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N,*N*'-Mono substituted acyclic thioureas: efficient ligands for the palladium catalyzed Heck reaction of deactivated aryl bromides

ABSTRACT

iodobenzene with styrene).



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ARTICLE INFO

A series of N.N'-mono substituted acyclic thiourea ligands are found to be highly active phosphine-free

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Introduction

The palladium-catalyzed arylation of olefins is an important method for the C–C bond formation in many organic transformations, finding several applications in the synthesis of natural products and fine chemicals.^{1–5} This reaction was usually performed with 1–5 mol % of palladium catalyst in the presence of the phosphine ligands.^{6,7} However, the phosphine ligands are generally expensive and air sensitive. A number of phosphine-free catalysts^{8–13} have been employed in the Heck reaction, among them N-heterocyclic carbene ligands,^{14,15} and palladacycle catalysts^{16,17} have shown excellent activity. Therefore, the development of phosphine-free catalysts is an important topic of research. Thioureas are air and moisture stable solids and have been employed as ligands in organometallic chemistry.^{18–24} These ligands act as efficient catalysts in palladium catalyzed Heck and Suzuki–Miyaura cross coupling reaction.^{25–28}

Compared to other phosphine-free ligands, steric and electronic properties of thiourea or urea ligands allow a variety of possible coordination modes when bonding to a metal. The catalytic activities of thiourea ligands can be varied by a variety of substitutions on nitrogen and their structure. Dan Yang and co-workers reported bulky thiourea–Pd complex and acyclic bis (thiourea) ligands for Heck and Suzuki reaction of aryl halides. The Pd complex of NH moiety containing acyclic mono thioureas shows no catalytic activity in the Heck reaction.^{27,28} Recently Khairul has reported NH

containing palladium(II) thiourea complex for the Heck cross-coupling reaction.²⁹

catalysts for palladium catalyzed Heck reaction of aryl iodides and bromides with olefins. We have

achieved high turnover numbers for aryl iodides with olefins (TONs up to 970,000 for the reaction of

Previously, we have reported homogeneous and heterogeneous thiopseudourea palladium(II) complexes as catalysts for Sonogashira, Suzuki–Miyaura, Heck, and Hiyama and Larock heteroannulation cross-coupling reactions.^{30–32}

Herein, we report that NH featuring *N*,*N*'-mono substituted acyclic thioureas are highly efficient ligands for the Pd-catalyzed Heck reaction of aryl iodides and bromides with olefins, which achieved very high turnover numbers for aryl iodides as well as aryl bromides.

Results and discussion

All the acyclic *N*,*N*⁻mono substituted thioureas (Fig. 1) can be easily synthesized in one step as shown in Scheme 1.³³ Ligands **1a–d** were prepared from in situ generated benzoyl derivatives such as aroyl isothiocyanates and aryl amines in acetone at 0 °C to afford products in quantitative yields under nitrogen atmosphere, which are obtained as white solids after purification by column chromatography. The resulting compounds were characterized by NMR, IR, and Mass spectroscopic techniques. Subsequently, the acyclic simple thiourea ligand **1e** was prepared by the reaction of commercially available phenyl isothiocyanate with picolyl amine in dichloromethane (DCM) (Scheme 2).³⁴

Further, we studied the catalytic activity of various *N*,*N*'-mono substituted thioureas for the Heck reaction between 4-bromoanisole and styrene at 130 °C (Table 1). The reactions were performed in the presence of 0.01 mol % of catalyst³⁵ (1:2 ratio of Pd(OAc)₂/





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Figure 1. Structures of thiourea ligands.



Scheme 1. Synthesis of *N*,*N*⁻mono substituted acyclic thiourea ligands.



Scheme 2. Synthesis of N,N'-mono substituted acyclic thiourea ligand (1e).

Pd(OAc)₂ / ligand

Table 1

Heck reaction between 4-bromoanisole and styrene

MeO + Ph LiOH.H ₂ O, DMF MeO							
Entry	Ligand	Base	Time (h)	Yield ^b (%)			
1	1a	NaOAc	10	62			
2	1a	K ₂ CO ₃	10	90			
3	1a	K_3PO_4	10	32			
4	1a	LiOH·H ₂ O	10	98			
5	1b	LiOH·H ₂ O	10	82			
6	1c	LiOH·H ₂ O	10	86			
7	1d	LiOH·H ₂ O	10	_			
8	1e	LiOH·H ₂ O	15	94			
9	1f	LiOH·H ₂ O	24	34			
10	1g	LiOH·H ₂ O	24	-			

^a Reaction conditions: 4-bromoanisole 1 mmol, styrene 2 mmol, base 2.0 mmol, 0.01 mol % of catalyst (Pd(OAc)₂/ligand = 1:2) in 2 mL DMF, reaction temperature 130 °C.

thiourea ligand (1a) in 2 mL DMF, using a variety of bases (2 mmol) for about 10 h (entries 1–4). Among these (entry 4), the LiOH·H₂O base gave the best results. In the series of thiourea ligands (1a–d) studied, the picolyl group containing ligand 1a (entry 4) resulted in excellent yields. When the picolyl group is replaced with the phenyl group (1b &1c), the yields were slightly lower (entries 5 & 6). No activity was observed for the ligand 1d, as the pyridine group was directly attached to nitrogen atom (entry 7). The ligand 1e (entry 8) gave an excellent yield, whereas 1f (commercially available) gave very low yield (entry 9). The ligand 1e is similar to the earlier reported one, wherein we exchanged the oxygen atom

with sulfur.³⁶ We also examined the simple thiourea **1g** system and found to be completely inactive (entry 10). According to Guo and co-workers an additional substituent on nitrogen atom in *N*-phenyl urea may cause steric hindrance, which we have also observed in case of **1f** ligand.³⁷ The ligand **1d** was completely inactive in the Heck reaction, which can be explained by the possible formation of highly stable bis-complex, wherein the formation of strongly coordinating sulfur and nitrogen bonds with Pd was expected.

Earlier, it was reported that N,N'-mono substituted acyclic N–H featuring thiourea ligands are completely inactive in Pd catalyzed Heck reaction.²⁶ But in our case, we highlight that the N–H featuring thiourea ligands (**1a–c**) act as good catalysts in the Heck reaction due to the presence of the carbonyl functional group adjacent to nitrogen atom. From the above results, it is clear that the position of heterocyclic ring and the carbonyl functional group on nitrogen atom in each thiourea ligand plays an important role in the catalytic activity of Pd(OAc)₂ in the Heck reaction.

The Heck coupling reaction of various aryl halides and olefins has been investigated in the presence of Pd(OAc)2/1a (1:2). The results are summarized in Table 2.³⁸ Deactivated and activated aryl bromides were reacted with different aromatic olefins to give moderate to excellent yields of the coupled products (0.001 mol % of Pd, 2 equiv LiOH·H₂O, DMF, 130 °C) (entries 1-7 & 10-15). Sterically hindered 2-bromoanisole and 2-bromotoluene could also be coupled in moderate yields by increasing the catalyst loading (0.01 mol % of Pd) (entries 16 and 17). Furthermore, aryl iodides were also excellent substrates suitable for our reaction conditions (entries 18–21). We have achieved high turnover numbers $(6.6 \times 10^5 \text{ and } 4.7 \times 10^5)$ with electron rich aryl bromides (entries 8 & 9) and aryl iodides $(9.7 \times 10^5 \text{ and } 9.5 \times 10^5)$ using as low as 0.0001 mol % of Pd (entries 18 & 19). The above optimized reaction conditions were less effective for the Heck reaction of aryl chlorides (entry 22).

Encouraged by these results, further we have examined the coupling reaction of aryl halides with *n*-butyl acrylate using Pd(OAc)₂/ **1a** (1:2) (Table 3).³⁹ When aryl iodides were used as substrates, excellent yields were obtained (entries 1–5). Aryl bromides resulted in moderate to excellent yields with *n*-butyl acrylate (entries 6–9). Poor yields were observed in case of aryl chlorides (entry 10).

In conclusion, we have accomplished phosphine-free *N*,*N*⁻-mono substituted acyclic thiourea ligands for Pd catalyzed Heck cross-coupling reactions. Compared to the earlier reports on thiourea ligands, ours is better for Heck reactions of deactivated aryl bromides. We have achieved high turnover numbers for both aryl iodides and aryl bromides. Since these ligands are inexpensive and easy to prepare, the present protocol has potential application for the synthesis of Heck products. Work is in progress in our laboratory to extend the application of these ligands to other palladium-catalyzed transformations.

^b Isolated yield.

Table 2 Heck reaction of aryl halides and styrenes^a

۸r	v 1		$\Pr(OAc)_2 / \text{lig}$	and (1:2)			
ALA $\stackrel{+}{\longrightarrow}$ $K \stackrel{+}{\longrightarrow}$ LiOH.H ₂ O, DMF, 130 °C Ar							
Entry	ArX		R	Pd/ mol %	Time (h)	Yield ^b (%)	
1	MeO	Br		0.001	10	97	
2	MeS	Br	\bigcirc	0.001	10	90	
3	MeS-	Br		0.001	10	94	
4	Me ₂ N	Br	$\bigcirc \frown$	0.001	48	60	
5		Br	\bigcirc	0.001	10	97	
6		Br		0.001	10	95	
7	MeO	Br		0.001	10	94	
8	MeO	Br	\bigcirc	0.0001	15	66	
9	MeS ⁻	Br	$\bigcirc \frown$	0.0001	20	47	
10	X	Br	$\bigcirc \frown$	0.001	10	95	
11	MeO	Br	$\bigcirc \frown$	0.001	10	90	
12	MeOO	Br	$\bigcirc \frown$	0.001	12	84	
13		Br	$\bigcirc \frown$	0.001	12	96	
14	\bigcirc	Br	N	0.001	10	64	
15	\bigcirc	Br		0.001	10	98	
16	\bigcirc	Br		0.01	10	82	
17	C	OMe		0.01	10	76	
18	\bigcirc	I		0.0001	10	97 ^c	
19	\int		\bigcirc	0.0001	10	95 ^c	
20	\bigcirc			0.001	10	98 ^c	
21	\bigcirc	I OMe	\bigcirc	0.001	10	95 ^c	
22	O ₂ N	Cl	$\bigcirc \frown$	1	10	42	

^a Reaction conditions: aryl halide 1 mmol, olefine 2 mmol, LiOH·H₂O 2.0 mmol, 0.001 mol % of Pd, DMF 2 mL.

^b Isolated yield.

^c Reaction temperature 120 °C.

Table 3

Heck reactions of aryl halides and n-butyl acrylate^a

R	$\int_{-\infty}^{\infty} + \sum_{n=1}^{\infty} CO_2^n Bu \frac{Pd(C)}{NaO}$	OAc) ₂ / ligand (1: OAc, DMF, 130 °C	$\frac{2}{C}$ R	CO2 ⁿ Bu
Entry	R	Pd/mol %	Time (h)	Yield ^b (%)
1		0.001	10	99°
2	I	0.001	10	96 ^c
3	CI	0.001	10	94 ^c
4	Γ, I	0.001	10	90 ^c
5	OMe	0.001	10	87 ^c
6	Br	0.001	10	86
7	EtOOC	0.01	12	90
8	MeO	0.01	12	74
9	Br	0.01	12	90
10	Cl	1	24	21

^a Reaction conditions: aryl halide 1 mmol, *n*-butyl acrylate 2 mmol, NaOAc 2.0 mmol 0.01 mol % of Pd catalyst in 2 mL DMF.

^b Isolated yield.

^c Reaction temperature 120 °C.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014. 09.053.

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- 33. General procedure for the preparation of ligands (1a-1d): To a solution of NH₄SCN (0.912 g, 12 mmol) in 20 mL acetone was added benzoyl chloride (0.14 g, 10 mmol) drop wise at 0 °C and the mixture was stirred for 30 min. To this aryl amine (10 mmol) was added at the same temperature and stirred for an additional 3 h. The mixture was concentrated, water (50 mL) was added, and extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous MgSO₄, and filtered, after

which the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1:3) as the eluent to give the desired product in 80-90% yield (**1a-d**).

- 34. General procedure for the preparation of ligands (1e): To a RB- flask containing picolylamine (1.08 g, 10 mmol) in 20 mL dichloromethane (DCM) was added drop wise a solution of 4-chlorophenyl isothiocyanate (1.5 equiv) in DCM (10 mL) at 0 °C and the resulting mixture was allowed to stir at room temperature for 10 h. The solvent was removed under reduced pressure and the residue was purified by repeated crystallization with ethyl acetate to give the desired product in 80% yield.
- 35. General procedure for the preparation of catalyst solution: A single-necked 25 mL RB-flask was charged with the ligand 1a (0.1 mmol), Pd(OAc)₂ (0.05 mmol), LiOH-H₂O (3 equiv), and methanol (5 mL). After stirring for 3 h at room temperature, a brown colored solution was observed. The resulting solid was washed with water (2 mL) to remove excess base (note: solid is insoluble in water). The solid was then washed with ethyl acetate to remove water and excess ligand. The resulting solid was dried under high vacuum to obtain the pure complex.

This solid is further diluted with DMF (500 mL) to make 5 mol% of stock solution (1 mL contains 0.01 mol% of Pd catalyst). For low catalyst loading reactions (0.001 mol% of Pd catalyst) we further diluted the above DMF stock solution.

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 General procedure for Heck reaction of aryl bromides with styrene: The 25 mL RB-flask was charged with aryl bromides (1 mmol), alkenes (2 mmol), LiOH·H₂O (2 mmol), and the catalyst (Pd(OAc)₂/1a = 1:2, 0.001 mol% in 2 mL N.N-dimethylformamide). The reaction mixture was heated at 130 °C for 10 h. Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with brine water. The combined organic phase was dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was subjected to column thromatography on silica gel using ethyl acetate and hexane to afford the Heck product in high purity.
- 39. General procedure for Heck reaction of aryl bromides with n-butyl acrylate: The 25 mL RB- flask was charged with aryl bromides (1 mmol), n-butyl acrylate (2 mmol), NaOAc (2 mmol), and 0.01 mol % catalyst (Pd(OAc)₂/1a (1:2) in 2 mL N,N-dimethylformamide). Then the experimental procedure was same as above.