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Efficient Mizoroki–Heck coupling reactions using phosphinemodified Pd(II)–picolinate complex

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ABSTRACT

Efficient Mizoroki–Heck couplings were obtained using a very easily synthesizable palladium(II) complex of hemilabile N–O ligand (picolinate), with high turnover frequencies up to >10,000 h⁻¹, in just 15 min, with high selectivity of >99% to the desired products. Wide applicability of the simple-looking palladium complex catalyst was established with differently functionalized substrates. Catalyst screening studies revealed intricate details of dependence of catalyst performance on different reaction parameters and conditions and arriving at the optimized facile methodology.

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KEYWORDS

Heck coupling; hemilabile N–O ligand; homogeneous catalysts; Pd(II)-complex; picolinate

GRAPHICAL ABSTRACT



Introduction

Palladium catalysts have been known for high performance in different types of C–C coupling reactions such as Mizoroki–Heck, etc., used in synthesis chemistry for natural product and pharmaceutical intermediates, polymer building units, specialty chemicals and pesticide building blocks, etc., and hence have gained importance in the last few decades.^[1] Typically during a Mizoroki–Heck-type C–C coupling, the reaction between an organic halide and alkene, role of the Pd-complex, is considered prime important in catalyst performance in terms of activity and selectivity. In addition, some important

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⁽⁾ Supplemental data (synthesis and characterization of all the reaction products [¹H and ¹³C NMR traces]) can be accessed on the publisher's website.

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2 🔄 S. SHARMA AND B. R. SARKAR

aspects like facile ligand synthesis and cost pertaining to that, and the stability of the metal complex, sensitivity to air/oxygen/aqueous environment, contribute greatly to overall economic viability of a metal complex catalyst for large-scale applications.^[2] Developmental approaches have been reported such as design of novel ligands/Pd-complexes having mvriad of donor centers (C, N, O, P, S, etc.), ligand denticity (mono-, bi-, polydentate, etc.), use of different media to assist catalyst-product separation, etc. with varied shares of advantages and drawbacks in their syntheses and applications. Majority of the highefficiency catalysts with ingenious phosphine-derived ligands reported are associated with multistep ligand-synthesis processes (including stoichiometric steps), and hence expensive mostly, have enhanced sensitivity to moisture and air, thus diminishing the chance of industrial viability.^[3] Among the other classes of ligands, phosphine-free ligands, typically functionalized N-heterocyclic carbenes/N-donor ligands were reported.^[4] Another important class of compounds named as Schiff's bases have also been used extensively for catalyzing different kinds of reactions.^[5] In a very recent report, complexes of different Schiff's base type N-O ligands were studied for Heck coupling reactions with promising results.^[6] In the same context, Pd-complexes of hemilabile N–O ligands might also play important roles in Mizoroki-Heck catalysis. In another report, new N-O ligand was reported for Pd-catalyzed Mizoroki-Heck coupling in water presenting good promise but with low TOF (<10 h⁻¹).^[7] As exemplified by Guo et al.,^[8] Pd-complexes of these ligands were found to have moderate to high activity under phosphine-free conditions. Phosphine-free bispicolinate complex of palladium has also been reported by Iyer et al. for the Heck reactions, but with moderate performance only.^[9] However, Pd-complexes of simple hemilabile N-O ligands such as picolinate along with another phosphine ligand have been found to catalyze hydroxycarbonylation reactions and Suzuki cross-coupling reactions with high efficiency and stability.^[10] We herein report the use of phosphinecontaining Pd-picolinate complex as efficient catalyst for Heck coupling reactions having high to excellent performance.

Phosphine-containing palladium picolinate complex [Pd–Pyca complex] was obtained by synthesis process as described elsewhere.^[10(a)] The complex was obtained as pale yellow powder and was used for the Mizoroki–Heck coupling reactions after proper purification and characterization which matched with the data in literature.^[(10a)] The reaction of iodobenzene with styrene was considered as model reaction for optimization of catalyst performance as shown in Scheme 1.

Table 1 contains the details of optimization of reaction parameters with respect to the solvent used, base, temperature. It was observed that the catalyst showed good performance with a relative ratio of 1:1.2 at 100 °C.

The conversion, selectivity (and hence GC yields) were calculated on the basis of quantification by a calibrated gas chromatographic technique. The selectivity in all the



Scheme 1. Mizoroki-Heck coupling of iodobenzene with styrene using palladium(II) picolinate complex.

Entry	Solvent	Base	Temperature (°C)	Time (min)	Yield, % ^b
1	MeOH	NaOAc	70	65	35.7
2	Toluene	NaOAc	100	60	40
3	Dioxane	NaOAc	100	60	45
4	EtOH	NaOAc	80	70	44
5	CH₃CN	NaOAc	80	30	50
6	Neat	NaOAc	80	60	20
7	DMSO	NaOAc	100	40	69
8	DMF	NaOAc	100	30	90.1
9	DMF	K ₂ CO ₃	100	50	72
10	DMF	Cs ₂ CO ₃	100	40	75
11	DMF	Et₃N	100	60	30
12	DMF	NaHCO ₃	100	30	58
13	DMF	Na ₂ CO ₃	100	60	65.2
14	DMF	NaOAc	80	40	80
15	DMF	NaOAc	120	15	99.8
16	DMF	NaOAc	130	15	99.8

 Table 1. Optimization of reaction conditions.^a

^aReaction conditions: lodobenzene: 1.0 mmol, Styrene: 1.2 mmol, Base: 1.5 mmol, Pd-catalyst: 0.007 mmol, Solvent: 3 mL, ^bGC Yield.

cases was found to be >99% toward the desired product only using this catalyst indicating a highly selective catalyst. Among the different solvents tested (Table 1, entries 1–7), dimethyl formamide (DMF) showed good conversions initially (90.1%). Almost all the solvents tested gave satisfactory conversions in the range of \sim 30–90% within very short reaction times indicating high catalyst efficiency. As we know, the catalytic performance is also dependent on the base used, we tested different bases to choose the best one (Table 1, entries 8–13). Optimization of the bases revealed that sodium acetate, NaOAc, was the most efficient one. Once the base and the solvent were fixed, the reaction was optimized with respect to the reaction temperature and 120 °C was considered as optimized among 80, 100, 120, and 130 °C, respectively (Table 1, entries 8, 14–16).

It was observed that the catalyst performance was enhanced with temperature from \sim 80% conversion at 80 °C till about 120 °C with \sim 99.8% conversion in just 0.25 h. On further rise to 130 °C, the catalyst performance did not change anyway. The optimized reaction conditions thus obtained were used for subsequent studies. The typical concentration-time profile of the optimized reaction of styrene and iodobenzene is presented in Figure 1, which shows the almost complete conversion of the limiting reagent, i.e., iodobenzene and no other side products other than the desired product stilbene.

To understand the efficiency of developed catalyst, another quantitative aspect of the catalytic reaction namely turnover frequency (TOF, h^{-1}) was used, which integrated the time required for the reactions and hence can be an indicator of the catalytic activity. With the understanding of the optimized reaction conditions, we wanted to explore the maximum efficiency boundary with respect to the catalyst performance (activity and selectivity). We varied the substrate-to-catalyst (S/C) ratio gradually within the workable handling limits, with slight increase in every step to obtain the activities (in TOF) for comparison and subsequent further increment. The results are tabulated in Table 2.

It was clearly observed that the Pd-pyca complex catalyst has a very high activity for Mizoroki–Heck coupling reaction with the highest observed TOF of $10,715 h^{-1}$ and may be considered as an efficient homogeneous Pd-complex catalyst with hemilabile N–O ligand for Mizoroki–Heck coupling reactions. The high TOF of the catalyst was mostly observed for the bromoarenes and iodoarenes, but we could not get impressive results



Figure 1. Concentration-time profile for optimized catalytic reaction.

for the Heck coupling involving chloroarenes (~36% conversion with chlorobenzene, entry 20, Table 3), and the scope of such experimentation is open. Having found this high activity for the coupling reactions, we wanted to demonstrate the applicability of the catalyst to various substituted substrates having a variety of functional groups as presented in Table 3. The study of the scope of application to various derivatives showed impressive results with majority of reactions showing more than 95% conversion within a very short reaction time of 15 min. The electron-donating groups as well as the electron-withdrawing substituents on the aryl ring showed almost comparable performance in the catalytic Heck couplings. The standard reaction had also been conducted (Table 3, Entry 21) in gram-scale to visualize larger scale application. It may be noted that the Pd–pyca complex outperforms the activity shown by the catalyst precursors alone, e.g., Pd(OAc)₂ alone (~31% conversion in 30 min) and Pd(OAc)₂/PPh₃ (~43% conversion in 30 min), and hence the role of picolinate ligand was observed to be vital in the performance of the Pd-catalyst for Mizoroki–Heck reactions.

The comparative study of the activity of present catalyst with the reported catalyst systems reveals that this work is a significant advancement in terms of use of an easily available cheap picolinate ligand in the Pd-complex, over the expensive ligands requiring multistep syntheses. Comparing the different catalyst systems described in the Bi- and multidentate P- or N-based ligands for the Mizoroki–Heck reactions in the review by Farina,^[2e] it can be stated that the majority of the reported catalysts work at 130–150 °C, showing very high TONs, but take

Entry	Subs, mmol	Cat, mmol	Yield, % ^b	Time, min	TOF, h ⁻¹
1	1	0.07	99	15	57
2	1	0.007	95	15	543
3	10	0.007	84	15	4,800
4	50	0.007	75	30	10,715

 Table 2.
 Variation of substrate-to-catalyst ratio.^a

^aReaction conditions: Reaction conditions: Substrates: iodobenzene, styrene in molar ratio of 1:1.2 solvent: DMF; NaOAc: 1.5 equivalents to iodobenzene, temperature: 120 °C. ^bGC Yield.

Entry	Arvl Halide		Product	Vield % ^b
1				98
	1a	2a	3a	
2	Me 1b	2a	Me 3b	94
3	Me 1b	Me 2b	Me 3c Me	93
4	MeO 1c	2a	MeO 3d	91
5	MeO 1c	2b Me	Meo 3e	90
6	Me 1d	2a	Me 3f	95
7	Me 1d	Zb Me	Me 3g	95
8	Br 1e	2a	3h	93
9	Br	Zb Me	CH ₃ 3i	92
10	OHC If	2a	OHC 3j	90
11	OHC If	Zb Me	OHC CH3	92

 Table 3.
 Heck coupling of different aryl halide and olefins.^a

(Continued)



^aReaction conditions: Aryl halide: 1 mmol; alkene: 1.2 mmol; NaOAc: 1.5 mmol, Pd-catalyst: 0.007 mmol; solvent: DMF; temperature: 120 °C; time: 15 min, ^bisolated yields, ^ctime: 25 min, ^dlarger-scale reaction: iodobenzene: 4.9 mmol; styrene: 5.9 mmol; NaOAc: 7.4 mmol, Pd-catalyst: 0.034 mmol, other conditions similar.

>20 h to completion, with some exceptions such as Pd/Tedicyp,^[11] Pd/bispyridine-based N–N ligand^[12] (higher TONs and TOFs observed than our present report). But in these cases, the synthesis routes to such ligands are complex multistep ones compared to the picolinate

ligand. The Pd-picolinate-phosphine complex thus opens up scope for making economically viable catalysts for large-scale applications, envisions potential use of the catalysts for other types of C-C coupling reactions, and also for development of associated separable catalyst systems.

As a conclusion, we would like to mention that the simple and facile palladium picolinate complex has emerged as a promising catalyst for Heck coupling with high efficiency.

Experimental details

All of the reagents and solvents are commercially available and were used as purchased without further purification. Solvents except laboratory reagent grade were dried and purified, when necessary. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel plates from Merck (silica gel 60, F 254, 0.25 mm) using 100% n-hexane as mobile phase (R_f for trans-stilbene was 0.62). Reaction products were purified by column chromatography using 100–200-mesh silica gel and eluting with n-hexane or n-hexane/ethyl acetate mixtures. Melting points of synthesized compounds were determined in *E*–*Z* melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded in Bruker-Avance II (400, 100 MHz) spectrometer and chemical shift is given in δ units with respect to TMS as internal standard. The proton multiplicities were mentioned as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, and m = multiplet.

General experimental procedure for the Heck reaction

A mixture of iodobenzene (1.0 mmol), styrene (1.2 mmol), NaOAc (1.5 mmol), catalyst (0.007 mmol), and DMF (3 mL) was added in a round-bottom flask (no inert gas protection was needed.). The reaction was performed at 120 °C for 15 min. Upon completion of reaction as indicated by TLC, the reaction mixture was poured in crushed ice-water, extracted with ethyl acetate, dried over anhydrous Na₂SO₄, concentrated in vacuum to give crude product which was purified through column chromatography on silica gel (100–200) to afford pure stilbenes in 90–98% yields. For GC analysis, after completion of the reaction (indicated by TLC), a measured quantity of the reaction mixture was analyzed in a Shimadzu 2014 GC instrument fitted with a RTX-5 column (30 m × 0.25 mm × 0.2 μ m). A calibrated method developed using known standards (starting materials, products) was used for quantitative analysis of reaction mixtures. Conversion and TOF were calculated as:

$$Conversion = \frac{\text{Moles of starting material consumed}}{\text{Initial moles of starting material}} \times 100$$
$$TOF = \frac{\text{Moles of starting material converted}}{\text{Moles of catalyst used} \times \text{time}}$$

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