H NMR, ^{13}C NMR, and ESI-mass spectrometry) and by elemental analysis. Elemental analysis of L_4 fully agreed with experimental analysis. The ^1H NMR spectrum of L_4 in DMSO-d_6 shows resonances at δ 2.13, 2.39, and 7.27 for the *p*- and *o*-methyl and the aromatic ring proton of the phenyl groups, respectively. Also the imidazolium proton of L_4 resonates at δ 10.13 in DMSO-d_6. The ESI mass spectrum of L_4 shows a molecular ion peak at m/z 497.4 $[M]^+$.

To investigate the reactivity of (L_{1-4}) as ligand, we first employed 4-acetylbromobenzene and *n*-butyl acrylate as the standard substrates. Their coupling reactions were carried out under a variety of palladium sources, bases and solvents. The results are summarized in Table 1. In a comparative study, we applied these salts in conjunction with $Pd(OAc)_2$ as pre-catalyst for the Heck coupling reaction of 4-acetylbromobenzene and *n*-butyl acrylate in DMF as solvent at 80 °C. Results (Table 1, entries 1–4) show that all four salts (L_{1-4}) are very efficient and suitable ligands for the Heck coupling reaction with Pd(II) as pre-catalyst. On the basis of higher yields for L_2 compared to others, this salt was selected as the ligand of choice for this reaction.

We then examined the effect of bases and among the tested bases, K_2CO_3 was the most effective base for the coupled product in presence of L_2 (Table 1, entry 8), while other bases, such as NaOAc, Na_2CO_3 and K_3PO_4 gave yields of 11%, 51% and 37%, respectively (Table 1, entries 5–7). Replacement of inorganic bases by the organic base Et_3N afforded low product yields (Table 1, entry 9). The next step was to optimize the conditions to select the best solvent from the commonly used ones. Solvents *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMAc) were found to

Table 1
The optimized reaction conditions for Pd-catalyzed Mizoroki–Heck reactions.[a]

Entry	Ligand	Base	Solvent	Pd source	Yield (%)[b]
1	L_1	K_2CO_3	DMF	$Pd(OAc)_2$	87
2	L_2	K_2CO_3	DMF	$Pd(OAc)_2$	96
3	L_3	K_2CO_3	DMF	$Pd(OAc)_2$	93
4	L_4	K_2CO_3	DMF	$Pd(OAc)_2$	91
5	L_2	NaOAc	DMF	$Pd(OAc)_2$	11
6	L_2	Na_2CO_3	DMF	$Pd(OAc)_2$	51
7	L_2	K_3PO_4	DMF	$Pd(OAc)_2$	37
8	L_2	K_2CO_3	DMF	$Pd(OAc)_2$	96
9	L_2	Et_3N	DMF	$Pd(OAc)_2$	Trace
10	L_2	K_2CO_3	DMAc	$Pd(OAc)_2$	95
11	L_2	K_2CO_3	H_2O/DMF	$Pd(OAc)_2$	81
12	L_2	K_2CO_3	H_2O	$Pd(OAc)_2$	21
13	L_2	K_2CO_3	*i*-PrOH	$Pd(OAc)_2$	41
14	L_2	K_2CO_3	Toluene	$Pd(OAc)_2$	63
15	L_2	K_2CO_3	Dioxane	$Pd(OAc)_2$	69
16	L_2	K_2CO_3	DMF	$PdCl_2$	79
17	L_2	K_2CO_3	DMF	$Pd(CH_3CN)_2Cl_2$	85
18	L_2	K_2CO_3	DMF	K_2PdCl_4	71

[a] Reaction conditions: 1.0 mmol of 4-acetylbromobenzene, 1.2 mmol of *n*-butyl acrylate, 2 mmol of base, 0.5 mol% Pd salt, 1.0 mol% imidazolium salt (L_{1-4}), 80 °C, 2 h, 3 mL solvent.
[b] Isolated yield.

Table 2
Heck reaction between aryl halides and olefins.[a]

Entry	ArX	Olefin	Yield (%)[b]	Entry	ArX	Olefin	Yield (%)[b]
1	PhI	$PhCH{=}CH_2$	98	10	4-MeCO–PhBr	$PhCH{=}CH_2$	94
2	PhI	$H_2C{=}CH{-}COOBu$	97	11	4-MeCO–PhBr	$H_2C{=}CH{-}COOBu$	96
3	PhI	$H_2C{=}CH{-}COOMe$	97	12	4-MeO–PhBr	$H_2C{=}CH{-}COOBu$	81
4	PhI	$H_2C{=}CH{-}COOEt$	98	13	4-MeO–PhBr	$PhCH{=}CH_2$	83
5	PhI	4-Me–$PhCH{=}CH_2$	98	14	2-MeO–PhBr	$H_2C{=}CH{-}COOBu$	72
6	PhI	4-MeO–$PhCH{=}CH_2$	96	15	PhBr	$H_2C{=}CH{-}COOBu$	55
7	4-MeO–PhI	$H_2C{=}CH{-}COOBu$	95	16	4-MeCO–PhCl	$PhCH{=}CH_2$	49
8	4-MeO–PhI	$PhCH{=}CH_2$	96	17	4-MeCO–PhCl	$H_2C{=}CH{-}COOBu$	46
9	2-MeO–PhI	$H_2C{=}CH{-}COOBu$	90	18	PhCl	$H_2C{=}CH{-}COOBu$	17

[a] Reaction conditions: 1.0 mmol of aryl halide, 1.2 mmol of olfins, 2 mmol of K_2CO_3, 0.5 mol% $Pd(OAc)_2$, 1.0 mol% imidazolium salt L_2, 80 °C, 3 mL DMF.
[b] Isolated yield.

Table 3
The optimized reaction condition for Pd-catalyzed Suzuki reaction.[a]

Entry	Base	Solvent	Yield (%)[b]	Entry	Base	Solvent	Yield (%)[b]
1	K_2CO_3	DMF	71	8	K_2CO_3	H_2O/*i*-PrOH	84
2	K_2CO_3	DMAc	65	9	KOH	H_2O/*i*-PrOH	97
3	K_2CO_3	H_2O	53	10	Na_2CO_3	H_2O/*i*-PrOH	69
4	K_2CO_3	*i*-PrOH	47	11	K_3PO_4	H_2O/*i*-PrOH	42
5	K_2CO_3	Toluene	31	12	NaOAc	H_2O/*i*-PrOH	75
6	K_2CO_3	Dioxane	21	13	Et_3N	H_2O/*i*-PrOH	63
7	K_2CO_3	H_2O/DMF	87				

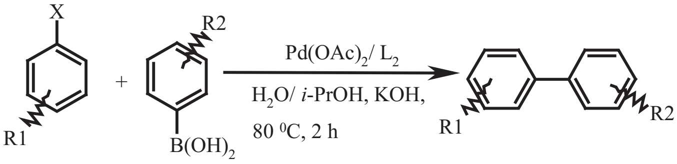
[a] Reaction conditions: 1.0 mmol of 4-acetylbromobenzene, 1.2 mmol of phenylboronic acid, 2 mmol of bases, 0.5 mol% $Pd(OAc)_2$, 1.0 mol% imidazolium salt L_2, 80 °C, 3 mL solvent.
[b] Isolated yield.

be of similar activity and more active than the other solvents, such as dioxane, toluene, H_2O, *i*-PrOH and a mixture of H_2O/DMF (2/1, v/v) in presence of K_2CO_3 as base catalyzed by $Pd(OAc)_2/L_2$ at 80 °C for 2 h (Table 1, entries 10–15). Then we carried out screening of palladium salts for better performance of the reaction and other palladium sources, including $Pd(OAc)_2$, proved to be less effective in the reaction of 4-MeCO-PhBr and *n*-butyl acrylate (Table 1, entries 16–18).

On the basis of the optimized conditions, we next carried out the Heck coupling reactions with a variety of aryl halides and alkene derivatives (Table 2). The coupling reactions of olefins and aryl iodides showed excellent yields (Table 2, entries 1–6). In the case of iodoanisole derivatives, sterically hindered 2-iodoanisole showed a slightly lower yield than 4-iodoanisole (Table 2, entries 7–9). Next, a variety of aryl bromides was employed as coupling partner with *n*-butyl acrylate and styrene in the Heck reaction using the $Pd(OAc)_2/L_2$ catalytic system. Aryl bromides having an electron withdrawing substituent gave the coupled product in good yields, and aryl bromides containing an electron donating group produced the corresponding coupled product in moderate yields (Table 2, entries 10–13). Among the bromoanisole derivatives, 2-bromoanisole exhibited the lowest yield (Table 2, entry 14). The coupling reactions of *n*-butyl acrylate with electron neutral aryl bromide, bromobenzene, gave the desired coupled product in 55% yield (Table 2, entry 15). We also tried the coupling reaction using aryl chlorides and found that the coupling of 4-acetylchlorobenzene with styrene and *n*-butyl acrylate resulted in moderate yields (Table 2, entries 16, 17). Unfortunately, the catalytic system $Pd(OAc)_2/L_2$ showed no activity for the Heck coupling reaction of chlorobenzene and trace amounts of coupling product was observed (Table 2, entry 18). The Heck coupling reaction of olefins with aryl halides showed the desired *E*-isomeric products as the only product.

Further, we investigated the Suzuki coupling reaction using the imidazolium salt L_2 as the ligand and Pd $(OAc)_2$ as the catalyst. We initially investigated the effect of bases and solvents on Suzuki reaction using 4-acetylbromobenzene and phenylboronic acid as substrates to optimize the reaction conditions (Table 3). The solvents, such as DMF, DMAc, H_2O, *i*-PrOH, dioxane and toluene, gave low to moderate yields ranging from 21% to 71% as illustrated in Table 3 (entries 1–6). However, when we adopted the organic/aqueous co-solvent, satisfactory results were obtained and a mixture of H_2O/*i*-PrOH (1/1, v/v) was found to be the best of choice (Table 3, entry 8). The merit of the co-solvent is attributed to the good solubility of the organic reactants and the inorganic bases. Among the tested bases, KOH is the best choice as compared to the other bases in a mixture of H_2O/*i*-PrOH (1/1, v/v) as solvent. The activity toward cross-coupled product was decreased when K_2CO_3 was replaced with Na_2CO_3, K_3PO_4, NaOAc, and Et_3N (Table 3, entries 10–13).

Table 4
Suzuki–Miyaura cross-coupling reaction of aryl halides with aryl boronic acids.[a]



Entry	R_1	X	R_2	Yield (%)[b]
1	H	Br	H	95
2	4-$COCH_3$	Br	H	97
3	H	Br	2-CH_3O	71
4	H	Br	4-CH_3O	90
5	4-$COCH_3$	Br	2-CH_3O	73
6	4-$COCH_3$	Br	4-CH_3O	94
7	4-$COCH_3$	Cl	H	67
8	H	Cl	H	48

[a] Reaction conditions: 1.0 mmol of aryl halides, 1.2 mmol of aryl boronic acids, 2 mmol of KOH, 0.5 mol% $Pd(OAc)_2$, 1.0 mol% imidazolium salt L_2, 80 °C, 3 mL mixture of H_2O/*i*-PrOH (1:1, v/v).
[b] Isolated yield.

The cross-coupling of a variety of aryl halides with phenylboronic acids in presence of the $Pd(OAc)_2/L_2$ catalytic system was carried out at 80 °C using mixture of H_2O/*i*-PrOH (1/1, v/v) as solvent (Table 4). The aryl bromides with electron-withdrawing group, 4-acetylbromobenzene, could efficiently couple with phenylboronic acids. Also, the coupling reaction could be efficiently executed of aryl boronic acids with methoxy as an electron-donating group (Table 4, entries 3–6). Using 4-methoxyphenylboronic acid led to good yields of the desired products. Although, due to crowding effect of phenylboronic acids substituted at *ortho* position, 2-methoxyphenylboronic acid led to low yields (Table 4, entries 3 and 5). The aryl chlorides tested afforded the corresponding products in moderate to good yields (Table 4, entries 7 and 8).

4. Conclusion

In conclusion, we have developed a new combination of $Pd(OAc)_2$/imidazolium salts (L_{1-4}),which is proved to be efficient for Heck reactions of various aryl iodides, bromides, and chlorides with various substituted alkenes and Suzuki–Miyaura reactions of various aryl bromides and chlorides with aryl boronic acids under the appropriate reaction conditions. It also demonstrates great tolerance to a wide range of groups on all substrates of aryl halides, alkenes and arylboronic acids.

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