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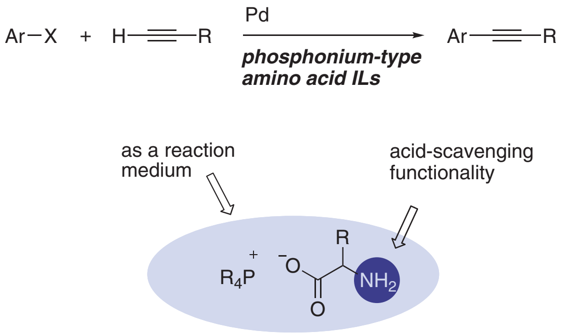
Copper-free Sonogashira Coupling Reaction in Phosphonium Amino Acid Ionic Liquids

Takahide Fukuyama,* Md. Taifur Rahman, Shinji Maetani, and Ilhyong Ryu*
Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531

(Received July 1, 2011; CL-110557; E-mail: ryu@c.s.osakafu-u.ac.jp)

Phosphonium amino acid ionic liquids were found to be useful for the copper-free and amine-free Sonogashira coupling reaction. A hydrophobic and lipophobic ionic liquid permitted easy separation of the product from ionic liquid and catalyst, and the recovered ionic liquid containing Pd catalyst could be reused.

Palladium–copper-catalyzed coupling reaction of aryl halides and terminal alkynes, namely the Sonogashira coupling reaction, provides a powerful tool for access to a wide range of disubstituted alkynes.[1] The origin of palladium-catalyzed reaction for the same transformation is back in 1975, for which Cassar[2] and the Heck group[3] independently reported the reaction proceeded in the presence of strong base such as $NaOCH_3$ or amine as solvent. In 2002 we reported that the copper-free Sonogashira coupling reaction (Cassar/Heck reaction) was successfully carried out in ionic liquids,[4] such as $[bmim]PF_6$ to give good yields of disubstituted alkynes,[5–7] and can create an effective catalyst recycling system coupled with a microflow technology. The Sonogashira coupling reactions, irrespective of with or without copper, often employ a volatile and odorous amine, as solvent and/or a base to scavenge the acid (HX) by-product. We herein report an amine-free protocol in which phosphonium-based amino acid ionic liquids[8] would serve as polar reaction media ensuring a copper-free system and an acid-scavenger (Scheme 1).

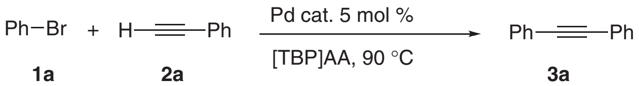


Scheme 1. Copper-free Sonogashira coupling reaction using amino acid ionic liquid.

We investigated the reaction of bromobenzene (**1a**) with phenylacetylene (**2a**) as a model of copper-free and amine-free Sonogashira reaction using a variety of tetrabutylphosphonium amino acid ionic liquids. Thus, when the reaction of **1a** with **2a** was carried out in the presence of a catalytic amount of $[PdCl_2(PPh_3)_2]$ (5 mol %) in [TBP][Gly] as a solvent at 90 °C for 7 h, the coupling product, diphenylacetylene (**3a**), was formed in 39% yield (Table 1, Entry 1), after biphasic workup using hexane. [TBP][Ala] and [TBP][Val] gave similarly poor results. However, good yields of the coupling product **3a** was obtained when [TBP][Met], [TBP][Phe], or [TBP][Ile] was used as a solvent (Entries 4–9).

We then investigated the scope of the copper-free Sonogashira coupling reaction using [TBP][Ile] as the solvent and $[Pd(PPh_3)_4]$ as the catalyst.[9] The results are shown in Table 2. The reaction of **1a** with *p*-tolylacetylene (**2b**) gave **3b** in 88% yield (Entry 2). Under similar conditions, 4-bromoanisole (**1b**) also worked well to give the corresponding product **3c**. The reaction of iodobenzenes **1c**–**1g** with phenylacetylene gave the corresponding disubstituted acetylenes in good yields (Entries 4–8). *p*-Chloroiodobenzene (**1g**) reacted with **2a** to give **3f**, with the chloride functionality remaining intact (Entry 8). Aliphatic acetylene, such as 1-octyne, could be employed as a coupling partner to afford hexylphenylacetylene (**3g**) in 96% yield.

Table 1. Copper-free Sonogashira coupling reaction of **1a** with **2a** using tetrabutylphosphonium amino acid ionic liquids[a]



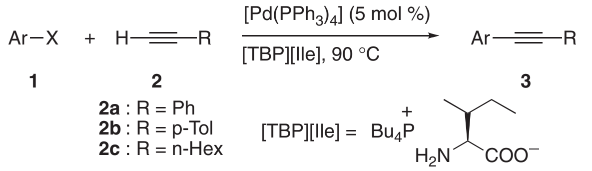
1a **2a** **3a**

Entry	AA	Pd cat.	Time/h	Yield[b]/%
1	Gly	$[PdCl_2(PPh_3)_2]$	7	39
2	L-Ala	$[PdCl_2(PPh_3)_2]$	3	18
3	L-Val	$[PdCl_2(PPh_3)_2]$	5	37
4	L-Met	$[PdCl_2(PPh_3)_2]$	3	68
5	L-Met	$[Pd(PPh_3)_4]$	4	79
6	L-Phe	$[PdCl_2(PPh_3)_2]$	5	88
7	L-Phe	$[Pd(PPh_3)_4]$	6	84
8	L-Ile	$[PdCl_2(PPh_3)_2]$	3	68
9	L-Ile	$[Pd(PPh_3)_4]$	3	99

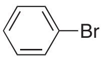
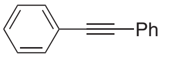
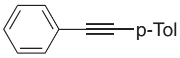
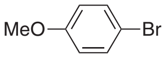
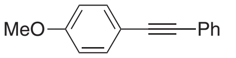
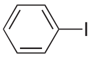
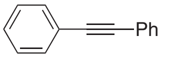
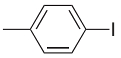
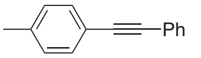
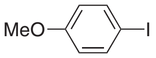
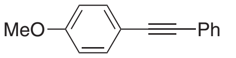
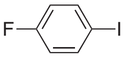
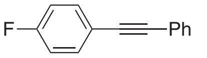
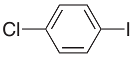
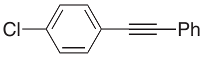
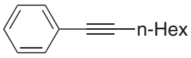
[a]Conditions: **1a** (0.25 mmol), **2a** (1.2 equiv), Pd cat. (5 mol %), ionic liquid (0.5 mL), 90 °C. [b]NMR yield using 1,4-dimethoxybenzene as an internal standard.

To recycle the Pd catalyst and the ionic liquid, removal of HX from the solvent by aqueous inorganic base was carried out. However, the water solubility of [TBP][Ile] made the separation difficult. Therefore, modification of ionic liquid structure was necessary to enhance the hydrophobic character of the ionic liquid. For this purpose, we prepared several phosphonium amino acid ionic liquids having longer alkyl chains on phosphorus and nitrogen atoms and found that ionic liquid prepared from tributyldecylphosphonium salt and *N*-heptylphenylalanine[10] was both hydrophobic and lipophobic for hexane. Using the ionic liquid, catalyst recycling study was carried out (Scheme 2). The first reaction of **1a** with **2a** gave the coupling product **3a** in 95% isolated yield. While $[PdCl_2(PPh_3)_2]$ showed a low solubility in the ionic liquid at the initial stage of the reaction, a homogeneous solution was obtained after the reaction. After extraction with hexane to separate the products from the ionic liquid, HI was removed by biphasic treatment

Table 2. Copper-free Sonogashira coupling reaction of aryl halides with terminal alkynes using [TBP][Ile][a]



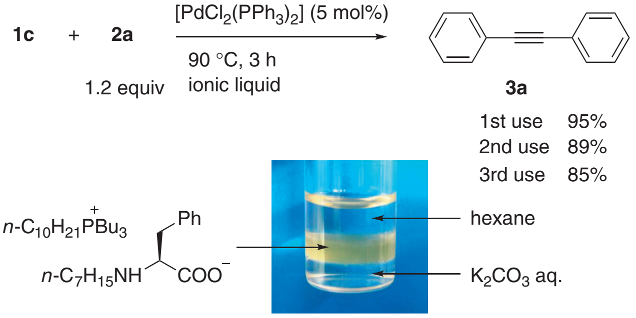
2a : R = Ph
2b : R = p-Tol
2c : R = n-Hex

Entry	1	2	Time/h	3	Yield/%[b]
1	 **1a**	**2a**	3	 **3a**	99[c]
2	**1a**	**2b**	8	 **3b**	88
3	 **1b**	**2a**	3	 **3c**	84
4	 **1c**	**2a**	2	 **3a**	87
5	 **1d**	**2a**	1	 **3d**	98
6	 **1e**	**2a**	2	 **3c**	98
7	 **1f**	**2a**	6	 **3e**	67
8	 **1g**	**2a**	2	 **3f**	96
9	**1a**	**2c**	8	 **3g**	96

[a]Conditions: **1** (0.25 mmol), **2** (1.2 equiv), $[Pd(PPh_3)_4]$ (5 mol %), [TBP][Ile] (0.5 mL), 90 °C. [b]Isolated yield after flash chromatography on SiO_2. [c]NMR yield.

with aqueous saturated K_2CO_3. The recovered ionic liquid containing the Pd catalyst was able to be reused successfully with only a slight loss in its activity.

In conclusion, phosphonium amino acid ionic liquids were found to be useful for the copper-free and amine-free Sonogashira coupling reaction. Among them, a hydrophobic and lipophobic ionic liquid permitted easy separation of the product from ionic liquid and catalyst, and the recovered ionic liquid containing Pd catalyst could be reused. Detailed study on the present copper- and amine-free Sonogashira coupling reaction and other applications using amino acid ionic liquids are currently underway in this laboratory.



Scheme 2. Recycling study using a hydrophobic and lipophobic ionic liquid.

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9 To a 10 mL flask was added tributyldecylphosphonium *N*-heptyl-L-phenylalanine salt (540.5 mg), $[PdCl_2(PPh_3)_2]$ (9.2 mg, 0.013 mmol), **1c** (52.0 mg, 0.25 mmol), and **2a** (31.2 mg, 0.31 mmol). The flask was evacuated and subsequently flushed with argon, and the reaction mixture was stirred at 90 °C for 3 h. After the reaction, the product was extracted with hexane (5 × 3 mL). The combined hexane layer was evaporated and the residue was purified by column chromatography on silica gel (hexane) to give **3a** (42.3 mg, 95%). Ionic liquid solution was washed with a saturated K_2CO_3 aqueous solution (3 × 2 mL). The ionic liquid layer was dried under reduced pressure and used for the next cycle.

10 Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, $J = 7.8$ Hz, 2H), 7.19 (t, $J = 7.3$ Hz, 2H), 7.10 (t, $J = 7.3$ Hz, 1H), 3.27 (t, $J = 6.7$ Hz, 1H), 3.09 (dd, $J = 13.8$, 5.5 Hz, 1H), 2.83 (dd, $J = 13.8$, 7.8 Hz, 1H), 2.65–2.59 (m, 1H), 2.44–2.35 (m, 10H), 1.51–1.41 (m, 18H), 1.29–1.19 (m, 20H), 0.97–0.83 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 140.9, 129.0, 127.0, 124.5, 65.8, 48.3, 40.4, 31.2, 30.3, 29.9, 28.7, 28.4, 26.9, 23.3, 22.0, 21.3, 18.2, 17.8, 13.5, 12.9. IR (neat): 3313.1, 1575.6 cm^{-1} MS: FAB (+) $m/z = 343$, $[C_{22}H_{48}P]^+$, FAB (−): m/z 262, $[C_{16}H_{24}NO_2]^-$.