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Palladium-Catalyzed Double Carbonylation Reactions of *o*-Dihaloarenes with Amines in Phosphonium Salt Ionic Liquids

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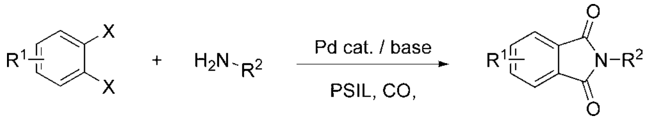
ABSTRACT



Palladium-catalyzed double carbonylation of *o*-dihaloarenes with amines in phosphonium salt ionic liquids proceeds efficiently to give the corresponding N-substituted phthalimides. This process can tolerate a wide array of functional groups and affords products in excellent yields. The recyclability of the catalytic system was also investigated.

As a new replacement of traditional organic solvents, phosphonium salt-based ionic liquids (PSILs) have attracted increasing attention by organic chemistry researchers in recent years. Compared to their ammonium counterparts, PSILs display increased stability toward thermal and chemical degradation, making them ideal for use at high temperatures or in processes in which the products can be removed by distillation.[1] PSILs are also nonvolatile, economical, and available on an industrial scale. In the past several years, McNulty and other groups successfully investigated the application of PSILs, in general, and specifically for palladium-catalyzed processes.[2] Recently, we also reported several palladium-catalyzed reactions in PSILs.[3]

Building on our previous research about palladium-catalyzed carbonylation reactions to synthesize heterocyclic compounds[4] and aiming to explore the unique capabilities of PSILs, we designed a reaction to obtain a seven-membered ring lactam through a palladium-catalyzed one-pot Heck and intramolecular carbonylation reactions. We chose 1,2-dibromobenzene and allylamine as the substrates for the model reaction. Under the conditions shown below, we found that, in PSIL 102, trihexyl(tetradecyl)phosphonium bromide, with $Pd(OAc)_2$ as the catalyst, Cs_2CO_3 as the base, and without additional phosphine ligand, the reaction provided two different products other than the target lactam: the doubly carbonylated product **A** (the phthalimide derivative) and the monocarbonylated product **B** (the allylamide) (Scheme 1).

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(1) (a) Bradaric, C. J.; Downard, A.; Kennedy, C.; Robertson, A. J.; Zhou, Y. *Green Chem.* **2003**, *5*, 143. (b) Kim, Y. J.; Varma, R. S. *J. Org. Chem.* **2005**, *70*, 7882.

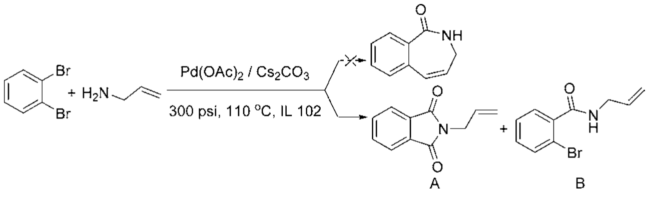
(2) (a) McNulty, J.; Capretta, A.; Wilson, J.; Dyck, J.; Adjabeng, G.; Robertson, A. J. *Chem. Commun.* **2002**, 1986. (b) Gerritsma, D. A.; Robertson, A. J.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 7629. (c) McNulty, J.; Capretta, A.; Cheekoori, S.; Clyburne, J. A. C.; Robertson, A. *J. Chem. Oggi* **2004**, *22*, 13. (d) McNulty, J.; Cheekoori, S.; Nair, J. J.; Larichev, V.; Capretta, A.; Robertson, A. J. *Tetrahedron Lett.* **2005**, *46*, 3641. (e) McNulty, J.; Nair, J. J.; Cheekoori, S.; Larichev, V.; Capretta, A.; Robertson, A. J. *Chem.*—*Eur. J.* **2006**, *12*, 9314. (f) McNulty, J.; Cheekoori, S.; Bender, T. P.; Coggan, J. A. *Eur. J. Org. Chem.* **2007**, *9*, 1423. (g) McNulty, J.; Nair, J. J.; Robertson, A. J. *Org. Lett.* **2007**, *9*, 4575.

(3) (a) Yang, Q.; Alper, H. *J. Org. Chem.* **2010**, *75*, 948. (b) Cao, H.; McNamee, L.; Alper, H. *J. Org. Chem.* **2008**, *73*, 3530. (c) Yang, Q.; Robertson, A.; Alper, H. *Org. Lett.* **2008**, *10*, 5079. (d) Cao, H.; McNamee, L.; Alper, H. *Org. Lett.* **2008**, *10*, 5281.

(4) (a) Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 35. (b) Dong, C.; Alper, H. *J. Org. Chem.* **2004**, *69*, 5011. (c) Lu, S. M.; Alper, H. *J. Am. Chem. Soc.* **2005**, *127*, 14776. (d) Cao, H.; Xiao, W. J.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1807. (e) Lu, S. M.; Alper, H. Eur. *J. Org. Chem.* **2007**, *13*, 5908. (f) Zheng, Z. Y.; Alper, H. *Org. Lett.* **2008**, *10*, 829. (g) Lu, S. M.; Alper, H. *J. Am. Chem. Soc.* **2008**, *130*, 6451.

10.1021/ol101714p

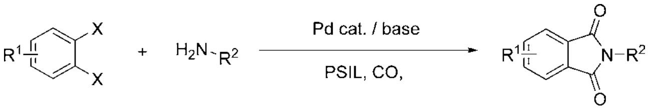
Scheme 1



Phthalimide derivatives have been used extensively in synthetic chemistry, with a wide range of applications, particularly in biological chemistry. Some phthalimides display pharmacological activities as anticonvulsants,[5] anti-inflammatories,[6] analgesics,[7] herbicidal[8] and insecticidal[9] agents. Typically, phthalimide derivatives are synthesized via the condensation of amines with phthalic anhydride in refluxing organic solvents. High boiling point solvents such as acetic acid, DMF, and dioxane are commonly used.[10] Synthesis in solvent-free conditions can be achieved by refluxing a mixture of phthalic anhydride with the amine or by using a catalyst such as DABCO at room temperature.[11] There has also been work on using microwave irradiation as a heating method.[12] Few publications have appeared concerning the synthesis of phthalimides by palladium-catalyzed carbonylation reactions, and the method has suffered from a limitation of solvents.[13]

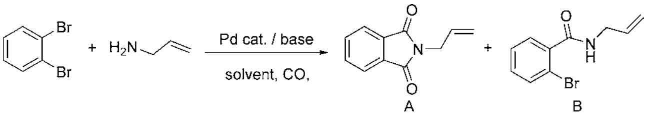
Herein we report the first examples of synthesizing the phthalimide derivatives by the palladium-catalyzed double carbonylation reaction of *o*-dihaloarenes and allylamines in PSILs, which can tolerate a wide array of functional groups and afford products in good to excellent yields (Scheme 2).

Scheme 2



To improve the reaction selectivity for compound **A**, 1,2-dibromobenzene and allylamine were chosen as the substrates for the model reaction and for optimization of the reaction conditions. The results are presented in Table 1. First, the nature of the neutralizing base plays an important role in this reaction. Use of the hindered amine DBU gave the best result in comparison with using Cs_2CO_3 and TEA (Table 1, entries 1, 3, and 8). In PSIL 102, without any ligand, both $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ were useful in catalyzing the reaction and provided compound **A** as the main product while $Pd_2(dba)_3$ gave inferior selectivity and yields (Table 1, entries 3, 6, and 7). We also found that higher CO pressure or longer reaction times did not benefit the reaction. The double carbonylation reaction of *o*-dibromobenzene in PSIL 102 proceeded even more efficiently under 1 atm CO and afforded 83% yield of **A** with $Pd(OAc)_2$ as the catalyst without any added ligand. With $PdCl_2(PPh_3)_2$ as the catalyst, the yield of **A** was 90% (Table 1, entries 9 and 10). In this study, the phosphonium salt ionic liquid also showed better efficiency for the reaction when compared with THF. By using $Pd(OAc)_2$ as the catalyst but no added ligand, there was no reaction in THF (Table 1, entries 2 and 11).

Table 1. Optimization of the Palladium-Catalyzed Dicarbonylation Reaction of 1,2-Dibromobenzene and Allylamine[a]



entry	catalyst	base	solvent	CO	time (h)	**A**	**B**
1	$Pd(OAc)_2$	Cs_2CO_3	IL 102	300 psi	24	42%	38%
2	$Pd(OAc)_2$	Cs_2CO_3	THF	300 psi	24	ND	ND
3	$Pd(OAc)_2$	DBU	IL 102	300 psi	24	70%	7%
4	$Pd(OAc)_2$	DBU	IL 102	600 psi	24	54%	13%
5	$Pd(OAc)_2$	DBU	IL 102	300 psi	48	65%	6%
6	$Pd_2(dba)_3$	DBU	IL 102	300 psi	24	27%	15%
7	$PdCl_2(PPh_3)_2$	DBU	IL 102	300 psi	24	80%	8%
8	$PdCl_2(PPh_3)_2$	TEA	IL 102	300 psi	24	Messy	
9	$PdCl_2(PPh_3)_2$	DBU	IL 102	1 atm	24	90%	trace
10	$Pd(OAc)_2$	DBU	IL 102	1 atm	24	83%	trace
11	$Pd(OAc)_2$	DBU	THF	1 atm	24	ND	ND

[a] Reaction conditions: dibromobenzene (1 mmol), allylamine (1.2 mmol), Pd catalyst (0.05 mmol), base (2 mmol), IL 102 (2.0 g), 110 °C. All yields are isolated yields.

A variety of PSILs were also screened for the carbonylation reaction of 1,2-dibromobenzene and allylamine (Table 2). The reactions were conducted under 1 atm of CO, 110 °C, with $PdCl_2(PPh_3)_2$ as the catalyst and DBU as the base. PSIL 102 is the best PSIL for the reaction and furnished the target product in 90% isolated yield, while other PSILs gave the double carbonylated products in appreciably lower yields (21−64%).

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(5) Abdel-Hafez, A. A. *Arch. Pharm. Res.* **2004**, *27*, 495.

(6) (a) Lima, L. M.; Castro, P.; Machado, A. L.; Fraga, C. A. M.; Lugnier, C.; Gonc, V. L.; Barreiro, E. J. *Bioorg. Med. Chem.* **2002**, *10*, 3067. (b) Collin, X.; Robert, J.; Wielgosz, G.; Le Baut, G.; Bobin-Dubigeon, C.; Grimaud, N.; Petit, J. *Eur. J. Med. Chem.* **2001**, *36*, 639. (c) Groutas, W. C.; Chong, L. S.; Venkataraman, R.; Kuang, R.; Epp, J. B.; Houser-Archield, N.; Huang, H.; Hoidal, J. R. *Arch. Biochem. Biophys.* **1996**, *332*, 335.

(7) Antune, R.; Buttista, H.; Strivastuva, R. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3071.

(8) Kawagushi, S.; Ikeda, O. Jpn. Pat. Appl. JP2001328911, 2001.

(9) Ebihara, K.; Oora, T.; Nakaya, M.; Shiraishi, S.; Yasui, N. Jpn. Pat. Appl. JP08245585, 1996.

(10) (a) Perry, C. J.; Parveen, Z. *J. Chem. Soc., Perkin Trans. 2* **2001**, 512. (b) Lima, L. M.; Brito, F. C. F.; Souza, S. D.; Miranda, A. L. P.; Rodrigues, C. R.; Fraga, C. A. M.; Barreiro, E. J. *Bioorg. Med. Chem.* **2002**, *12*, 1533. (c) Zhang, C.; Ping, Q.; Zhang, H.; Shen, J. *Eur. Polym. J.* **2003**, *39*, 1629. (d) Sinkeldam, R. W.; Houtem, M. H. C. J.; Koeckelberghs, G.; Vekemans, J. A. J. M.; Meijer, E. W. *Org. Lett.* **2006**, *8*, 383.

(11) Heravi, M. M.; Shoar, R. H.; Pedram, L. *J. Mol. Catal. A* **2005**, *231*, 89.

(12) (a) Mogilaiah, K.; Reddy, G. R. *Indian J. Chem., Sect. B* **2004**, *43*, 882. (b) Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* **2003**, *5*, 1851. (c) Li, H.; Zhang, J.; Zhau, Y.; Li, T. *Synth. Commun.* **2002**, *32*, 927. (d) Vidal, T.; Petit, A.; Loupy, A.; Gedye, R. N. *Tetrahedron* **2000**, *56*, 5473. (e) Borah, H. N.; Boruah, R. C.; Sandhu, J. S. *J. Chem. Res. (S)* **1998**, S272.

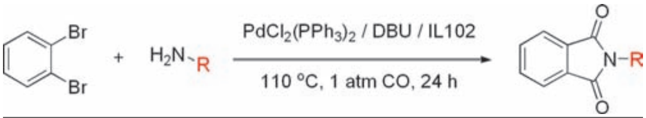
(13) (a) Mori, M.; Chiba, K.; Ohta, N.; Ban, Y. *Heterocycles* **1979**, *13*, 329. (b) Perry, R. J.; Turner, S. R. *J. Org. Chem.* **1991**, *56*, 6573.

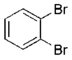
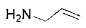
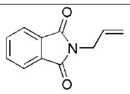
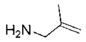
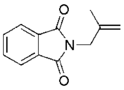
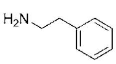
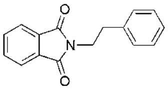
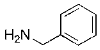
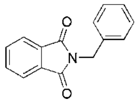
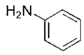
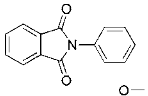
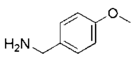
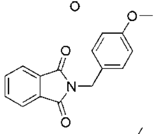
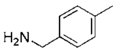
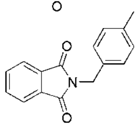
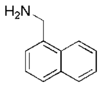
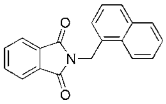
Table 2. Palladium-Catalyzed Dicarbonylation Reactions between 1,2-Dibromobenzene and Allylamine in Various PSILs[a]

entry	catalyst	solvent	**A**	**B**
1	$PdCl_2(PPh_3)_2$	IL101	21%	ND
2	$PdCl_2(PPh_3)_2$	IL 102	90%	trace
3	$PdCl_2(PPh_3)_2$	IL106	64%	12%
4	$PdCl_2(PPh_3)_2$	IL109	33%	5%
5	$PdCl_2(PPh_3)_2$	IL110	45%	ND
6	$PdCl_2(PPh_3)_2$	IL163	59%	13%

[a] IL101: $C_{14}H_{29}(C_6H_{13})_3P^+Cl^-$. IL102: $C_{14}H_{29}(C_6H_{13})_3P^+Br^-$. IL106: $C_{14}H_{29}(C_6H_{13})_3P^+OTs^-$. IL109: $C_{14}H_{29}(C_6H_{13})_3P^+NTf_2^-$. IL110: $C_{14}H_{29}(C_6H_{13})_3P^+PF_6^-$. IL163: $(C_4H_9)_4P^+Br^-$.

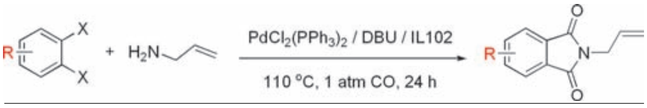
Table 3. Reactions of Amines with 1,2-Dibromobenzene[a]

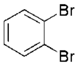
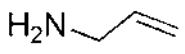
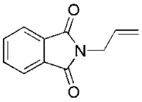
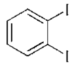
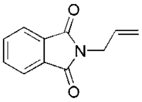
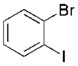
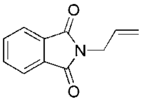
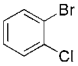
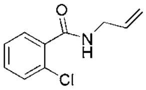
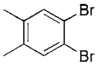
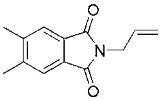
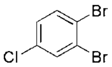
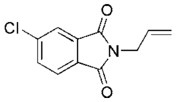


entry	dihalide arene	amine	A	yield
1				90%
2				65%
3				91%
4				75%
5				92%
6				74%
7				75%
8				85%

[a] Reaction conditions: 1,2-dibromobenzene (1 mmol), amines (1.2 mmol), CO 1 atm, DBU (2 mmol), $PdCl_2(PPh_3)_2$ (0.05 mmol), PSIL 102 (2 g), 110 °C, 24 h.

Table 4. Reactions of Allylamine with Different Dihalobenzenes[a]



entry	dihalide arene	amine	A	yield
1				90%
2				78%
3				75%
4				77%
5				79%
6				63%

[a] Reaction conditions: 1,2-dihalobenzene (1 mmol), allylamine (1.2 mmol), CO 1 atm, DBU (2 mmol), $PdCl_2(PPh_3)_2$ (0.05 mmol), PSIL 102 (2 g), 110 °C, 24 h.

The study of the scope of this palladium-catalyzed dicarbonylation reaction in PSIL 102 was extended to a series of amines and 1,2-dihalobenzenes (Tables 3 and 4). Table 3 shows that a wide variety of amines readily react with dibromobenzene to give substituted phthalimides. Both the aromatic and aliphatic amines were active for these reactions, and in all cases, good yields (65−92%) of isolated products were obtained from the reaction mixtures.

Using the standard conditions established for the reaction, different dihalobenzenes were also used for this double carbonylation reaction (Table 4). 1,2-Diiodobenzene and 1-bromo-2-iodobenzene reacted with allylamine to form *N*-allylphthalimide in 78 and 75% isolated yields, respectively, while 1-bromo-2-iodobenzene only afforded the monocarbonylated product, *N*-allyl-2-chlorobenzamide, in 77% yield after 24 h (Table 4, entries 2−4). Substituents on the haloaromatic ring may also influence the outcome of the reaction, with electron-donating groups providing better yields than electron-withdrawing groups. Without any substituents, the reaction provided the best yield of the phthalimide (Table 4, entried 1, 5, and 6).

Catalyst reuse was also investigated in this work. After the reaction (Table 3, entries 1 and 3), the ionic liquid was partitioned with hexane, and the substituted phthalimide product was extracted into hexane. The IL phase containing active Pd catalysts was dried under vacuum and recharged with starting material and base. After 24 h, the target products were isolated in 65 and 73% yield.

In conclusion, we have discovered an effective method for the synthesis of N-substituted phthalimides under mild conditions. PSIL 102, trihexyl(tetradecyl)phosphonium bromide, is a particularly effective general reaction media for the palladium-catalyzed double carbonylation reactions of dihaloarenes and amines and affords products in excellent yields.

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Supporting Information Available: Full experiment details, characterization for all compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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