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Palladium-catalyzed tandem allylic substitution/cyclization and cascade hydrosilylated reduction: the influence of reaction parameters and hydrosilanes on the stereoselectivity[†]

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To shed light on the influence of reaction parameters on palladium-catalyzed tandem allylic alkylation in the presence of Fei-Phos (a chiral *trans*-1,2-diaminocyclohexane-derived phosphine ligand), the effect of different phosphine ligands, inorganic or organic bases, Brønsted acids, and other additives on the asymmetric palladium-catalysed alkylation of catechol with allylic diacetate was investigated. In this reaction, 2-vinyl-2,3-dihydro-benzo[1,4]dioxin products with promising enantioselectivity were achieved in good yields. In addition, a novel palladium-catalyzed three-component and one-pot allylic substitution/cyclization/reduction reaction assisted by methylphenylsilane was reported with good selectivity.

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Introduction

Transition-metal-catalyzed allylic substitution reactions are an extremely useful class of organic transformation, revealed several decades ago, and offer simple and practical approaches for the synthesis of alkene-substituted molecular frameworks.¹ Notably, the allylic substitution reaction has been proven to be one of the most important and fundamental C–C bond-forming processes in organic synthesis.² In this regard, the catalytic asymmetric version of allylic alkylation has also become a powerful carbon–carbon or carbon–heteroatom bond-forming approach to a range of structurally diverse allyl-substituted compounds. These are prevalent functional molecules and building blocks for the construction of natural products and biologically important complexes in synthetic chemistry.³ In this approach, it is well-known that catalytic asymmetric allylic substitution largely relies on the capability for stereoselective induction of the chiral ligands.⁴ In fact, numerous phosphine ligands have been utilized as they are extremely effective and are key factors in this allylic substitution reaction, including allylic cyclization.^{1–5} However, it is still highly desirable to search for a highly efficient ligand, which is needed to accommodate low-

reactivity substrates for catalytic asymmetric allylic substitution reactions with improved activity and stereoselectivity. Despite the recent success in allylic alkylation of various carbon- or heteroatom-based nucleophiles, including cyanoacetate, alcohols, and heterocycles,⁶ transition-metal-catalyzed asymmetric allylic substitutions of functional molecules with structurally varied allylic acetates continue to receive much attention from synthetic chemists. Thus the development of new reaction systems with good yields and stereoselectivity is a valuable topic and is still highly desirable.

Among allylic substitution reactions, the stereoselective allylic alkylation of oxygen-nucleophiles, such as alcohols, is one of the most important C–O bond-forming transformations for the construction of chiral ether-containing compounds.⁷ Notably, in this context, palladium complexes with bidentate phosphine or phosphite ligands have been proven to be effective catalysts for the construction of different C–O bonds and chiral ethers with good stereoselectivity.⁷ For example, we developed the chiral *trans*-1,2-diaminocyclohexane-derived multiple stereogenic and multifunctional CycloN2P2-Phos (also called Fei-Phos) for catalytic asymmetric allylic substitutions of benzyl alcohols and silanols with allylic acetates.⁸ Good to excellent yields and high enantioselectivities (up to 99% ee) were achieved in this reaction, which motivated us to expand the synthetic functions of Fei-Phos in palladium catalysis.⁹ Although asymmetric palladium-catalyzed allylic alkylation of catechol with (Z)-2-butene-1,4-diylbis(methylcarbonate) gave the desired 2-vinyl-1,4-benzodioxane with up to 45% ee in the presence of chiral ligands such as BINAP was realized by Sinou in 1994,¹⁰ the use of simple allylic acetates as the electrophiles

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in this reaction has not been described yet. In addition, it is surprising that limited progress has been made so far on the tandem allylic alkylation of catechol with allylic reagents for the synthesis of chiral 2-vinyl-2,3-dihydro-benzo[1,4]dioxanes.¹¹ Thus in this work, we continue to carry out further investigations on the catalytic asymmetric allylic substitution of catechol with allylic diacetates in the presence of a palladium catalyst with Fei-Phos or other P-ligands. This approach could be useful for the construction of 1,4-benzodioxane ring systems that are found in various natural products and are key skeletons in pharmaceutical candidates possessing important biological activities.¹² In addition, the effect of various phosphine ligands, inorganic or organic bases, Brønsted acids, and other additives, on the asymmetric palladium-catalysed alkylation of catechol with allylic diacetate was investigated in this work.

Results and discussion

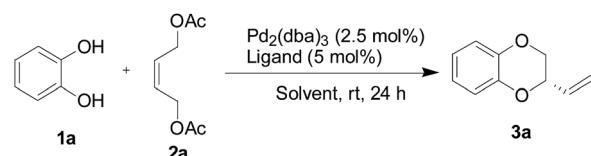
Palladium-catalyzed tandem allylic alkylation of catechol with allylic compounds

Firstly, the allylic substitution/cyclization reaction of benzene-1,2-diol **1a** with the (*Z*)-but-2-ene-1,4-diol-derived allylic acetate **2a** was used as a model reaction at room temperature in the presence of a palladium complex which was generated *in situ* by mixing Pd₂(dba)₃ [tris(benzylideneacetone)dipalladium] with various phosphine ligands (Scheme 1). It should be noted that there is no effective phosphine ligand previously reported for this reaction.^{10,11} To evaluate the feasibility of the tandem allylic alkylation reactions, we wanted to explore the potential of commercially available phosphine ligands and our P-ligands, which we have reported in the past few years,¹³ including Fei-Phos. Results from the optimization studies employing the

phosphine ligands are summarized in Table 1. Notably, most of the phosphine ligands gave poor or no yield of the corresponding product **3a**. Only **L3**, **L8**, and **L12** (Fei-Phos) were proven to be effective in this reaction (entries 3, 8, and 12, respectively), and **L3** and **L8** gave low to moderate yields (30–50%) as well as low enantioselectivity (25–39% ee). Interestingly, our Fei-Phos is still the best choice in this reaction in comparison with the other P-ligands evaluated in this work (entry 12, 60% yield and 39% ee). Notably, when the reaction temperature was decreased to 0 or –20 °C, both the yield and enantioselectivity decreased obviously (entries 17 and 18). With the optimized ligand in THF, the solvent effect was also evaluated in the catalytic asymmetric allylic substitution/cyclization reaction (Table 1, entries 19–22). Although this tandem allylic substitution reaction occurred smoothly to deliver 2-vinyl-2,3-dihydro-benzo[1,4]dioxane (**3a**) with good yields (70%) in 1,4-dioxane, the solvents evaluated in this work gave inferior performance in comparison with THF.

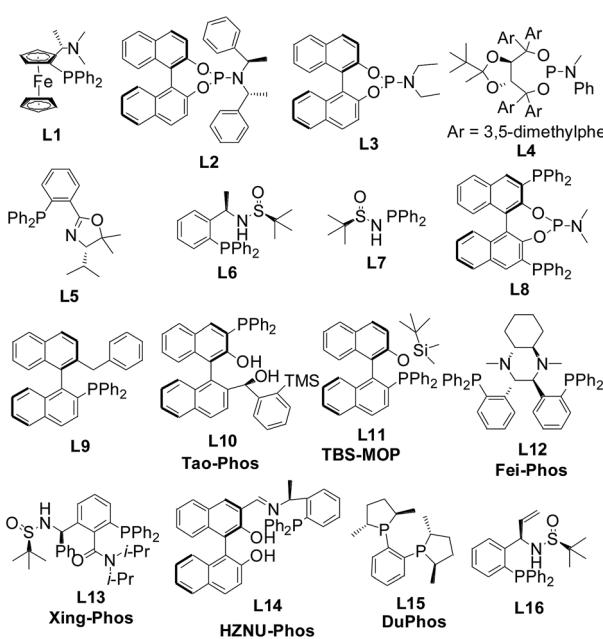
Then, we continued to investigate the effect of the palladium catalyst precursors or other transition metal catalysts on the

Table 1 The effect of the various phosphine ligands on the palladium-catalyzed allylic substitution/cyclization reaction of benzene-1,2-diol **1a** with the (*Z*)-but-2-ene-1,4-diol derived allylic acetate **2a**



Entry ^a	Ligand	Solvent	Yield ^d (%)	ee ^{e,f} (%)
1	L1	THF	n.r	—
2	L2	THF	<5	—
3	L3	THF	50	39
4	L4	THF	n.r	—
5	L5	THF	n.r	—
6	L6	THF	n.r	—
7	L7	THF	n.r	—
8	L8	THF	30	25
9	L9	THF	n.r	—
10	L10	THF	n.r	—
11	L11	THF	n.r	—
12	L12	THF	60	39
13	L13	THF	n.r	—
14	L14	THF	n.r	—
15	L15	THF	n.r	—
16	L16	THF	n.r	—
17 ^b	L12	THF	24	31
18 ^c	L12	THF	5	33
19	L12	1,4-Dioxane	72	35
20	L12	DCM	<5	—
21	L12	DCE	12	n.d
22	L12	DMSO	n.r	—

^a Reaction conditions: **1a** (0.25 mmol), **2a** (1.4 eq.), Pd₂(dba)₃ (2.5 mol%) and Fei-Phos (5 mol%), N₂, rt, 24 h. ^b The temperature was 0 °C. ^c The temperature was –20 °C. ^d Isolated yields after silica gel chromatography. ^e Determined using chiral HPLC. n.r is no reaction; a trace is represented by <5% yield; n.d is not determined. ^f Determined by the sign of the specific rotation.¹⁴



Scheme 1 The various phosphine ligands evaluated in the palladium-catalyzed tandem allylic alkylation of benzene-1,2-diol **1a** with the (*Z*)-but-2-ene-1,4-diol derived allylic acetate **2a**.



catalytic asymmetric allylic alkylation. As shown in Table 2, most of the palladium salts were not suitable for this tandem allylic alkylation reaction, in which only $[\text{Pd}(\eta\text{-C}_3\text{H}_5)\text{Cl}]_2$ and $\text{Pd}(\text{PPh}_3)_4$ had the ability to promote tandem allylic substitution to give the corresponding 2-vinyl-2,3-dihydro-benzo[1,4]dioxane (**3a**) in moderate yield (35–58%). Interestingly, other palladium salts or transition metal salts, such as $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, $\text{Pd}(\text{OAc})_2$, $[\text{RhCl}(\text{cod})]_2$, $[\text{Ir}(\text{cod})\text{OMe}]_2$, or $\text{RuCl}(\text{PPh})_3$, were not suitable catalyst precursors in this reaction. These experimental results showed that the enhancement of enantioselectivity in the palladium-catalyzed allylic substitution/cyclization reaction of benzene-1,2-diol **1a** with the (*Z*)-but-2-ene-1,4-diol derived allylic acetate **2a** is not an easy task. The major reason possibly originated in the acidity of catechol because we have found that the equilibrium acidity (pK_a) is an important factor in the reactivity of structurally diverse alcohols.⁹

Therefore, on the basis of the above findings, the modification of the reaction parameters by the addition of acidic or basic additive to tune the acidity is not trivial in this work. Initially, the $\text{Pd}/\text{Fei-Phos}$ -catalyzed tandem allylic substitution of benzene-1,2-diol **1a** with the (*Z*)-but-2-ene-1,4-diol derived allylic acetate **2a** was carried out in the presence of various inorganic bases or organic bases at room temperature. As shown in Fig. 1, the effect of the bases on the enantioselectivity in the palladium/Fei-Phos catalyzed allylic substitution/cyclization reaction provided direct information that this reaction largely relied on the acidity of the reaction system (Table S6 of ESI†). For example, when KF or Na_2CO_3 was used as the base,

Table 2 The effect of palladium salts or other transition metal salts on the catalytic asymmetric allylic alkylation of benzene-1,2-diol **1a** with the (*Z*)-but-2-ene-1,4-diol derived allylic acetate **2a** in the presence of Fei-Phos

Entry ^a	Catalyst	Yield ^b (%)	ee ^c (%)
1	$[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$	58	35
2	$(\text{Ph}_3\text{P})_4\text{Pd}$	35	19
3	$\text{PdCl}_2(\text{CH}_3\text{CN})_2$	n.r	—
4	$\text{PdCl}_2(\text{PhCN})_2$	<5	—
5	$\text{Pd}(\text{OAc})_2$	n.r	—
6	$\text{RhCl}(\text{PPh}_3)$	n.r	—
7	$[\text{RhCl}(\text{coe})]_2$	n.r	—
8	$[\text{RhCl}(\text{cod})]_2$	n.r	—
9	$[\text{RhCl}_2(\text{pmcpcd})]_2$	n.r	—
10	$\text{RuCl}(\text{PPh})_3$	n.r	—
11	$[\text{Ir}(\text{cod})\text{OMe}]_2$	n.r	—

^a Reaction conditions: the reaction of **1a** (0.25 mmol) and **2a** (1.4 eq.) was carried out under N_2 at room temperature for 24 h by mixing with $[\text{Pd}]$ (5 mol%), $[\text{Rh}]$ (5 mol%), $[\text{Ru}]$ (5 mol%), or $[\text{Ir}]$ (5 mol%) and the chiral ligand (5 mol%). ^b Isolated yields after silica gel chromatography. ^c Determined using chiral HPLC.

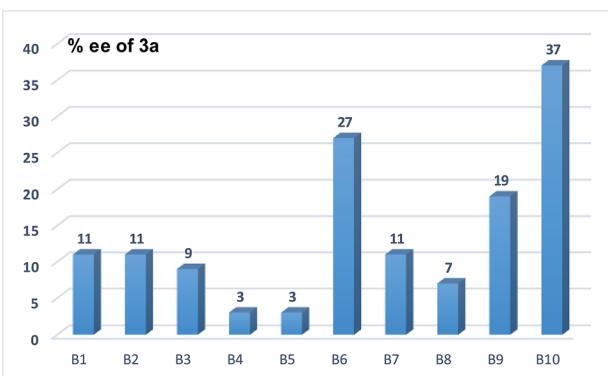
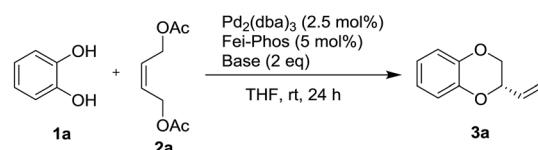


Fig. 1 The effect of base (B1–B10) on the enantioselectivity in the Pd-catalyzed tandem allylic substitution/cyclization: B1 (K_2CO_3), B2 (KHCO_3), B3 (K_3PO_4), B4 (KF), B5 (Na_2CO_3), B6 (NaHCO_3), B7 (Cs_2CO_3), B8 (DBU), B9 (Et_3N) and B10 (DIPEA).

almost no enantioselectivity was observed and almost all the bases decreased the stereoselectivity (3–37% ee).

Similarly, the effect of organic acids on the enantioselective Pd-catalyzed allylic alkylation was also performed under the optimized reaction conditions. As shown in Fig. 2, it was found that all the chiral organic acids, such as mandelic acid and proline, gave the desired product **3a** with a low enantioselectivity (5–25% ee). Interestingly, the absolute configuration of the chiral organic acid played important role in the influence of the additive, for example, (*S*)-(+)-mandelic acid or *L*-(–)-proline gave higher enantioselectivity than (*R*)-(–)-mandelic acid or *D*-(–)-proline. Although most of the organic acids had no ability to improve the enantioselectivity, the experimental results clearly supported the theory that the organic acids could affect the catalytic efficiency of the palladium catalyst in this reaction. Gratifyingly, among the different organic acids used as additives in this reaction, phenylboronic acid was determined to be an excellent additive for the enhancement of enantioselectivity.

As shown in Fig. 3, phenylboronic acid improved the enantioselectivity from 39% ee to 51% ee when 10 mol% of $\text{PhB}(\text{OH})_2$ was used in this reaction. However, the yield was quite low in this case (10% isolated yield). Inspired by this finding, the role of various arylboronic acids in the palladium-catalyzed tandem allylic substitution of benzene-1,2-diol **1a** with the (*Z*)-but-2-ene-1,4-diol derived allylic acetate **2a** was then investigated using a series of experimental studies. As shown in Table S7 (see the ESI†) about 20 examples revealed that phenylboronic acid was still the best additive in this reaction.

Then the effect of the amount of phenylboronic acid on the enantioselectivity was further investigated. Unfortunately, it was difficult to exceed 51% ee when larger amounts of phenylboronic acid were used as the additive in the palladium-catalyzed allylic substitution/cyclization reaction (Fig. 4).



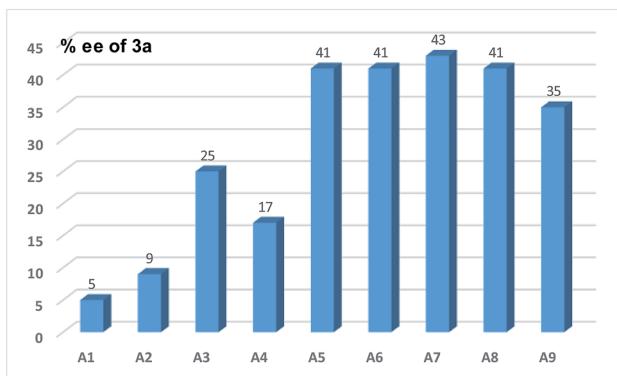
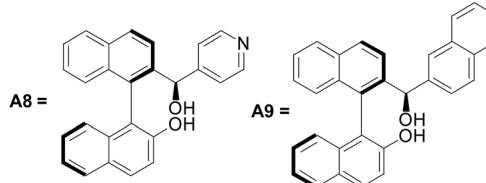
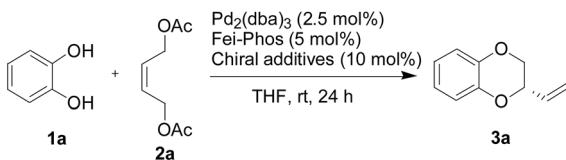


Fig. 2 The effect of chiral organic acids on the enantioselectivity in the Pd-catalyzed tandem allylic substitution/cyclization: A1 [(S)-(+)-mandelic acid], A2 [(R)-(+)-mandelic acid], A3 [L-(-)-proline], A4 [D-(+)-proline], A5 [(S)-BINOL], A6 [(R)-BINOL], A7 (race-BINOL), A8, and A9.¹⁵

It is well-known that the leaving group is also an important factor in the palladium-catalyzed allylic alkylation reaction.¹¹ Thus its effect on the enantioselectivity of the allylic

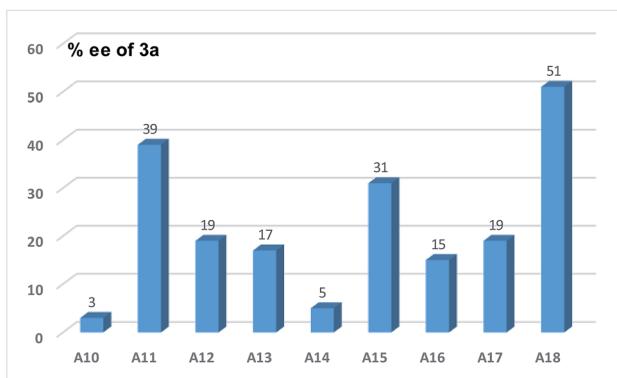
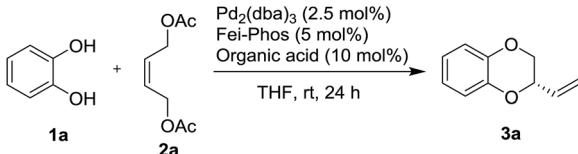


Fig. 3 The effect of organic acids on the enantioselectivity in the Pd-catalyzed tandem allylic substitution/cyclization: A10 (benzoic acid), A11 (2-methylbenzoic acid), A12 (abietic acid), A13 (ascorbic acid), A14 (pivalic acid), A15 (boric acid), A16 (cyclopropylboronic acid), A17 (2-naphthaleneacetic acid) and A18 (phenylboronic acid).

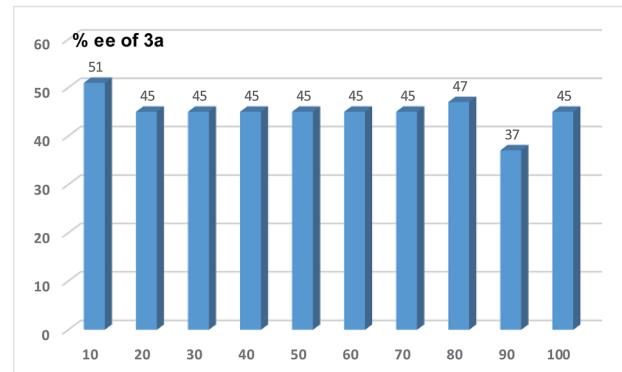
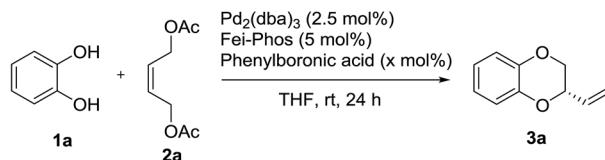


Fig. 4 The effect of the amount of phenylboronic acid on the enantioselectivity in the Pd-catalyzed tandem allylic substitution/cyclization.

substitution/cyclization reaction is shown in Fig. 5. The results indicate that the benzoyl group as the leaving group has the best enantioselectivity (45% ee). In addition, the enantioselectivity due to the leaving group was influenced largely by whether it was an electron-donating group, for example, with a *p*-

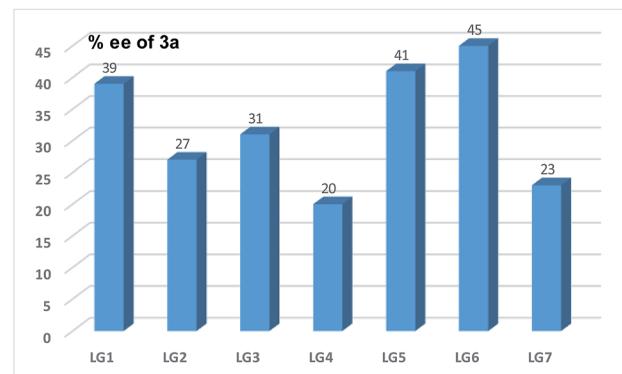
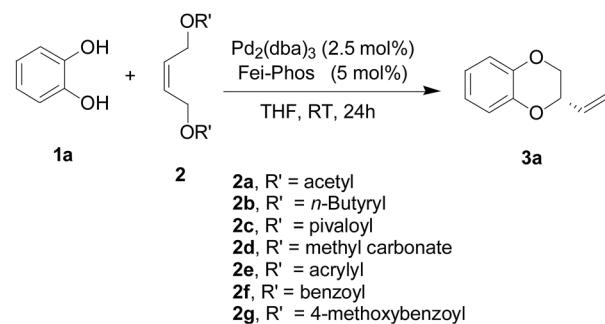
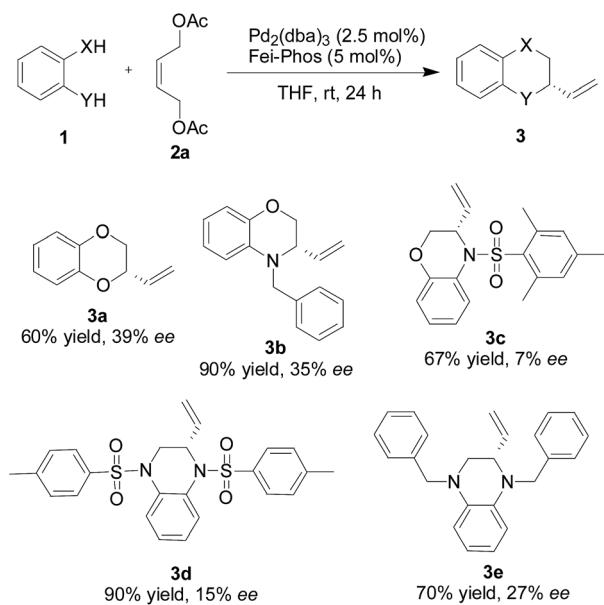


Fig. 5 The effect of the leaving group of substrate 2 on the enantioselectivity in the Pd-catalyzed tandem allylic substitution/cyclization: LG1 (acetyl), LG2 (n-butyryl), LG3 (pivaloyl), LG4 (methyl carbonate), LG5 (acrylyl), LG6 (benzoyl) and LG7 (4-methoxybenzoyl).



Scheme 2 Fei-Phos ligand-controlled palladium-catalyzed tandem allylic alkylation of different 1,2-bifunctional nucleophiles **1** with the (Z)-but-2-ene-1,4-diol derived allylic acetate **2a**: a representative substrate scope.

methoxybenzyl group as the leaving group, the enantioselectivity of the reaction system reduced to 23% ee. However, other fatty acids and unsaturated fatty acids other than acetic acid esters had no significant enhancement on the enantioselectivity of the tandem allylic alkylation. Moreover, under the optimized reaction conditions, all these leaving groups decreased the yields to lower than that with the acetyl group.

Therefore, under the optimized reaction conditions shown in Table 1, we further investigated the substrate scope of the catalytic asymmetric tandem allylic substitution/cyclization reaction of different 1,2-bifunctional nucleophiles **1** with the (Z)-but-2-ene-1,4-diol derived allylic acetate **2a**. As shown in Scheme 2, good yields and promising ee values were obtained for various substituted 2-heterocycles **3** (up to 7–39% ee). Although the enantioselectivity is not good enough, the present method is quite simple and features good yields. In addition, the reaction information described above provides a spring-board to modify the reaction conditions of the palladium-catalyzed tandem allylic alkylation reactions in the near future.

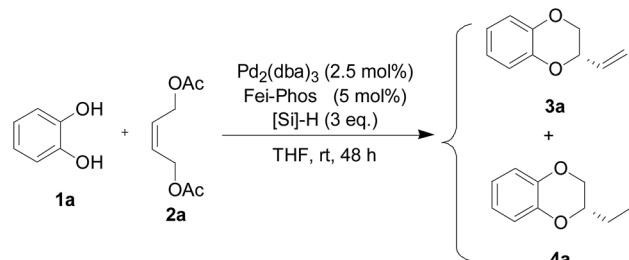
Palladium-catalyzed three-component tandem allylic substitution/cyclization and cascade hydrosilylated reduction

Encouraged by the experimental results for the palladium-catalyzed tandem allylic alkylation of different 1,2-bifunctional nucleophiles **1** with the (Z)-but-2-ene-1,4-diol-derived allylic acetate **2a** shown in Scheme 2, we turned our attention to the design of a novel one-pot multicomponent asymmetric allylic alkylation and cascade hydrosilylated reduction. In fact, we found that 2-vinyl-2,3-dihydro-benzo[1,4]dioxane (**3a**) and the other products **3** were not stable enough in the presence of the palladium catalyst. We proposed that the palladium-

promoted isomerisation of the alkene group resulted in the deceased enantioselectivity.¹⁶ Therefore, the reduction of the vinyl group by hydrosilane would be an interesting topic because the palladium complex associated with Fei-Phos would be effective in this reaction. However, to the best of our knowledge, despite the previous success of Pd-catalyzed tandem reactions,¹⁷ there are no past reports on a palladium-catalyzed cascade allylic alkylation/hydrosilylated reduction. In addition, the different activities of hydrosilanes makes this reaction quite difficult and unpredictable. Herein, with commercially available hydrosilanes to hand, including PMHS (polymethylhydrosiloxane), Ph_2SiH_2 , MePhSiH_2 , PhSiH_3 , and MePh_2SiH , a one-pot palladium-catalyzed asymmetric allylic alkylation and cascade hydrosilylated reduction reaction was attempted under optimized reaction conditions (see Table 3 and Table S10 in the ESI;† 2.5 mol% of palladium catalyst, $\text{Pd}_2(\text{dba})_3$, 5 mol% of Fei-Phos, and 3 equiv. hydrosilane in THF were determined as the optimal reaction conditions).

To our delight, the palladium catalyst with Fei-Phos was also highly effective in the asymmetric tandem allylic alkylation of benzene-1,2-diol **1a** with the (Z)-but-2-ene-1,4-diol derived allylic acetate **2a**. The results presented in Table 3 clearly demonstrate the efficiency of Fei-Phos in this multicomponent allylic alkylation transformation. The corresponding product **4a** could be obtained with varied yields with better enantioselectivity (45% ee), which supported our hypothesis that the direct reduction of 2-vinyl-2,3-dihydro-benzo[1,4]dioxane (**3a**) could inhibit the isomerization of the double carbon–carbon bond in this reaction. In particular, when MePhSiH_2 was used as a reductive hydrosilane, only the desired product **4a** was obtained, while other hydrosilanes gave poor chemoselectivity or had no activity for the cascade hydrosilylated reduction.

Table 3 The activities of various hydrosilanes in the asymmetric palladium-catalyzed tandem allylic alkylation of benzene-1,2-diol **1a** with the (Z)-but-2-ene-1,4-diol derived allylic acetate **2a**

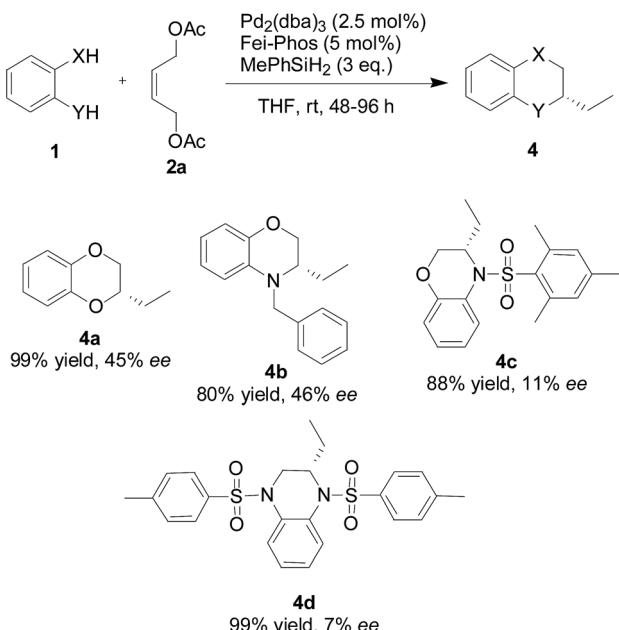


Entry ^a	Silane	Yield ^b (%)	3a : 4a ^c
1	PMHS	99%	1 : 0.48
2	Ph_2SiH_2	99%	1 : 0.59
3	MePhSiH_2	99%	0 : 1
4	PhSiH_3	n.r.	—
5	MePh_2SiH	87%	1 : 0

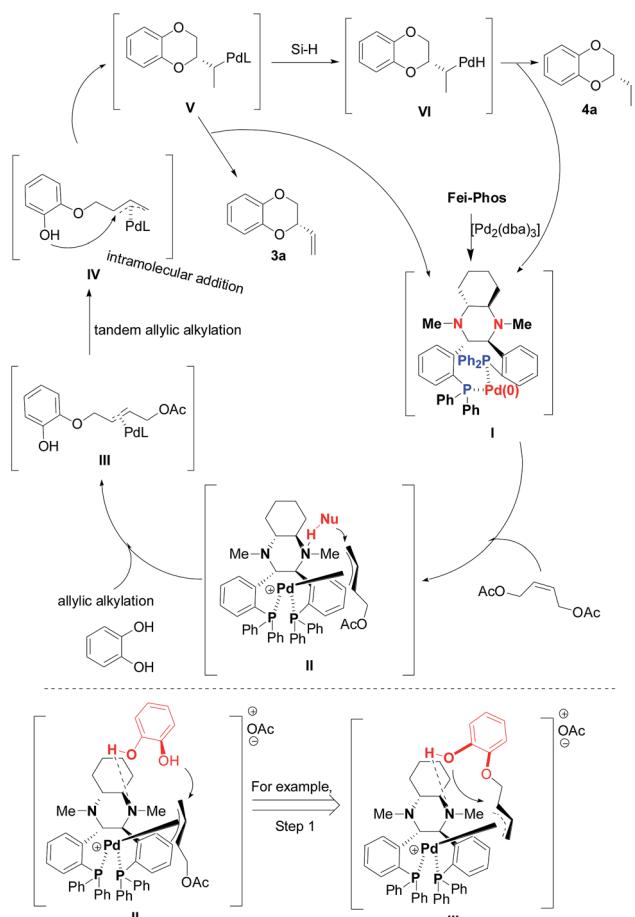
^a Reaction conditions: **1a** (0.25 mmol), **2a** (1.4 eq.), $\text{Pd}_2(\text{dba})_3$ (2.5 mol%), hydrosilane (3 eq.), Fei-Phos (5 mol%), N_2 , rt, 48 h.

^b Isolated yields after silica gel chromatography. ^c Determined from GC-MS analysis.





Scheme 3 Palladium-catalyzed multicomponent allylic substitution/cyclization and cascade reduction with hydrosilane (MePhSiH_2).



Scheme 4 The proposed mechanism for asymmetric palladium-catalyzed allylic substitution/cyclization and cascade hydrosilylated reduction in the presence of hydrosilane.

Therefore, we have successfully developed a novel strategy for the asymmetric palladium-catalyzed multicomponent allylic alkylation and one-pot reduction of an alkene product.

Finally, under the optimized reaction conditions that were established, shown in Table 3, the substrate scope of this palladium-catalyzed multicomponent allylic substitution/cyclization and cascade reduction with hydrosilane (MePhSiH_2) was examined with the representative 1,2-bifunctional nucleophiles 1. As summarised in Scheme 3, all the corresponding heterocycle products 4 were obtained in excellent yields (80–99% isolated yields) with moderate to low enantioselectivities (up to 46% ee).

On the basis of the experimental results and the generally accepted mechanism for palladium-catalyzed allylic alkylation,¹⁸ we proposed a mechanistic procedure with the corresponding transition-state model, as shown in Scheme 4. In the first step, there was an initial oxidative addition of the low valent palladium species ($\text{Pd}(0)\text{L}_2$), which formed *in situ* from $\text{Pd}_2(\text{dba})_3$ and Fei-Phos, to the (*Z*)-but-2-ene-1,4-diol derived allylic acetate 2a (electrophile) and then nucleophilic attack on the corresponding allylic $\text{Pd}(\text{II})$ cation. Subsequently, the reductive elimination of the palladium intermediate II that had coordinated with the ligand resulted in the formation of the single alkylation intermediate III, and then intramolecular allylic alkylation led to the regeneration of the $\text{Pd}(0)$ complex when intermediate IV liberated the product.

Conclusions

In summary, we have determined the stereoselective activity of Fei-Phos in the asymmetric palladium-catalyzed tandem allylic alkylation of 1,2-bifunctional nucleophiles 1 with the (*Z*)-but-2-ene-1,4-diol derived allylic acetate 2a. In addition, the influence of the reaction parameters on palladium-catalyzed tandem allylic alkylation in the presence of Fei-Phos, including the effect of various phosphine ligands, inorganic or organic bases, Brønsted acids, and other additives on the asymmetric palladium-catalysed alkylation of catechol with allylic diacetate, was investigated in detail. Under optimized reaction conditions, the corresponding 2-vinyl-2,3-dihydro-benzo[1,4]dioxin products were achieved with promising enantioselectivity in good yields. In addition, a novel one-pot allylic substitution/cyclization and cascade reduction with the aid of methyl-phenylsilane was further developed in this work. It provides an interesting example of the concept of silicon-mediated organic synthesis (SiMOS) because the three-component reaction is precisely controlled by certain hydrosilanes. Finally, on the basis of the present work, we believe that the modification of Fei-Phos would be an effective strategy for the improvement of asymmetric palladium-catalyzed transformations.

Conflicts of interest

There are no conflicts to declare.

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