

Mechanical Stirring Speed in Water/Hexane Biphasic Catalyst Controls Regioselectivity of Pd-catalyzed Allylation Reaction

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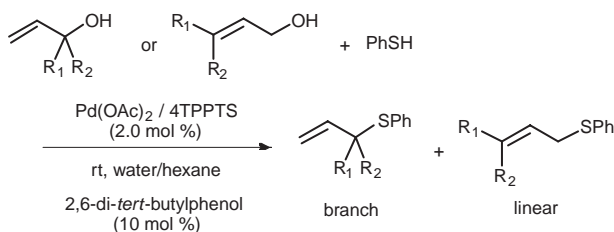
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Vigorous mechanical mixing of the water/hexane biphasic Pd-catalyzed allylation of benzenethiol gave sterically congested allyl sulfides, due to high reactivity of the enforced orientation of the η^1 -allylpalladium intermediate at the solvent interface.

Water/organic solvent biphasic media system in catalysis attracts growing interests, because of easy separation of products from catalysts and decrease of harmful organic solvents.¹ We previously reported a highly active and re-usable water-soluble palladium catalyst for allylation of thiols using allylic alcohols in a biphasic water/organic solvent system.² The reaction is believed to proceed via an η^3 -allylpalladium intermediate.³ During our continuing study on water-soluble organometallic compounds,⁴ we accidentally found the fact that stirring speed of the water/organic solvent biphasic system affects the regioselectivity in allylation of benzenethiol. Namely, the more the stirring speed is increased, the more branched allylic carbon reacts to give branched allyl phenyl sulfide. Such a phenomenon, where the selectivity is controlled by mechanical mixing speed, is unexpected and is not known to date.⁵

When 1,1-dimethylallyl alcohol reacted with benzenethiol in the presence of Pd(OAc)₂ (2 mol %)/TPPTS (10 mol %) in water/hexane biphasic reaction media under nitrogen, smooth allylation took place to give a mixture of 3-methyl-2-butenyl and 1,1-dimethylallyl phenyl sulfides, which can be separated by decantation of the hexane phase (Scheme 1).⁶

Table 1 shows the results of the palladium-catalyzed allylation under various stirring speeds. Under stirring speed over 750 rpm, the ratio of 1,1-dimethylallyl phenyl sulfide to prenyl phenyl sulfide ($R = [\text{branch}]/[\text{linear}]$) was approximately 4, but on lowering the stirring speed, the ratio R dramatically decreased. Figure 1 shows the relation between the ratio R and the stirring speed. The absolute rate of the reaction actually decreased under slow mixing speed owing to insufficient mixing of catalyst with reagents as expected, since collision probability of catalyst with substrates should decrease. Similar trends were also obtained when 3-methyl-2-butenyl alcohol was employed, suggesting that a common allylpalladium(II) intermediate is



Scheme 1.

Table 1. Allylation of benzenethiol with several allylic alcohols^a

Allylic alcohol	Stirring speed /rpm	Time /h	Yield/%		R^b
			branch	linear	
1,1-Dimethylallyl alcohol	1500	5	76	18	4.1
	1000	12	80	20	4.0
	750	8	76	21	3.7
	500	8	72	26	2.7
	400	24	57	40	1.4
	300	24	41	53	0.80
	200	48	35	61	0.58
3-Methyl-2-butenyl alcohol	1500	24	42	12	3.5
	300	24	17	10	0.58
2-Butenyl alcohol (E/Z = 95/5)	1500	5	62	35	1.8
				(E/Z = 92/8)	
	300	24	28	65	0.43
1-Methylallyl alcohol	1500	3	61	36	1.7
				(E/Z = 75/25)	
	300	24	25	68	0.38
				(E/Z = 73/27)	

^aReaction conditions: Pd(OAc)₂ (0.02 mmol), TPPTS (0.10 mmol), allylic alcohol (1.0 mmol), benzenethiol (1.0 mmol), 2,6-di-*tert*-butylphenol (0.10 mmol), solvent = water 4.0 mL, hexane 4.0 mL, 30 °C.
^b R is the ratio of branch isomer to linear isomer: $R = [\text{branch}]/[\text{linear}]$.

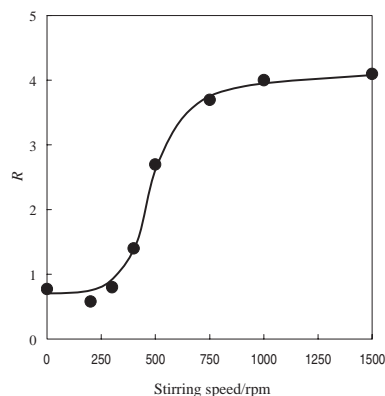


Figure 1. Relationships between the ratio R and the stirring speed for the reaction of benzenethiol with 1,1-dimethylallyl alcohol. R is the ratio of branch isomer to linear isomer: $R = [\text{branch}]/[\text{linear}]$.

involved in this reaction.³ Reactions using 2-butenyl and 1-methylallyl alcohols also gave similar results. Though slow radical isomerization of the branched product to linear was observed,⁷ addition of 2,6-di-*tert*-butylphenol as radical trapping

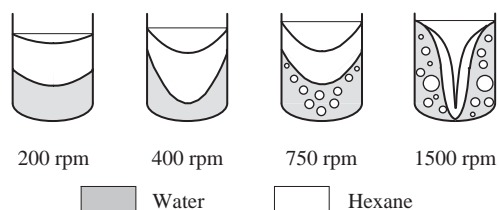


Figure 2.

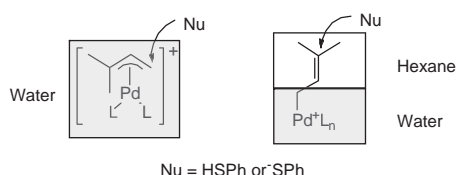


Figure 3.

reagent in the dark significantly inhibited this isomerization. Thus, only minor apparent isomerization of 1,1-dimethylallyl phenyl sulfide to 3-methyl-2-butenyl phenyl sulfide was observed under the reaction conditions.

In order to get further insights of this mechanism, apparent mixing conditions of the reaction solution in the flask were visually analyzed (Figure 2). Under the slow stirring rate below 500 rpm, where low selectivity for the branched product was observed, the clear interface of water and hexane was always observed. However, when the stirring speed was raised more than 750 rpm, small lumps of solvents started to appear. Under the fast stirring conditions, more than 1000 rpm by our apparatus,⁸ two phases could not be apparently distinguished and the system was filled with innumerable small solvent lumps. This fact does not mean a difference of microscopic interface structure at a molecular level, but simply indicates the increase of interface area by mechanical stirring.

A possible mechanism for this allylation is initial formation of allylpalladium(II) intermediate, which is formed from allylic alcohol and Pd⁰ species, followed by the reaction with nucleophile such as thiol or thiolate anion to give corresponding sulfide. We propose from the microscopic point of view that the water-soluble allylpalladium(II) intermediate in the water/hexane interface should have a highly oriented structure as shown in Figure 3, where the allyl moiety exists as η^1 -3-methyl-2-butenyl (or 2-butenyl)palladium(II).⁹ Namely the more hydrophilic TPPTS ligand side of the allylpalladium intermediate should stay in the water phase, but the hydrophobic allyl moiety side is facing toward the hexane phase. The allyl ligand may exist in an η^1 -fashion probably due to effective invasion to the hexane phase or possible steric congestion by water solvation, and thus the 3-methyl-2-butenyl structure would be favored in comparison with the 1,1-dimethylallyl. S_N2' reaction of the allyl ligand with thiol or thiolate anion would selectively give branched product. The allylation reaction within water medium may also take place, where an η^3 -allylpalladium(II) intermediate exists. In this case the less congested carbon of the η^3 -allyl moiety may selectively react to give mainly less substituted product as expected in allylation via an η^3 -allylpalladium intermediate.

Since the interface area should increase with increasing stirring rate, the product ratio of the branched to linear product (*R*) also increases. The catalyst activity in the interface should be higher than that in water phase, since nucleophile exist in hexane phase.

Such a phenomenon displays a novel aspect in the chemical reaction and raises the importance of mechanical mixing in controlling the reaction selectivity of biphasic catalyses. Diverse applications toward many chemical reactions is expected. Further mechanistic studies are required to clarify the origin of the present novel interface effect.

References and Notes

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- 6 Typical procedure for catalytic allylation as follows. In a 25-mL Schlenk tube, Pd(OAc)₂ (4.5 mg, 0.020 mmol) and trisodium salt of tris(*m*-sulfonatophenyl)phosphine (TPPTS, 56.5 mg, 0.100 mmol) were placed under nitrogen atmosphere. Degassed pure water (4 mL) was introduced, and the mixture was stirred vigorously at 30 °C for several minutes, then the aqueous solution became a clear yellow solution. Allylic alcohol (0.100 mL, 1.00 mmol) was added via a syringe. After about 10 min stirring, benzenethiol (0.100 mL, 1.00 mmol) and 2,6-di-*tert*-butylphenol (0.0206 g, 0.1 mmol) in hexane (4 mL) were added. Biphenyl (0.1545 g, 0.999 mmol) was added as an internal standard to the solution. After stirring the organic layer was analyzed by GLC.
- 7 The reaction in the absence of 2,6-di-*tert*-butylphenol gave a 65:35 mixture of 1,1-dimethylallyl phenyl sulfide and 3-methyl-2-butenyl phenyl sulfide.²
- 8 Reactions were performed in the test tube type Schlenk flask, whose inside diameter is 2.0 cm, using a standard 1.5 cm long teflon-covered magnetic stirring bar with an outside diameter of 0.5 cm.
- 9 Orientation of solvent molecules in the water/hydrophobic interface is theoretically proposed to be well-organized and have charged structure. Allylpalladium catalyst in the interface may also have similar orientation. K. N. Kudin, R. Car, *J. Am. Chem. Soc.* **2008**, *130*, 3915.