Cryptand-22 as an Efficient Ligand for the Palladium-Catalyzed Mizoroki-Heck Reaction under Air

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Abstract:

An efficient catalytic system using an air- and thermally-stable $PdCl_2$-C22 complex for the Mizoroki-Heck cross-coupling reaction was developed. The complex has been shown to be a highly active catalyst for coupling reactions of aryl iodides, bromides as well as chlorides with various olefins.

Key words:

Heck reaction; cross-coupling reaction; $PdCl_2$/cryptand-C22 complex; aryl halides; olefins

1. Introduction

Palladium-catalyzed cross-coupling reactions between aryl halides and terminal acetylenes (commonly referred to as the Mizoroki-Heck reaction) is a highly versatile, powerful and popular tool for the synthesis of substituted olefins, dienes and precursors of conjugated polymers.[1] This reaction has also been utilized for the preparation of natural products,[2] and pharmaceuticals.[3] Unlike other carbon-carbon bond forming reactions that involve a polar addition, the Mizoroki-Heck reaction can be accomplished with any sensitive functionality such as aldehyde, ketone, cyano, amino, hydroxyl, carboxy, ester, and nitro groups.[4] The traditional Mizoroki-Heck reaction is typically performed with 1-5 mol% of a palladium catalyst along with a phosphine [5] or phosphorus[6] ligand in the presence of a suitable base. However, phosphine ligands are toxic, expensive, unrecoverable, and unstable at high temperatures; thus the development of a phosphine-free palladium catalyst is a topic of enormous interest. Moreover, the Mizoroki-Heck reaction still shows some limitations, especially in relation to the use of certain reagents. In particular, a major restriction of palladium-catalyzed coupling processes has been the poor reactivity of cheaper and readily available aryl chlorides and aryl bromides in comparison with more active aryl iodides. Therefore, the search for efficient catalysts for the cross-coupling of olefins with deactivated aryl bromide and towards activated aryl chloride is under progress. In recent years, utilization of selenium-[7] and nitrogen-based[8] catalysts, sulfur-based palladacycles[9] and *N*-heterocyclic carbene (NHC) ligands[10] as catalyst systems have also been introduced for the Mizoroki-Heck reaction, with an emphasis on air and thermally stable palladium catalysts. However, these non-phosphine ligands are not commercially available and some are tedious and cumbersome to prepare.

In cross-coupling reactions, amines are generally used as bases, but they can also serve to stabilize the reactive palladium intermediates.[11] Due to stronger σ-donation which favors both oxidative addition and slow reductive-elimination step in the catalytic cycle, ligands of N,N-type as compared to those of P,P-type ligands have demonstrated excellent properties for palladium complexation as well as catalysts for cross-coupling reactions.[12] Very recently as part of our studies to find a robust and easily prepared system to catalyze carbon-carbon bond forming reaction of terminal alkynes with acyl halides, we demonstrated that a Pd(II) catalyst system based on a commercially available diazacrown ether or cryptand-22, $PdCl_2$-C22, is a very active homogeneous catalyst under aerobic conditions.[13] With some modifications, this catalyst can be readily prepared based on the method described by Sun et al.[14] The remarkable chelating effect of this N- and O-containing ligand and its flexibility facilitate the stabilization of the reactive palladium intermediates,[11]and suppress the Pd black formation even at high temperature under air. The FT-IR spectrum of the complex displays $\nu_{N\text{-}H}$ stretch at 3224 cm^{-1} which is at a lower frequency than that of the free ligand (3327 cm^{-1}), indicating coordination of the cryptand nitrogens to Pd(II) ion.

Herein, we introduce this homogeneous air- and thermally-stable $PdCl_2$-C22 complex, as a highly efficient catalytic system for the Mizoroki-Heck reaction without using phosphorus ligands. A literature survey revealed that the reaction condition such as base, solvent, and reaction temperature have a great influence on this reaction. Our investigation began with an effort to optimize reaction conditions for the cross-coupling reaction.

2. Results and discussion

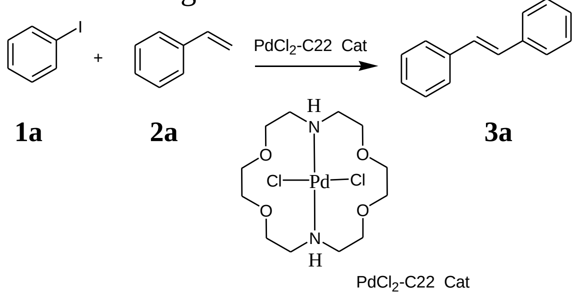
Iodobenzene and styrene were chosen as the coupling partners under various reaction conditions catalyzed by $PdCl_2$-C22 complex (0.9 mol%) in air (Table 1). The reaction rates were found to be strongly dependent on the base, solvent, temperature, and palladium concentration employed. Different organic and inorganic bases were screened as the role of the base is neutralizing and removing HI. The yield of the cross-coupling products was reduced when inorganic bases such as K_2CO_3, Na_2CO_3 or KO^tBu were employed (entries 13-15, Table 1). Moreover, a considerable increase in the product formation was observed in the presence of an organic base such as Et_3N in DMF at high temperature. Several other solvents including tetrahydrofuran (THF), *N*-methylpyrrolidone (NMP), dimethylacetamide (DMAc), and dimethyl sulfoxide (DMSO) were also surveyed under similar conditions but compared to *N*,*N*-dimethylformamide (DMF), all of them gave inferior results (entries 1-4, Table 1). Also, low palladium concentrations gave decreased yields (entries 6 and 7, Table 1). An increase in the catalyst concentration (1.1 mol%) did not have any significant effect on the product yield (entry 8, Table 1). It was concluded that Et_3N as base in DMF at 130 °C in the presence of 0.9 mol% of the catalyst is the optimized condition for the coupling reaction, which, after 15 min, gave the product in 97% yield as a *trans*-stilbene (entry 11, Table 1).

After developing the optimized reaction condition, the scope of this methodology was extended to the coupling reaction of activated, non- and deactivated aryl halides with different vinylic substrates (styrene, 4-methoxy styrene, *n*-butyl acrylate and acrylamide) using DMF/Et_3N at 130 °C in the presence of 0.9 mol% of the catalyst (Table 2).[15] Only trans products were selectively obtained in all cases. The results indicated that the $PdCl_2$-C22 catalytic system is remarkably active and tolerant of a range of functionalities. As expected, the reaction of iodobenzene, 4-iodotoluene, 4-iodoanisol, 1-iodonaphthalene, and 2-iodothiophene were performed very smoothly within 0.25-2 h giving the desired products in 80-97% isolated yields. However, the reaction of sterically hindered 2-iodotoluene with styrene gave a diminished yield (entry 6, Table 2). Under the same reaction conditions, the coupling reaction of bromobenzene with styrene gave a very poor yield (16 %) after 48 h (entry 11, Table 2); therefore, reaction conditions for the cross-coupling between aryl bromides/chlorides and alkenes were in need of tetra-*n*-butyl ammonium bromide (TBAB, 1 equiv) as an additive. Activated aryl bromides such as 1-bromo-4-nitrobenzene, 4-bromobenzonitrile, and 4-bromobenzaldehyde were rapidly coupled in high yields (entries 14, 15, 18, and 19, Table 2). The Mizoroki-Heck cross-coupling reaction of activated aryl chlorides such as 4-chloroacetophenone and 4-chlorobenzonitrile as well as the non-activated electron neutral chlorobenzene with styrene was also investigated under similar reaction conditions (entries 20-22, Table 2) using TBAB (1 equiv). However, compared to the bromo analogues, the reactions gave moderate yields and took longer reaction times.

3. Conclusion

In summary, the $PdCl_2$-C22 complex has been introduced as a potential catalyst for Mizoroki-Heck reaction of aryl halides with terminal olefins under phosphine-free conditions. This catalyst has the following advantages: thermal stability, facile synthesis, inexpensiveness, easy handling, and catalytic performance in air. Furthermore, cryptand-22 might act as a ligand to stabilize the Pd(0) species in the Mizoroi-Heck reaction.

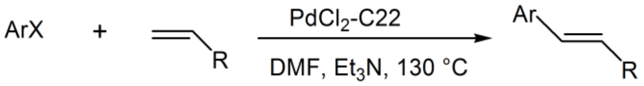
Table 1. Screening of the Reaction Conditions[a]



Entry	Solvent	Cat. (mol%)	T (°C)	Base	Time (h)	Yield (%)[b]
1	THF	0.9	115	Et_3N	6	31
2	DMSO	0.9	115	Et_3N	1.5	84
3	NMP	0.9	115	Et_3N	3	63
4	DMAc	0.9	115	Et_3N	2	60
5	DMF	0.9	115	Et_3N	1.5	87
6	DMF	0.7	115	Et_3N	2.75	80
7	DMF	0.5	115	Et_3N	4	71
8	DMF	1.1	115	Et_3N	1	89
9	DMF	0.9	100	Et_3N	2	84
10	DMF	0.9	60	Et_3N	4	37
11	DMF	0.9	130	Et_3N	0.25	97
12	DMF	0.9	130	DIPEA	1.5	77
13	DMF	0.9	130	K_2CO_3	4.5	68
14	DMF	0.9	130	Na_2CO_3	7	64
15	DMF	0.9	130	KO^tBu	1	61

[a] Reaction conditions: Iodobenzene (1 mmol), styrene (1.1 mmol), base (1.1 mmol), solvent (1 mL) under air; [b] Isolated yield.

Table 2 PdCl$_2$-C22-Catalyzed Mizoroki-Heck Coupling Reaction of Aryl Halides and Olefins[a]



Entry	ArX	R	Product	Time (h)	Isolated yield[c] (%)
1	PhI	Ph	**3a**	0.25	97[8a]
2	PhI	4-MeOC$_6$H$_4$	**3b**	0.75	80[10b]
3	PhI	CONH$_2$	**3c**	2	84[16]
4	PhI	CO$_2$Bu^n	**3d**	1	91[8a]
5	4-MeC$_6$H$_4$I	Ph	**3e**	1	90[2a]
6	2-MeC$_6$H$_4$I	Ph	**3f**	3	72[17]
7	4-MeOC$_6$H$_4$I	Ph	**3g**	1	80[18]
8	1-I-Naphtalene	Ph	**3h**	1.5	82[19]
9	4-MeC$_6$H$_4$I	CO$_2$Bu^n	**3i**	1	92[8a]
10	2-I-Thiophene	CO$_2$Bu^n	**3j**	1	94[20]
11	PhBr	Ph	**3k**	48	16[8a]
12	PhBr	Ph	**3k**[b]	4	73[8a]
13	PhBr	CO$_2$Bu^n	**3l**[b]	3.5	69[8a]
14	4-NO$_2$C$_6$H$_4$Br	Ph	**3m**[b]	2	85[8a]
15	4-NO$_2$C$_6$H$_4$Br	CO$_2$Bu^n	**3n**[b]	3	81[8a]
16	4-MeOC$_6$H$_4$Br	Ph	**3o**[b]	3.5	70[10b]
17	4-MeOC$_6$H$_4$Br	CO$_2$Bu^n	**3p**[b]	4.5	62[8a]
18	4-CNC$_6$H$_4$Br	Ph	**3q**[b]	3	82[21]
19	4-CHOC$_6$H$_4$Br	Ph	**3r**[b]	3	85[22]
20	PhCl	Ph	**3s**[b]	8	51[8a]
21	4-CH$_3$COC$_6$H$_4$Cl	Ph	**3t**[b]	5	64[23]
22	4-CNC$_6$H$_4$Cl	Ph	**3u**[b]	4	66[24]

[a] Unless otherwise indicated, the reaction conditions were as follows: aryl halide (1 mmol), olefin (1.1mmol), Et$_3$N (1.1 mmol), PdCl$_2$-C22 (0.9 mol%), DMF (1 mL), 130 °C under air.

[b] TBAB (1 mmol) was added.

[c] References for known compounds.

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[15] **General Procedure***:* A 5 mL RB-flask was charged with aryl halide (1 mmol), alkene (1.1 mmol), $PdCl_2$-C22 (0.009 mmol, 0.9 mol %), triethylamine (1.1 mmol), and DMF (1 mL) (for aryl bromides and chlorides 1 mmol of TBAB was added); the reaction mixture was stirred at 130 °C for the appropriate time (Table 2) and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to r.t., poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification by preparative TLC (silica gel, eluent *n*-hexane or *n*-hexane-EtOAc, 9:1) gave the pure product.

3e: White solid; mp 119-122 °C (lit.[2a] mp 120-122 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.13 (s, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 126.45, 126. 49, 127.5, 127.7, 128.65, 128.7, 129.5, 134.6, 137.55, 137.57.

3f: Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H), 7.08 (d, *J* = 16.1 Hz, 1H), 7.26-7.47 (m, 7H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 125.4, 126.3, 126.6, 126.7, 127.65, 127.69, 128.8, 130.1, 130.5, 135.9, 136.5, 137.8.

3g: White solid; mp 136-137 °C (lit.[18] mp 135-137 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.89-6.94 (m, 2H), 6.99 (d, *J* = 16.3 Hz, 1H), 7.09 (d, *J* = 16.3 Hz, 1H), 7.23-7.28 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.45-7.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 114.1, 126.3, 126.6, 127.2, 127.7, 128.2, 128.7, 130.1, 137.7, 159.3.

3i: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.43 (sext, *J* = 7.4 Hz, 2H), 1.70 (quin, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 4.20 (t, *J* = 6.6 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 19.2, 21.4, 30.8, 64.3, 117.2, 128.0, 129.6, 131.7, 140.5, 144.5, 167.2.

3j: Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.43 (sext, *J* = 7.2 Hz, 2H), 1.68 (quin, *J* = 6.8 Hz, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 6.24 (d, *J* = 15.7 Hz, 1H), 7.04 (t, *J* = 4.9 Hz, 1H), 7.24-7.27 (m, 1H), 7.36 (d, *J* = 4.9 Hz, 1H), 7.77 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.8, 19.2, 30.8, 64.4, 117.0, 128.1, 128.3, 130.8, 137.0, 139.6, 166.9.

3q: White solid; mp 115-118 °C (lit.[21] 116-118 °C); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.09 (d, *J* = 16.3 Hz, 1H), 7.23 (d, *J* = 16.3 Hz, 1H), 7.26-7.42 (m, 3H), 7.53-7.66 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 110.6, 119.1, 126.7, 126.88, 126.94, 128.7, 128.9, 132.4, 132.5, 136.3, 141.8.

3r: Pale yellow solid; mp 117-118 °C (lit.[22] mp 115-116 °C); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.15 (d, *J* = 16.3 Hz, 1H), 7.28 (d, *J* = 16.3 Hz, 1H), 7.32-7.42 (m, 3H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.88 (d, *J* = 7.7 Hz, 2H), 10.0 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 126.9, 127.3, 128.5, 128.9, 130.3, 132.2, 135.3, 136.5, 143.4, 191.7.

3t: Pale yellow solid; mp 143-145 °C (lit.[22] mp 144-145 °C); ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.62 (s, 3H), 7.13 (d, *J* = 16.3 Hz, 1H), 7.24 (d, *J* = 16.3 Hz, 1H), 7.28-7.33 (m, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.96 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 26.6, 126.5, 126.8, 127.4, 128.3, 128.8, 128.9, 131.5, 135.9, 136.7, 142.0, 197.5.

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