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Catalytic Allylic Arylation of Cinnamyl Carbonates over Palladium Nanoparticles Supported on a Thermoresponsive Polymer in Water

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Poly(NIPAM-*co*-4-VP) undergoes phase transition at low critical solution temperature with a change from hydrophilic to hydrophobic core in hydrophilic solvent. Palladium nanoparticles supported on such thermoresponsive polymer support were demonstrated to catalyze the Tsuji-Trost reaction for the arylation of various cinnamyl carbonates by arylboronic acids. Therefore, a protocol developed under mild reaction conditions demonstrates the recyclability of the catalyst in an eco-friendly solvent such as water.

Introduction

Allylic substitution catalyzed by palladium has been explicitly researched for the asymmetric organic synthesis of many natural products[1] and various biologically active compounds.[2] Such allylic substitutions, referred to as the Tsuji-Trost reaction, are proficient to introduce C-C, C-N, and C-O bonds in organic carbocyclic synthesis[3] and in heterocycles synthesis[4] with good regio-, chemo-, and stereoselectivities.[5] Following this trend, heterogeneous palladium catalysts have excelled in organic synthesis compared to homogeneous catalysis due to their advantages including less contamination, ease of separation, and recyclability. Recently, versatile materials such as carbon,[6] silica,[7] clay minerals[8] and polymers[9] have been used as a support for palladium. Resin supporter with an elongated reaction time under harsh conditions has been reported.[9] Previously, Y. Uozumi and co-workers employed amphiphilic resin as a polymer support for palladium in order to facilitate allylic substitution in aqueous media.[10] Likewise, we recently developed palladium on thermoresponsive poly(N-isopropylacrylamide-*co*-4-vinylpyridine) (poly(NIPAM-*co*-4-VP)) for cross coupling reactions.[11] Though both resin and hydrogel supports to assist the reaction, poly(NIPAM-*co*-4-VP) has a special low critical solution temperature (LCST) feature that imparts an additional control to accelerate the reaction. Pd(0) nanoparticles have been proved to be active catalyst for allylic substitution in water or THF[12] but a thermoresponsive support like poly(NIPAM-*co*-4-VP) could help to recycle the catalyst as well as participate in the reaction. Allylic substitution by Pd nanoparticles runs smoothly but sometimes its scope is limited by the use of stabilizer like TBAB.[13] Based on these studies and our work of the first Pd-catalyzed allylic benzylation of *N,N*-ditosylbenzylamines with arylboronic acids,[14] we focused on the development of a competent heterogeneous Pd catalyst for allylic substitution in aqueous media.

First, we developed a Pd(0) catalyst by immobilizing Pd(II) on hydrogels by shaking a dispersion of Pd(II) acetate and the polymer support in dry deoxygenated THF, followed by the reduction of Pd(II) by $NaBH_4$ in methanol,[15] as shown in Figure 1.

Experimental

Materials and methods

All reagents were purchased from commercial sources (Aldrich, TCI). *N*-Isopropylacrylamide (NIPAM, Aldrich 97%), *N,N′*-methylenebisacrylamide (MBAAm, Aldrich 99%), palladium acetate(II), sodium borohydrate, ethyl acetate, methanol, toluene and diethyl ether were used as received. 4-Vinylpyridine (4-VP, Aldrich 99%) was distilled under reduced pressure before use.

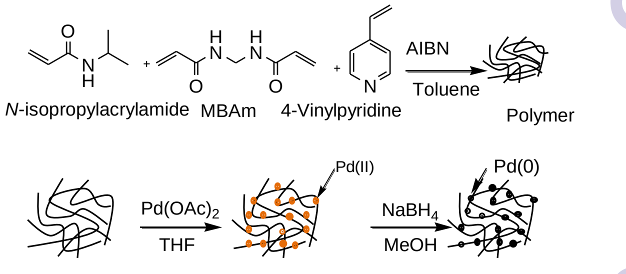

Figure 1 Preparation of the Pd(0) catalyst supported on poly(NIPAM-*co*-4-VP).

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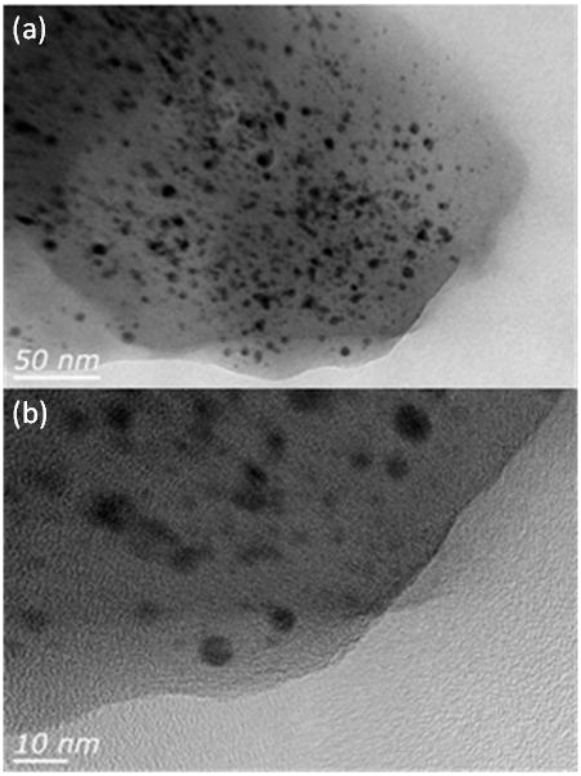


Figure 2 Transmission Scanning Spectroscopy (TEM) images of Pd(0) catalyst supported on poly(NIPAM-*co*-4-VP).

SEM and EDAX measurements were performed on a HRTEM JEOL electron microscope at an acceleration of 300 kV. The loading value of Pd(0) in the catalyst was estimated by ICP analysis with a JY Ultima2C. ICP also helped to check for leaching out after every recycle test. The low critical solution temperature (LCST) of the synthesized hydrogels was characterized with DSC measurements (TA Instrument, DSC 2010). All the hydrogels were immersed in pH 10 buffer solution at room temperature for 24 h to reach the equilibrium state. The DSC analysis of the swollen hydrogels were performed from 0 °C to 60 °C at a heating rate of 2 °C/min under nitrogen atmosphere with a purge rate of 40 mL/min.

General procedure for the preparation of palladium catalyst

Preparation of poly(*N*-isopropylacrylamide-*co*-4-VP). Poly(NIPAM-*co*-4-VP) hydrogels were prepared using *N*-isopropylacrylamide (NIPAM) and 4-vinylpyridine (4-VP) at a 1:1 monomer feed ratio in toluene[11] that has low critical solution temperature 47 ˚C (DSC measurement).

Coordination of Pd(0) catalyst on supported polymer and subsequent reduction. An oven-dried 50 mL jacketed vial was charged with poly(NIPAM-*co*-4-VP) (0.1 g), palladium acetate(II) (10.0 mg, 0.045 mmol) and THF (20 mL) under an argon atmosphere and subjected to shaking at 1100 rpm for 12 h at 60 ˚C. The resulting material was then dispersed in methanol, filtered, washed with THF and dried *in vaccuo*. The reduction of Pd (II) in the collected material was carried out by treating it with sodium borohydride (0.010 g, 0.264 mmol) in methanol (20 mL) by stirring at room temperature for 12 h. The catalyst was then filtered, washed with methanol and water, and dried, and collected as black beads of nano-sized palladium(0) immobilized on poly(*N*-isopropylacrylamide-*co*-4-VP) polymer with a loading value of 0.184 mmol Pd/g polymer (verified by ICP mass).

General procedure for the synthesis of cinnamyl carbonates

In a typical experiment to synthesize cinnamyl methyl carbonate, cinnamyl alcohol (2.68 g, 20.0 mmol) in CH_2Cl_2 (30 mL), pyridine (15 mL), *N,N*-dimethylaminopyridine (0.183 g, 1.5 mmol) and methyl chloroformate (2.835 g, 30.0 mmol) were added to a 100 mL round-bottom flask at 0 ˚C. The mixture was stirred for 2 h at room temperature and monitored by thin layer chromatography (TLC) until completion. The reaction mixture was then washed with water, dried over $MgSO_4$, concentrated *in vacuo*, and purified by silica gel column chromatography to yield pure cinnamyl methyl carbonate **1a**. The product was analyzed by ^1H NMR spectroscopy.

General procedure for application of Pd(0) catalyst

General procedure for the allylic coupling of cinnamyl methyl carbonate with arylboronic acid. An oven dried 10 mL jacket vial was charged with cinnmayl methyl carbonate **1a** (0.192 g, 1.0 mmol), phenylboronic acid **1b** (0.183 g, 1.5 mmol), K_2CO_3 (0.414 g, 3.0 mmol), H_2O (2 mL), and Pd catalyst (0.271 g, 5 mol %) and subjected to shaking at 80 °C. The reaction was monitored by TLC and GC. Upon completion, the reaction mixture was cooled down to room temperature and diluted with ethyl acetate (5 mL). The catalyst was filtered off and collected while the organic mixture was washed with brine and water, dried over $MgSO_4$, and concentrated under reduced pressure. The pure product **3a** was obtained by silica gel column chromatography and analyzed by ^1H NMR spectroscopy.

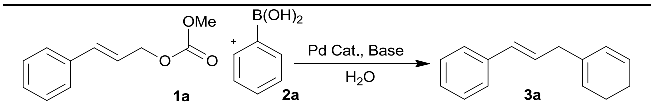
Recycling experiments for allylic arylation. Recycling experiments were carried out by the general procedure described for the allylic coupling of cinnamyl methyl carbonate **1a** and toluylboronic acid **2b**. The catalyst was recovered and recycled for the following experiment. The filtrate was collected and analyzed by ICP. Ten such repetitions of the reaction with an output of 89-94 % yields of the product **3b** were demonstrated.

Result and Discussion

Polymer behaviour and morphology

According to differential scanning calorimetry (DSC) studies, the polymer coils around itself and result in behavioural changes from hydrophilic to hydrophobic polymer core in hydrophilic solvent like water.

Table 1 Optimization study results for the allylic substitution of carbonates[a]



Entry	Pd Cat. (mol%)	Base (equiv.)	Temp. (°C)	Time (h)	Yield[b] (%)
1	5	---	80	6	78
2	5	Et_3N (3)	80	6	72
3	5	K_2CO_3 (1)	80	6	86
4	5	K_2CO_3 (2)	80	6	85
5	5	KF (2)	80	6	83
6	5	KF (3)	80	6	94
7	1	K_2CO_3 (3)	60	24	77
8	5	K_2CO_3 (3)	60	18	86
9	10	K_2CO_3 (3)	60	12	84
10	1	K_2CO_3 (3)	80	8	94
11	5	K_2CO_3 (3)	80	6	95
12	10	K_2CO_3 (3)	80	4	88

[a] Reaction conditions: Cinnamyl methyl carbonate (0.5 mmol, 1.0 equiv.), phenylboronic acid (0.75 mmol, 1.5 equiv.), H_2O (2 mL). [b] Isolated yield.

This change is brought up by the dominant hydrophobic interactions among poly(*N*-isopropylacrylamide) (PNIPAM) chains above LCST that leads to the expulsion of water molecules trapped in polymer beads. This stage is perfectly suitable to set organic reaction in water that does not need any phase transfer catalyst to assist interactions between two phases.

The prepared catalyst was analyzed by transmission electron microscopy (TEM), scanning electron microscopy (SEM), energy dispersive X-ray analysis (EDXA), and inductively coupled plasma (ICP) to evaluate its morphology and behaviour, and estimate the catalytic efficiency (provided in the Supporting Information).

Catalytic properties

For this study, allylic carbonates derived from allylic alcohols were used as the active substrates for allylic substitution. The outset of the optimization study for the allylic substitution reactions was set by the reactions at temperatures above LCST of the polymer support, which showed productive results. However, the reaction progress was slow. Changing the reaction parameters including the catalyst loading and temperature affected the product yields, as shown in Table 1. Therefore, the combination of temperature, catalyst loading and appropriate base enhanced the catalysis to introduce C-C coupling of aryl and allylic units.

By applying the optimized conditions, allylic arylation of a variety of cinnamyl carbonates by different arylboronic acids was explored. Both of the reactants cinnamyl carbonates and arylboronic acids, irrespective of the attached electron withdrawing and electron donating substituents, showed active participation in the reaction with the sole product of 1,3-diaryl-1-propene, as shown in Table 2. An active antimicrobial agent obtusastyrene **3e**,[16] originally isolated from heartwood of *Dalbergia obtuse*,[17] was also successfully synthesized.

Recyclability. Another desirable quality of a heterogeneous catalyst is its ability to be recycled. The catalyst evaluated in this study showed remarkable recyclability with negligible leaching of palladium (approx. 20ppm as verified by ICP analysis) and product yields of 89-94%, as shown in Table 3. The schematic representation of the recyclability is shown in the Figure 3.

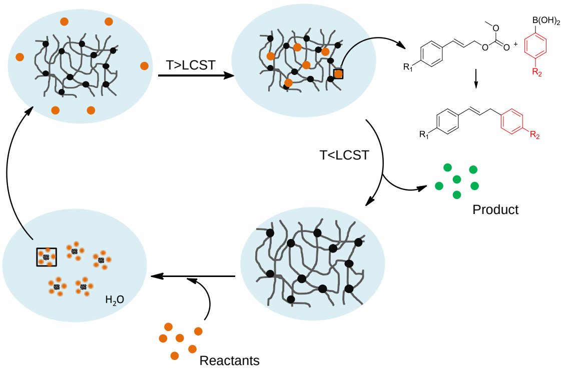
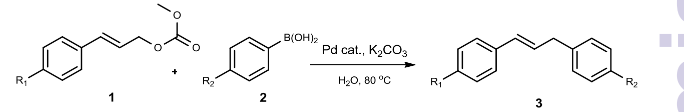
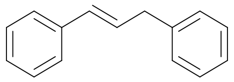
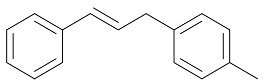
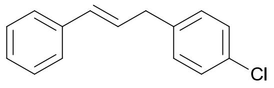
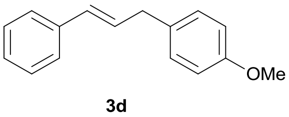
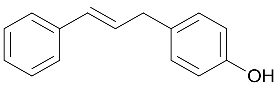
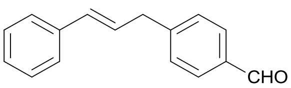
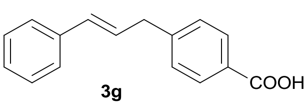
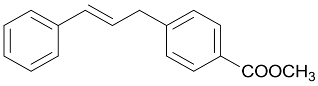
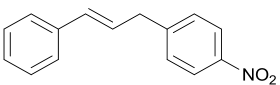
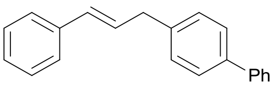
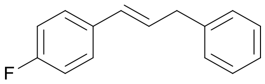
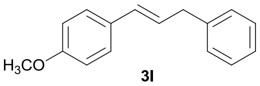


Figure 3 The schematic representation of recyclability.

Table 2 Scope of the allylic arylation of cinnamyl carbonate derivatives with arylboronic acids in water[a]

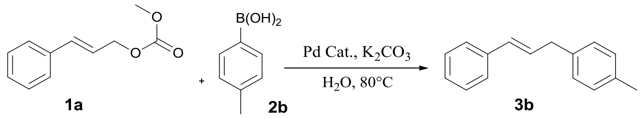


Entry	R_1 R_2	Product	Time (h)	Yield (%)[b]
1	**1a** (R_1 = H), **2a** (R_2 = H)	 **3a**	6	95
2	**1a** (R_1 = H), **2b** (R_2 = CH_3)	 **3b**	3	94
3	**1a** (R_1 = H), **2c** (R_2 = Cl)	 Cl **3c**	3	96

4	**1a** (R_1 = H), **2d** (R_2 = OCH_3)	 **3d**	9	91
5	**1a** (R_1 = H), **2e** (R_2 = OH)	 **3e**	9	92
6	**1a** (R_1 = H), **2f** (R_2 = CHO)	 **3f**	12	90
7	**1a** (R_1 = H), **2g** (R_2 = COOH)	 **3g**	20	86
8	**1a** (R_1 = H), **2h** (R_2 =$COOCH_3$)	 **3h**	24	86
9	**1a** (R_1 = H), **2**i (R_2 = NO_2)	 **3i**	24	84
10	**1a** (R_1 = H), **2j** (R_2 = Ph)	 **3j**	6	95
11	**1b** (R_1 = F), **2a** (R_2 = H)	 **3k**	10	93
12	**1c** (R_1 = OCH_3), **2a** (R_2 = H)	 **3l**	3	92

[a] Reaction conditions: Cinnamyl methyl carbonates (1, 0.5 mmol, 1.0 equiv.), arylboronic acids (2, 0.75 mmol, 1.5 equiv.), Pd catalyst (5 mol%, 0.271 g), K_2CO_3 (1.5 mmol, 3.0 equiv.), H_2O (2 mL). [b] Isolated yield

Table 3 Recycling tests for allylic arylation[a]



Run	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Yield[b]	94	94	93	92	92	91	90	90	90	89

[a] Reaction conditions: Cinnamyl methyl carbonate (0.5 mmol, 1.0 equiv.), 4-methylphenylboronic acid (0.75 mmol, 1.5 equiv.), Pd catalyst (5 mol%, 0.271 g), K_2CO_3 (1.5 mmol, 3.0 equiv.), H_2O (2 mL). [b] Isolated yield.

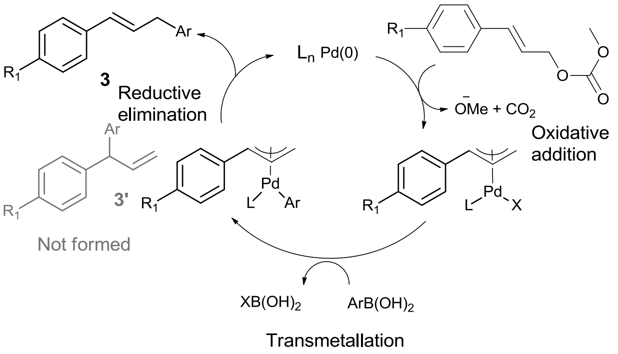


Figure 4 Presumed mechanism of the Tsuji-Trost reaction of cinnamyl carbonates and arylboronic acids.

A tentative mechanism is proposed in which the π-allylpalladium complex undergoes substitution with the nucleophilic aryl group from arylboronic acid. According to the mechanism, the addition of the aryl group can result in two regioisomers. However, steric preference led to the regioselective production of compound **3** (Figure 4).

Conclusions

We successfully demonstrated the allylic arylation of cinnamyl carbonates by Pd(0) nanoparticles supported on a thermoresponsive support under mild conditions in a water solvent. The steric effect of the aryl group helped to afford the least substituted regio-isomer. Moreover, the mild reaction conditions aided the tolerance of different functional groups on the aryl moieties. The eco-friendly solvent like water and recyclability of the catalyst are the noticeable features of this study.

Acknowledgements

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Table of Contents

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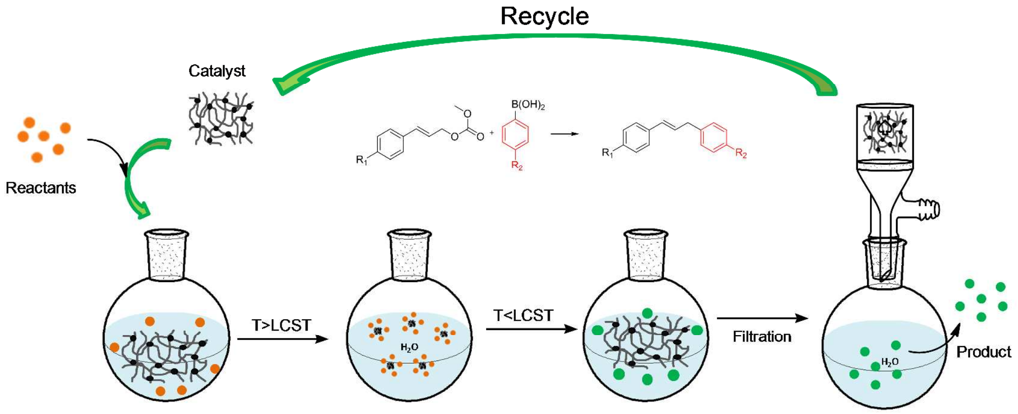

Palladium nanoparticles were supported on a thermoresponsive polymer and used as a catalyst for the allylic arylation of the cinnamyl carbonates in water.