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Full Paper

Thermoregulated Aqueous Biphasic Catalysis of Sonogashira Reactions

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A water-based thermoregulated system for Pd-catalyzed Sonogashira reactions is presented, which allows for not only a highly efficient homogeneous catalytic reaction, but also an easy separation/recovery of the catalyst. The novel catalytic system exhibits high efficiency and excellent reusability. In addition, the Sonogashira reactions are performed with $Pd(OAc)_2$ without a copper co-catalyst.

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Introduction

Homogeneous palladium catalysts have drawn particular attention due to their catalytic properties.[1–6] However, the main disadvantage of these homogeneous catalysts is the problem of separation and recycling the catalyst from the reaction mixture. To deal with this problem, a lot of strategies have been developed.[7–9] Among them, biphasic systems have many potential advantages and meet several goals of green chemistry, and have gained increasing attention as a promising reaction media.[10,11] One of the representative features of thermoregulated biphasic systems is that it provides a means to perform monophasic catalysis at one temperature, while catalyst/product separation is carried out at room temperature. Up to this point, numerous thermomorphic catalytic systems have been reported.[12–15] Unfortunately, while biphasic conditions facilitate catalyst separation and reuse, multiple phases introduce kinetic barriers and mass transfer limitations. Moreover, the traditional thermoregulated phase-transfer catalysis suffers from requirement of organic solvents or special palladium catalysts such as palladacycles.

The Sonogashira reaction, a carbon–carbon coupling reaction of major relevance in synthetic organic chemistry, is usually performed at elevated temperatures. Therefore, it is particularly suitable for the use of thermoregulated catalytic processes. Thermomorphic systems for palladium-catalyzed Sonogashira reaction have been reported by the groups of Bergbreiter,[16] Chiba,[17] and Lu.[18] However, these methods require either a copper co-catalyst or an organic co-solvent. Water is a desirable reaction medium for reasons of low cost, safety, and environmental concerns. Hence, water-based catalytic systems have many potential advantages and follow the principles of green chemistry.[19] Disappointingly, a limited number of neat water-based thermoregulated biphasic catalytic reactions have been reported. Phosphate ligands containing polyethylene glycol (PEG) moieties have been used as thermoregulated ligands for Sonogashira coupling in pure water, which was reported by Jin's group in 2011.[20] Our group has a long-standing interest in developing efficient temperature-dependent biphasic systems for various organic reactions.[21–24] Recently, we reported a new PEG-based dicationic ionic liquid (PEG-DAIL, as shown in Chart 1) exhibiting temperature-dependent phase behaviour.[25]

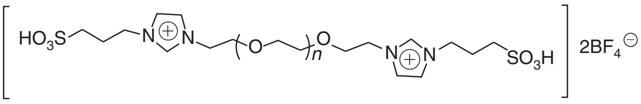


Chart 1. The thermoregulated ligand, PEG-DAIL[BF_4].

The nature of the strong electron-donating abilities of *N*-heterocyclic carbene (NHC) ligands facilitates tighter binding of the ligand to the metal, which significantly enhances the catalyst's lifetime and efficiency.[26–28] Hence, NHC ligands have been applied in versatile catalytic reactions due to its excellent physicochemical properties. In the present paper, we report the use of a PEG-based imidazolium salt as NHC thermoregulated ligand precursors for Sonogashira reactions, being organic solvent-free and copper-free. To the best of our knowledge, the palladium-catalyzed Sonogashira coupling reaction in a thermoregulated system using water as sole medium, promoted by a PEG-bound NHC thermoregulated ligand, has not been reported.

Experimental

All chemicals were from commercial sources and used without any pretreatment. All reagents were of analytical grade. ^1H NMR spectra were recorded on a Bruker 400 MHz spectrometer with TMS as an internal standard. All the products were known compounds and characterized by comparing their ^1H NMR spectra (see Supplementary Material) with those reported in the literature.

Typical Procedure for the Preparation of Thermoregulated Ligand (PEG-DAIL[BF$_4$])

The thermoregulated ligand (PEG-DAIL[BF$_4$]) was prepared according to the reference reported by our group.[25] ν_{max} (KBr)/cm^{-1} 3849, 3400, 3020, 2883, 1732, 1591, 1456, 1431, 1377, 1122, 1109, 972, 883, 798, 677, 577. δ_H (D$_2$O) 2.15 (4H, t, J 7.0, $2 \times CH_2$), 2.77–2.81 (4H, m, $2 \times CH_2$), 3.45–3.66 (90H, m, $(OCH_2CH_2)_n$), 3.74 (4H, d, J 4.0, $2 \times CH_2$), 4.21–4.30 (8H, m, $4 \times NCH_2$), 7.41 (4H, s, $4 \times CH$), 8.71 (2H, s, $2 \times CH$). δ_C (D$_2$O) 25.2, 47.7, 47.9, 49.1, 68.6, 68.7, 69.6, 122.3, 123.1, 136.0.

General Conditions for Sonogashira Reactions

A solution of Pd(OAc)$_2$ (0.34 mg, 0.0015 mmol) and ligand PEG-DAIL[BF$_4$] (4.5 mg, 0.003 mmol) in deoxygenated H_2O (2 mL) was stirred at room temperature for 30 min in air. Et_3N (101 mg, 1 mmol), aryl halide (0.5 mmol), and terminal alkyne (0.75 mmol) were then successively added. The reaction mixture was heated in an oil bath with magnetic stirring. After cooling to room temperature, the reaction mixture was added to brine (15 mL) and extracted with diethyl ether (3 × 15 mL). The solvent was concentrated under vacuum and the product was isolated by short column chromatography on silica gel.

Catalyst Recycling for the Sonogashira Reaction

When the reaction was completed, the reaction mixture was cooled to room temperature and extracted with diethyl ether (2 mL). Et_3N (101 mg, 1 mmol), bromobenzene (0.5 mmol), and phenylacetylene (0.75 mmol) were added to the aqueous phase that was separated from the previous catalytic run, and reacted at 80°C.

Results and Discussion

Literature reports reveal that a palladium-NHC complex could be explored using an imidazolium salt as an NHC precursor with a homogeneous Pd source.[29–31] Hence, a water-soluble palladium complex was generated in situ from PEG-DAIL[BF$_4$] and Pd(OAc)$_2$ in water at room temperature and was directly applied to the copper-free Sonogashira reaction between aryl halides and terminal alkynes. It was important to note that no precautions against catalyst oxidation need to be taken: all the reactions and separations were run in air.

Fig. 1 demonstrates the process of the Sonogashira reaction between aryl halides and terminal alkynes in water catalyzed by the thermoregulated ligand-Pd(OAc)$_2$. Aqueous solutions of thermo-responsive ligand and Pd(OAc)$_2$ exhibit a temperature-dependent behaviour. On heating to the reaction temperature (>80°C), the catalyst transfers into the substrate phase and catalyzes the reaction homogeneously. Upon cooling the reaction mixture to room temperature, the catalyst returns to the water phase and the product precipitates to the bottom. The water phase containing the catalyst can be separated simply from the product and reused in the next run.

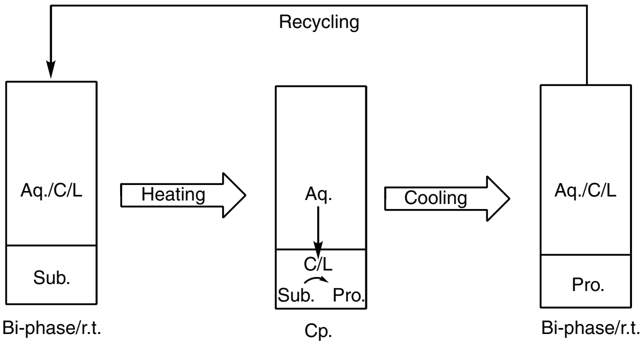
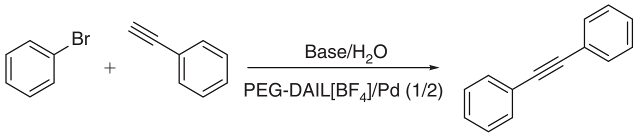


Fig. 1. The thermoregulated ligand (PEG-DAIL[BF$_4$])-Pd(OAc)$_2$ catalyzed Sonogashira reaction in water (Aq. = aqueous; Sub. = substrate; Pro. = product; Cp. = cloud point; C = catalyst; L = ligand).

Table 1. Sonogashira reaction of bromobenzene with phenylacetylene[A]



Entry	Base	Temperature [°C]	Pd source	Yield[B] [%]
1	Et_3N	25	Pd(OAc)$_2$	10
2	Et_3N	45	Pd(OAc)$_2$	69
3	Et_3N	65	Pd(OAc)$_2$	50
4	Et_3N	80	Pd(OAc)$_2$	93
5	Pyridine	80	Pd(OAc)$_2$	76
6	Morpholine	80	Pd(OAc)$_2$	78
7	Piperidine	80	Pd(OAc)$_2$	80
8	K_2CO_3	80	Pd(OAc)$_2$	62
9	NaOAc	80	Pd(OAc)$_2$	58
10	KF	80	Pd(OAc)$_2$	44
11	Et_3N	80	$PdCl_2$	90
12	Et_3N	80	$Pd_2(dba)_3$	55
13	Et_3N	80	Pd/C	45

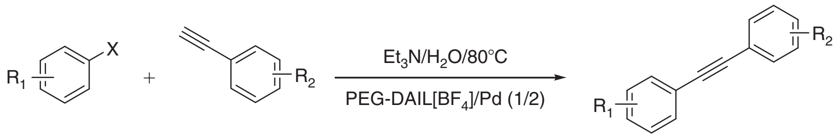
[A] Reaction conditions: bromobenzene (1.0 mmol), phenylacetylene (1.5 mmol), base (2.0 mmol), H_2O (2 mL), PEG-DAIL[BF$_4$]/Pd = 1/2 (molar ratio, 0.3 mol-% Pd(OAc)$_2$), 3 h.

[B] Gas chromatography (GC) yield.

Initially, the cross-coupling between bromobenzene and phenylacetylene was chosen as a model reaction for screening the best reaction conditions. As shown in Table 1, the reaction temperature was found to play a crucial role in the Sonogashira reactions. The cross-coupling was slow at room temperature (Table 1, entry 1). By increasing the reaction temperature from 25 to 65°C, the yield of the product increased slowly from 10 to 50 %, while a sharp rate of acceleration was observed at 80°C (Table 1, entries 2–4). The results indicated that the palladium catalyst stayed in the aqueous phase at lower temperatures (<80°C) and transferred into the substrate phase at higher temperatures (>80°C).

According to the published literature,[16–18] the choice of base was a significant factor that determined the efficiency of the Sonogashira reaction. Therefore, various bases were investigated and the results showed that the use of an inorganic base, such as K_2CO_3, NaOAc (Table 1, entries 8–10), afforded the desired products in moderate yields. In contrast, organic bases afforded good to excellent yields (Table 1, entries 4–7). Among them, Et_3N provided a much better result than others at 80°C (Table 1, entry 4). The palladium source was also important to the catalytic efficiency. As shown in Table 1, Pd^{II} sources such as Pd(OAc)$_2$ or $PdCl_2$ exhibited higher catalytic activity than Pd^0 sources (Table 1, entries 4 and 11–13). Therefore, Pd(OAc)$_2$

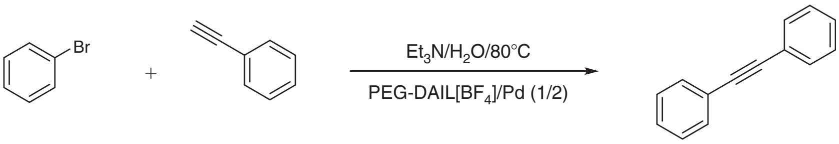
Table 2. Sonogashira reaction between aryl halides and terminal alkynes in water[A]



Entry	R_1	X	R_2	Time[B] [h]	Yield[C,D] [%]
1	4-OMe	I	H	1.5	97 (94)
2	4-H	I	H	1.5	99 (95)
3	4-COMe	I	H	1.5	99 (93)
4	4-Me	Br	H	3	90 (86)
5	2-Me	Br	H	3	85 (80)
6	2-Me, 3-Me	Br	H	3	82 (78)
7	4-OMe	Br	H	3	91 (88)
8	4-Cl	I	H	2	93 (90)
9	4-Br	I	H	2	92 (88)
10	4-COOMe	Br	H	2	95 (80)
11	4-NO_2	Br	H	2	99 (95)
12	4-CN	Br	H	2	96 (90)
13	4-COMe	Br	H	2	93 (88)
14	2-bromothiophene	Br	H	6	75 (70)
15	4-COMe	Br	4-NH_2	4	84 (80)
16	4-COMe	Br	4-CF_3	4	87 (80)
17	4-NO_2	Cl	H	12	18[E]

[A] Reaction condition: ArX (1.0 mmol), terminal alkyne (1.5 equiv.), Et_3N (2.0 equiv.), H_2O (2 mL), and PEG-DAIL$[BF_4]$/Pd = 2/1 (molar ratio, 0.3 mol-% $Pd(OAc)_2$).
[B] The reaction was monitored by GC.
[C] GC yield.
[D] Isolated yields given in parentheses.
[E] Palladium loading of 0.5 mol-%.

Table 3. Recycling experiments for Sonogashira coupling between bromobenzene and phenylacetylene[A]



Run	1	2	3	4	5
Yield[B] [%]	93	90	88	75	70

[A] Reaction conditions: bromobenzene (1.0 mmol), phenylacetylene (1.5 mmol), Et_3N (2.0 mmol), H_2O (2 mL), and PEG-DAIL$[BF_4]$/Pd = 2/1 (molar ratio, 0.3 mol-% $Pd(OAc)_2$).
[B] GC yield.

was chosen as the desired palladium catalyst. Overall, the best reaction conditions of the model Sonogashira reaction was using $Pd(OAc)_2$ as a catalyst with Et_3N as a base at 80°C in water.

The scope of the Sonogashira coupling reaction was thoroughly investigated under the established reaction conditions. As shown in Table 2, the results illustrated that the aryl iodides with electron-donating or electron-withdrawing groups both could afford the corresponding products in excellent yields in short reaction times (Table 2, entries 1–3). In contrast, the electronic effects of substituent groups on aryl bromides made some difference to the coupling yields. Generally, aryl bromides with electron-withdrawing groups such as 4-NO_2 and 4-CN afforded the corresponding products in high yield (Table 2, entries 10–13), while aryl bromides with electron-donating groups such as methyl and methoxy groups required prolonged reaction time to obtain good yields (Table 2, entries 4–7). It should also be noted that aryl iodides can be selectively coupled in the presence of aryl bromides or aryl chlorides. When the substrate contains iodo, bromo and/or chloro substituents, phenylacetylene coupled readily only with the iodo side (Table 2, entries 8 and 9). Interestingly, the present thermoregulated protocol was also suitable for sterically hindered 1-bromo-2,3-dimethylbenzene (Table 2, entry 6). To our delight, aryl bromides bearing a heterocyclic aromatic substituent was also found to afford the desired product in 75 % yield (Table 2, entry 14). The coupling reactions of 4-bromoacetophenone with 4-ethynylaniline or 1-ethynyl-4-(trifluoromethyl)-benzene also showed excellent yields (Table 2, entries 15 and 16). However, efforts to activate aryl chloride in the thermoregulated system to reach a high yield were unsuccessful, even after prolonging the reaction time to 12 h and using a palladium loading of 0.5 mol-% (Table 2, entry 17).

The recycling and recovery of a catalytic system are a very important issue from both practical and environmental points of view. To evaluate the reusability of the thermoregulated ligand-$Pd(OAc)_2$ catalyst, recycling studies were carried out for the cross-coupling of bromobenzene with phenylacetylene using the optimal reaction conditions. After the reaction was complete and cooled to room temperature, the product was extracted with diethyl ether and the water phase containing the catalyst was loaded with the reactants and bases for the next run. As shown in Table 3, the catalytic system could be recycled three times while still maintaining a satisfactory yield. A significant decrease in the catalytic activity was observed in the fourth and fifth recycling experiments.

Conclusions

We have described an environmentally friendly water-based catalytic system for Sonogashira reactions that allow product/catalyst separation by simple variation of temperature without the need of any organic solvent. The novel catalytic system exhibits high efficiency and excellent reusability. In addition, the Sonogashira reactions are performed in air, catalyzed with $Pd(OAc)_2$, and without a copper co-catalyst.

Supplementary Material

Experimental procedures, characterization data, and copies of the ^1H NMR spectra of all cross-couplings are available on the Journal's website.

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