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Ionic liquid/water as a recyclable medium for Tsuji–Trost reaction assisted by microwave

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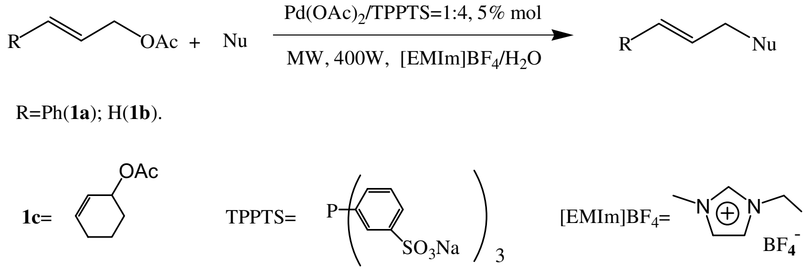
Abstract—An efficient microwave protocol is described for allylic substitution with various carbon and heteronucleophiles catalyzed by $Pd(OAc)_2$/TPPTS in an $[EMIm]BF_4/H_2O$ medium. The ionic liquid/water containing catalyst system can be recycled eight times without loss of activity.

The Tsuji–Trost reaction is a reliable and widely used method for constructing C–C, C–N, and C–O bonds in organic syntheses, with high chemo-, regio-, and stereoselectivities.[1] The reaction often employs Pd(0) complexes and activated allyl alcohol derivatives, in particular, allylic halides, acetates, and carbonates. A variety of nucleophiles such as, carbanions,[2,3] amines,[2,4] sulfides,[2,5] and sulfinates,[2,6] have been shown to couple efficiently with palladium π-allyl complexes. In recent years, allylic substitutions catalyzed by Pd(0) in water or an aqueous–organic medium have been reported.[7]

The chemical and pharmaceutical industry is under an accelerating pressure to find environmentally friendly organic reaction methodologies. Because water is one of the most suitable solvents for realizing safe, harmless, economical, and environmentally friendly processes for the production of fine chemicals, organic reactions in water have recently attracted much attention.[8] Among a variety of possible 'green' solvent alternatives for catalytic reactions, room-temperature ionic liquid (RTIL) reaction media continue to be an area of increasing research activity.[9] Ionic liquids of the dialkylimidazolium class may simplify metal catalyst recycling techniques and allow to develop some new reaction protocols due to their high polarity and special properties. The rising number of publications is indicative of the potential of RTILs as 'neoteric solvents' for various chemical reactions.

Since the appearance of microwave assisted synthesis in 1986,[10] this technique has been accepted as a common method for reducing reaction time by several orders of magnitude and for increasing yields of product compared to conventional methods.[11] The ionic liquids are also suitable for microwave chemistry.[12] We have focused on the application of the Tsuji–Trost reaction in a mixture of water and ionic liquid ($[EMIm]BF_4$),[13]



Scheme 1.

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a new 'green' solvent, which has a wide solubility to organic materials and inorganic materials. Herein, we reported allylic substitution with various carbon and heteronucleophiles catalyzed by palladium(0)-TPPTS assisted by microwave irradiation. The reaction has a great advantage in terms of catalyst recycling, since the product could be readily separated from the [EMIm]BF_4/H_2O containing catalysts via simple extraction with a conventional organic solvent (see Scheme 1).

Firstly, the reaction of cinnamyl acetate with sodium azide was carried out in ionic liquid ([EMIm]BF_4), in the presence of a catalytic amount of $Pd(OAc)_2$ and TPPTS, no reaction proceeded. Using [EMIm]BF_4/H_2O instead of [EMIm]BF_4, the desired product was obtained in good yield. The water plays presumably an important role in the process because of good water solubility to $Pd(OAc)_2$ and TPPTS. Control experiments indicated that, in the absence of TPPTS, no product was observed. Furthermore, the different ratios of [EMIm]BF_4 and H_2O in the reaction were investigated. It is found that the ratio from 1:1 to 1:2 did not affect the yield. The effect of MW power level on this reaction was examined too (Table 1). An efficient power reduced the reaction time from 11 min to 3.5 min. So we chose the power 400 W as operation parameter for follow-up experiments.

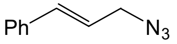
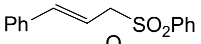
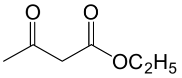
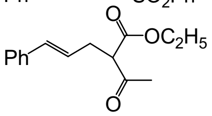
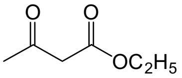
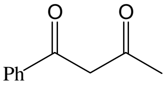
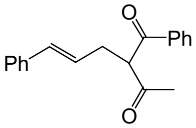
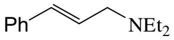
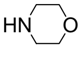
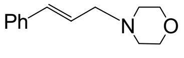
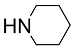
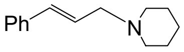
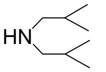
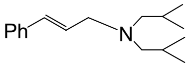
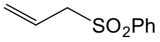
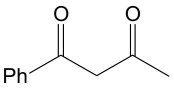
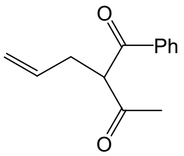
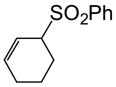
Table 1. Reaction at different MW power levels[a]

Power (W)	80	160	240	320	400
Time (min)	11	8	6	5	3.5

[a] $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), TPPTS (56.8 mg, 0.1 mmol)), [EMIm]BF_4 (1 ml), H_2O (2 ml), cinnamyl acetate (88 mg, 0.5 mmol), NaN_3 (48.75 mg, 0.75 mmol).

The results concerning the reaction of allylic acetate with various nucleophiles catalyzed by palladium(0)-TPPTS in an ionic liquid/water medium via assisted by microwave irradiation are summarized in Table 2. All are α-products with *E*-configuration except entry 12. Reaction of compounds **1a**, **b**, or **c** with sodium azide (entry 1) or *p*-toluene sulfinate (entries 2, 10, 12), which are soluble in water,

Table 2. Reaction of allylic substrates with various nucleophiles[a]

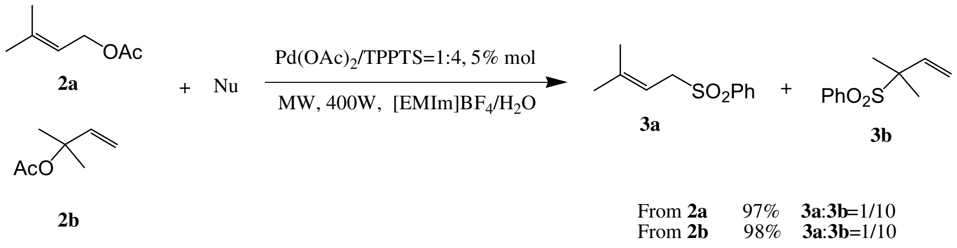
	Allylic	Nucleophile	Base	Product	Time (min)	Yield (%)[b]
1	**1a**	NaN_3	None		3.5	75
2	**1a**	$NaSO_2Ph$	None		1.5	99
3[c]	**1a**		Et_3N		3	93
4[c]	**1a**		None	None	10	0
5[c]	**1a**		Et_3N		4	99
6[d]	**1a**	$HNEt_2$	None		3.5	95
7[d]	**1a**		None		5.5	83
8[d]	**1a**		None		4.5	95
9[d]	**1a**		None		10	80
10[c]	**1b**	$NaSO_2Ph$	None		2	99
11[c]	**1b**		DBU		9	81
12[c]	**1c**	$NaSO_2Ph$	None		2.5	97

[a] Reaction conditions: $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), TPPTS (56.8 mg, 0.1 mmol), H_2O (2 ml), [EMIm]BF_4 (1 ml), allylic acetate (0.6 mmol), nucleophile (0.5 mmol), base (1.5 equiv), MW (400 W).

[b] Isolated yields. All products were identified by NMR and mass spectrometry.

[c] Allylic acetate (0.5 mmol) and nucleophile (0.6 mmol) were employed.

[d] [EMIm]BF_4 (1 ml), H_2O (4 ml).



Scheme 2.

Table 3. Recycle of [EMIm]BF$_4$/H$_2$O reaction medium[a]

Isolated yield (%)							
Run1[b]	Run2	Run3	Run4	Run5	Run6	Run7	Run8
99	99	99	99	99	99	99	99

[a] Pd(OAc)$_2$ (5.6 mg, 0.025 mmol), TPPTS (56.8 mg, 0.1 mmol), [EMIm]BF$_4$ (1 ml), H$_2$O (2 ml), cinnamyl acetate (88 mg, 0.5 mmol), and NaSO$_2$Ph·2H$_2$O (100 mg, 0.5 mmol).

[b] Run 1, NaSO$_2$Ph·2H$_2$O (150 mg, 0.75 mmol) was added.

gave the corresponding allyl azide or sulfone in good yields using this system. Alkylation of acetate needed the presence of a base such as triethylamine (entries 3 and 5) or better DBU (1,8-diazabicyclo [5,4,0] undec-7-ene) (entry 11). No desired product had been detected even after prolonging reaction time to 10 min in the absence of Et$_3$N (entry 4). Secondary amines reacted with **1a** leading to the products of corresponding monoalkylation in good yields (entries 6–9). In entry 9, the reaction rate decreased largely due to the steric hindrance. Detailed reaction procedure can be seen in Ref. 14.

Prenyl acetate **2a** and its regioisomer **2b**, 2-methylbut-3-en-2-yl acetate, yielded a mixture of isomeric sulfones **3a** and **3b** in the same ratio (identified by ^{1}H NMR), suggesting that the reaction proceeds via the π-allyl intermediate (Scheme 2).

Catalyst recycling studies were also carried out. After extraction with diethyl ether to separate the product from the catalyst, the resulting [EMIm]BF$_4$/H$_2$O was pumped for several minutes and reused for the next reaction directly. The resulting [EMIm]BF$_4$/H$_2$O containing the Pd catalyst can be reused successfully eight times without any reduction of its catalytic activity (Table 3).

In summary, we have developed a facile methodology to assist Tsuji–Trost reaction via palladium(0)/TPPTS-catalyzed in ionic liquid/water by using microwave irradiation. The 'green' solvent is harmless, economical, and environmentally friendly. The catalyst system was very easy to separate from the reaction product, so it can be used repeatedly. The microwave irradiation is very favorable for Tsuji–Trost reactions in [EMIm]BF$_4$/H$_2$O and it assists this reaction greatly.

Acknowledgements

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13. [EMIm]BF_4 is soluble to water at any ratio.
14. General procedure: 0.025 mmol $Pd(OAc)_2$ and 0.1 mmol TPPTS were added to a mixture of [EMIm]BF_4 (1 ml) and H_2O (2 ml) in a sealed vessel. The mixture was stirred until $Pd(OAc)_2$ soluted completely. Then 0.6 mmol cinnamyl acetate (**1a**), 0.5 mmol acetoacetate and 0.75 mmol Et_3N (1.5 equiv) were added into the vessel. After flushed with argon for 1 min, the vessel was put into a beaker and then placed in the center of a microwave apparatus (domestic microwave). The reaction mixture is irradiated by microwaves (400 W) for 20 s. After the reaction vessel was cooled down to room temperature, it is irradiated for 20 s again. When the reaction was completed, the product was extracted by diethyl ether (3×10 ml). The Pd(0)-TPPTS was kept in [EMIm]BF_4/H_2O. The diethyl ether layer was combined and concentrated in vacuum. The product was purified by column chromatography. (*Z*)-Ethyl 2-acetyl-5-phenylpent-4-enoate: ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.26 (t, $J = 7.2$ Hz, 3H), 2.26 (s, 3H), 2.75 (t, $J = 7.2$ Hz, 2H), 3.59 (t, $J = 7.2$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 6.09–6.15 (m, 1H), 6.46 (d, $J = 15.9$ Hz, 1H), 7.21–7.31 (m, 5H); ^{13}C NMR (75 Hz, $CDCl_3$, δ ppm): 202.4, 169.2, 137.0, 132.7, 128.5 (2C), 127.4, 126.1 (2C), 125.7, 61.4, 59.5, 31.5, 29.2, 14.1; MS: $m/z = 246$ (M^+, 7), 228 (8), 203 (12), 173 (9), 157 (37), 129 (25), 117 (24), 91 (30), 77 (9), 43 (100).