Aqueous-Phase, Palladium-Catalyzed Heck Reaction: The Significant Role of CN-containing Counter Anion[†]

Cai, Yueqin^a(蔡月琴) Song, Gonghua^{*,b}(宋恭华) Zhou, Xiaoying^b(周晓英)

^a School of Chemistry and Molecular Engineering, East China University of Science and Technology, Shanghai 200237, China

^b Shanghai Key Laboratory of Chemical Biology, Institute of Pesticides & Pharmaceuticals, East China University of Science and Technology, Shanghai 200237, China

Water-soluble diol-functionalized imidazolium ionic liquid **1**, prepared from 2,2-bis(1-methyl-methyl-imidazolium)propane-1,3-diol bromide, potassium hydroxide, and malononitrile, was used as an efficient phosphine-free ligand for palladium-catalyzed arylation of aryl halides with acrylates in aqueous phase under mild conditions. It was found that the synergistic coordinating action of diol-functionalized imidazolium cation with CN-containing anion played the key role in improving the activity and stability of the catalyst.

Keywords homogeneous catalysis, acylation, Heck reaction, phosphine-free ligand, nitrile group

Introduction

It has been estimated that about 80% of chemical waste resulted from use of flammable, toxic, and nonrenewable organic solvents.^[1] Thus, replacing organic solvents with more environmentally acceptable alternatives becomes one of the major tasks of green chemistry.^[2] Among the efforts on this subject, using water as a reaction medium has received great attention since water has the advantages of low cost, nontoxicity, nonflammability, and being a renewable resource.^[3] The palladium-catalyzed Heck reaction has now become a widely used synthetic methodology for forming carboncarbon bonds and been found numerous applications in synthetic organic chemistry.^[4-7] However, most of the previously reported Heck reactions were carried out in organic solvents.^[4] As amendments following the first report of cross-coupling reactions catalyzed by Pd(TPPMS)₃,^[8] several examples of Pd-catalyzed Heck cross-coupling reactions in aqueous solvents have been demonstrated by using water-soluble phosphine ligands.^[9-13] These phosphine ligands give synthetically useful yields indeed. However, most of P-containing ligands have suffered from the following shortcomings: highly toxic and air sensitive. So a number of phosphine-free catalytic systems, such as wool-Pd,^[14] phosphine-free catalytic systems, such as wool-Pd, N,O-bidentate compounds,^[15] 4-aminopyridine resin-immobilized Pd,^[16] pyridylbenzoimidazole,^[17] palla-dium immobilized on silica gel,^[18] N,N-dimethyl- β -alanine,^[19] and so on,^[20-22] have been used for palladium catalyzed Heck reaction in recent years. Among them, most of the reactions were carried out in organic solvents like DMF or NMP.

We recently reported two diol-functionalized imidazolium ionic liquids (ILs), namely 2,2-bis(1-methylmethylimidazolium)propane-1,3-diol hexafluorophosphate and 1-(2,3-dihydroxypropyl)-3-methylimidazolium hexafluorophosphate,^[23-25] which were also proved to be efficient phosphine-free ligands for palladium-catalyzed Heck reaction of aryl halides with acrylates under aerobic condition in DMF. The predominant advantage of diol-functionalized imidazolium ILs lies in the multiple coordinating sites in the cation. Besides an excellent O,O-ligand for the metal resulting from the ethylene glycol group,^[26] imidazolium skeleton can generate *N*-heterocyclic carbene (NHC) *in situ*, which is beneficial to the stabilization of Pd.^[27,28] On the other hand, Rach and Kühn^[29] have pointed out that CN group could ligate transition metal with weakly coordinating counter anions and improve the catalysis reactivity significantly. Their usefulness results from the labile coordination mode of the CN group, which can be easily replaced by more strongly coordinating ones, other metal cores, or by substrates.

To date, functionalized imidazolium-based ILs have been rapidly developed as the ligands for the palladium-catalyzed Heck reaction. However, most of these ligands are developed with advance in *N*-heterocyclic carbenes (NHCs)^[30,31] or with coordinating sites in the cations.^[23-25] The investigation on the effects of anions

2819

^{*} E-mail: ghsong@ecust.edu.cn; Tel.: 0086-021-64253452; Fax: 0086-021-64253452 Received July 4, 2012; accepted July 20, 2012; published online October 30, 2012.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.20120675 or from the author.

[†] Dedicated to the 60th Anniversary of East China University of Science and Technology.

FULL PAPER

of ILs in catalytic chemistry is only in its infancy. To the best of our knowledge, there is no detailed report about the co-actions of ILs-based ligands with complexible counter anions, although they are highly worthy to be investigated. Herein, we report a new phosphinefree IL ligand 1 composed of a diol-functionalized imidazolium cation and a CN-containing anion. The IL ligand was prepared from 2,2-bis(1-methyl-methylimidazolium)propane-1,3-diol bromide, potassium hydroxide, and malononitrile (Scheme 1). The CN-containing anion moiety was introduced into the ligand, which could also weakly coordinate with the palladium and lead to the superior retention of the palladium. The application of it to the palladium-catalyzed Heck reaction of aryl halides with acrylates was investigated in detail. Compared to the ILs published before which were applied as the ligands in the Heck reaction in DMF,^[23-25] using IL ligand 1 in water-DMF medium, efficient conversion of aryl iodides/bromides with acrylates to the corresponding cross products was conducted under mild reaction conditions. The recycling of the catalytic species was also practicable. The high stability and activity of catalyst was owing to the synergistic coordinating action of diol-functionalized imidazolium cation with CN-containing anion.

Scheme 1



Experimental

Synthesis of ionic liquid ligand 1

A mixture of 1.32 g malononitrile (20 mmol) and 1.12 g potassium hydroxide (20 mmol) in 10 mL CH₃CN was added 4.26 g of 2,2-bis(1-methyl-methyl-imidazolium)propane-1,3-diol bromide (10 mmol) and stirred at room temperature for 48 h. The solution was concentrated under vacuum; ethanol was added to the residue for extracting the product, which was dried *in vacuo* to give 3.04 g of (77%) yellow oil. ¹H NMR (DMSO-*d*₆, 500 MHz) δ : 3.09 (s, 4H), 3.48 (s, 2H), 3.84 (s, 6H), 4.20 (s, 4H), 5.15 (s, 2H), 7.65 (s, 2H), 7.75 (s, 2H), 8.61 (s, 2H); IR (KBr) *v*: 3370, 3152, 3109, 2957, 2155, 1622, 1571, 1513, 1350, 1167, 1027 cm⁻¹; ESI-MS *m/z*: 421.2 (M + Na)⁺, 265.1 (M - [(CNCHCN)₂]-H)⁺, 133.1 ((CNCHCN)₂+3H)⁺.

General procedure for Heck reaction and recovery of catalyst

In a typical experiment, to a mixture of 1.02 g phenyl iodide (5 mmol) with 0.86 g methyl acrylate (10 mmol) in 1.5 mL water and 0.5 mL DMF was added **1** (1.0 mol%), 0.69 g K₂CO₃ (5 mmol), and 0.009 g PdCl₂ (1.0 mol%). The mixture was reacted at 80 °C for 1 h. On completion monitored by TLC and GC, the reaction mixture was extracted with ethyl ether (10 mL×3). The combined organic extracts were dried with Na₂SO₄, filtered and concentrated under vacuum to give the desired product 0.79 g (97%). ¹H NMR (DMSO-*d*₆, 500 MHz) δ : 4.20 (s, 3H), 6.40 (d, *J*=6 Hz, 1H), 7.40—7.50 (m, 5H), 7.70 (d, *J*=6 Hz, 1H); MS (70 eV) *m/z* (%): 162 (M⁺, 30), 147 (15), 131 (100), 103 (50), 77 (25), 51 (10).

The remaining liquid phase composed of PdCl₂, ligand and the formed salt of K_2CO_3 was used directly without further treatment for the next run through treated with phenyl iodide (1.02 g, 5 mmol), methyl acrylate (0.86 g, 10 mmol), and K_2CO_3 (0.69 g, 5 mmol) again.

Results and Discussion

The coupling of phenyl iodide and methyl acrylate was chosen as the prototypical reaction for the optimization of reaction conditions.

We began the investigation by conducting Heck reaction in the presence of water. It is worth mentioning that using water alone as a solvent would lead to remarkable Pd precipitation with a very low yield of 20% (Table 1, Entry 1). Therefore, DMF was selected as co-solvent to increase both the stability of catalyst and solubility of hydrophobic substrates in the solvent. The results showed that the activity of catalyst increased notably with the addition of DMF (Table 1, Entries 2—5). Changing water/DMF volume ration from 9 : 1 to 3 : 1 caused a surprising increase in reaction yield from 51% to 97%. Hence, subsequent reactions were performed in the mixed solution of water-DMF (V : V = 3 : 1).

Further inspection revealed that the base, catalyst, temperature, and the loading of catalyst also affected the reaction quite notably. It was found that the best results were obtained with the combination of K_2CO_3 as base and PdCl₂ as catalyst. The application of other bases, for example, (*n*-Bu)₃N, Et₃N, pyridine, NaHCO₃, Na₂CO₃, or NMP (Table 1, Entries 6—11), or other catalysts such as Pd(OAc)₂ and Pd₂(dba)₃ (Table 1, Entries 12, 13) would result in lower yields. Decreasing reaction temperature or palladium loading showed a remarkably slowing down of the reaction rate (Table 1, Entries 14, 15).

On the other hand, the nature of IL ligands also played an important role in affecting the coupling reaction. To demonstrate the effects of IL ligands, the

		catliga	ind	COOMe
		Base/DMF	F/H ₂ O	
Entry	Cat. (Dosage/mol%)	Base	$V(H_2O)$: $V(DMF)$	Yield ^b /%
1	PdCl ₂ (1.0)	K_2CO_3	Pure water	20
2	PdCl ₂ (1.0)	K_2CO_3	9:1	51
3	PdCl ₂ (1.0)	K_2CO_3	17:3	63
4	PdCl ₂ (1.0)	K_2CO_3	4:1	83
5 ^{<i>c</i>}	PdCl ₂ (1.0)	K_2CO_3	3:1	97
6	PdCl ₂ (1.0)	(<i>n</i> -Bu) ₃ N	3:1	44
7	PdCl ₂ (1.0)	Et_3N	3:1	61
8	PdCl ₂ (1.0)	Pyridine	3:1	65
9	PdCl ₂ (1.0)	NaHCO ₃	3:1	54
10	PdCl ₂ (1.0)	Na ₂ CO ₃	3:1	58
11	PdCl ₂ (1.0)	NMP	3:1	38
12	$Pd_2(dba)_3 (0.5)^d$	K_2CO_3	3:1	35
13	Pd(OAc) ₂ (1.0)	K_2CO_3	3:1	56
14^e	PdCl ₂ (1.0)	K_2CO_3	3:1	63
15 ^f	PdCl ₂ (0.5)	K_2CO_3	3:1	60
16 ^g	PdCl ₂ (1.0)	K_2CO_3	3:1	58
17^{h}	PdCl ₂ (1.0)	K_2CO_3	3:1	63
18 F	$PdCl_2(CH_3CN)_2$ (1.0)	K_2CO_3	3:1	70

^{*a*} The molar ratios of phenyl iodide/methyl acrylate/base/are 1 : 2 : 1, the molar ratio of ligand **1** to PdCl₂ is 1 : 1, temperature 80 °C, reaction time 1 h. ^{*b*} Isolated yields. ^{*c*} Pd precipitations are not found. ^{*d*} dba, dibenzylidene acetone. ^{*e*} Temperature 60 °C. ^{*f*}Reaction time 15 h. ^{*g*} Ligand **2**. ^{*h*} Ligand **3**.

analogous Br and PF₆ anion-containing ILs, 2,2-bis(1methyl-methylimidazolium)propane-1,3-diol bromide (2) 2,2-bis(1-methyl-methylimidazolium)prpane-1,3and diol hexafluorophosphate $(3)^{[25]}$ (Scheme 2) were synthesized and applied to the model reaction. It was found that the CN-containing anion IL 1 showed the highest activity (Table 1, Entry 5), while ILs 2 and 3 gave lower yields of products probably due to Pd precipitation (Table 1, Entries 16 and 17). The higher capacity for immobilization of the palladium complex and better catalytic activity of IL 1 probably resulted from the co-action of its cation ligand and counteranion. In addition to the coordination of diol-functionalized imidazolium cation, the CN-containing anion moiety could also weakly coordinate with the palladium, which led to the superior retention of the palladium and high activity in catalyzing Heck reaction.

Furthermore, another catalyst with a CN-containing anion, $PdCl_2(CH_3CN)_2$ was adopted without ligand **1** (Table 1, Entry 18). Lower yield of 70% and Pd precipitation were obtained. Thus, the experimental results clearly demonstrated that the synergistic effect of diolScheme 2



functionalized imidazolium cation and CN-containing anion on stabilization and catalysis of palladium was the key element to the success of Heck reaction in this case.

Recyclability of the catalyst PdCl₂-1 was also investigated. After each cycle, the product was extracted with ethyl ether, and the aqueous phase containing catalyst PdCl₂-1 was reused directly for the next catalytic run. Recycling experimental results indicated that the catalytic activity of the recycled catalyst was lower because the time required to obtain the same conversion was double. However, this catalytic system could be reused at least 5 times without significant loss of activity (Table 2). The good performance of the catalyst is ascribed to the strong chelating coordination of both cation and anion with the metal center, which makes catalyst exhibit good thermal and oxidative stability in practice.

 Table 2
 Recycling of PdCl₂-1 catalyst^a

Run	Yield ^b /%	Time/h
1	97	1
2	95	1
3	93	1
4	94	2
5	92	2

^{*a*} PdCl₂ 1.0 mol%, ligand **1** 1.0 mol%, phenyl iodide 5 mmol, methyl acrylate 10 mmol, H₂O/DMF (1.5/0.5 mL), K₂CO₃ 5 mmol (additionally added per pass). ^{*b*} Isolated yield.

To explore the scope of $PdCl_2$ -1 catalytic system in catalyzing Heck coupling reactions in H₂O/DMF, methyl or ethyl acrylate was coupled with various substituted aryl halides. As can be seen from Table 3, in the cases of bromides/iodides, all the reactions proceeded with high selectivity and moderate to good yields. According with the earlier reports, aryl bromides/iodides with an electron-withdrawing substituent (Table 3, Entries 5, 6, 11, 12) gave higher yields than those with an electron-donating substituent (Table 3, Entries 3, 4, 7—

10, 13, 14). Unfortunately, however, as to the activation of chlorides, relatively poor activity was observed (Table 3, Entries 15, 16) probably due to poorer activity of chlorides. To some degrees, some heterogeneous catalysts like $Pd/C^{[32]}$ are even good for coupling aryl chlorides compared with the catalyst $PdCl_2$ -1. But the recyclability of the heterogeneous catalysts is discounted owing to the aggregation and agglomeration of Pd particles into less active large particles during the reaction.^[14]

Table 3	Heck reactions	of haloarenes	with acrylates ^{<i>a</i>}
I able 5	ficer reactions	or maioarches	with act yithes

R ¹	K + ∕∕⊂COOF	$R^2 \frac{1}{K_2C}$	PdCl ₂ O ₃ /DI	-1 MF/H ₂ O R ¹	COOR ²
Entry	\mathbb{R}^1	\mathbb{R}^2	Х	Time/h	Yield ^b /%
1	Н	Me	Ι	1	97
2	Н	Et	Ι	1	98
3	<i>p</i> -OCH ₃	Me	Ι	6	80
4	<i>p</i> -OCH ₃	Et	Ι	6	76
5	p-NO ₂	Me	Ι	0.5	96
6	p-NO ₂	Et	Ι	0.5	98
7	<i>p</i> -CH ₃	Me	Ι	4	84
8	<i>p</i> -CH ₃	Et	Ι	4	81
9	o-CH ₃	Me	Ι	10	69
10	o-CH ₃	Et	Ι	10	70
11	p-NO ₂	Me	Br	2	95
12	p-NO ₂	Et	Br	2	94
13	<i>p</i> -CH ₃	Me	Br	24	70
14	<i>p</i> -CH ₃	Et	Br	24	68
15	p-NO ₂	Me	Cl	24	24
16	p-NO ₂	Et	Cl	24	21

 a PdCl₂ 1.0 mol%, ligand **1** 1.0 mol%, haloarene 5 mmol, acrylate 10 mmol, K₂CO₃ 5 mmol, H₂O/DMF (1.5/0.5 mL). b Isolated yields.

Conclusions

In summary, an excellent catalytic system was formed by the chelating coordination of a diol-functionalized imidazolium ionic liquid involving a CNcontaining anion with the readily available PdCl₂. With this catalytic system, the arylation of aryl iodides/bromides with acrylates could proceed smoothly in aqueous media under air conditions. The good thermal, moist and oxidative stability of catalyst was attributed to the synergistic action of diol-functionalized imidazolium cation and CN-containing anion. Moreover, effective recycling of PdCl₂-1 was also achieved.

Acknowledgement

We acknowledge the National Natural Science Foundation of China (No. 20676033), the China Postdoctoral Science Foundation (No. 20070410169) and the Shanghai Leading Academic Discipline Project (No. B507) for financial support.

References

- Shaughnessy, K. H.; Devasher, R. B. Curr. Org. Chem. 2005, 9, 585.
- [2] Clark, J. H. Green Chem. 1999, 1, C1.
- [3] Chanda, A.; Fokin, V. V. Chem. Rev. 2009, 109, 725.
- [4] Yin, L.; Liebscher, J. Chem. Rev. 2007, 107, 133.
- [5] Rothenberg, G.; Cruz, S. C.; van Strijdonck, G. P. F.; Hoefsloot, H. C. J. *Adv. Synth. Catal.* **200**4, *346*, 467.
- [6] Burello, E.; Rothenberg, G. Adv. Synth. Catal. 2003, 345, 1334.
- [7] Cruz, S. C. Chem. Phys. 2003, 5, 4455.
- [8] Casalnuovo, A. L.; Calabrese, J. C. J. Am. Chem. Soc. 1990, 112, 4324.
- [9] Vallin, K. S. A.; Larhed, M.; Hallberg, A. J. Org. Chem. 2001, 66, 4340.
- [10] Wüllner, G.; Jänsch, H.; Kannenberg, S.; Schubert, F.; Boche, G. *Chem. Commun.* **1998**, *998*, 1509.
- [11] Li, C. J. Acc. Chem. Res. 2002, 35, 533.
- [12] Genêt, J. P.; Savignac, M. J. Organomet. Chem. 1999, 576, 305.
- [13] Devasher, R. B.; Moore, L. R.; Shaughnessy, K. H. J. Org. Chem. 2004, 69, 7919.
- [14] Wu, S.; Ma, H. C.; Jia, X. J.; Zhong, Y. M.; Lei, Z. Q. *Tetrahedron* 2011, 67, 250.
- [15] Cui, X.; Li, J.; Zhang, Z. P.; Fu, Y.; Liu, L.; Guo, Q. X. J. Org. Chem. 2007, 72, 9342.
- [16] Wu, X. M.; Pei, W. Chin. J. Chem. 2009, 27, 963.
- [17] Chen, W. X.; Xi, C. J.; Wu, Y. W. J. Organomet. Chem. 2007, 692, 4381.
- [18] Wang, Z. L.; Wang, L.; Yan, J. C. Chin. J. Chem. 2008, 26, 1721.
- [19] Cui, X.; Li, Z.; Tao, C. Z.; Xu, Y.; Li, J.; Liu, L.; Guo, Q. X. Org. Lett. 2006, 8, 2467.
- [20] Zhang, Z. H.; Zha, Z. G.; Gan, C. S.; Pan, C. F.; Zhou, Y. Q.; Wang, Z. Y.; Zhou, M. M. J. Org. Chem. 2006, 71, 4339.
- [21] Wang, L.; Li, H.; Li, P. Tetrahedron 2009, 65, 364.
- [22] Zheng, P.; Zhang, W. J. Catal. 2007, 250, 324.
- [23] Cai, Y. Q.; Lu, Y.; Liu, Y.; Gao, G. H. Catal. Lett. 2007, 154, 119.
- [24] Cai, Y. Q.; Lu, Y.; Liu, Y.; He, M. Y.; Wan, Q. X. Catal. Commun. 2008, 9, 1209.
- [25] Cai, Y. Q.; Lu, Y. Catal. Commun. 2009, 10, 1390.
- [26] Kwong, F. Y.; Klapars, A.; Buchwald, S. I. Org. Lett. 2002, 4, 581.
- [27] Calo, V.; Nacci, A.; Monopoli, A.; Fornaro, A.; Sabbatini, L.; Cioffi, N.; Ditaranto, N. Organometallics 2004, 23, 5154.
- [28] Calo, V.; Nacci, A.; Monopoli, A.; Ieva, E.; Cioffi, N. Org. Lett. 2005, 7, 671.
- [29] Rach, S. F.; Kühn, F. E. Chem. Rev. 2009, 109, 2061.
- [30] Diez-González, S.; Nolan, S. P. Coord. Chem. Rev. 2007, 251, 874.
- [31] Gade, L. H.; Bellemin-Loponnaz, S. Coord. Chem. Rev. 2007, 251, 718.
- [32] Mukhopadhyay, S.; Rothenberg, G.; Joshi, A.; Baidossi, M.; Sasson, Y. Adv. Synth. Catal. 2002, 344, 348.

(Zhao, C.)