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Poly(ethylene glycol) (PEG) as a Reusable Solvent Medium for Organic Synthesis. Application in the Heck Reaction[†]

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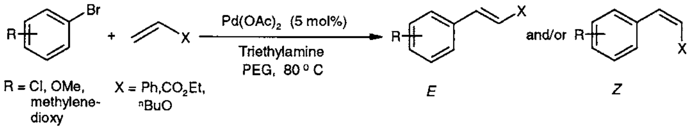
ABSTRACT



PEG has been used as a solvent medium for regioselective Heck reactions with easy recyclability of solvent and Pd catalyst for the first time.

Solvents are widely used in organic synthesis and have been a cause of major concern due to their associated environmental hazards. The major disadvantages are their pyrophoric nature, volatility, and poor recovery. To address some of these issues, attempts have been made to develop solvent-free chemistry, which to some extent has been successful for a few transformations.[1] However, in performing the majority of organic transformations, solvents play a critical role in making the reaction homogeneous and allowing molecular interactions to be more efficient. In recent times ionic liquids have been in the forefront of research, and several publications and reviews have already appeared.[2] Even though ionic liquids offer some advantages, the tedious preparation of ionic liquids (and raw materials for ionic liquids) and their environmental safety is still debated. To address the concerns raised by volatile organic solvents, we initiated a new program to identify whether any available liquid polymers or low melting polymers can be used as solvents.[3] We herein report the application of poly(ethylene glycol) (PEG) having molecular weight 2000 (or lower) as an efficient reaction medium for Pd-catalyzed C−C bond formation, namely, the Heck reaction.[4,5] We have noticed that this transformation is more rapid and high yielding, and the catalyst is easily recycled with high efficiency. Interestingly, the stereo- and regioselectivities are also different from those with conventional solvents and ionic liquid media. The

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(1) (a) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159. (b) Toda, F.; Tanaka, K. *Chem. Rev.* **2000**, *100*, 1025. (c) Cave, G. W. V.; Raston, C. L. *Chem. Commun.* **2000**, 2199. (d) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. (e) Toda, F. *Synlett* **1993**, 303.

(2) (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3773. (c) Gordon, C. M. *Appl. Catal., A* **2001**, *222*, 101. (d) Sheldon, R. *Chem. Commun.* **2001**, 2399.

(3) (a) Santaniello, E.; Manzocchi, A.; Sozzani, P. *Tetrahedron Lett.* **1979**, *47*, 4581. (b) Buchardt, J.; Meldal, M. *Tetrahedron Lett.* **1998**, *39*, 8695. (c) Badone, D.; Jommi, G.; Pagliarin, R.; Tavecchia, P. *Synthesis* **1987**, 920. (d) Babonneau, M. T.; Jacquier, R.; Lazaro, R.; Viallefont, P. *Tetrahedron Lett*, **1989**, *30*, 2787. (e) Heiss, L.; Gais, H. J. *Tetrahedron Lett.* **1995**, *36*, 3833. (f) Ebert, C.; Gardossi, L.; Linda, P.; Vesnaver, R.; Bosco, M. *Tetrahedron* **1996**, *52*, 4867. (g) Namboodiri, V. N.; Varma, R. S. *Green Chem.* **2001**, *3*, 146.

(4) (a) Dick, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (b) Jeffery, T. *Chem. Commun.* **1984**, 1287. (c) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379. (d) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(5) (a) Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091. (b) Carmichael, A. J.; Earle, M. J.; Holbry, J. D.; McComac, P. M.; Seddon, K. R. *Org. Lett.* **1997**, *1*, 997. (c) Xu, L.; Chen, W.; Xiao, J. *Organometalics* **2000**, *19*, 1123. (d) Hagiwara, H.; Shimizu, Y.; Hoshi, T.; Suzuki, T.; Ando, M.; Ohkubo, K.; Yokoyama, C. *Tetrahedron Lett.* **2001**, *42*, 4349. (e) Deshmukh, R. R.; Rajagopal, R.; Srinivasn, K. V. *Chem. Commun.* **2001**, 1544.

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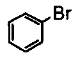
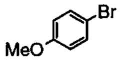
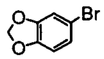
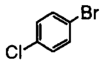
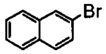
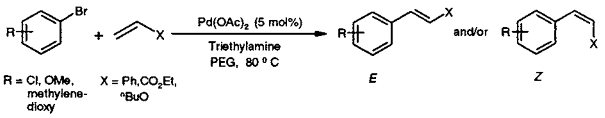
Table 1. Pd-Catalyzed Heck Reaction of Electron-Deficient and Electron-Rich Olefins in Polyethylene Glycol

Entry	Aryl bromide	Alkene	Product	Time	% Yield[a] (*E*:*Z*)
1		Ethyl acrylate	Ethyl cinnamate **(1a)**	8	90
		Styrene	Stilbene **(1b)**	10	93
		n-Butyl vinyl ether	1-(2-butoxy-(E)-1-ethenyl) benzene **(1c)**	12	88 (80:20)
2		Ethyl acrylate	4-methoxy-ethyl cinnamate **(2a)**	12	91
		Styrene	4-methoxy stilbene **(2b)**	12	85
		n-Butyl vinyl ether	1-(2-butoxy-(E)-1-ethenyl) - 4- methoxy-benzene **(2c)**	16	82 (70:30)
3		Ethyl acrylate	3,4-methylenedioxy ethyl cinnamate **(3a)**	12	95
		Styrene	3,4-methylenedioxystilbene **(3b)**	13	89
		n-Butyl vinyl ether	1-(2-butoxy-(E)-1-ethenyl) -3, 4-methylenedioxybenzene **(3c)**	15	80 (75:25)
4		Ethyl acrylate	4-chloro-ethyl cinnamate **(4a)**	8	90
		Styrene	4-chloro-stilbene **(4b)**	9	89
		n-Butyl vinyl ether	1-(2-butoxy-(E)-1-ethenyl)- 4-chlorobenzene **(4c)**	14	90 (100:0)
5		Ethyl acrylate	Ethyl 3-(4a,8a-dihydro-2-naphthalenyl)-(E)-2-propenoate **(5a)**	10	89
		Styrene	1-(naphthyl)-2-phenyl(E)-1-ethene **(5b)**	12	90
		n-Butyl vinyl ether	1-(2-butoxy-(E)-1-ethenyl) naphthalene **(5c)**	15	87 (75:25)

[a] Yields calculated after column chromatography and characterized by ^{1}H NMR and mass spectrometry.

results are presented herein. We first tested the Heck coupling between bromobenzene (**1**) and ethyl acrylate, wherein both the substrates (1:1), $Pd(OAc)_2$ (3 mol %), and TEA (1 equiv) were taken in PEG (MW 2000) and subjected to heating at 80 °C for 8 h. The reaction mixture was allowed to cool to room temperature, diluted with ether, and cooled to 0 °C to precipitate out PEG. The ether layer was characterized after workup to identify the clean formation of ethyl cinnamate (**1a**) in 90% yield and 90% purity. To further explore the effect of the reaction medium in the Heck coupling, bromobenzene was reacted with less reactive electron-rich vinyl butyl ether to observe the clean formation of butyl styryl ether (**1c**) with exclusive attack of aryl palladium species at the β-carbon of butyl vinyl ether. This is in sharp contrast to results obtained when the reaction is performed in ionic liquids.[6] Interestingly, when the reaction is conducted in conventional solvents (DMF, DMSO, CH_3CN) mixtures of products are obtained with varying ratios.[7] *Thus PEG is unique in obtaining a single regioisomer with good diastereoselection* (80/20 *E*/*Z*). In the third instance, bromobenzene was reacted with styrene to isolate *trans*-stilbene (**1b**) exclusively in 93% isolated yield.

To understand the role of PEG as a reaction medium, bromoanisole (**2**) was subjected to the Heck reaction with all the three olefins, namely, ethyl acrylate, styrene, and butyl vinyl ether. In all three cases, once again excellent regio- and stereoselectivities were obtained (**2a**, **2b**, and **2c**). When 4-chlorobromobenzene was reacted with butyl vinyl ether (**4c**), exclusive formation of *E*-geometrical olefin was achieved. These results indicate that electronic factors in the aryl system control the geometry of the olefin to a certain extent. The other olefinic partners, styrene and ethyl acrylate, behaved normally. In the case of naphthyl bromide (**5**), the products obtained have similar selectivities as in the case of bromobenzene. 3,4-Methylenedioxybenzene reacted well with butyl vinyl ether to yield a single regioisomer (β attack) with 75% diastereoselectivity of the *E*-isomer. In all of the cases studied, the coupling was performed in the absence of any ligand. Additionally, no external PTC was added as was required in the earlier reports.[8] We envisage that PEG not only acted as an efficient solvent medium but also as a PTC for smooth C−C bond formation.



To check the reusability of the solvent as well as the catalyst, after initial experimentation the reaction mixture was extracted with dry ether[9,10] and the PEG and $Pd(OAc)_2$

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[6] Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3*, 295.

[7] (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S. *J. Org. Chem.* **1992**, *57*, 1481. (b) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1993**, *58*, 7421. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858.

[8] (a) Morales-Morales, D.; Redon, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.

were solidified and subjected to a second run of the Heck reaction by charging with the same substrates (bromobenzene, ethyl acrylate, and triethylamine). The results of this experiment and four subsequent experiments were almost consistent in yields (88%, 82%, 80%, 74%, 73%, 70%). After five runs, the PEG layer retained 90% of the palladium (residual analysis, which is within limits of experimental error). In conclusion, low molecular weight PEG has been utilized for the first time as a new solution medium for the Heck reaction, which required no additional PTC or ligands. Also, the reaction works very well for electron-deficient and electron-rich olefins, with equal ease and with high regio- and stereoselectivities.

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(9) Extraction with dry ether is essential to avoid loss of palladium species in the organic layer. No attempt has been made to make PEG free of salts as the salts have never hampered the rate of reaction.

(10) **Typical Procedure.** A mixture of aryl bromide (1 mmol), olefin (1 mmol), PEG-2000 (2 g), TEA (1 mmol), and Pd $(OAc)_2$ (0.05 mmol) was placed in a 10-mL round-bottomed flask and was stirred and heated at 80 °C. After completion of the reaction (monitored by TLC) the reaction mixture was cooled, extracted with cold diethyl ether (3 × 10 mL), and purified by column chromatography.