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Fei-Phos ligand-controlled asymmetric palladium-catalyzed allylic substitutions with structurally diverse nucleophiles: scope and limitations†

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To shed light on the scope and limitations of palladium-catalyzed allylic alkylation in the presence of chiral *trans*-1,2-diaminocyclohexane-derived Fei-Phos as an effective phosphine ligand, the asymmetric palladium-catalysed alkylation of structurally diverse hard/soft nucleophiles, including allylic etherification of alcohols and the allylic alkylation of activated methylene compounds, indoles, and aromatic amines were investigated in this study; the corresponding products with various functional groups were achieved in good yield and with high enantioselectivity (up to 99% ee).

Introduction

Allyl-substituted compounds are an extremely useful class of molecules that have been used as widespread building blocks in organic synthesis for more than 40 years.[1] Among the synthetic methods for the preparation of allyl-substituted compounds by alkylation reactions, transition-metal-catalyzed allylic alkylations offer one of the simplest and most practical approaches for the construction of allyl-substituted molecular frameworks.[2] Accordingly, the allylic alkylation reaction has become a fundamental carbon–carbon bond-forming reaction in synthetic chemistry. Of especial importance, the catalytic asymmetric allylic alkylation is now a classic, powerful and useful carbon–carbon and carbon–heteroatom bond forming reaction which has satisfied the growing demand for enantioselective synthesis of a range of structurally and stereochemically rich functional alkenes in recent decades.[3] In particular, the resulting substituted alkenes are prevalent intermediates in numerous natural products and biologically important building blocks in organic synthesis. In this respect, recent research has focused on transition-metal-catalyzed asymmetric allylic alkylation with varied allylic acetates. In this approach, the catalytic asymmetric allylic alkylation usually relies on the rational design of chiral ligands.[4] In this regard, numerous phosphine ligands have been found to play extremely effective roles in catalytic asymmetric allylic alkylation reactions. Although numerous chiral ligands have been reported in the catalytic asymmetric allylic alkylation reaction in recent years,[1–5] it is still highly desirable to add a highly efficient ligand to this list that can readily accommodate substrates for a wide of catalytic asymmetric allylic alkylation reactions. Also, the catalysis chemistry of asymmetric allylic alkylation reactions with improved catalytic activity and performance as well as stereoselectivity continues to receive much attention from synthetic chemists.

Despite the recent success of the general allylic alkylation of carbon nucleophiles, the development of new palladium complexes with extremely high enantioselectivity and activity is a hot topic and is also highly sought after. In addition, the palladium-catalyzed asymmetric allylic alkylation of heteroatom-based nucleophiles, such as alcohols, cyanoacetates, and heterocycles, with high levels of enantioselectivity has not been widely reported, probably due to unfavorable deactivation of the metal–ligand complexes.[6] Among catalytic asymmetric alkylation reactions, the catalytic asymmetric allylic alkylation of alcohols is one of the most important C–O bond cleavage and new C–O bond forming transformations for the synthesis of chiral ethers. In this context, various palladium catalyst systems associated with bidentate phosphine or phosphite ligands have afforded the chiral ethers with moderate to good stereoselectivity.[7]

In 2013, we developed a new multidentate and multifunctional phosphine with multiple stereogenic centers (CycloN2P2-Phos), also called Fei-Phos in this work, derived from chiral *trans*-1,2-diaminocyclohexane, for the catalytic asymmetric alkylation of allylic acetates with benzyl alcohols and silanols (Scheme 1).[8] Also in this work, it was found that catalytic allylic alkylation of alcohols and silanols resulted in good to excellent yields and high enantioselectivities (up to 99% ee). However, the

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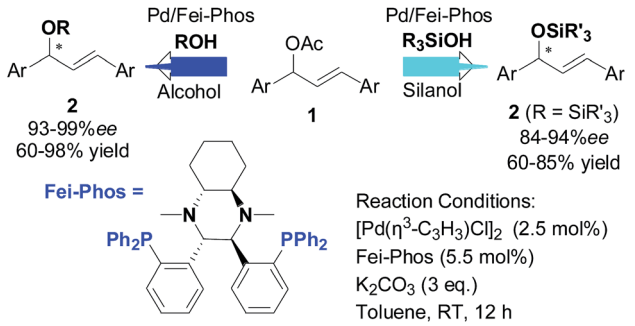


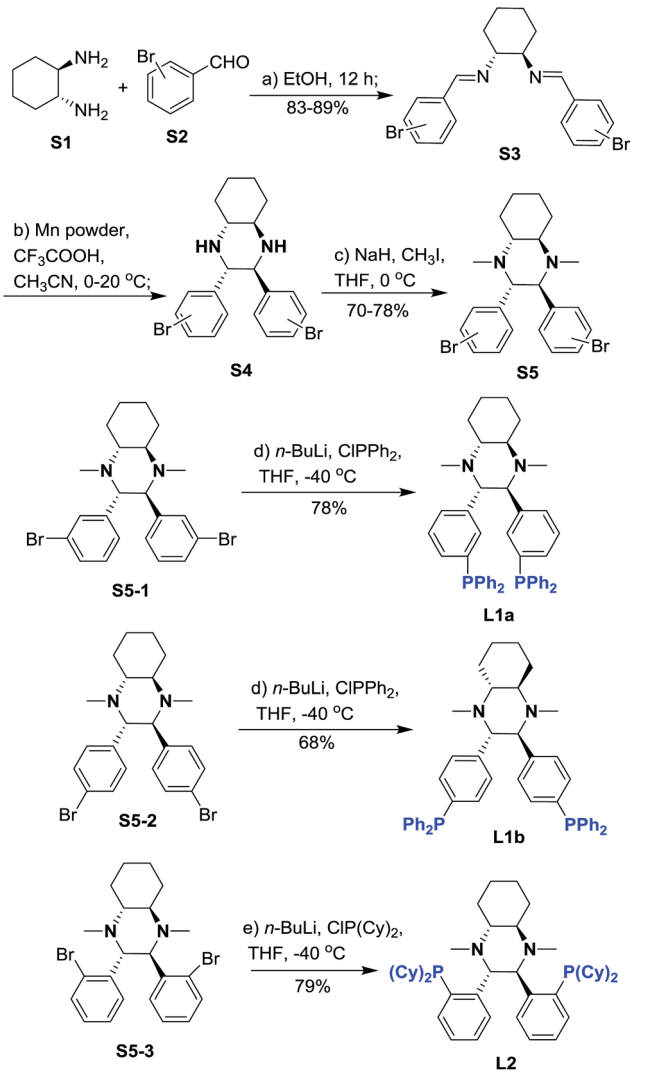
Scheme 1 Pd/Fei-Phos catalyzed asymmetric allylic etherification/silylation of allylic acetate with alcohols or silanols.

detailed catalytic activity and possible substrate scope as well as the limitations of Fei-Phos in the allylic substitution reaction remain unclear. Meanwhile, in order to expand the synthetic application of Fei-Phos in asymmetric palladium catalysis, especially the stereoselectivity of Fei-Phos in the catalytic asymmetric allylic alkylation and the determination of the privileged role of the Pd/Fei-Phos catalyst system in such reactions, the clarification of the corresponding asymmetric catalysis chemistry based on related reaction results is an interesting task in this field. In addition, we became intrigued by the possibility of generating a coordinated palladium/Fei-Phos complex by a nitrogen or phosphine center, a true catalyst that heretofore has not been clarified in previous studies; this prompted us to carry out a comparative investigation of asymmetric palladium-catalyzed allylic alkylation with other ligands in this work.

Results and discussion

Pd/Fei-Phos-catalyzed allylic alkylation with activated methylene compounds

Although Fei-Phos has been introduced as a chiral ligand in palladium-catalyzed allylic substitutions, our previous work only focused on the allylic etherification/silylation reaction. In addition, it is unclear how the stereoselective allylic substitutions are induced by the multifunctional Fei-Phos because of the two nitrogen centers and two phosphine centers on this ligand. Therefore, it is necessary to investigate the catalytic functionality and stereoselective induction of Fei-Phos in various allylic substitutions and its potential applications in organic synthesis. To exclude the possibility of two molecular ligands with one palladium catalyst (PdL_2), we wished to prepare the analogous ligands from the same chiral source, *trans*-1,2-diaminocyclohexane, for the corresponding catalytic allylic alkylation of various nucleophiles; we felt it would also be useful to indirectly compare studies of the intermolecular coordination (Pd/Fei-Phos) and intramolecular interaction (PdL_2). In addition, to determine the importance of the phosphorous atom on the Fei-Phos, we carried out the synthesis of diamine-derived multifunctional biphosphines **L1a** and **L1b**. As shown in Scheme 2, the synthesis of the two novel multifunctional biphosphine ligands started with the preparation of Schiff base **S3** *via* the simple condensation of *trans*-1,2-diaminocyclohexane with *meta*-bromobenzaldehyde or *para*-bromobenzaldehyde. Then, similarly to a previous report,[8] the resulting Schiff base **S3** was converted into the substituted diphenylpiperazine **S4** by a reductive coupling reaction.[9] The methylation of secondary amine **S4** to tertiary amine **S5** was subsequently performed with MeI in the presence of strong base. Then, in the last step, bromide–lithium exchange followed by reaction with $ClPPh_2$ gave the desired biphosphine ligands **L1a** and **L1b**. Similarly, we also prepared the ligand **L2** (Scheme 2), an analogue of Fei-Phos ligand, with a dicyclohexylphosphine moiety. Therefore, these ligands could be applied to the comparative study of catalytic asymmetric allylic alkylations with or without Fei-Phos ligand.

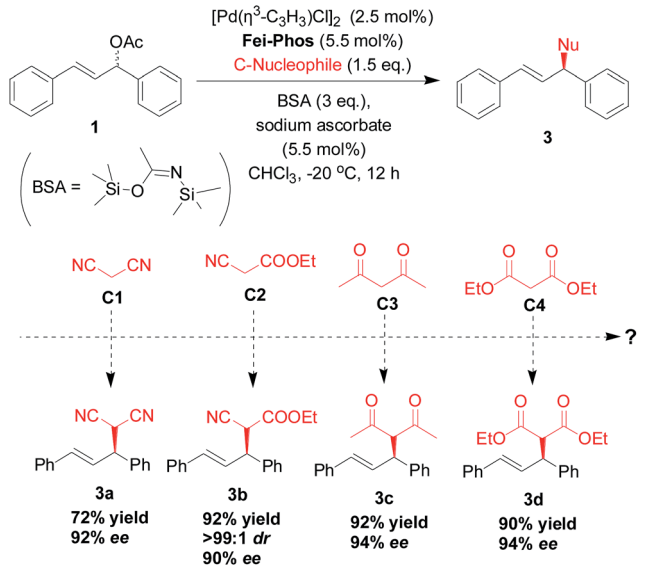


Scheme 2 Synthesis of diamine-derived multifunctional biphosphines L1 and L2.

The catalytic asymmetric allylic alkylation of activated methylene compounds is one of the most attractive and important approaches for the synthesis of chiral allyl-substituted carbonyl derivatives. To better understand the observed trends corresponding to the powerful potential of Fei-Phos related to the catalytic activity of Pd/Fei-Phos complex in

various asymmetric allylic alkylation reactions, further evaluation of the substrate scope was performed to probe the general structure of nucleophiles; we anticipated good enantioselectivity in catalytic asymmetric allylic alkylation with activated methylene compounds. With the optimized reaction conditions in hand (see Tables S1–S4 of the ESI†), a variety of activated methylene compounds were used in the catalytic asymmetric allylic alkylation reaction (Scheme 3). Gratifyingly, various methylene nucleophiles (C1–C4) reacted smoothly with 1,3-diphenyl-2-propenyl acetate (**1**) to deliver highly optically pure allylic methylene compounds (90% to 94% ee), with good yields of the isolated products (72% to 92% yield). As shown in Scheme 3, this approach is potentially useful for the enantioselective construction of important compounds containing aromatic alkenes and unsaturated carbonyl groups. Notably, all the activated methylene compounds with various relative acidities of their α-hydrogen atoms (pK_a = 11.1 to 16.4)[10] gave the desired products at almost the same high level of enantioselectivity (90% to 94% ee) with undifferentiated induction. The electronic properties of the activated methylene compounds show no significant impact on the selectivity and reactivity of the allylic alkylation, which possibly reveals the high level of stereoselectivity of the multifunctional Fei-Phos ligand in the allylic alkylation reaction of activated methylene compounds.

In addition, to the best of our knowledge, there are only a few examples of the asymmetric palladium-catalyzed allylic alkylation of 2-cyanoaetates with allylic acetates;[11] unfortunately, the yields and enantioselectivities in previous reports were not good. In fact, chiral ligands with good catalytic activity were still insufficient for the allylic alkylation of unsubstituted 2-cyanoacetates.[11b,c] Very recently, we reported an efficient palladium-catalyzed asymmetric allylic alkylation of alkyl-2-cyanoacetates using a BINOL-derived multifunctional *N*,*O*,*P*-ligand (HZNU-Phos), in which the Pd/HZNU-Phos complex exhibited high diastereo- and enantioselectivity (up to >99 : 1 dr and up to 96% ee) in this reaction.[12]



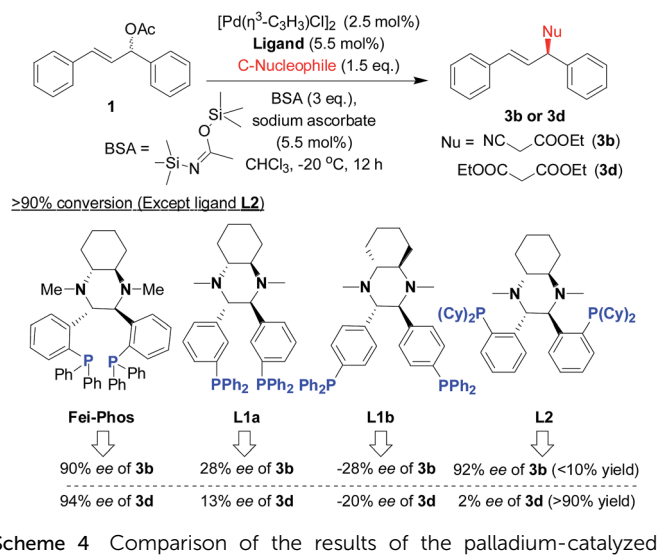
Scheme 3 Pd/Fei-Phos catalyzed asymmetric allylic alkylation of activated methylene compounds (carbon-based nucleophiles).

However, except for methyl or ethyl-2-cyanoacetate, substituted alkyl-2-cyanoacetates with other groups on their ester moieties, such as i-Pr, *n*-Bu, *t*-Bu, or Bn, gave a mixture of diastereoisomers with low diastereoselectivity (52 : 48).

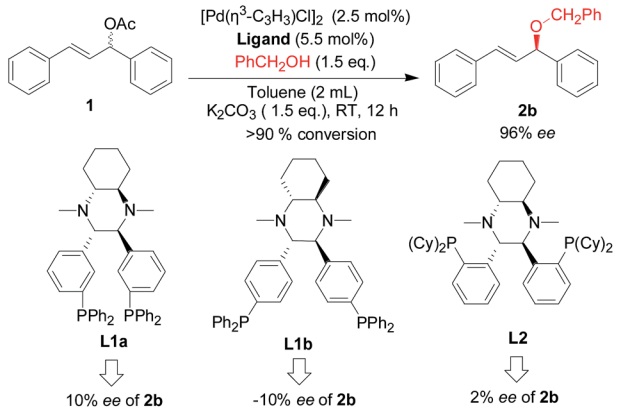
The asymmetric allylic alkylation of activated methylene compounds with 1,3-diphenyl-2-propenyl acetate (**1**) using **L1**–**L2** (Scheme 4) and chiral Schiff base-based *P*,*N*-ligands as chiral ligands was also investigated. Although the catalytic reactivities of these ligands were comparable to that of Fei-Phos in the catalytic asymmetric allylic alkylation of ethyl-2-cyanoacetate (Scheme 3), the expected products **3b**, **3d**, or **3e** were still obtained with low enantioselectivity. For example, only 28% ee of **3b** was achieved in the presence of ligand **L1a** or **L1b**. As a ESI† experiment, we also investigated the palladium-catalyzed allylic etherification of benzylic alcohol in the presence of the new ligands **L1** and **L2** (Scheme 2). These observations in Scheme 5 are consistent with the allylic etherification, where biphosphines **L1** and **L2**, derived from *trans*-1,2-diaminocyclohexane, exhibited inferior stereocontrol in this reaction; this indirectly provides useful information that Fei-Phos is a structurally reasonable phosphine ligand in palladium catalysis.

Furthermore, we have also investigated the reactivity of chiral Schiff base-based *P*,*N*-ligands that were obtained from *in situ* condensation of (*S*)-1-(2-(diphenylphosphino)phenyl) ethanamine[12] with simple aromatic aldehydes (Scheme 6) in the palladium-catalyzed allylic alkylation of ethyl-2-cyanoacetate. However, in contrast to the multifunctional P,N-type Fei-Phos ligand, these chiral *P*,*N*-ligands resulted in poor yields (10% to 65%) and inferior enantioselectivities (0% to 90% ee) in this reaction. The above results provided indirect evidence that the effects of nitrogen and phosphorous atoms on the Fei-Phos backbone in the palladium-catalyzed allylic alkylation are not as simple as imagined, which also supports the privileged role of multifunctional Fei-Phos in this reaction.

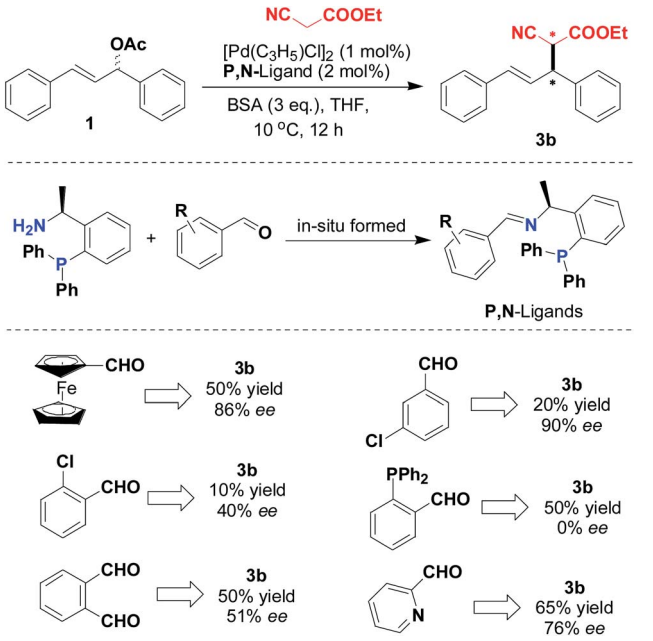
Therefore, under the optimized reaction conditions, we further investigated the substrate scope of the Pd/Fei-Phos-



Scheme 4 Comparison of the results of the palladium-catalyzed allylic alkylation of activated methylene compounds in the presence of Fei-Phos and its analogues.



Scheme 5 Catalytic activity of diamine-derived multifunctional biphosphines **L1a** and **L1b** in palladium-catalyzed allylic etherification.

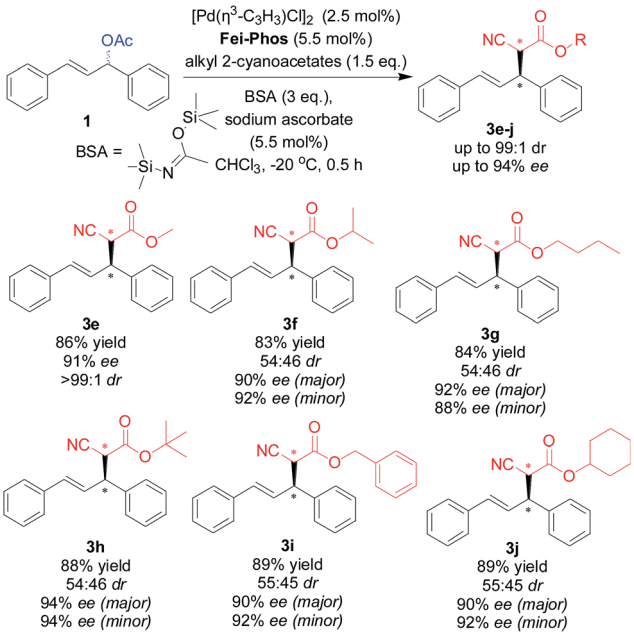


Scheme 6 Chiral Schiff base-based *P,N*-ligand-controlled palladium-catalyzed allylic alkylation of ethyl-2-cyanoacetate: a comparison with multifunctional Fei-Phos.

promoted asymmetric allylic alkylation reaction of various alkyl-2-cyanoacetates with 1,3-diphenyl-2-propenyl acetate (**1**). As shown in Scheme 7, good yields and high ee values were obtained for various substituted 2-cyanoacetates (up to 94% ee). Similarly to previous reports,[11,12] other alkyl groups on 2-cyanoacetates, such as i-Pr, *n*-Bu, *t*-Bu, or Bn, gave mixtures of diastereoisomers with low diastereoselectivity (about 55 : 45). Notably, the ee values of these isomers were good to excellent (Scheme 7, 90% to 94% ee).

Pd/Fei-Phos-catalyzed allylic alkylation with indole compounds

Encouraged by these experimental results, we then turned our attention to the asymmetric allylic alkylation of indoles. The



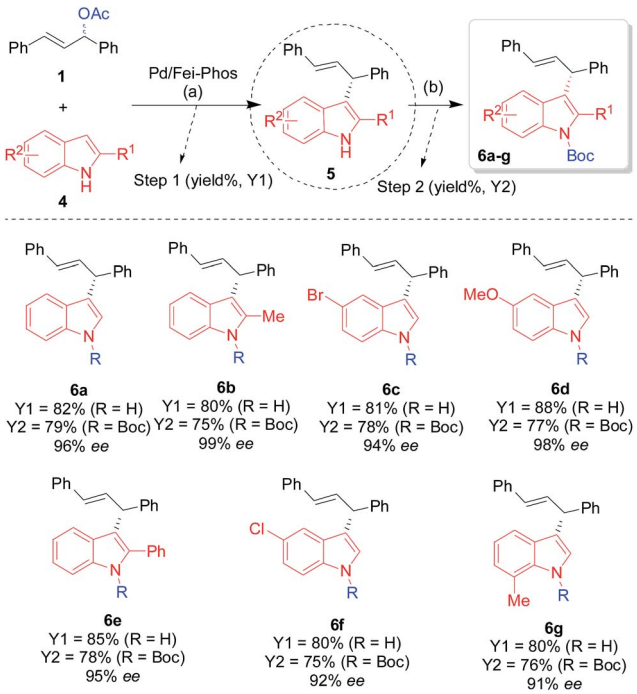
Scheme 7 Pd/Fei-Phos catalyzed asymmetric allylic alkylation of alkyl-2-cyanoacetates.

synthesis of indole derivatives is of significant importance because they are commonly found in bioactive natural products and fine chemicals.[13,14] In this regard, although numerous chiral palladium–phosphine complexes have been reported to catalyze enantioselective intra- or intermolecular allylic alkylations of indoles that afforded important indole-based chiral molecules/heterocycles,[15] there are only a few examples related to the intermolecular palladium-catalyzed allylic alkylation of indoles with high enantioselectivities (>95% ee).[16] Herein, with commercial available indoles **4** in hand, palladium-catalyzed asymmetric allylic alkylation was attempted under the optimized reaction conditions (see Table S5 of the ESI† and Scheme 7; 2.5 mol% of palladium catalyst, $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$, 5.5 mol% of Fei-Phos, and 3 equiv. K_2CO_3 in toluene were determined to be the optimal reaction conditions).

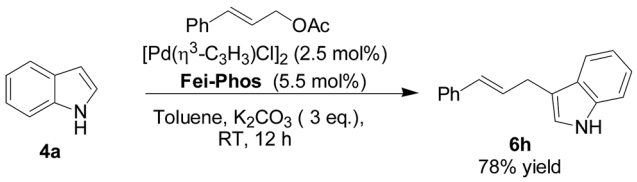
To our delight, Fei-Phos was also highly effective in the asymmetric allylic alkylation of indoles with allylic acetate. The results presented in Scheme 8 clearly demonstrate the efficiency of Fei-Phos in this catalytic asymmetric transformation. The corresponding products **5** or **6** were obtained with good yields and excellent enantioselectivities (91% to 99% ee).[17] Therefore, we have succeeded in the development of a highly efficient strategy for the palladium-catalyzed asymmetric allylic alkylation of indoles with the highest level of enantioselective induction to date in certain cases (for example, 99% ee for **5b**/**6b**). Notably, when acetic acid 3-phenyl-allyl ester was used in the palladium/Fei-Phos-catalyzed allylic alkylation of indole (**4a**), only the linear product **6h** was obtained in good yield (Scheme 9).

Pd/Fei-Phos-catalyzed allylic amination with aromatic amines

Chiral allylic amines are very important compounds in organic synthesis because they are useful synthetic intermediates for



Scheme 8 Pd/Fei-Phos-catalyzed asymmetric allylic alkylation of indoles (a) $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ (2.5 mol%), Fei-Phos (5.5 mol%), toluene, K_2CO_3 (3 eq.), RT, 12 h. (b) Boc_2O, DMAP (1 mol%), DCM.

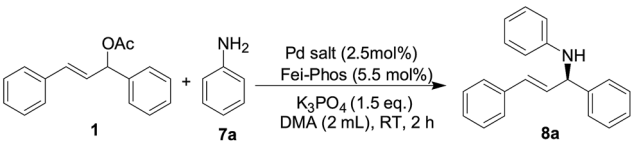


Scheme 9 Palladium/Fei-Phos-catalyzed allylic alkylation of indole (**4a**) with acetic acid 3-phenyl-allyl ester.

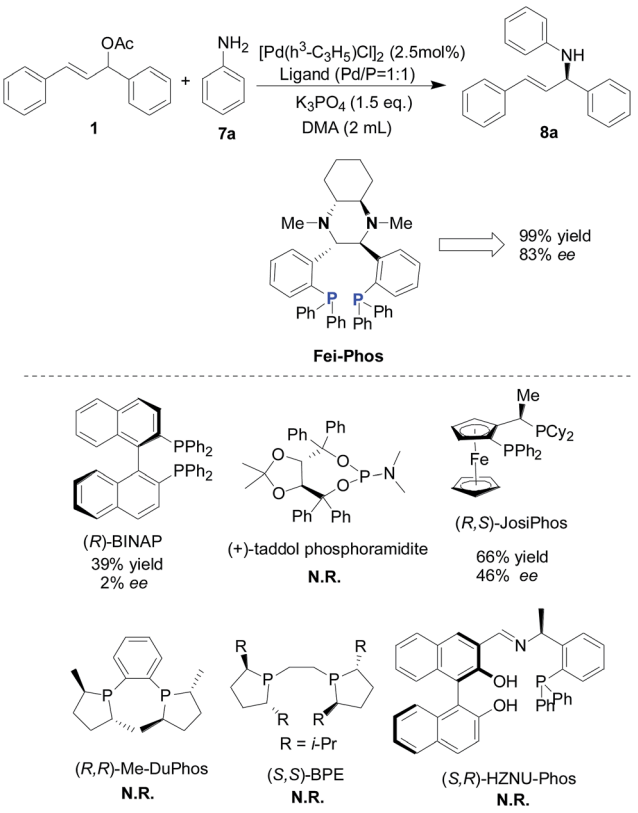
the preparation of natural products and drug candidates.[18] Accordingly, finding a reliable and efficient entry into chiral allylic amines is a highly important task. In this regard, the palladium-catalyzed allylic amination of allylic acetates with amines has been developed to address this task with the aid of chiral ligands.[19] Multifunctional Fei-Phos-controlled catalytic asymmetric allylic amination reactions for accessing chiral allylic amines should be useful for the development of new synthetic methods as well as for further determination of the scope, limitation, and mechanistic understanding of the palladium/Fei-Phos-catalyzed alkylation of various nucleophilies in the near future.

Based on the experimental studies described above that aimed at accessing allyl-substituted compounds with the synthetic strategy of palladium-catalyzed allylic alkylation, we envisioned that catalytic asymmetric allylic amination using the Pd/Fei-Phos catalyst system could also afford the corresponding products in good yields and with promising stereoselectivity. Initial attempts of catalytic allylic amination reactions to generate allylic amines revealed that various Pd-based catalysts, including $Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3\cdot CHCl_3$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, could promote the desired transformation in excellent yields (Table 1). Among the palladium catalysts evaluated in this work, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and $Pd_2(dba)_3\cdot CHCl_3$ gave the best enantioselectivity in the presence of Fei-Phos (entry 6 of Table 1). Then, a broad screen of commercially available P-based ligands, including our HZNU-Phos ligand, which exhibited good performance in the allylic alkylation of alkyl-2-cyanoacetate,[12] was carried out for a comparative study to identify Fei-Phos as the privileged ligand in this reaction (Scheme 10).

Table 1 Screening of palladium salts in the catalytic asymmetric amination of 1,3-diphenyl-2-propenyl acetate with aniline



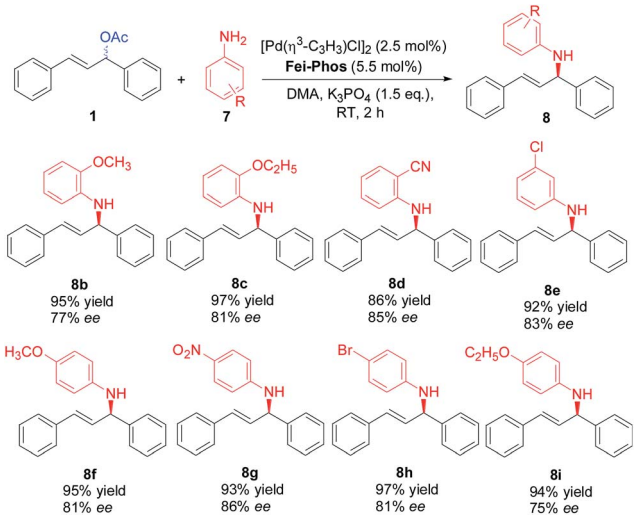
Entry	Cat. Pd	Yield (%)	ee (%)
1	$Pd(OAc)_2$	99	81
2	$PdCl_2$	99	80
3	$Pd_2(dba)_3\cdot CHCl_3$	99	83
4	$Pd(PPh_3)_4$	94	52
5	$Pd(PPh_3)_2Cl_2$	99	81
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	99	83



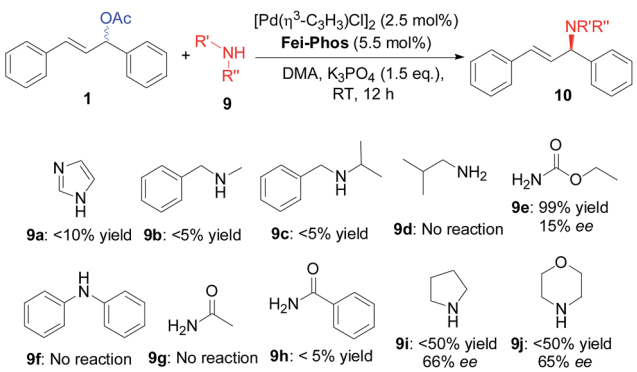
Scheme 10 Comparison of the results of the palladium-catalyzed asymmetric allylic amination with aniline.

Under the optimized reaction conditions that were established in the screening of solvents, temperatures, and other factors (see Tables S6–S9 of the ESI†), the substrate scope of this palladium-catalyzed allylic amination with aromatic amines was examined. As summarized in Scheme 11, for the aromatic amines, substituents on different positions of the phenyl moiety were well tolerated in this reaction, and all the corresponding products **8** were obtained in excellent yield (86% to 97% isolated yields) with moderate to good enantioselectivity (75% to 86% ee).

Although the asymmetric palladium-catalysed alkylation of structurally diverse nucleophiles, including the allylic etherification of alcohols and the allylic alkylation of activated methylene compounds, indoles, and aromatic amines, has supported the powerful potential of the enantioselective induction of Fei-Phos ligand in palladium catalysis, this ligand still has unavoidable limitations in the palladium-catalyzed allylic alkylation of nitrogen-based nucleophiles. As shown in Scheme 12, we have found that heterocycles (such as imidazole), alkyl amines, secondary aromatic amine, amide, and carbamate are not suitable substrates in this allylic amination. In other words, these negative results are useful for understanding how the Pd/Fei-Phos catalyst system-involved mechanistic procedure is affected by the electronic and steric factors of hard/soft substrates in this reaction.



Scheme 11 Palladium-catalyzed asymmetric allylic amination of 1,3-diphenyl-2-propenyl acetate with aromatic amines.



Scheme 12 Negative results in the palladium-catalyzed asymmetric allylic amination of 1,3-diphenyl-2-propenyl acetate with various nitrogen-based nucleophiles.

Conclusions

In summary, we have determined the beneficial features of Fei-Phos in the palladium-catalyzed asymmetric allylic etherification of alcohols and the asymmetric allylic alkylation of activated methylene compounds, indoles, and aromatic amines. All these catalytic transformations resulted in good to excellent yields and high enantioselectivities (up to 99% ee), which also demonstrates that this catalytic system, Pd/Fei-Phos complex, affords a high level of enantioselectivity. In view of the established utility of the Pd/Fei-Phos catalyst system in various allylic alkylation reactions, we anticipate that it will be necessary to carry out further mechanistic studies on the Pd catalysis in this reaction in the near future. Finally, we believe that Fei-Phos is an effective ligand in synthetically useful palladium-catalyzed asymmetric transformations because of the incorporation of a tertiary diamine onto the diphosphine-type ligand.

Acknowledgements

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