Tetramethylguanidine as an Inexpensive and Efficient Ligand for the Palladium-Catalyzed Heck Reaction

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Received 6 May 2005

Abstract: An inexpensive and efficient $Pd(OAc)_2$/tetramethylguanidine (TMG) or $PdCl_2$/TMG catalytic system has been developed for the Heck reaction of an olefin with an aryl halide. The TONs were up to 1000000 when iodobenzene was used as the substrate with butyl acrylate as the reactant. In addition, $[Pd(TMG)_4]Cl_2(H_2O)_8$, an air-stable compound, effectively promoted the Heck reaction, which demonstrated that TMG acted as a ligand in this reaction system.

Key words: tetramethylguanidine, Heck reaction, palladium, aryl halides, ligand

The palladium-catalyzed coupling of olefins with aryl or vinyl halides, known as the Heck reaction,[1] is one of the most versatile tools for carbon–carbon bond formation in organic synthesis. This reaction has attracted considerable attention because it presents one of the simplest ways to obtain variously substituted olefins, dienes, and other unsaturated compounds, many of which are useful as dyes,[2] pharmaceuticals, etc. The Heck reaction is typically performed with 1–5 mol% of a Pd catalyst along with phosphine[3] or phosphorus[4] ligands in the presence of a suitable base. Phosphine ligands are expensive, toxic, and unrecoverable; therefore, the development of a phosphine-free Pd catalyst is a topic of enormous interest. To date, there have been a number of reports on sulfur-based palladacyles,[5] selenium-based catalysts,[6] nitrogen-based catalysts,[7] and nucleophilic carbene ligands[8] as catalyst systems in relation to the development of the Heck reaction. However, most of these new ligands are not commercially available and some are cumbersome to synthesize. It is desirable to have simple, inexpensive, easily prepared, and stable catalysts for these reactions.

Tetramethylguanidine $HN{=}C[N(CH_3)_2]_2$ (TMG) is an organic base, this material has attracted much attention in organic synthesis,[9] due to the multiplicity of coordination positions present and its strongly basic character. A comparison of the structure of TMG with phosphines led us to test the effectiveness of TMG as a ligand in the Heck reaction. To the best of our knowledge, TMG has not been reported as ligand for the Heck reaction, although the coordination complex $[Pd(TMG)_4]Cl_2$ was published by Drago in 1965.[10]

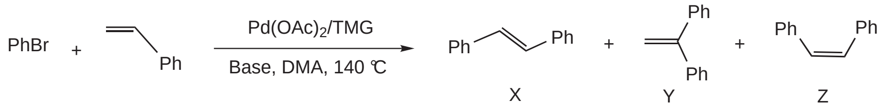
We first tested the catalytic activity of $Pd(OAc)_2$/TMG in the Heck reaction between styrene and bromobenzene, and the results are summarized in Table 1. No conversion was observed when Et_3N was used as the base (Table 1, entry 1). However, when several inorganic bases were used in place of Et_3N, all the reactions examined led to some conversion, and NaOAc gave the best result. Thus, when using $Pd(OAc)_2$ (0.1 mol%)/TMG (0.4 mol%) as catalyst and NaOAc as base in *N*,*N*-dimethylacetamide (DMA) at 140 °C for 20 hours, the coupling of bromobenzene with styrene gave the product in 99% yield as a *trans*-stilbene (>95% selectivity). In the absence of TMG, a 66% yield of the corresponding coupling product was obtained (Table 1, entry 5). Decreasing the catalyst loading to 0.01 mol% still resulted in quantitative conversion and high selectivity, even though the reaction times were prolonged to 40 hours. When the catalyst loading was reduced to 0.0004 mol%, the yield was poor even when the reaction time was extended. Noteworthy is that $PdCl_2$ (0.1 mol%)/TMG (0.4 mol%) gave the same result as $Pd(OAc)_2$/TMG (Table 1, entry 10).

A search for the most appropriate solvent for this reaction led us to conclude that the reaction rates were solvent-dependent. Though numerous solvents could be used, polar solvents such as DMF and DMA proved to be most effective (Table 2), with DMA as the solvent of choice. It is believed that the high solvent polarity of DMA helps solubilize all catalytic components and this is the principal influence of the solvent in the present reaction.

After establishing the high catalytic efficiency of the $PdCl_2$/TMG-system in the Heck reaction, we next examined the coupling of other representative aryl halides with different olefins, and the results are summarized in Table 3. As expected the activated substrates such as iodobenzene or bromobenzene with electron-withdrawing groups reacted very smoothly. When iodobenzene was used as the substrate with butyl acrylate, a yield of 42% was still achieved even when the Pd loading was reduced to 0.00004 mol%; the TON could be up to 1000000 (Table 3, entry 4). For the reaction between activated aryl bromides (Table 3, entry 11, 12) and styrene, quantitative conversions were observed with a Pd loading of 0.1 mol% and a reaction time of 20 hours. 3-Bromopyridine was also efficiently coupled with styrene to afford the desired

SYNLETT 2005, No. 12, pp 1885–1888
Advanced online publication: 07.07.2005
DOI: 10.1055/s-2005-871581; Art ID: U13605ST

Table 1 Pd-Catalyzed Heck Reaction of Bromobenzene and Styrene[a]



Entry	Catalyst (mol%)	Base	T (h)	Yield (%)[b]	TON
1	0.1	Et_3N	20	0	0
2	0.1	K_3PO_4	20	39	390
3	0.1	K_2CO_3	20	51	510
4	0.1	NaOAc	20	99	990
5[c]	0.1	NaOAc	20	66	660
6	0.01	NaOAc	20	75	7500
7	0.01	NaOAc	40	99	9900
8	0.004	NaOAc	24	67.8	17000
9	0.0004	NaOAc	72	15	40000
10	$PdCl_2$ (0.1)/TMG	NaOAc	20	99	990

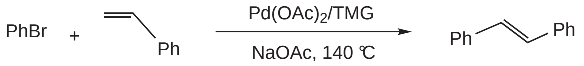
[a] Unless otherwise indicated, the reaction conditions were as follows: $Pd(OAc)_2$/TMG (1:4), bromobenzene (5 mmol), styrene (6 mmol), base (6 mmol), DMA (5 mL), 140 °C.

[b] *trans*-Stilbene > 95%, [GC, diethyleneglycol–Bu_2O as the internal standard].

[c] No TMG added.

product in 92% yield (0.1 mol% Pd). When the catalyst loading was increased (0.5 mol%), a remarkably high yield (90%) in the reaction between 4-methyl-bromobenzene and styrene could be achieved although 4-methyl-bromobenzene is a deactivated aryl bromide; this was the best result when compared with the reports in the literature on nitrogen-based catalysts.[7b,k] Aryl chlorides with electron-withdrawing groups were also effective in these system, we found that when 4-nitrochlorobenzene reacted with butyl acrylate, the yield was up to 90% in the absence of additives [such as $N(Bu)_4Br$[11]]. The results indicated that the addition of TMG resulted in a highly efficient Heck reaction.

Table 2 Effect of the Solvent on Pd-Catalyzed Heck Reaction of Bromobenzene and Styrene[a]



Entry	Solvent	Yields (%)[b]
1	DMSO	76
2	DMF	92
3	DMA	99
4	Dioxane	81
5	CH_3CN	21
6	Ethylene glycol	83

[a] Reaction conditions: bromobenzene (5 mmol), styrene (6 mmol), NaOAc (6 mmol), catalyst (0.1 mol%), $Pd(OAc)_2$/TMG (1:4), solvent (5 mL), 140 °C.

[b] GC yield [diethyleneglycol–$(Bu)_2O$ as GC standard]; average of two runs.

To figure out the precise function of TMG in the Heck reaction, the compound $[Pd(TMG)_4]Cl_2(H_2O)_8$ was synthesized from one equivalent of $PdCl_2$ and four equivalents of TMG in dichloromethane at room temperature, according to the literature method.[10] Single crystals of $[Pd(TMG)_4]Cl_2(H_2O)_8$[12] were obtained by slow diffusion of hexane into a dichloromethane solution of $PdCl_2$/TMG. Its molecular structure is shown in Figure 1. The complex $[Pd(TMG)_4]Cl_2(H_2O)_8$ was used in the coupling of aryl halide and olefin. We found that similar results were obtained (Table 2, entry 20, 21, 22) when compared with those of $PdCl_2$/TMG. This implies that TMG might act as a ligand to stabilize the Pd(0) species during the course of the reaction.

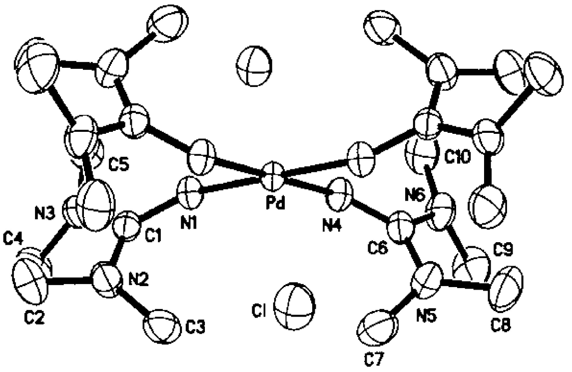
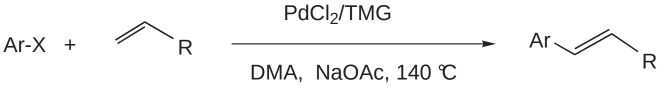


Figure 1 The molecular structure of $[Pd(TMG)_4]Cl_2(H_2O)_8$. Hydrogen atoms and H_2O are omitted for clarity.

Table 3 PdCl$_2$/TMG-Catalyzed Heck Reaction of Aryl Halides and Olefins[a,13]



Entry	Aryl halide	R	Catalyst (mol%)	T (h)	Yield (%)[b]	TON
1	PhI	CO_2Bu	0.1	2	100	1000
2	PhI	CO_2Bu	0.01	5	100	10000
3	PhI	CO_2Bu	0.0004	30	81	200000
4	PhI	CO_2Bu	0.00004	56	42	1000000
5[c]	PhI	Ph	0.004	24	96	24000
6[c]	PhI	CO_2Bu	0.01	2	92	9200
7	PhBr	Ph	0.1	20	99	990
8	*p*-MeC_6H_4Br	Ph	0.1	20	65	650
9	*p*-MeC_6H_4Br	Ph	0.5	20	90	180
10	*p*-MeC_6H_4Br	CO_2Bu	0.1	20	76	760
11	*p*-$(CHO)C_6H_4Br$	Ph	0.1	20	96	960
12	*p*-$NO_2C_6H_4Br$	CO_2Bu	0.1	20	100	1000
13	*p*-$NO_2C_6H_4Br$	CO_2Bu	0.004	30	96	24000
14	*p*-$NO_2C_6H_4Br$	Ph	0.01	20	100	10000
15	*p*-$NO_2C_6H_4Cl$	Ph	0.01	35	80	8000
16	*p*-$NO_2C_6H_4Cl$	CO_2Bu	0.01	35	90	9000
17	PhCl	Ph	0.1	20	36	360
18	3-Br-Pyridine	CO_2Bu	0.1	20	98	980
19	3-Br-Pyridine	Ph	0.1	20	92	920
20[d]	PhBr	Ph	0.1	20	99	990
21[d]	*p*-MeC_6H_4Br	CO_2Bu	0.1	20	82	820
22[d]	*p*-$NO_2C_6H_4Cl$	Ph	0.1	20	92	920

[a] Unless otherwise indicated, the reaction conditions were as follows: aryl halide (5 mmol), olefin (6 mmol), NaOAc (7.5 mmol), PdCl$_2$/TMG (1:4), DMA (5 mL), 140 °C.

[b] Average of isolated yields of two runs.

[c] *trans*-Stilbene > 95%, *trans*-cinnamic acid butyl ester >99% (GC, diethyleneglycol–Bu$_2$O as the internal standard).

[d] $[Pd(TMG)_4]Cl_2(H_2O)_8$ as catalyst.

In summary, an air-stable, inexpensive, and easily prepared TMG/Pd catalyst has been developed for the Heck reaction of aryl halide with terminal olefins. TONs could be up to 1000000 for the reaction of iodobenzene with butyl acrylate. This nitrogen-based catalyst showed a high activity when aryl bromides and actived aryl chlorides were used as substrates. Furthermore, TMG might act as a ligand to stabilize the Pd(0) species in the Heck reaction. Further studies aimed at the utility of these catalysts in Pd-catalyzed reactions are in progress.

Acknowledgment

We thank the National Science Foundation of China (No. 20474061) for financial support.

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(12) Single crystals of complex $[Pd(TMG)_4]Cl_2(H_2O)_8$ suitable for X-ray diffraction were obtained by slow diffusion of hexane into a dichloromethane solution of $PdCl_2$/TMG. The compound crystallizes in the triclinic space group P–1 with $a = 8.9997$ (11) Å, $b = 10.3817$ (13) Å, $c = 11.6080$ (14) Å, $\alpha = 78.040$ (2)°, $\beta = 68.603$ (2)°, $\gamma = 82.922$ (2)°, V = 986.5 (2) $Å^3$, $R1 = 0.0309$, $wR = 0.0894$.

(13) Typical Procedure for the Heck Reaction: An oven-dried Schlenk flask was charged under N_2 with styrene (6.0 mmol), bromobenzene (5.0 mmol), and NaOAc (6.0 mmol). A solution of catalyst $Pd(OAc)_2$/TMG (1:4) or $PdCl_2$/TMG (1:4) in DMA (5.0 mL, 1.0×10^{-6} M) was then added via syringe. The flask was sealed and placed in a 140 °C oil bath and stirred for 20 h. The course of the reaction was monitored by periodically taking samples and analyzing them by gas chromatography [di(ethylene glycol)–Bu_2O as internal standard]. After cooling to r.t., the reaction mixture was poured into H_2O (50 mL) and extracted with EtOAc (3×40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography on silica gel (hexanes–CH_2Cl_2, 1:1) gave *trans*-stilbene (859 mg, 95.5%), estimated to be >99% pure by ^1H NMR and GC.