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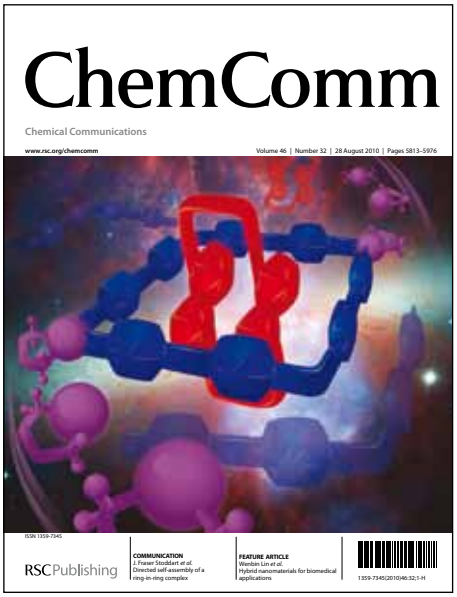

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Communication

Pd-Catalyzed stereospecific allyl□aryl coupling of allylic alcohols with arylboronic acids

Jiang Ye, Jingming Zhao, Jing Xu, Yuxue Mao and Yong Jian Zhang*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
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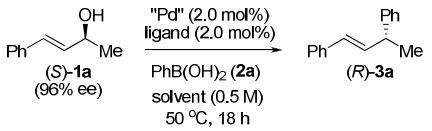
An efficient method for Pd-catalyzed stereospecific allyl□aryl coupling of allylic alcohols with arylboronic acid has been described. The reactions proceeded smoothly in the presence of $Pd_2(dba)_3$•$CHCl_3$ and racemic BINAP under mild and neutral conditions, affording allyl□aryl coupling products in moderate to high yields with excellent stereospecificities.

Transition metal-catalyzed cross-coupling reactions of allylic electrophiles with aryl nucleophiles are powerful tools for the construction of valuable allyl□aryl coupling compounds by the formation of a new C□C bond.[1,2] The allyl□aryl coupling reaction with arylboronic acid derivatives has emerged as being advantageous in light of their availability, stability, and ease of handling.[3] Although some transition metal such as Rh-,[4] Pd(II)-[5] and Cu[6]-catalyzed stereoselective allylic arylation reactions using arylboronic acids or their derivatives have been reported, Pd-catalyzed Suzuki□Miyaura coupling of allylic electrophiles have mostly been confined to afford linear allyl□aryl coupling products.[7] In contrast, the coupling reaction of 1,3-disubstituted secondary and potentially enantioenriched allylic partners have been much less explored despite the reaction provides the coupling products with a stereogenic center. Until recently, Uozimi,[8] Tian[9] and our group[10] accomplished respectively Pd-catalyzed stereospecific allyl□aryl coupling reactions of enantioenriched allylic electrophiles with arylboronic acids, offering allyl□aryl coupling products with high stereospecificity.

Direct cross-coupling between readily available allylic alcohols and arylboronic acids is undoubtedly an atom-economical and greener process due to avoid further activation of allylic alcohols to their esters, carbonates or phosphonates et al.[11] In this context, although hydroxyl group is a reluctant leaving group, some approaches for transition metal-catalyzed cross-coupling of allylic alcohols with arylboronic acids have been established.[12] However, the reactions have mostly been limited for primary allylic alcohols. Tsukamoto and co-workers investigated that Pd-catalyzed allyl□aryl coupling reaction of chiral secondary allylic alcohol with phenylboronic acid, but the reaction afforded a racemic product.[12a] In spite of chiral allylic alcohols are readily accessible by the numerous asymmetric synthetic methods, to our knowledge, the corresponding stereospecific cross-coupling of enantioenriched allylic alcohols with arylboronic acids are unknown. Based on our recent success in Pd-catalyzed stereospecific cross-coupling of allylic carbonates with arylboronic acids,[10] herein we disclose corresponding stereospecific coupling reaction directly using allylic alcohols, a greener and practical protocol that allows rapid access to allyl□aryl coupling products with high stereospecificities.

Initially, we conducted the reaction of enantioenriched allylic alcohol **1a** (96% ee) as a standard substrate with phenylboronic acid (**2a**) under our previous conditions[10] for the coupling reaction of allylic carbonates (Table 1, entries 1 and 2). However, the reaction conditions were not effective for the direct coupling of allylic alcohol **1a**. Remarkably, by

Table 1 Optimization studies for Pd-catalyzed stereospecific allyl□aryl coupling of (*S*)-**1a** with **2a**[a]



entry	Pd	ligand	solvent	conv. (%)[b]	ee (%)[c]
1	$Pd(OAc)_2$	-	H_2O	10	ND
2	$Pd(OAc)_2$	*rac*-BINAP	THF[d]	21	ND
3	$[Pd(allyl)Cl]_2$	*rac*-BINAP	THF	0	-
4	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	THF	86 (78)	95
5	$Pd(PPh_3)_4$	-	THF	68 (48)	5
6	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	toluene	99 (91)	96
7	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	CyH	65 (54)	96
8[e]	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	toluene	85 (73)	96
9[f]	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	toluene	99 (85)	62
10	$Pd_2(dba)_3$•$CHCl_3$	PPh_3	toluene	79 (74)	8
11	$Pd_2(dba)_3$•$CHCl_3$	PCy_3	toluene	46 (43)	71
12	$Pd_2(dba)_3$•$CHCl_3$	$P(C_6F_5)_3$	toluene	0	-
13	$Pd_2(dba)_3$•$CHCl_3$	DPPE	toluene	27 (20)	96
14	$Pd_2(dba)_3$•$CHCl_3$	DPPB	toluene	45 (41)	92
15	$Pd_2(dba)_3$•$CHCl_3$	DPPF	toluene	68 (63)	86
16	$Pd_2(dba)_3$•$CHCl_3$	Xantphos	toluene	44 (30)	65
17[g]	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	toluene	68 (67)	96
18[h]	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	toluene	99 (92)	81
19[i]	$Pd_2(dba)_3$•$CHCl_3$	*rac*-BINAP	toluene	99 (91)	56

[a] Conditions: Pd (2.0 mol%), ligand (2.0 mol% for bisphosphines; 4.0 mol% for monophosphines), **1a** (0.4 mmol), **2a** (0.6 mmol), solvent (0.8 mL), 50 °C, 18 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. Isolated yields are shown in parentheses. [c] Determined by chiral HPLC analysis. The absolute configuration was determined by comparison the sign of optical rotation with that of the reported data.[10] [d] With 5 equiv. of H_2O. [e] The reaction was conducted at 40 °C. [f] The reaction was conducted at 70 °C. [g] 1 mol% of catalyst loading. [h] 4 mol% of catalyst loading. [i] 8 mol% of catalyst loading. CyH: cyclohexane. ND: not determined.

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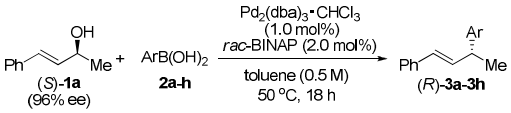
means of further screening of palladium source (entries 3□5), we found that the reaction proceeded well in the presence of $Pd_2(dba)_3$•$CHCl_3$ (1 mol%) and racemic BINAP (2 mol%) in THF at 50 °C for 18 h, affording coupling product **3a** in 78% yield with complete regioselectivity and high enantiospecificity (95% ee) with inversed absolute configuration, and no *E*/*Z* isomerization and *β*-hydride elimination were observed (entry 4). However, the reaction with $Pd(PPh_3)_4$ as a catalyst gave almost racemic product (entry 5). Further investigation of solvent effect demonstrated that toluene is a best solvent for the reaction, giving product **3a** in 91% yield with complete enantiospecificity (96% ee, entry 6). However, the reactions did not work at all in CH_2Cl_2, ether, pentane, acetonitrile, methanol or pure water. We also demonstrated that 50 °C is an ideal temperature for the reaction. Lowering the reaction temperature to 40 °C resulted in lower conversion (entry 8), and higher reaction temperature led to erosion of enantioselectivity (entry 9). The reaction efficiency was also sensitive to the nature of the phosphine ligand. When using PPh_3 as a ligand, the reaction gave almost racemic product (entry 10). The reaction with *σ*-donating tricyclohexylphosphine resulted in low conversion and enantioselectivity (entry 11), and the reaction did not proceed at all in the presence of electronic deficient phosphine ligand, $P(C_6F_5)_3$ (entry 12). Bisphosphine ligands such as DPPE, DPPB, DPPF and Xantphos promoted reaction with good to excellent enantiospecificities, but the reactions led to low conversions (entries 13□16). Notably, bisphosphine ligands played an important role for high stereospecificities in the coupling reaction.[13] The reason can be explained that Pd(0) complex with PPh_3 acts as a nucleophile to isomerize *π*-allylpalladium intermediates via S_N2-type attack leading to loss of stereospecificity in allylic substitutions reported by Bäckvall and Granberg.[14] This isomerization due to Pd-Pd displacement can be inhibited by the use of chelated bidentate ligand.[14] To prove this explanation, we examined the reaction under different catalyst loading (entries 17□19). Clearly, the stereospecificities were significantly decreased with increasing catalyst loading; 56% ee was observed when the reaction proceed in the presence of 4 mol% of $Pd_2(dba)_3$•$CHCl_3$ and 8 mol% of racemic BINAP (entry 19).

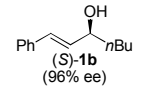
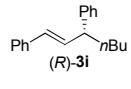
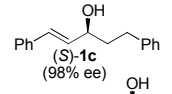
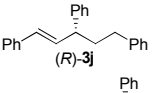
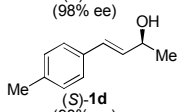
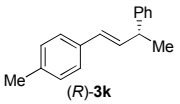
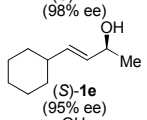
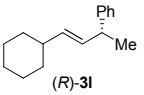
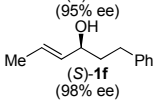
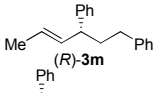
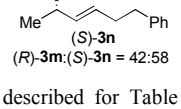
Table 2 Pd-Catalyzed stereospecific allyl□aryl coupling of (*S*)-**1a** with various arylboronic acids **2**[a]



entry	Ar	yield (%)[b]	ee (%)[c]	es (%)[d]
1	Ph (**2a**)	91	96	100
2	2-MeC_6H_4 (**2b**)	81	94	98
3	3-$MeOC_6H_4$ (**2c**)	84	95	99
4[e]	4-MeC_6H_4 (**2d**)	47	95	99
5[e]	4-$^tBuC_6H_4$ (**2e**)	60	95	99
6[e]	4-$MeOC_6H_4$ (**2f**)	45	95	99
7[e]	4-ClC_6H_4 (**2g**)	63	89	93
8	2-naphthyl (**2h**)	91	94	98

[a] Conditions: **1a** (0.4 mmol), **2** (0.6 mmol), toluene (0.8 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Enantiospecificity (es) = $ee_{product}/ee_{substrate} \times 100\%$. [e] The reactions were carried out for 24 h.

Table 3 Pd-Catalyzed stereospecific allyl□aryl coupling of various allylic alcohols (*S*)-**1** with **2a**[a]

entry	allylic alcohol	product	yield (%)[b]	ee (es) (%)[c]
1	 (*S*)-**1b** (96% ee)	 (*R*)-**3i**	76	94 (98)
2	 (*S*)-**1c** (98% ee)	 (*R*)-**3j**	68	91 (93)
3	 (*S*)-**1d** (98% ee)	 (*R*)-**3k**	86	91 (93)
4	 (*S*)-**1e** (95% ee)	 (*R*)-**3l**	82	93 (98)
5	 (*S*)-**1f** (98% ee)	 (*R*)-**3m**	91[d]	96 (98)
		 (*S*)-**3n** (*R*)-**3m**:(*S*)-**3n** = 42:58	91[d]	97 (99)

[a] The reaction conditions as described for Table 2. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Total isolated yield of (*R*)-**3m** and (*S*)-**3n**.

With the optimized conditions in hand, the reaction scope of the allyl□aryl coupling reaction with respect to substituted arylboronic acids was evaluated. As shown in Table 2, the coupling reaction of enantioenriced allylic alcohol **1a** (96% ee) with various substituted arylboronic acids with different electronic or steric natures proceeded to the corresponding allyl□aryl coupling product (*R*)-**3a**□**3h** in moderate to high level of isolated yields with complete regioselectivities and excellent enantiospecificities, no *E*/*Z* isomerizations and *β*-hydride eliminations were observed for all of the examples. The reactions with *para*-substituted arylboronic acids exhibited relatively low conversions.

Next, we further investigated the coupling reaction of various allylic alcohols **1** with phenylboronic acid (**2a**) under our optimized conditions (Table 3). The reactions of chiral allylic alcohols **1b**□**1e** with **2a** gave corresponding coupling products **3i**□**3l** as single regioisomers in good yields with excellent enantiospecificities (93□98% es, entries 1□4). The coupling reaction of the sterically less differentiated **1f** (98% ee) with **2a** furnished a mixture of the two regioisomers, **3m** and **3n** with a ratio of 42:58 in 91% of total yield with excellent chirality transfer for the two isomers (entry 5). These results indicated that the regioselectivity of the coupling reaction is controlled by the steric differences of the 1- and 3-substituents of the allylic alcohols.[2]

To gain more mechanistic information for the stereospecific allyl□aryl coupling process, we examined the reaction of enantioenriched (*S*)-**1a** using both enantiomers of ligand. As shown in Eq. 1, there were a slight level of double diastereodifferentiation but both reactions afforded the product with inversed configuration as the predominant outcome. These results indicated that the stereochemistry of the reaction exclusively depended on the configuration of allylic alcohol. On the other hand, performing the reactions of

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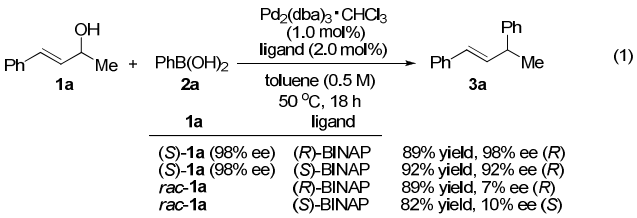

racemic allylic alcohol **1a** with both enantiomers of BINAP afforded coupling product **3a** with poor enantioselectivities.

Although an in-depth investigation remained to be conducted, the plausible reaction pathway for the cross-coupling of allylic alcohols with arylboronic acids can be proposed as outlined in Figure 1.[10,11,12a] Firstly, hydroxyl group of allylic alcohol **1a** is activated by arylboronic acid, and then π-allylpalladium species is formed by the oxidative addition of Pd-complex to the activated chiral (*S*)-**1a** from the back side stereospecifically. Palladium intermediate **II** subsequently takes place the transmatalation to form allylarylpalladium **III**, which undergo reductive elimination at the sterically less hindered side to furnish the inversed allyl□aryl coupling product (*R*)-**3a** with excellent stereospecificity.

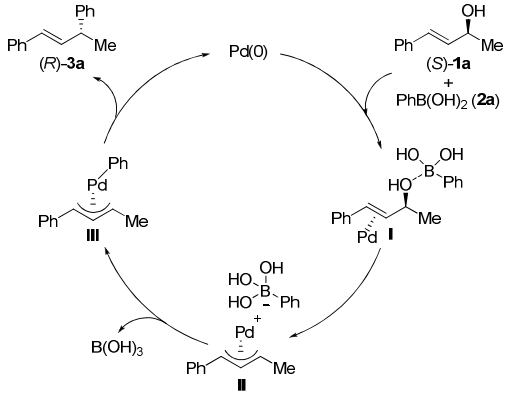

Figure 1. Possible reaction pathway

In conclusion, we have developed an atom-economical method for Pd-catalyzed stereospecific allyl□aryl coupling reaction directly using chiral secondary allylic alcohols with arylboronic acids. The reactions proceeded smoothly in the presence of $Pd_2(dba)_3$•$CHCl_3$ and racemic BINAP under mild and neutral conditions, affording allyl□aryl coupling products in moderate to high yields with excellent enantiospecificities with inversed stereochemistry. Further studies on the exploration of the scope and the mechanism of the reaction are currently underway, and will be reported in due course.

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Notes and references

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

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