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Polyethylene Glycol as Support and Phase Transfer Catalyst in Aqueous Palladium-catalyzed Liquid-phase Synthesis

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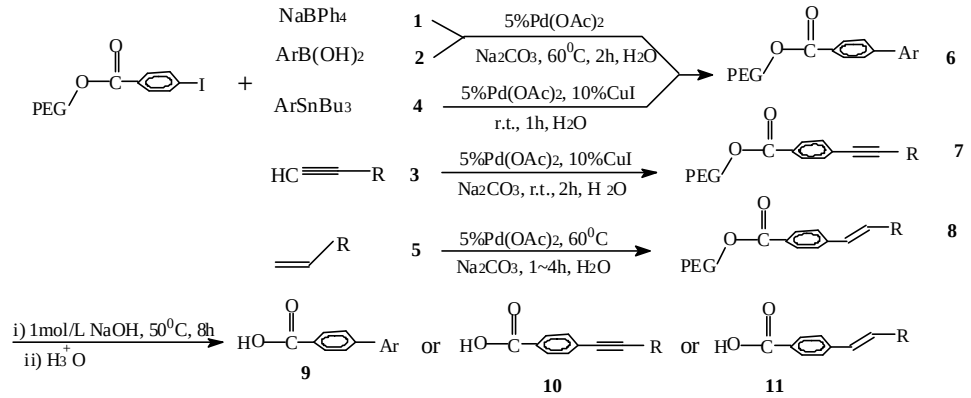
Abstract: Excellent yields and purity were obtained in the aqueous medium Suzuki, Sonogashira, Stille and Heck reactions using palladium (II) as catalyst in liquid phase synthesis. Polyethylene glycol (PEG) acted as soluble polymeric support and phase transfer catalyst as well.

Keywords: Aqueous medium, palladium-catalyzed, polyethylene glycol, liquid-phase synthesis.

Recently, the liquid-phase synthesis of small organic compounds has been a preferable strategy due to its combination with the advantage of solution-phase and solid-phase methods[1]. Among the various soluble polymers, polyethylene glycol (PEG) is the most useful as support. It has been reported that PEG bound substrates could also play the role of phase-transfer catalyst (PTC) in some reactions[2]. Herein we reported that palladium-catalyzed coupling reactions could be taken place smoothly in aqueous medium using PEG as PTC and polymer support under mild conditions (**Scheme 1**).

Aqueous medium offers a safe, economic and environmentally benign alternative in organic synthesis, but it is often limited by spare solubility of reactants, so that the additional phase-transfer catalysts are indispensable. However, due to the intrinsic solubility and PTC properties of the polymeric support, the coupling involved with PEG supported 4-iodobenzoate provides improved yields than the analogues reactions in solution phase (**Table 1**). As it was shown in **Table 1**, in the absence of additional PTC, palladium-catalyzed Heck, Suzuki, Sonogashira and Stille coupling reactions could be carried out smoothly in water. After precipitation, the precipitate was washed with ether, the PEG bound products were cleavaged efficiently from the support with 1 mol/L NaOH aqueous solution at 50°C for 8 hours and acidified with 5 mol/L HCl aqueous solution to pH within 3~4 before routine workup. The yields of products were good to excellent. It is potential for these reactions to be assumed for the combinatorial synthesis on the soluble support.

Scheme 1



2a Ar=Ph, **2b** Ar=*p*-$CH_3C_6H_4$, **3a** R=Ph, **3b** R=CH_2OH, **4a** Ar=Ph, **4b** Ar= *p*-$CH_3C_6H_4$, **5a** R=Ph, **5b** R=COOH

Table 1 Palladium-catalyzed reactions through solution phase and liquid phase in water without additional PTC

Entry	Substrate	Time (h)	Temp. (°C)	Yield (%)[a]	Yield (%)[b]	Purity (%)[c]
1	1	2	60	89	61	99.18
2	2a	2	60	92	63	99.43
3	2b	2	60	86	58	98.88
4	3a	1	r.t.	91	61	98.13
5	3b	2	r.t.	84	54	98.34
6	4a	1	r.t.	90	73	99.17
7	4b	1	r.t.	86	59	98.65
8	5a	0.5	60	83	54	94.33
9	5b	4	60	71	32	75.74

a. the yields in liquid phase; b. the yields in solution phase; c. based on HPLC analysis

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