# Green Chemistry

## PAPER

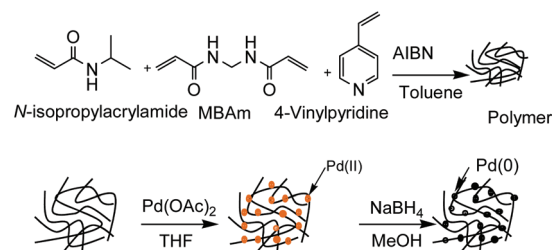CrossMark
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# Catalytic allylic arylation of cinnamyl carbonates over palladium nanoparticles supported on a thermoresponsive polymer in water†

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Poly(NIPAM-*co*-4-VP) undergoes a phase transition at the low critical solution temperature with a change from the hydrophilic to the hydrophobic core in a hydrophilic solvent. Palladium nanoparticles supported on such a 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 using 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 heterocycle synthesis[4] with good regio-, chemo-, and stereoselectivities.[5] Following this trend, heterogeneous palladium catalysts have excelled in organic synthesis compared to homogeneous catalysts due to their advantages including less contamination, the ease of separation, and recyclability. Recently, versatile materials such as carbon,[6] silica,[7] clay minerals[8] and polymers[9] have been used as supports for palladium. A 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 proven to be the active catalyst for allylic substitution in water or THF[12] but a thermoresponsive support

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

like poly(NIPAM-*co*-4-VP) could help in recycling the catalyst as well as participating in the reaction. Allylic substitution by Pd nanoparticles occurs smoothly but sometimes its scope is limited by the use of a stabilizer like TBAB.[13] Based on these studies and our work on 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(ıı) on hydrogels by shaking a dispersion of Pd(ıı) acetate and the polymer support in dry deoxygenated THF, followed by the reduction of Pd(ıı) by NaBH₄ in methanol,[15] as shown in Fig. 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(ıı), sodium borohydride, ethyl acetate, methanol,
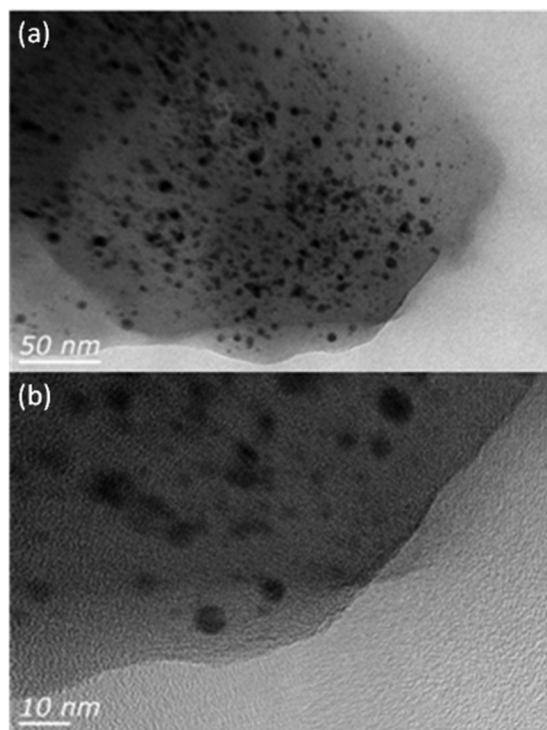
**Fig. 2** Transmission Electron Microscopy (TEM) images of the Pd(0) catalyst supported on poly(NIPAM-*co*-4-VP).

toluene and diethyl ether were used as received. 4-Vinylpyridine (4-VP, Aldrich 99%) was distilled under reduced pressure before use.

TEM and EDXA measurements were performed on a HRTEM JEOL electron microscope at an acceleration voltage of 300 kV (Fig. 2). The loading value of Pd(0) in the catalyst was estimated by ICP analysis with a JY Ultima 2C. ICP also helped in checking for leaching out after every recycle test. The low critical solution temperature (LCST) of the synthesized hydrogels was characterized by DSC measurements (TA Instrument, DSC 2010). All the hydrogels were immersed in a pH 10 buffer solution at room temperature for 24 h to reach the equilibrium state. The DSC analysis of the swollen hydrogels was performed from 0 °C to 60 °C at a heating rate of 2 °C min$^{-1}$ under a nitrogen atmosphere at a purge rate of 40 mL min$^{-1}$.

### 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 1 : 1 monomer feed ratio in toluene[11] that has the low critical solution temperature of 47 °C (DSC measurements).

**Coordination of Pd(0) catalyst on the 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 vacuo*. 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 the poly(*N*-isopropylacrylamide-*co*-4-VP) polymer with a loading value of 0.184 mmol Pd per g polymer (verified by ICP mass analysis).

### 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$_2$Cl$_2$ (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 $^1$H 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 cinnamyl methyl carbonate **1a** (0.192 g, 1.0 mmol), phenylboronic acid **1b** (0.183 g, 1.5 mmol), K$_2$CO$_3$ (0.414 g, 3.0 mmol), H$_2$O (2 mL), and a 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 $^1$H 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% yield of the product **3b** were demonstrated.

## Results and discussion

### Polymer behaviour and morphology

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

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 for setting an organic reaction in water that does not need any phase transfer catalyst to assist with 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) spectroscopy to evaluate its morphology and behaviour, and to estimate the catalytic efficiency (provided in the ESI†).

## 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 an 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 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 1,3-diaryl-1-propene, as shown in Table 2. An active antimicrobial agent
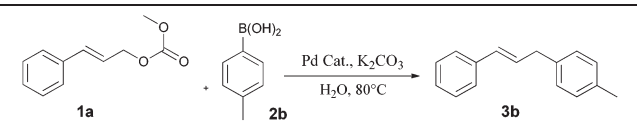
**Table 1** Optimization study results for the allylic substitution of carbonates[a]



| Entry | Pd Cat. (mol%) | Base (equiv.) | Temp. (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 5 | — | 80 | 6 | 78 |
| 2 | 5 | Et$_3$N (3) | 80 | 6 | 72 |
| 3 | 5 | K$_2$CO$_3$ (1) | 80 | 6 | 86 |
| 4 | 5 | K$_2$CO$_3$ (2) | 80 | 6 | 85 |
| 5 | 5 | KF (2) | 80 | 6 | 83 |
| 6 | 5 | KF (3) | 80 | 6 | 94 |
| 7 | 1 | K$_2$CO$_3$ (3) | 60 | 24 | 77 |
| 8 | 5 | K$_2$CO$_3$ (3) | 60 | 18 | 86 |
| 9 | 10 | K$_2$CO$_3$ (3) | 60 | 12 | 84 |
| 10 | 1 | K$_2$CO$_3$ (3) | 80 | 8 | 94 |
| 11 | 5 | K$_2$CO$_3$ (3) | 80 | 6 | 95 |
| 12 | 10 | K$_2$CO$_3$ (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$_2$O (2 mL). [b] Isolated yield.

**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) | 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) **2i** (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$_2$CO$_3$ (1.5 mmol, 3.0 equiv.), H$_2$O (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.
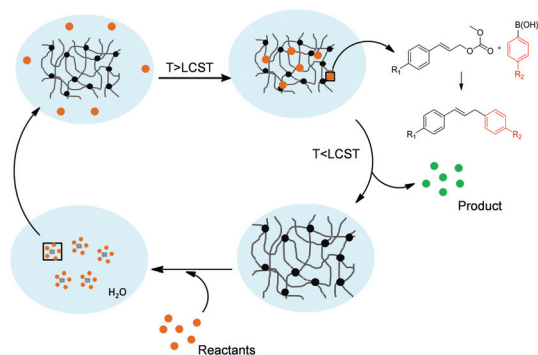


**Fig. 3** The schematic representation of recyclability.

obtusastyrene **3e**,[16] originally isolated from heartwood of *Dalbergia obtusa*,[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. 20 ppm 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 Fig. 3.

A tentative mechanism is proposed in which the π-allyl-palladium 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** (Fig. 4).

## Conclusions

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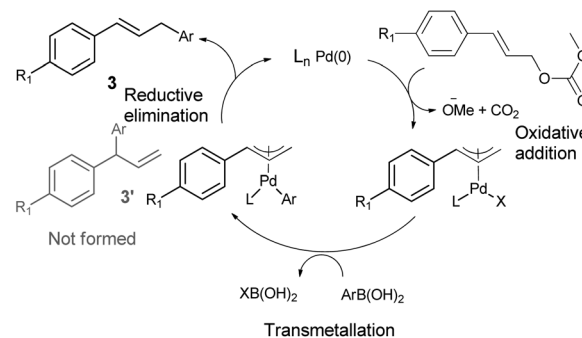


**Fig. 4** Presumed mechanism of the Tsuji–Trost reaction of cinnamyl carbonates and arylboronic acids.

## Acknowledgements

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