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Stereospecific Allyl–Aryl Coupling Catalyzed by *in situ* Generated Palladium Nanoparticles in Water under Ambient Conditions

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Abstract: A practical process for the stereospecific cross-coupling of secondary allylic carbonates with arylboronic acids has been developed. The reaction is catalyzed by *in situ* generated palladium nanoparticles (PdNPs) without any ligands and additional stabilizers in water under ambient conditions and furnishes the allyl–aryl coupling products in high isolated yields with high stereospecificities as well as excellent chemo-, regio- and *E*/*Z*-selectivities. The *in situ* generated PdNPs showed extraordinary catalytic activity (S/C up to 5000) even for the allyl–aryl coupling reactions of easily eliminated allylic carbonates under aqueous ambient conditions. The mechanism of the process has also been investigated.

Keywords: allyl–aryl coupling; asymmetric synthesis; cross-coupling; palladium nanoparticles; stereospecificity

Introduction

The Suzuki–Miyaura coupling has emerged as one of the most versatile transformations for C–C bond formation.[1] While the coupling reaction has most often been applied to sp^2-hybridized halides and pseudohalides, significant progress toward extending the coupling method to secondary sp^3-electrophiles has been achieved using Ni catalysts since the ground-breaking work by Fu in 2004.[2,3] Pd is the primarily used catalyst for the cross-coupling reaction, and yet it is not effective for the coupling reaction of secondary alkyl electrophiles due to the high energy barrier of the oxidative addition.[4,5] In contrast, secondary allylic alcohol derivatives are expected to be applicable as electrophiles for the coupling reaction because Pd can be readily oxidized with allylic partners forming allylpalladium intermediates.[6] However, the protocols for the coupling reaction of secondary and potentially enantiomerically enriched allylic electrophiles are surprisingly less explored, mainly due to the propensity for allylpalladium intermediates to undergo β-hydride elimination delivering the conjugated diene.[7] Nevertheless, pioneering work by Uozumi and Hayashi,[8] as well as the most recent efforts by Uozumi and Yamada,[9] Tian,[10] and our group,[11] respectively, demonstrated the feasibility of the Pd-catalyzed Suzuki–Miyaura coupling of secondary allylic electrophiles with arylboronic acids. The method also offered a possibility to conduct the stereoselective allyl–aryl coupling through the stereospecific cross-coupling of chiral secondary allylic electrophiles.[10,11,12] Whereas the stereospecificity of the coupling reaction is largely affected by the ligand, and some issues, such as higher catalyst loading, requirement of achiral ligand, and/or high reaction temperature, need to improve for practical use of the process in asymmetric synthesis.

In recent years amelioration of the cross-coupling reaction has been directed towards the more efficient, economic and greener techniques.[13] Since the first report of ligand-free Pd-catalyzed Suzuki–Miyaura coupling by Beletskaya,[14] simple Pd salts such as $PdCl_2$ or $Pd(OAc)_2$ in the absence of phosphane ligands are increasingly being used in Suzuki–Miyaura aryl–aryl couplings.[15] The mechanism studies by Reetz and de Vries demonstrated that the Pd salts indeed decompose to give palladium nanoparticles (PdNPs) at high temperature, and the catalysis takes place on the surface of PdNPs.[16] Indeed, PdNPs-catalyzed cross-coupling reactions have recently attracted great attention due to their high catalytic activity and the fact of allowing for ligand-free synthesis.[17] However, PdNPs are generally prepared by complicated processes and additional stabilizers are required in

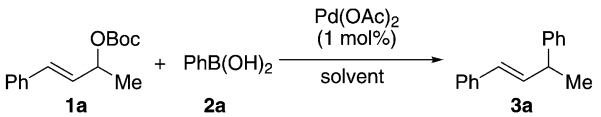
order to prevent the formation of Pd black precipitates, as well as the fact that the reactions typically need to be performed at high temperature.[18]

Given that great efforts in the development of greener process for Suzuki–Miyaura aryl–aryl couplings, we recently questioned whether the stereospecific allyl–aryl coupling could also be addressed with PdNPs as catalyst without phosphane ligands using chiral secondary allylic electrophiles. Indeed, chiral secondary allylic alcohols are readily accessible by the numerous approaches that have been reported for the asymmetric synthesis of optically active secondary allylic alcohols, such as the addition of vinyl-metal reagents to aldehydes,[19] ketone reduction,[20] allylic substitution of primary allylic carbonates,[21] Sharpless kinetic resolution,[22] and lipase resolution.[23] In this paper, we report the successful execution of these ideals and present a practical method for the stereospecific allyl–aryl coupling of secondary allylic carbonates with arylboronic acids catalyzed by *in situ* generated PdNPs without any ligands and additional stabilizers in water at ambient temperature. Although there are a few reports on asymmetric reactions catalyzed by metal NPs with chiral ligands as stabilizers,[24] to the best of our knowledge, this is the first example of a stereospecific reaction catalyzed by metal NPs. Furthermore, we have expanded the substrate scope to more challenging secondary allylic carbonates with 1-benzyl, allyl or carbonylmethyl groups, which are largely unexplored allylic partners even for the allylic substitution reaction, coupling them with arylboronic acids to furnish allyl–aryl coupling products in high yields with complete chemo- and regioselectivities.

Results and Discussion

As in our previous report,[11] the coupling reaction of allylic carbonate **1a** with phenylboronic acid (**2a**) proceeded well in the presence of $Pd(OAc)_2$ and PPh_3 in wet THF at 50 °C giving coupling product **3a** in 87% yield with excellent selectivities (Table 1, entry 1). However, under otherwise identical conditions but at ambient temperature, the reaction did not work at all (entry 2). In contrast, the reaction proceeded in the absence of phosphane ligand giving the allyl–aryl coupling product **3a** in 33% conversion (entry 3). Surprisingly, with the replacement of wet THF solvent by pure water, the substrates were completely converted to the coupling product **3a** in 99% isolated yield using 1 mol% of $Pd(OAc)_2$ as a catalyst at ambient temperature for 4 h (entry 4). Nevertheless, when the reactions were carried out in organic solvents such as THF and MeOH, low conversions were observed (entries 5 and 6). Next, we examined the allyl–aryl coupling reaction of enantiomerically enriched allylic carbonate (*S*)-**1a** (97% *ee*) with phenylboronic acid (**2a**)

Table 1. Allyl–aryl coupling of allylic carbonate **1a** with phenylboronic acid (**2a**).[a]



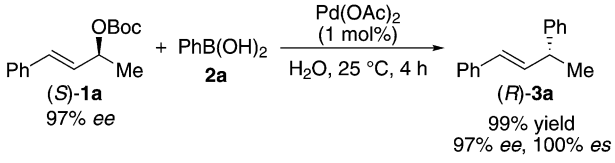
1a 2a 3a

Entry	Ligand	Solvent	*T* [°C]/ *t* [h]	Conv. [%][b]	Yield [%][c]
1	PPh_3	THF/H_2O[d]	50/24	100	87
2	PPh_3	THF/H_2O[d]	25/4	0	–
3	–	THF/H_2O[d]	25/4	33	–
4	–	H_2O	25/4	100	99
5	–	THF	25/4	16	–
6	–	MeOH	25/4	50	–

[a] *Reaction conditions:* $Pd(OAc)_2$ (1 mol%), PPh_3 (2 mol%) **1a** (0.50 mmol), **2a** (0.75 mmol), solvent (0.5 mL).
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] The yields are of isolated material.
[d] Using 5 equiv. of water to **1a**.

in the presence of 1 mol% of $Pd(OAc)_2$ in water at ambient temperature. Gratifyingly, the reaction furnished allyl–aryl coupling product **3a** in quantitative yield with complete enantiospecificity with inversion of the absolute configuration, and no *E*/*Z* isomerization and β-H elimination were observed (Scheme 1).

Interestingly, we found that the reaction mixture turned black after a few minutes. Based on general knowledge, if the Pd black forms in the early stage of the reaction, the reaction usually stops before full conversion. In order to recognize the real catalytic species and mechanism, we tried to monitor the reaction by transmission electron microscopy (TEM). Firstly, the sample was made by mixing $Pd(OAc)_2$ (5 μmol) and phenylboronic acid (0.75 mmol) in water (0.5 mL) and the mixture was stirred for 5 min at ambient temperature. The TEM analysis indicated that PdNPs were generated and dispersed well with an average particle size of 2.6 nm[25] (Figure 1a). We also found that the reaction gave a trace amount of biphenyl as determined by ^1H NMR. These results demonstrated that $Pd(OAc)_2$ was reduced to form PdNPs by homo-coupling of phenylboronic acid,[26] and the PdNPs are likely stabilized by phenylboronic acid.[27] For further investigation of the catalytic behavior, the standard coupling reaction of **1a** with **2a** in water was monitored by TEM. Remarkably, the average particle



Scheme 1. Stereospecific allyl–aryl coupling catalyzed by $Pd(OAc)_2$ in water under ambient temperature.

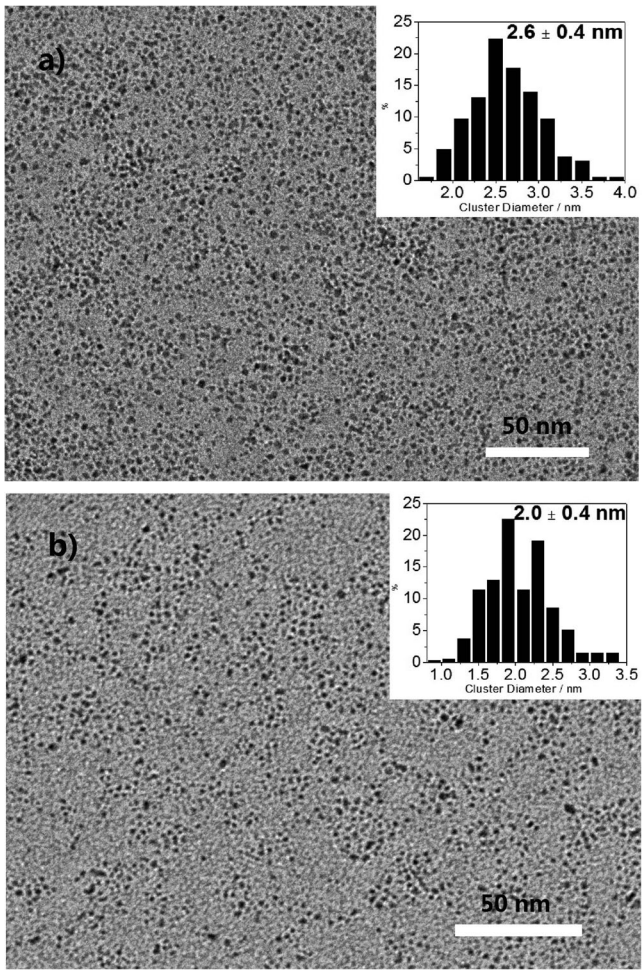


Figure 1. TEM image of PdNPs. **a**) A sample of PdNPs formed by mixing of $Pd(OAc)_2$ and phenylboronic acid (**2a**) in water. **b**) A sample of PdNPs after full conversion of the coupling reaction of **1a** with **2a** (2 h).

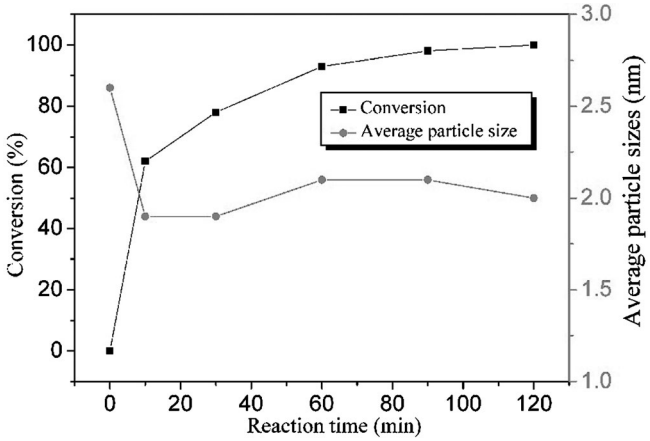


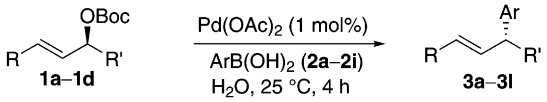
Figure 2. Plot of the conversion and the average particle size of PdNPs *vs.* reaction time for the coupling reaction of **1a** with **2a**.

size was reduced to 1.9 nm after the reaction had been carried out for 10 min[28] and the average size of PdNPs remained in the range of 1.9 to 2.1 nm until full conversion of the reaction after 2 h, and no Pd black was observed (Figure 1b and Figure 2). The size decreases maybe due to the fact that Pd atoms leach from Pd clusters during the oxidative addition to release active π-allylPd(II) species and that PdNPs are reaggregated after the reductive elimination.[29] In addition, in the kinetic study for the coupling reaction (Figure 2), the reaction showed extremely high catalytic activity in initial stage giving 62% conversion in just 10 min. These results indicate that the highly reactive leached Pd species might be the real catalytic species. In order to get more evidences for this hypothesis, we tried to monitor the reaction by ^{1}H NMR using D_2O as a solvent, however, no peaks for the starting material **1a**, the coupling product **3a** and any intermediates were observed because allylic carbonate **1a** and product **3a** are not soluble in water. Stoichiometric studies were performed by mixing PdNPs *in situ* generated from $Pd(OAc)_2$ and phenylboronic acid, and allylic carbonate **1a** in CD_3OD. However, by ^{1}H NMR monitoring of the reaction, a π-allylpalladium species was not observed, perhaps because the intermediate is very unstable.

With the mechanism insight in hand, the PdNPs-catalyzed allyl–aryl coupling reaction was applied to various combinations of chiral allylic carbonates **1a**–**1d** and arylboronic acids **2a**–**2i** in water at ambient temperature. As illustrated in Table 2, all of the reactions gave allyl–aryl coupling products **3a**–**3k** in high yields with complete regioselectivities and excellent enantiospecificities (95–100% *es*) with inversion of the absolute configurations, and no *E*/*Z* isomerizations and β-H eliminations were observed. The reaction can tolerate sterically hindered arylboronic acids such as **2b** and **2i** to furnish the products in high yields and excellent selectivities. The reaction with arylboronic acids containing electron-withdrawing groups gave slightly lower yields in comparison with those containing electron-donating groups (**3c** and **3d** *vs.* **3e**, **3f** and **3g**). The reaction of aliphatic allylic carbonate **1d** with phenylboronic acid (**2a**) provided coupling product **3l** in moderate yield with complete regio- and *E*/*Z* selectivities and stereospecificity.

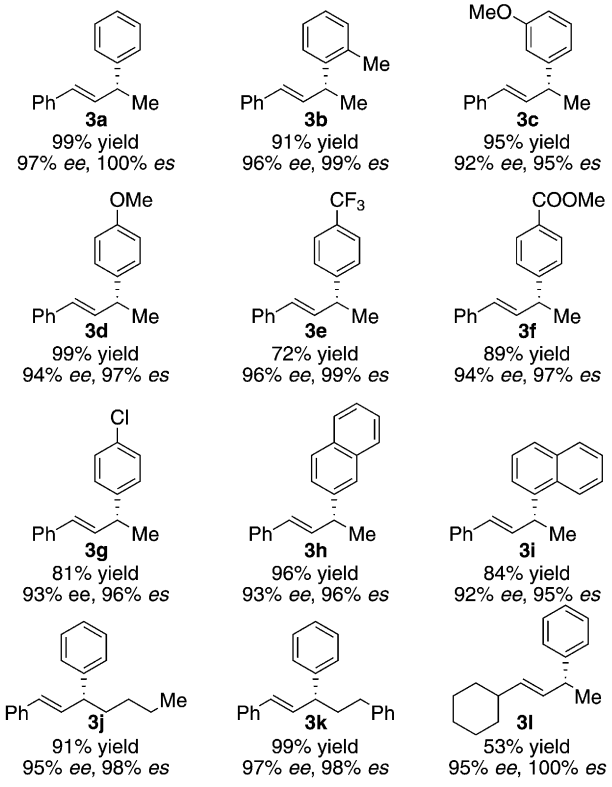
In order to further examine the regioselectivity of the coupling reaction, the reaction conditions were applied to the aliphatic allylic carbonates **1e** and **1f** (Scheme 2). The coupling reaction of the sterically less differentiated, 1-(2-phenyl)ethyl 3-methylallylic carbonate **1e** with phenylboronic acid (**2a**) gave a mixture of the two regioisomers of **3m** and **4a** with a ratio of 42:58 in 73% yield. The reaction of 1-(2-phenyl)-ethyl allylic carbonate **1f** with **2a** afforded linear product **4b** as a major product. These results indicate that the regioselectivity of the allyl–aryl coupling re-

Table 2. Stereospecific allyl–aryl coupling of allylic carbonates with arylboronic acids catalyzed by *in situ* generated PdNPs.[a]



1a, R = Ph, R' = Me, 97% *ee*
1b, R = Ph, R' = *n*-Bu, 97% *ee*
1c, R = Ph, R' = CH_2CH_2Ph, 99% *ee*
1d, R = cyclohexyl, R' = Me, 95% *ee*

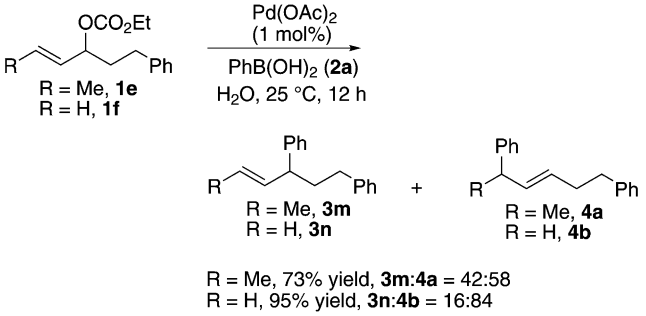
2a, Ar = Ph
2b, Ar = 2-Me-C_6H_4
2c, Ar = 3-MeO-C_6H_4
2d, Ar = 4-MeO-C_6H_4
2e, Ar = 4-CF_3-C_6H_4
2f, Ar = 4-MeO_2C-C_6H_4
2g, Ar = 4-Cl-C_6H_4
2h, Ar = 2-naphthyl
2i, Ar = 1-naphthyl



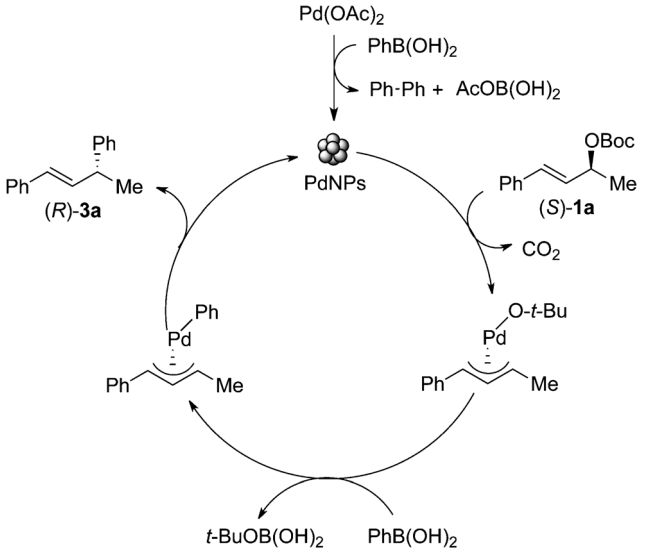
[a] *Reaction conditions:* $Pd(OAc)_2$ (1 mol%), **1** (0.50 mmol), **2** (0.75 mmol), water (0.5 mL), 25 °C, 4 h. The yields are of isolated material. The enantiomeric excesses were determined by chiral HPLC analysis. The absolute configurations were determined by comparing the sign of the optical rotation with reported values.[10,11,30] Enantiospecificity $(es) = ee_{product}/ee_{substrate} \times 100\%$. All of the reactions gave coupling products with complete chemo-, regio- and *E*/*Z*-selectivities.

action is controlled by the steric differences of the 1- and 3-substituents of the allylic carbonates.

Based on these studies, a mechanism and stereochemical mode of the coupling reaction could be proposed as shown in Scheme 3. The active π-allylpalladium species is formed *via* leaching from PdNPs by the oxidative addition to chiral allylic carbonate (*S*)-



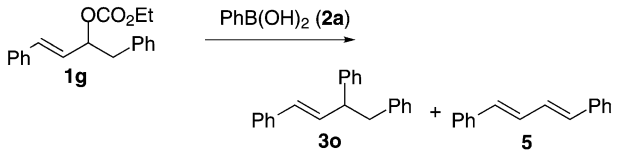
Scheme 2. PdNPs-catalyzed allyl–aryl coupling of allylic carbonates **1e** and **1f** with **2a**.



Scheme 3. Proposed reaction mechanism.

1a from the back side stereospecifically. The active Pd species subsequently takes part in a transmatalation with phenylboronic acid, and reductive elimination occurs at the sterically less hindered side of the π-allylpalladium complex to furnish the inversed allyl–aryl coupling product (*R*)-**3a** with complete regioselectivity and stereospecificity. The released Pd(0) species is reaggregated to form PdNPs. Water plays a significant role for the acceleration of the transmetalation step.[1] The coupling reaction is likely to occur at the interface of the organic substrate and water, the released boronic acid monobutoxide dissolves in water and plays a role for the stabilization of PdNPs.

The success of the highly selective allyl–aryl coupling reaction catalyzed by *in situ* generated PdNPs in water under ambient temperature prompted us to examine the coupling reaction of more challenging substrates such as 1-benzyl-3-phenylallylic carbonate **1g**, which is a largely unexplored substrate even for the allylic substitution reaction. The main reason likely is that its π-allylpalladium complex greatly tends to undergo β-hydride elimination to form highly conjugat-



With previous conditions:[11]
$Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), wet THF, 50 °C, 24 h
100% conversion, **3o**:**5** = 29:71
With conditions in this work:
$Pd(OAc)_2$ (1 mol%), H_2O, 25 °C, 12 h
99% isolated yield of **3o**
100% chemo-, regio- and *E*/*Z* selectivities

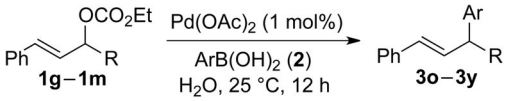
Scheme 4. PdNPs-catalyzed chemo- and regioselective allyl–aryl coupling of **1g** with **2a**.

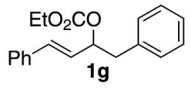
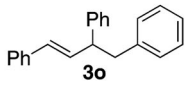
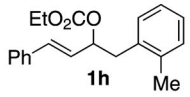
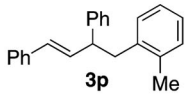
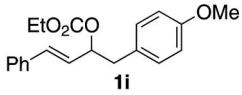
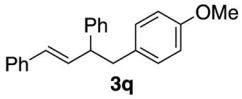
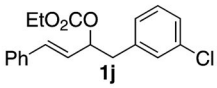
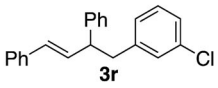
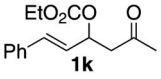
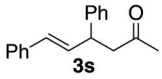
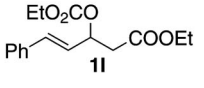
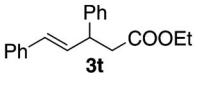
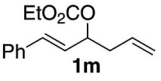
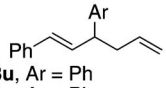
ed 1,4-diphenyl-1,3-butadiene (**5**). As shown in Scheme 4, with our previously reported reaction conditions,[11] the reaction with $Pd(OAc)_2$ and PPh_3 in wet THF at 50 °C for 24 h afforded the eliminated 1,3-butadiene **5** as a major product as determined by ^1H NMR of the crude reaction mixture. Remarkably, the reaction of allylic carbonate **1g** with phenylboronic acid (**2a**) under our PdNPs-catalyzed reaction conditions gave allyl–aryl coupling product **3o** in 99% isolated yield with complete regio- and *E*/*Z*-selectivities, and no 1,3-diene **5** was observed.

For further investigation on the scope of this type of substrates for the coupling reaction, various substrates were synthesized and applied to the allyl–aryl coupling reaction. As shown in Table 3, the reaction of allylic carbonates **1g**–**1j** with 1-benzyl groups with different substituents on the phenyl ring with phenylboronic acid (**2a**) in the presence of 1 mol% of $Pd(OAc)_2$ in water under ambient temperature for 12 h[31] proceeded with full conversion to the corresponding allyl–aryl coupling products in quantitative yields with complete chemo-, regio- and *E*/*Z* selectivities (entries 1–4). The reaction of 1-carbonylmethyl allylic carbonates **1k** and **1l**, which also readily undergo β-hydride elimination to form α,β,γ,δ-conjugated carbonyl compounds, still worked well giving allyl–aryl coupling products in high yields with excellent chemo-, regio- and *E*/*Z*-selectivities[32] (entries 5 and 6). Finally, we examined the coupling reaction of 1-allyl-3-phenylallylic carbonate **1m** with arylboronic acids. Under the standard reaction conditions, the reaction with **2a** afforded the allyl–aryl coupling product **3u** in almost quantitative yield (entry 7). The reaction still proceeded well when the catalyst loading was reduced to 0.1 mol% (entry 8). When further reducing the catalyst loading to 0.02 mol% (S/C = 5000), the reaction gave coupling product **3u** in 79% yield with complete selectivities within 72 h (entry 9). The reactions of allylic carbonate **1m** were efficiently performed with arylboronic acids exhibiting different steric and electronic properties giving allyl–aryl coupling products **3v**–**3y** in high yields with complete chemo-, regio- and *E*/*Z*-selectivities (entries 10–13). These results demonstrated that this aqueous PdNPs-catalyzed process is an extraordinarily active catalytic system for the allyl–aryl coupling reaction. Notably, these are the first efficient examples for the reaction of the easily eliminated substrates as allylic partners.

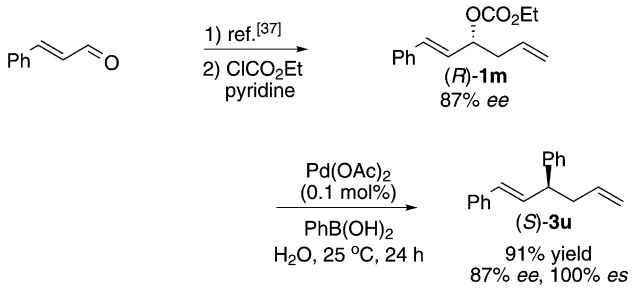
The efficiency for the allyl–aryl coupling reaction of the easily eliminated substrates prompted asymmetric synthesis of 1,5-diene using this method of the stereospecific allyl–aryl coupling of enantiomerically

Table 3. Allyl–aryl coupling of easily eliminated allylic carbonates with arylboronic acids catalyzed by *in situ* generated PdNPs.[a]



Entry	Allylic carbonate (**1**)	Product (**3**)	Yield [%][b]
1	 **1g**	 **3o**	99
2	 **1h**	 **3p**	99
3	 **1i**	 **3q**	99
4	 **1j**	 **3r**	99
5	 **1k**	 **3s**	88
6	 **1l**	 **3t**	84
7	 **1m**	 **3u**, Ar = Ph	98
8		**3u**, Ar = Ph	90[c]
9		**3u**, Ar = Ph	79[d]
10		**3v**, Ar = 3-MeO-C_6H_4	93
11		**3w**, Ar = 4-MeOOC-C_6H_4	85
12		**3x**, Ar = 1-naphthyl	94
13		**3y**, Ar = 2-naphthyl	96

[a] *Reaction conditions:* $Pd(OAc)_2$ (1 mol%), **1** (0.50 mmol), **2** (0.75 mmol), water (1.0 mL), 25 °C, 12 h.
[b] The yields are of isolated material.
[c] The reaction was carried out in the presence of 0.1 mol% of $Pd(OAc)_2$ in water (0.5 M) at ambient temperature for 24 h.
[d] The reaction was carried out in the presence of 0.02 mol% of $Pd(OAc)_2$ in water (0.5 M) at ambient temperature for 72 h.



Scheme 5. Asymmetric synthesis of 1,5-diene (*S*)-**3u**.

enriched **1m**. 1,5-Dienes are abundant in naturally occurring terpenes,[33] and these compounds have been proved to be highly versatile intermediates and synthetic building blocks.[34] Although there are some approaches for the preparation of 1,5-dienes,[35] the asymmetric synthesis of chiral 1,5-dienes has been achieved in recent years by the asymmetric allyl–allyl coupling reaction.[36] As illustrated in Scheme 5, the chiral 1-allyl-3-phenylallylic alcohol was readily synthesized by Krische's Ir-catalyzed transfer hydrogenative carbonyl allylation method,[37] and subsequently underwent carbonation with ethyl chloroformate to afford enantiomerically enriched allyl carbonate (*R*)-**1m** with 87% *ee*. The reaction of (*R*)-**1m** with phenylboronic acid (**2a**) in the presence of 0.1 mol% of $Pd(OAc)_2$ in water under ambient temperature for 24 h afforded chiral 1,5-diene (*S*)-**3u** in 91% yield with complete stereospecificity.

Conclusions

In conclusion, we have developed an efficient method for the highly selective and stereospecific allyl–aryl coupling of secondary allylic carbonates with arylboronic acids catalyzed by *in situ* generated PdNPs without any ligands and additional stabilizers in water at ambient temperature. The *in situ* generated PdNPs showed extraordinary catalytic activity even for the coupling reaction of easily eliminated allylic carbonates under aqueous ambient conditions. The mechanism of the process was investigated by TEM and kinetic studies. We believe that this study provides a new aspect of the practical process for asymmetric synthesis. Further studies will focus on gaining a better understanding of the reaction mechanism.

Experimental Section

General Procedure for the Allyl–Aryl Coupling

To 10-mL Schlenck flask equipped with a stir bar, was added $Pd(OAc)_2$ (0.005 mmol), **1** (0.5 mmol), **2** (0.75 mmol), H_2O (0.5 mL or 1 mL). The mixture was stirred at 25 °C for 4 or 12 h. Then the mixture was extracted with CH_2Cl_2 (2.0 mL × 4). The organic layer was dried over Na_2SO_4, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate: petroleum ether, 1:100–500) to furnish corresponding allyl-aryl coupling products.

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References

[1] a) A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854; *Angew. Chem. Int. Ed.* **2011**, *50*, 6722; b) G. A. Molander, B. Canturk, *Angew. Chem.* **2009**, *121*, 9404; *Angew. Chem. Int. Ed.* **2009**, *48*, 9240; c) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11; d) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[2] J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 1340.
[3] For a review of the cross-coupling of secondary alkyl electrophiles, see: A. Rudolph, M. Lautens, *Angew. Chem.* **2009**, *121*, 2694; *Angew. Chem. Int. Ed.* **2009**, *48*, 2656.
[4] I. D. Hills, M. R. Netherton, G. C. Fu, *Angew. Chem.* **2003**, *115*, 5927; *Angew. Chem. Int. Ed.* **2003**, *42*, 5749.
[5] For examples of the Pd-catalyzed Suzuki–Miyaura coupling of activated secondary alkyl electrophiles, see: a) A. Hu, J. R. Falck, *J. Am. Chem. Soc.* **2010**, *132*, 2524; b) N. Rodríguez, C. R. de Arellano, G. Asensio, M. Medio-Simón, *Chem. Eur. J.* **2007**, *13*, 4223.
[6] a) S. Norsikian, C.-W. Chang, *Curr. Org. Synth.* **2009**, *6*, 264; b) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395.
[7] a) H. Tsukamoto, T. Uchiyama, T. Suzuki, Y. Kondo, *Org. Biomol. Chem.* **2008**, *6*, 3005; b) D. Bouyssi, V. Gerusz, G. Balme, *Eur. J. Org. Chem.* **2002**, 2445; c) H. Chen, M.-Z. Deng, *J. Organomet. Chem.* **2000**, *603*, 189; d) Y. Kobayashi, R. Mizojiri, E. Ikeda, *J. Org. Chem.* **1996**, *61*, 5391; e) J. Tsuji, T. Yamakawa, M. Kaito, T. Mandai, *Tetrahedron Lett.* **1978**, 2075.
[8] Y. Uozumi, H. Danjo, T. Hayashi, *J. Org. Chem.* **1999**, *64*, 3384.
[9] a) Y. M. A. Yamada, S. M. Sarkar, Y. Uozumi, *J. Am. Chem. Soc.* **2012**, *134*, 3190; b) S. M. Sarkar, Y. Uozumi, Y. M. A. Yamada, *Angew. Chem.* **2011**, *123*, 9609; *Angew. Chem. Int. Ed.* **2011**, *50*, 9437.
[10] M.-B. Li, Y. Wang, S.-K. Tian, *Angew. Chem.* **2012**, *124*, 3022; *Angew. Chem. Int. Ed.* **2012**, *51*, 2968.
[11] C. Li, J. Xing, J. Zhao, P. Huynh, W. Zhang, P. Jiang, Y. J. Zhang, *Org. Lett.* **2012**, *14*, 390.
[12] For Pd(II)-catalyzed γ-selective stereospecific cross-coupling of chiral secondary allylic acetates with arylboronic acids, see: a) Y. Makida, H. Ohmiya, M. Sawa-

mura, *Chem. Asian J.* **2011**, *6*, 410; b) D. Li, T. Tanaka, H. Ohmiya, M. Sawamura, *Org. Lett.* **2010**, *12*, 3344; c) H. Ohmiya, Y. Makida, D. Li, M. Tanabe, M. Sawamura, *J. Am. Chem. Soc.* **2010**, *132*, 879; d) H. Ohmiya, Y. Makida, T. Tanaka, M. Sawamura, *J. Am. Chem. Soc.* **2008**, *130*, 17276.

[13] For selected recent reviews, see: a) Á. Molnár, *Chem. Rev.* **2011**, *111*, 2251; b) V. Polshettiwar, A. Decottignies, C. Len, A. Fihri, *ChemSusChem* **2010**, *3*, 502; c) B. H. Lipshutz, A. R. Abela, Z. V. Boskovic, T. Nishikata, C. Duplais, A. Krasovskiy, *Top. Catal.* **2010**, *53*, 985; d) B. H. Lipshutz, S. Ghorai, *Aldrichimica Acta* **2008**, *41*, 59; e) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133.

[14] N. A. Bumagin, V. V. Bykov, I. P. Beletskaya, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1989**, *38*, 2206.

[15] For selected recent examples, see: a) J. Qiu, L. Wang, M. Liu, Q. Shen, J. Tang, *Tetrahedron Lett.* **2011**, *52*, 6489; b) C. Liu, Q. Ni, F. Bao, J. Qiu, *Green Chem.* **2011**, *13*, 1260; c) W.-J. Zhou, K.-H. Wang, J.-X. Wang, Z.-R. Gao, *Tetrahedron* **2010**, *66*, 7633; d) B. Basu, K. Biswas, S. Kundu, S. Ghosh, *Green Chem.* **2010**, *12*, 1734; e) A. Del Zotto, F. Amoroso, W. Baratta, P. Rigo, *Eur. J. Org. Chem.* **2009**, 110–116.

[16] a) J. G. de Vries, *Dalton Trans.* **2006**, 421; b) M. T. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559; c) A. Alimardanov, L. Schmieder-van de Vondervoort, A. H. M. de Vries, J. G. de Vries, *Adv. Synth. Catal.* **2004**, *346*, 1812; d) J. G. de Vries, A. H. M. de Vries, *Eur. J. Org. Chem.* **2003**, 799; e) M. T. Reetz, E. Westermann, *Angew. Chem.* **2000**, *112*, 170; *Angew. Chem. Int. Ed.* **2000**, *39*, 165.

[17] For selected recent reviews on Pd nanocatalysis for the cross-coupling reaction, see: a) M. Pérez-Lorenzo, *J. Phys. Chem. Lett.* **2012**, *3*, 167; b) A. Fihri, M. Bouhrara, B. Nekoueishahraki, J.-M. Basset, V. Polshettiwar, *Chem. Soc. Rev.* **2011**, *40*, 5181; c) A. Balanta, C. Godard, C. Claver, *Chem. Soc. Rev.* **2011**, *40*, 4973; d) R. Narayanan, C. Tabor, M. A. El-Sayed, *Top. Catal.* **2008**, *48*, 60; e) J. Durand, E. Teuma, M. Gómez, *Eur. J. Inorg. Chem.* **2008**, 3577; f) D. Astruc, *Inorg. Chem.* **2007**, *46*, 1884; g) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609.

[18] For PdNPs-catalyzed Suzuki–Miyaura couplings under ambient temperature, see: a) Z. Du, W. Zhou, F. Wang, J.-X. Wang, *Tetrahedron* **2011**, *67*, 4914; b) W. Han, C. Liu, Z. Jin, *Adv. Synth. Catal.* **2008**, *350*, 501; c) A. K. Diallo, C. Ornelas, L. Salmon, J. R. Aranzaes, D. Astruc. *Angew. Chem.* **2007**, *119*, 8798; *Angew. Chem. Int. Ed.* **2007**, *46*, 8644; d) R. Tatumi, T. Akita, H. Fujihara, *Chem. Commun.* **2006**, 3349; e) F. Lu, J. Ruiz, D. Astruc, *Tetrahedron Lett.* **2004**, *45*, 9443.

[19] a) I. Sato, N. Asakura, T. Iwashita, *Tetrahedron: Asymmetry* **2007**, *18*, 2638; b) D. Tomita, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4138; c) J. L. von dem Bussche-Hünnefeld, D. Seebach, *Tetrahedron* **1992**, *48*, 5719; d) W. Oppolzer, R. N. Radinov, *Tetrahedron Lett.* **1988**, *29*, 5645.

[20] N. Arai, K. Azuma, N. Nii, T. Ohkuma, *Angew. Chem.* **2008**, *120*, 7567; *Angew. Chem. Int. Ed.* **2008**, *47*, 7457.

[21] I. Lyothier, C. Defieber, E. M. Carreira, *Angew. Chem.* **2006**, *118*, 6350; *Angew. Chem. Int. Ed.* **2006**, *45*, 6204.

[22] P. R. Carlier, W. S. Mungall, G. Sohröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 2978.

[23] a) K. Bogar, P. H. Vidal, A. R. A. Leon, J.-E. Backvall, *Org. Lett.* **2007**, *9*, 3401; b) A. Ghamen, H. Y. Aboul-Enein, *Tetrahedron: Asymmetry* **2004**, *15*, 3331; c) K. Faber, *Biotransformations in Organic Chemistry*, 5th edn., Springer, Berlin, **2004**; d) K. Drauz, H. Waldmann, *Enzyme Catalysis in Organic Synthesis*, Wiley-VCH, Weinheim, **1995**; e) C.-H. Wong, G. M. Whitesides, *Enzymes in Organic Chemistry*, Pergamon, Oxford, **1994**.

[24] a) K. Sawai, R. Tatumi, T. Nakahodo, H. Fujihara, *Angew. Chem.* **2008**, *120*, 7023; *Angew. Chem. Int. Ed.* **2008**, *47*, 6917; b) D. Han, X. Li, H. Zhang, Z. Liu, G. Hu, C. Li, *J. Mol. Catal. A* **2008**, *283*, 15; c) I. Favier, M. Gomez, G. Muller, M. R. Axet, S. Castillon, C. Claver, S. Jansat, B. Chaudret, K. Philippot, *Adv. Synth. Catal.* **2007**, *349*, 2459; d) S. Jansat, D. Picurelli, K. Pelzer, K. Philippot, M. Gomez, G. Muller, P. Lecante, B. Chaudret, *New J. Chem.* **2006**, *30*, 115; e) G. Szollosi, A. Mastalir, Z. Kiraly, I. Dekany, *J. Mater. Chem.* **2005**, *15*, 2464; f) S. Jansat, M. Gomez, K. Philippot, G. Muller, E. Guiu, C. Claver, S. Castillon, B. Chaudret, *J. Am. Chem. Soc.* **2004**, *126*, 1592; g) M. Tamura, H. Fujihara, *J. Am. Chem. Soc.* **2003**, *125*, 15742.

[25] Mixing $Pd(OAc)_2$ (5 μmol) and phenylboronic acid (0.75 mmol) in an organic solvent (0.5 mL) such as THF and MeOH still formed PdNPs with an average particle size of 3.0 and 2.9 nm, respectively, (see the Supporting Information).

[26] M. Moreno-Mañas, M. Pérez, R. Pleixats, *J. Org. Chem.* **1996**, *61*, 2346.

[27] a) R. Narayanan, M. A. El-Sayed, *J. Phys. Chem. B* **2004**, *108*, 8572; b) R. Narayanan, M. A. El-Sayed, *J. Am. Chem. Soc.* **2003**, *125*, 8340.

[28] For the TEM images for monitoring of the coupling reaction, see the Supporting Information.

[29] a) ref.[17]; b) P.-P. Fang, A. Jutand, Z.-Q. Tian, C. Amatore, *Angew. Chem.* **2011**, *123*, 12392; *Angew. Chem. Int. Ed.* **2011**, *50*, 12184; c) A. V. Gaikwad, A. Holuigue, M. B. Thathagar, J. E. ten Elshof, G. Rothenberg, *Chem. Eur. J.* **2007**, *13*, 6908.

[30] L. K. Thalén, A. Sumic, K. Bogár, J. Norinder, A. K. A. Persson, J.-E. Bäckvall, *J. Org. Chem.* **2010**, *75*, 6842.

[31] The reaction time was not optimized.

[32] The reaction of **1k** with **2a** (entry 5 of Table 3) gave a trace amount of the elimination product (4%) as determined by ^{1}H NMR of the crude mixture.

[33] a) K. C. Nicolaou, T. Montagnon, *Molecules that Changed the World*, Wiley-VCH, Weinheim, **2008**; b) E. Breitmaier, *Terpenes – Flavors, Fragrances, Pharmaca, Pheromones*, Wiley-VCH, Weinheim, **2006**.

[34] For selected examples of organic synthesis by using 1,5-dienes, see: a) J. A. Feducia, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 592; b) Y.-J. Zhao, S.-S. Chng, T.-P. Loh, *J. Am. Chem. Soc.* **2007**, *129*, 492; c) T. J. Donohoe, S. Butterworth, *Angew. Chem.* **2003**, *115*, 978; *Angew. Chem. Int. Ed.* **2003**, *42*, 948; d) H. Nakamura, Y. Yamamoto, in: *Handbook of Organopalladium*

Chemistry for Organic Synthesis, Vol. ,2 (Eds.: E.-i. Negishi, A. de Meijere), Wiley-Interscience, West Lafayette, **2002**, p 2919; e) R. C. D. Brown, J. F. Keily, *Angew. Chem.* **2001**, *113*, 4628; *Angew. Chem. Int. Ed.* **2001**, *40*, 4496; f) L. E. Overman, F. M. Knoll, *J. Am. Chem. Soc.* **1980**, *102*, 865.

[35] a) A. Jiménez-Aquino, E. F. Flegeau, U. Schneider, S. Kobayashi, *Chem. Commun.* **2011**, *47*, 9456; b) E. F. Flegeau, U. Schneider, S. Kobayashi, *Chem. Eur. J.* **2009**, *15*, 12247; and references cited therein.

[36] a) L. A. Brozek, M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2011**, *133*, 16778; b) P. Zhang, H. Le, R. E. Kyne, J. P. Morken, *J. Am. Chem. Soc.* **2011**, *133*, 9716; c) P. Zhang, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc.* **2010**, *132*, 10686.

[37] a) I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 6340; b) I. S. Kim. M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14891.

