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Synthetic Methods

Tsuji–Trost Reaction of Non-Derivatized Allylic Alcohols

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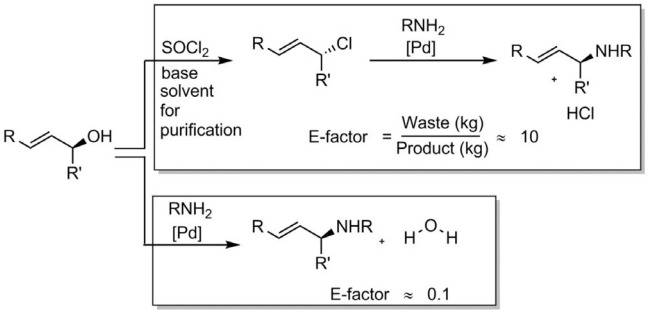
In memory of Prof. Takao Ikariya

Abstract: Palladium-catalyzed allylic substitution of non-derivatized enantioenriched allylic alcohols with a variety of uncharged N-, S-, C- and O-centered nucleophiles using a bidentate BiPhePhos ligand is described. A remarkable effect of the counter ion (X) of the XPd[κ^2-BiPhePhos][η^3-C_3H_5] was observed. When ClPd[κ^2-BiPhePhos][η^3-C_3H_5] (complex **I**) was used as catalyst, non-reproducible results were obtained. Study of the complex by X-ray crystallography, ^{31}P NMR spectroscopy, and ESI-MS showed that a decomposition occurred where one of the phosphite ligands was oxidized to the corresponding phosphate, generating ClPd[κ^1-BiPhe-Phosphite-phosphate][η^3-C_3H_5] species (complex **II**). When the chloride was exchanged to the weaker coordinating OTf^- counter ion the more stable Pd[κ^2-BiPhePhos][η^3-C_3H_5]$^+$ + [OTf]$^-$ (complex **III**) was formed. Complex **III** performed better and gave higher enantiospecificities in the substitution reactions. Complex **III** was evaluated in Tsuji–Trost reactions of stereogenic non-derivatized allylic alcohols. The desired products were obtained in good to excellent yields (71–98%) and enantiospecificities (73–99%) for both inter- and intramolecular substitution reactions with only water generated as a by-product. The methodology was applied to key steps in total synthesis of (*S*)-cuspareine and (+)-lentiginosine. A reaction mechanism involving a palladium hydride as a key intermediate in the activation of the hydroxyl group is proposed in the overall transformation.

Introduction

The Tsuji–Trost reaction is one of the most powerful synthetic tools to form carbon–carbon (C–C) or carbon–heteroatom (C–X) bonds in organic synthesis.[1] Traditionally, the hydroxyl (OH) group of easily accessible allylic alcohols is transformed into a better leaving group such as an ester, carbonate, or halide in a separate reaction step prior to the reaction to promote the C–O bond cleavage (Scheme 1a). This derivatization step generates waste and lowers the atom economy and increases the environmental factor (E-factor).[2] The substitution of the OH group was recently voted the second most desired transformation that a round table of pharmaceutical companies wanted greener alternatives for.[3]

During the last two decades, development of direct substitution reactions of allylic alcohols without prior derivatization has attracted considerable attention with respect to lowering the number of reaction steps and increasing the atom economy and thereby the environmental friendliness of the overall transformation. In such reactions, the only by-product generated is water (Scheme 1b). One successful strategy has been to employ an activator such as a Lewis or Brønsted acid to promote the C–O bond cleavage of palladium-catalyzed Tsuji–Trost reactions.[4,5] Another successful strategy is to use electron-deficient phosphorous-based ligands (phosphites, phosphoamidates, phospholes, phosphaalkene) in combination with palladium to promote C–O bond cleavage of allylic alcohols (Figure 1).[4,6]



Scheme 1. Derivatization of the OH-group leads to a high E-factor and lower atom efficiency.

Stereospecific substitution of the OH-group of easily accessible enantioenriched allylic alcohol with chirality transfer to the product is an even more challenging reaction and also enantioenriched allylic compounds are versatile chiral building blocks. There is a correlation between the enantiospecificity of

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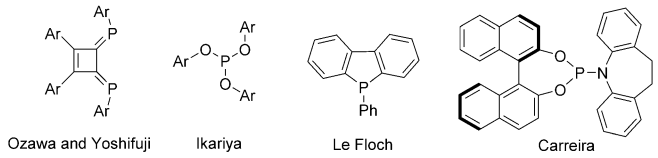
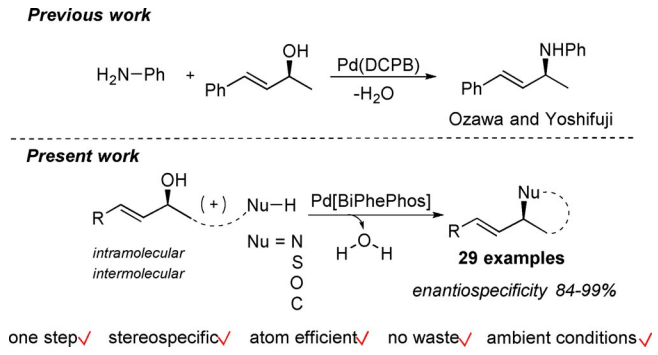


Figure 1. Successful ligands for direct substitution of the OH group of allylic alcohols.

Pd-catalyzed allylic substitutions and leaving group ability, in which poor leaving groups lead to worse results. The rational is that a poor leaving group will lower the rate of ionization and give a higher concentration of Pd^0 that is responsible for the racemization (vide infra).[7] In addition to the poor leaving group ability of the OH group, racemization of the stereocenter by η^3-η^1-η^3 isomerization of the π-allyl palladium intermediate may be an additional challenge depending on the substrate.[7] To our knowledge, only one single example is reported for a Pd-catalyzed intermolecular stereospecific amination of a non-derivatized allylic alcohol with water as the only by-product. Ozawa and Yoshifuji reported a stereospecific Pd-catalyzed intermolecular amination of an enantioenriched allylic alcohol without using acid activator at room temperature employing an electron-deficient bidentate diphosphinidene–cyclobutene (DPCB) ligand (Scheme 2).[6a] Elegant intermolecular cross-coupling reactions of optically active allylic alcohols with boronic acid (carbon nucleophile) have been reported by Ikariya, Tian, and Szabo.[8] A series of sophisticated enantioselective Tsuji–Trost reactions using a chiral catalyst to promote stereoinduction in which racemic mixtures of alcohols can be used to yield enantioenriched product have been reported.[9] Also, allylic substitutions in which a prochiral nucleophile is asymmetrically allylated have been reported.[10] In 2014, Beller and coworkers reported an enantioselective allylation of aniline derivatives to generate chiral allylic amines by employing a chiral phosphoric acid and a chiral palladium complex.[9a] An asymmetric allylic alkylation using an acetone nucleophile generated a chiral allylic compound was reported by Zhang et al.[9b] Recently, Tian also reported a kinetic resolution of racemic allylic alcohols through a palladium/sulfonyl-hydrazide-catalyzed enantioselective allylation.[9c] Asymmetric Tsuji–Trost type reaction catalyzed by Ir, Ru, and other metals has also been reported, by mainly Carreira.[11,12] Another environmental friendly route to synthesize enantioenriched allylic compounds is to use Lewis or Brønsted acid catalysis without the intermediacy of a π-allyl intermediate.[13–16] Enantioenriched allylic alcohols are easily accessible organic compounds.[17] Given that a round table of pharmaceutical companies voted the direct substitution of alcohols as the second most desired reaction that they wanted greener alternatives to, with a special emphasis on stereoselective/specific versions,[3] we thought it would be worthwhile to study and develop such chemistry. We here present a robust catalytic system for the enantiospecific substitution of the easily accessible non-derivatized enantioenriched allylic alcohols by O-, N-, S-, and C-centered nucleophiles with an exemplification to natural product synthesis from biomass derived allylic alcohol as well as the study on the Pd-BiPhePhos complexes.



Scheme 2. Tsuji–Trost reaction of non-derivatized stereogenic allylic alcohols.

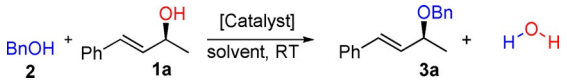
Results and Discussion

A. Catalyst studies

The catalyst screening was initially performed by mixing palladium precursor and ligands in situ and monitoring yield and stereospecificity. (*S*)-Cinnamyl alcohol **1a** and benzyl alcohol **2a** were used as substrates to screen the enantiospecificity in the intermolecular Tsuji–Trost reaction to yield **3a**. Oxygen nucleophiles are very challenging where only one previous report describes the intermolecular substitution using alcohols as nucleophiles via an π-allyl intermediate in which 30 mol% of a Pd-catalyst was used.[14a] $[Pd(\text{-allyl})Cl]_2$ was used as source of palladium to circumvent high concentrations of Pd^0 in the beginning of the reaction. Using $P(OPh)_3$ as ligand gave a very poor reactivity (Table 1, entry 1).[18] We hypothesized that a bidentate phosphite-based catalyst would be efficient with respect to stability and reactivity. Therefore, the $P(OPh)_3$ was exchanged for the BiPhePhos ligand.[19] The reaction gave high reactivity, however the stereospecificity differed between experiments (Table 1, entry 2). When the counter ion was changed to the less coordinating triflate (OTf), an efficient catalysis with high enantiospecificity was obtained (Table 1, entry 3). Bidendate phosphine ligands worked poorly (Table 1, entry 4). Using $Pd(dba)_2$ as palladium precursor gave lower enantiospecificity (Table 1, entry 5). Toluene was the best solvent of those tested for this reaction (Table 1, entries 3, 6, 7).

In order to understand the reaction better, the nature of the catalyst was studied. Crystals of $ClPd[\kappa^2\text{-BiPhePhos}][\eta^3\text{-}C_3H_5]$ (complex **I**) were grown and the molecular structure in Figure 2 shows a square planar geometry with a chloride weakly coordinating in the apical position (Pd–Cl, 2.67 Å). We found that the catalyst was rather unstable and that one of the phosphites readily was oxidized to generate $ClPd[\kappa^1\text{-BiPhePhos-oxo}][\eta^3\text{-}C_3H_5]$ (complex **II**), in which the chloride had exchanged the phosphorous coordinating to the palladium (Figure 2). This was observed in the ^{31}P NMR spectrum, where the intensity of complex **I** with a chemical shift at 148.5 ppm

Table 1. Optimization of reaction conditions.[a]



Entry	Pd source (mol%)	Ligand (mol%)	Solvent	Conv. [%][b]	*ee* [%]	e.s. [%][c]
1	$[Pd(allyl)Cl]_2$ (0.5)	$P(OPh)_3$ (8)	PhMe	<10	–	–
2	$[Pd(allyl)Cl]_2$ (0.5)	BiPhePhos (1.1)	PhMe	>95	11–94	12–95
3	$[Pd(allyl)Cl]_2$ (0.5)	BiPhePhos (1.1) AgOTf (1)	PhMe	>95	94	95
4	$[Pd(allyl)Cl]_2$ (0.5)	dppf (1.1)	PhMe	0	–	–
5	$[Pd(dba)_2]$ (5)	BiPhePhos (5.5)	PhMe	>95	47	48
6	$[Pd(allyl)Cl]_2$ (0.5)	BiPhePhos (1.1) AgOTf (1)	MTHF	0	–	–
7	$[Pd(allyl)Cl]_2$ (0.5)	BiPhePhos (1.1) AgOTf (1)	MTBE	<10	–	–

[a] Reaction conditions: 1a (99% *ee*) (0.5 mmol), 2 (0,75 mmol), $[Pd(allyl)Cl]_2$ (0.5 mol%), BiPhePhos (1.1 mol%), AgOTf (5 mol%), toluene (0.5 mL). [b] Conversion determined by ^1H NMR using xylene as an internal standard. [c] % enantiospecificity (% *ee* of product/% *ee* of substrate).

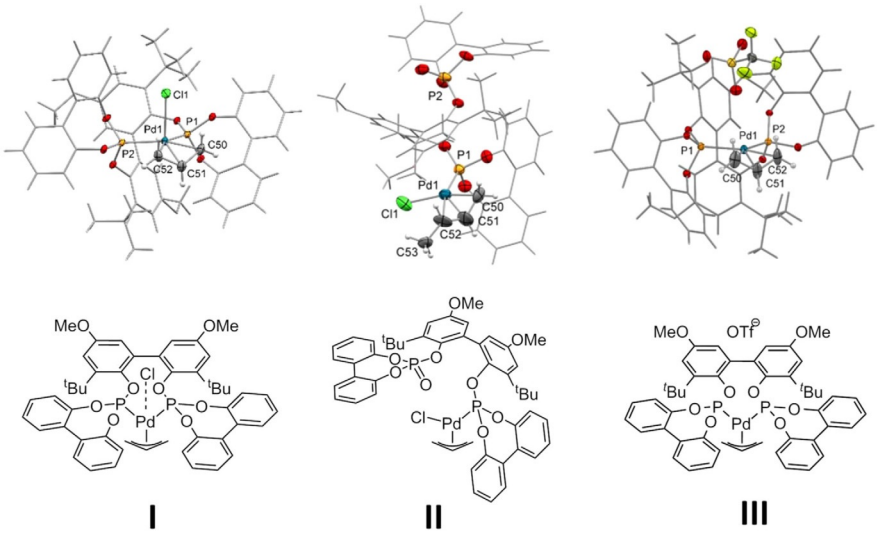


Figure 2. X-ray structure of Palladium complexes **I** (left), **II** (middle), and **III** (right) (top) and ChemDraw representations (below). For details see the supporting information.

decreased in favor of two new peaks in a 1:1 ratio at 136 and −2.8 ppm. Also other peaks were observed in the ^{31}P NMR spectrum. We were able to isolate complex **II** and grow crystals for X-ray crystallography (Figure 2). The decomposition of complex **I** to **II** was also observed during catalytic reactions.[20] Complex **II** was unreactive in the reaction with **1a** and **2a** to give **3a**, however became reactive after addition of AgOTf. Important to note, in this case no enantiospecificity was obtained. The complex obtained after addition of AgOTf to complex **I**, Pd[κ²-BiPhePhos][η³-C_3H_5]$^+$ + [OTf]$^-$, (complex **III**) was also crystallized. X-ray diffraction of complex **III** revealed the square planar geometry similar to that of **I** (Figure 3). The distance between the Pd-X differed between the two complexes where the Pd–Cl distance (2.67 Å) of complex **I** is significantly shorter than that of Pd-F where no interaction was observed (3.75 Å). The ^{31}P NMR spectrum of complex **III** showed two doublets with a coupling constant of J = 91.8 Hz at 145.7 and 147.0 ppm (vide infra). This pure complex gave high reactivity and enantiospecificity in the conversion of **1a** and **2a** to give **3a**. The Pd[κ²-BiPhePhos][η³-C_3H_5]$^+$ + [BF_4]$^-$ and Pd[κ²-BiPhePhos][η³-C_3H_5]$^+$ + [PF_6]$^-$ complexes also showed similar results as the triflate complex **III** (See Supporting Information).

Complexes **I** and **III** were more closely studied at variable temperatures using ^{31}P NMR spectroscopy. Complex **I** appeared as a singlet at 148.5 ppm at room temperature (Figure 3). When cooling down the NMR probe, the signal widened and at 0 °C appeared as a broad singlet. At −10 °C the signal split to two broad signals at 147.4 and 149.4 ppm. When cooling the probe to −20 °C the signals split to two distinguishable doublets. At −38 °C, the doublets are sharp with coupling constants of J = 91 Hz. The results from the variable temperature experiment with catalyst **I** is in accordance with that the chloride, that is loosely bound to the palladium (2.67 Å), is coordinating and decoordinating from the metal center forming a dynamic spectrum above −10 °C (vide infra).

Complex **III** shows two sharp doublets already at room temperature. When heating up the probe 100 °C, the two doublets remain. However at this temperature, complex **III** starts to decompose. This shows clearly that complexes **I** and **III** have different characteristics in which the chloride in complex **I** inter-

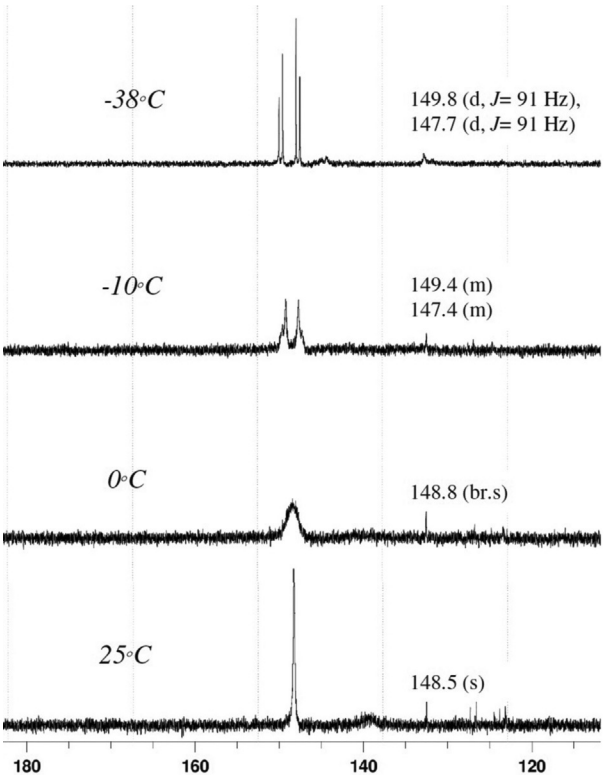


Figure 3. ^{31}P NMR spectra of complex I at −38 °C to 25° showing a dynamic behavior above −10 °C.

acts with the metal center at temperatures of which the catalytic experiments are performed.

The catalysts were also studied by ESI-MS in the reaction of **1a** and **2a** to generate **3a**. Reactions using complex **I** gave rise to several species, of which **II** and **II′** were observed as major complexes in the ESI-MS spectrum (Figure 4). When reactions were performed using complex **III**, the reaction was cleaner where only starting complex **III** and the complex from the first turn over (**III′**) where observed in the ESI-MS spectrum.

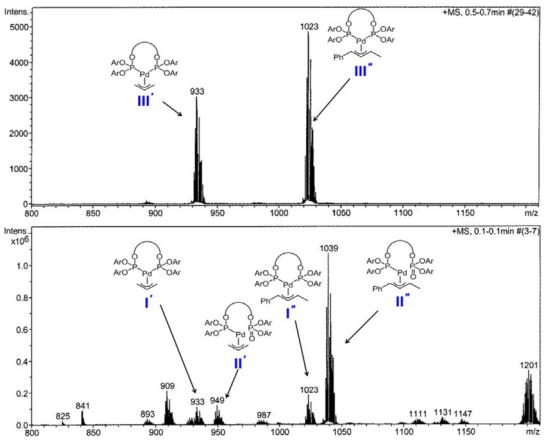


Figure 4. ESI-MS data for reactions using III that gives high chirality transfer, 95% e.s. (top) and for complex I that gave lower chirality transfer, 14% e.s. (bottom).

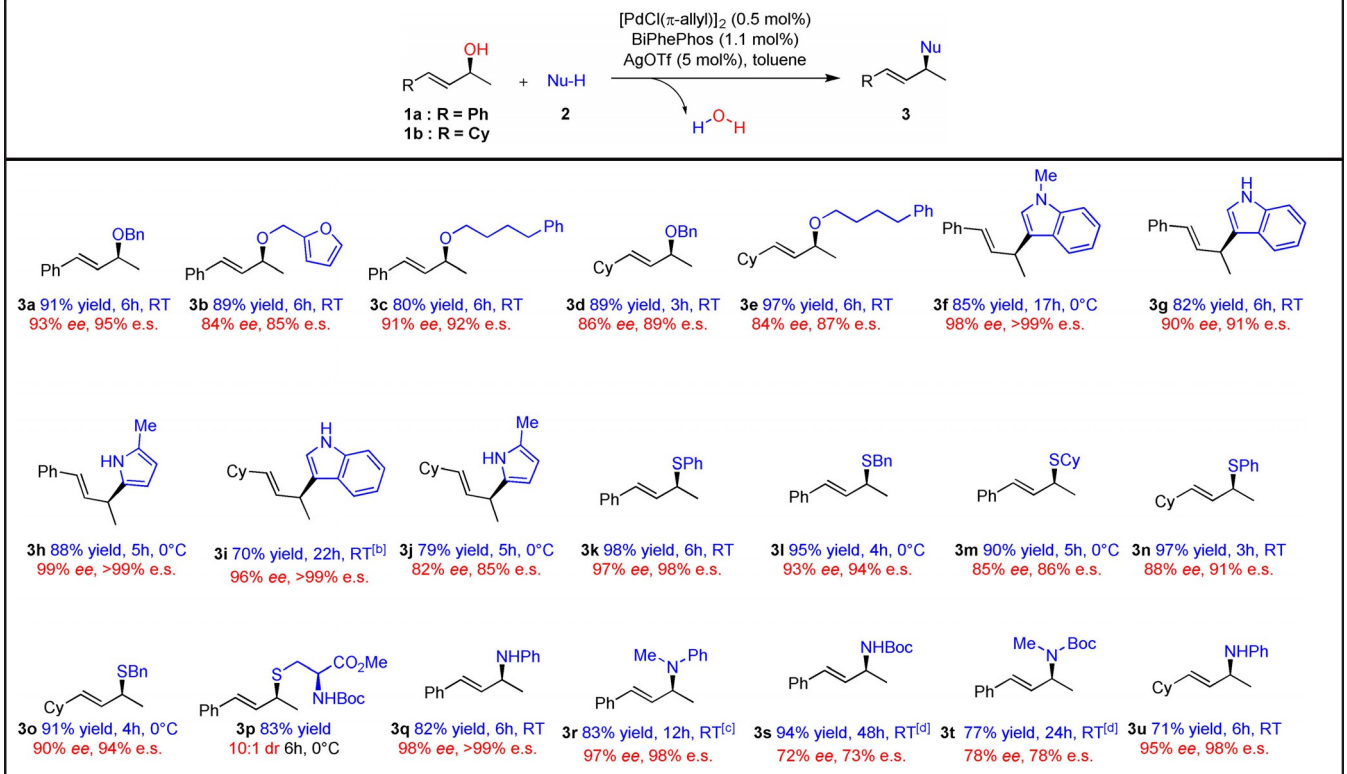
Important to note, no complexes with oxidized phosphates were observed when starting from complex **III**. A possible explanation for the higher stability of the triflate complex is that the non-coordinating triflate enhances the coordination between the phosphites and the palladium. The stronger coordinating chloride facilitate the decoordination of one of the phosphites and this would promote oxidation of the phosphite followed by decomposition of the complex to several species including complex **II** (vide infra).

B. Intermolecular Tsuji–Trost reaction of non-derivatized allylic alcohols

Complex **III** was readily generated in situ by mixing [Pd(π-allyl)Cl]$_2$, BiPhePhos, and AgOTf in DCM for 30 minutes followed by evaporation. The substrate scope of allylic substitution of the OH group by different nucleophiles and stereogenic allyl alcohols was examined. First oxygen-centered nucleophiles were used as nucleophiles. Benzylic, furfuryl, and aliphatic alcohols were tested as nucleophiles in the intermolecular substitution of (*E*,*S*)-4-phenylbut-3-en-2-ol ((*E*,*S*)-**1a**) and the non-aromatic (*E*,*S*)-4-cyclohexylbut-3-en-2-ol ((*E*,*S*)-**1b**). The reactions proceeded smoothly and products (*E*,*S*)-**3a-e** were obtained in good to excellent yields and with enantiospecificities above 85% (Table 2). Next, carbon-centered nucleophiles were trialed. The reaction was performed using *N*-methyl indole (**2f**) and the reaction proceeded to yield **3f** in 85% yield and an enantiospecificity >99%. Indole (**2g**) was used as substrate, and this substrate could potentially attack a π-allyl-palladium intermediate in the 1- or 3-position. Noteworthy, the indole attacked selectively in the 3-position to generate (*E*,*S*)-**3g** in high yield and excellent enantiospecificity. 2-Methylpyrrole as nucleophile gave corresponding product **3h**, with selective C-centered reactivity, in high yield and enantiospecificity. Reaction with less reactive **1b**, gave smooth reactions to yield **3i** and **3j** in moderate yields and high enantiospecificities. To our knowledge, these are the first reported examples of a stereospecific substitution of a non-derivatized allylic alcohol with a C-centered nucleophile in which water is generated as the only by-product. S-Centered nucleophiles are challenging substrates due to their susceptibility to coordinate and thus deactivate transition metal catalysts and have to our knowledge never been reported as a nucleophile in these reactions. Gratifyingly, the reaction of **2k** and (*E*,*S*)-**1a** generated substitution product (*E*,*S*)-**3k** in near quantitative yields and enantiospecificity. X-ray crystallography of the corresponding sulfone showed retention of configuration at the stereocenter of this novel compound (Figure 5).

Encouraged by this result, the reaction was performed with stronger nucleophiles. Both benzyl- and also alkyl thiols gave the corresponding products **3l** and **3m** in good to excellent yields and enantiospecificities. The reaction also worked well with less reactive **1b** to give products **3n** and **3o** in good to excellent yields and enantiospecificities. Inspired by this, protected (*R*)-cysteine was used as S-nucleophile. The reaction proceeded to give diastereomer (*R*,*S*)-**3p** in reasonable yields and high diastereoselectivity. Palladium-catalyzed allylic amina-

Table 2. Intermolecular allylic substitution.[a]



[a] Reaction condition: allylic alcohol **1a** (99% *ee*) or **1b** (96% *ee*) (0.5 mmol), nucleophile **2** (1 mmol), $[Pd(allyl)Cl]_2$ (0.5 mol%), BiPhePhos (1.1 mol%), AgOTf (5 mol%), toluene (0.5 mL), isolated yield was reported and % *ee* was measured by chiral HPLC, % e.s. is (% *ee* of product)/(% *ee* of substrate). [b] $[Pd(allyl)Cl]_2$ (2.5 mol%), BiPhePhos (5.5 mol%), AgOTf (2.5 mol%) were used. [c] $[Pd(allyl)Cl]_2$ (1 mol%), BiPhePhos (2.2 mol%), AgOTf (10 mol%) were used. [d] $[Pd(allyl)Cl]_2$ (2.5 mol%), BiPhePhos (5.5 mol%), AgOTf (25 mol%) were used and the reaction was run in MTBE (0.5 mL).

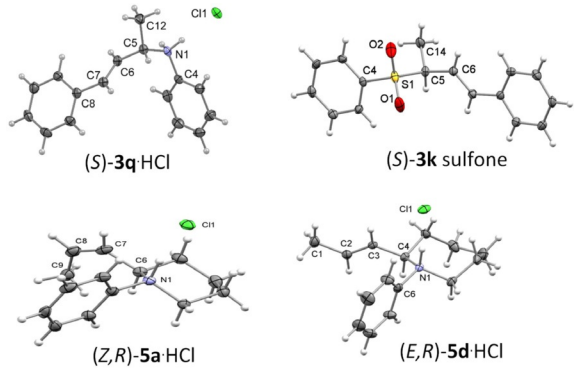
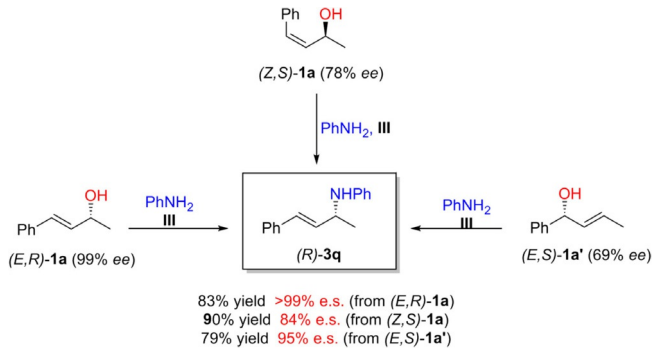


Figure 5. X-ray structures of novel compounds show that the reactions proceed with retention of configuration. ORTEP drawings, ellipsoids, are at 50% probability levels. For further crystallographic details see supporting information. Top left: (*S*)-**3q**.HCl. Top right: (*S*)-**3k**-sulfone. Bottom left: (*Z*,*R*)-**5a**.HCl Bottom right: (*E*,*R*)-**5d**.HCl.

tions by direct substitution of the OH group are challenging reactions for which only one single example has been reported.[5a] Taking into account the importance of stereogenic amines in the pharmaceutical and agricultural industries, we thought it would be worthwhile to explore these reactions. Allylic amination of (*E*,*S*)-**1a** by aniline (**2q**) gave product (*E*,*S*)-**3q** in 82% isolated yield and >99% enantiospecificity. The reactions proceed with retention of configuration at the stereocenter (determined by X-ray crystallography, see Figure 5). The reaction of (*E*,*S*)-**1a** with sterically hindered secondary *N*-methylaniline and (*E*,*S*)-**1a** gave (*E*,*S*)-**3r** in 83% yield and 98% enantiospecificity. Even weakly nucleophilic *N*-Boc and N(Me)-Boc worked as nucleophiles in the substitution reaction to yield products **3s** and **3t** in moderate to high yields and enantiospecificities. The scope of starting material was extended to the less reactive aliphatic allylic alcohol (*E*,*S*)-**1b**. Gratifyingly, product (*E*,*S*)-**3u** was obtained in a 71% yield and excellent enantiospecificity. It should be noted that all reactions in Table 2 proceeded to full conversion where no starting material and only desired product were observed in the ^{1}H NMR spectrum of the crude reaction mixtures.

As showed above, amination of (*E*,*R*)-**1a** proceeds with retention of configuration to yield (*E*,*R*)-**3q** in high yield and enantiospecificity. Using the corresponding *Z*-olefin (*Z*,*S*)-**1a** gave the inverted product (*E*,*R*)-**3q** in excellent yield and slightly lower enantiospecificity (Scheme 3).[5,6] This is consistent with an η^3-η^1-η^3 isomerization mechanism, where the palladium π-allyl isomerizes from the less stable *Z*-olefin to the more stable *E*-olefin.[7] When substrate (*E*,*R*)-**1a′** was used, in which the olefinic position has been transposed, the nucleophilic attack was selective to the olefinic position to give (*E*,*R*)-**3q** in excellent yield and chirality transfer via a formal S_N2' re-



Scheme 3. Absolut configuration of the product is dependent on both the absolute configuration of the substrate as well as the geometry of the olefin.

action. Thereby, the configuration of the stereocenter of the new C–N bond is, as expected, dependent on both the absolute configuration of chiral substrate and the geometry of the olefin.

B. Intramolecular Tsuji–Trost reaction of non-derivatized allylic alcohols

Even though a series of methodologies of Pd^{II}- and Au^{I}-catalyzed intramolecular substitution reactions of stereogenic alcohols by both N-, and O-centered nucleophiles with chirality transfer to generate 6-membered rings have been developed and studied by the Uenishi, Widenhoefer, Aponick groups, the corresponding intramolecular reactions proceeding through a π-allyl-palladium intermediate has been less studied.[14] In the case of Pd^{II}- and Au^{I}-catalyzed intramolecular reactions, a favored bicyclic transitions state is required for the reactivity.[14j] Because the present methodology proceeds through a π-allyl-palladium intermediate, we assumed that other ring-sizes would be possible, hence greatly expand the current substrate scope. Gratifyingly, substrate (*Z*,*S*)-**4a** was reacted to form the desired heterocycle (*E*,*S*)-**5a** as the major product in a good yield and excellent enantiospecificity (Table 3, entry 1). The corresponding *Z*-isomer was isolated as a minor side-product. The corresponding *E*-isomer, substrate (*E*,*R*)-**4a**, was reacted under the same reaction conditions to give a 3:1 ratio of products (*E*,*S*)-**5a** and (*Z*,*R*)-**5a**. The absolute configuration of (*Z*,*R*)-**5a** was determined by X-ray crystallography (Figure 5). Substrate **4b** has never been used in a substitution reaction with enantiospecificity, because the substrate is typically not susceptible towards formal S_N2 reactivity.[13–16] Using the current approach, the reaction proceeded smoothly to give (*E*,*S*)-**5b** with no loss in enantiospecificity. To expand this methodology to smaller ring sizes, substrate (*Z*,*S*)-**4c** was studied. The diastereomer of the corresponding 5-membered heterocycle (**5c**) was generated in a 14(*E*,*S*):1(*Z*,*R*) ratio. The generation of both 5-, and 6-membered cycles are favored kinetically and/or thermodynamically; in contrast, seven membered rings are not. To our knowledge the generation of a 7-membered ring from the corresponding stereogenic alcohol with has not yet been reported. Gratifyingly, we could generate (*E*,*R*)-**5d** as the single diastereomer in 85% yield and full enantiospecificity from substrate (*E*,*S*)-**4d** disclosing the strength of this catalytic system. The absolute configuration of the corresponding HCl salt was determined by X-ray crystallography (Figure 5).

Alcohols as nucleophiles also worked in the intramolecular stereoselective substitution reaction. When (*E*,*S*)-**4e** was run, the corresponding (*E*,*S*)-**5e** was obtained with excellent enantiospecificity through a formal S_N2' reaction.

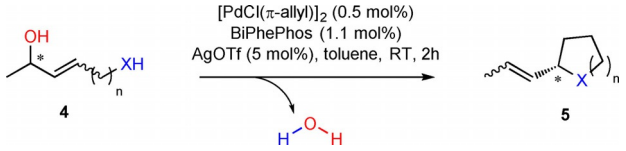
C. Natural product synthesis

To test the efficiency and the robustness of the Pd[BiPhePhos]-catalyzed stereospecific substitution we sought to apply the methodology in the total synthesis of natural products. (*S*)-cuspareine, tetrahydroquinoline alkaloid isolated from *Galipea officinalis*, which shows antiplasmodial activity,[21] was synthesized in 7 steps from commercially available **7** without needing any protecting groups. The synthesis starts out with a Grignard reaction, followed by reduction and a lipase-catalyzed kinetic resolution to generate stereogenic precursor **8** (Scheme 4). The stereospecific substitution reaction by complex **III** ring-closes the (*R*)-allylic alcohol intermediate **9** to generate tetrahydroquinoline **10** in 71 yield and 96% enantiomeric excess. (*S*)-cuspareine was finally obtained by hydrogenation of **10**. This demonstrates that a natural product can by prepared from an accessible chiral allylic alcohol.[22] Azasugar, (+)-lentiginosine isolated from *Astralagus lentiginosus*, which shows amyloglycosidase and Hsp90 inhibitory activities,[23] was synthesized from cheap and abundant D-galactose. The synthesis was carried out by applying the Bernet–Vasella reaction of the iodo-galacto pyronoside **12**[24] to yield oxime **13** in a one-pot transformation. The oxime **13** was reduced and transformed to Boc-protected amino allylic alcohol **14**. This key intermediate was then used in the complex **III**-catalyzed stereospecific substitution and ring-closure to give **15** in a high yield with excellent diastereospecificity (96% *ee*). The Boc group was exchanged for a butenyl group to generate intermediate **16**. The diene **16**, was ring-closed using Grubbs (2^{nd} generation) catalyst and this intermediate was then reduced and deprotected in one step by Pd-catalysis to give (+)-lentiginosine.[25] This synthetic route shows that the catalyst is quite robust even to demanding substrates having several functional groups and demonstrates the potential to use bio-based starting material as feedstock to produce a natural product.

Mechanistic discussion

The Pd[BiPhePhos] catalyst is an efficient catalyst for the C–O bond cleavage in the nucleophilic substitution of the OH group in allylic alcohols. We were intrigued by the counter ion effect, where complex **III**, with an OTf anion gave a more stable and efficient catalyst than the corresponding Cl complex **I**. From the X-ray crystal structure of complex **I** (Figure 2), a weak coordination of the chloride to palladium (2.67 Å) is observed. Thereby, an equilibrium (K_1) between κ^2-**I** and κ^1-**I** will be present in solution (Scheme 5). This equilibrium is apparent when complex **I** was studied by ^{31}P NMR at variable tempera-

Table 3. Intramolecular allylic substitution.[a]



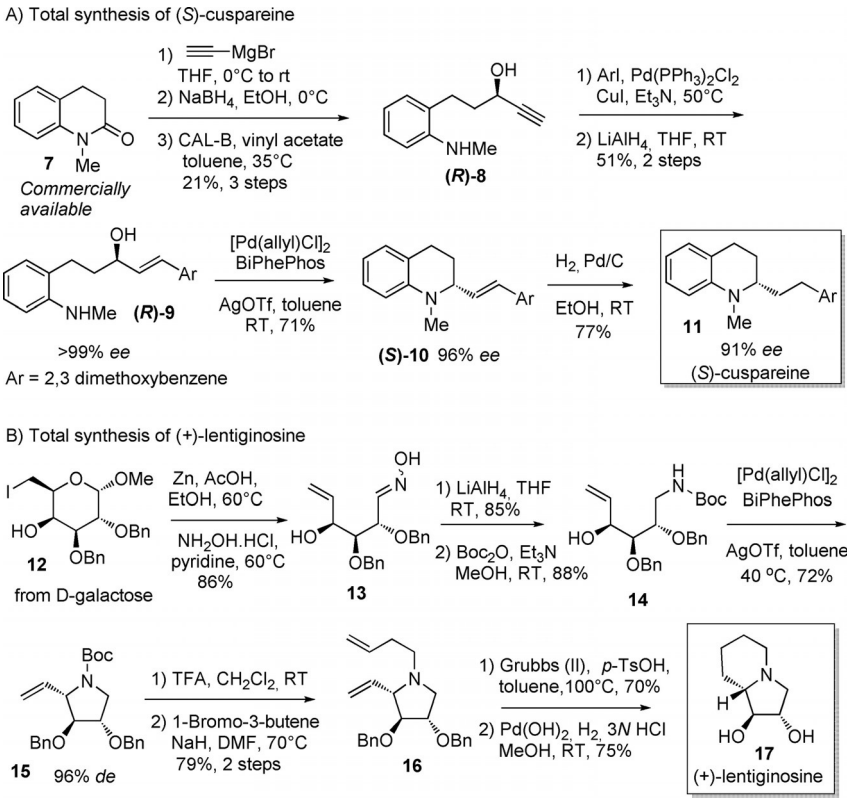
Entry	Substrate	Product	Yield (%)[b]	es (%)[c]
1	(*Z*,*S*)-**4a** (96% *ee*)	(*E*,*S*)-**5a** (96% *ee*)	74 (*E*/*Z* = 10:1)	> 99 (*E*) 97 (*Z*)
2	(*E*,*R*)-**4a** (95% *ee*)	(*E*,*S*)-**5a** (95% *ee*) (*Z*,*R*)-**5a** (91% *ee*)	86 (*E*/*Z* = 3:1)	> 99 (*E*) 96 (*Z*)
6	(*E*,*S*)-**4b** (77% *ee*)	(*E*,*S*)-**5b** (79% *ee*)	84	> 99
3	(*Z*,*S*)-**4c** (91% *ee*)	(*E*,*S*)-**5c** (90% *ee*)	87 (*E*/*Z* > 14:1)	99
4	(*E*,*S*)-**4d** (74% *ee*)	(*E*,*R*)-**5d** (74% *ee*)	75 (*E*/*Z* > 20:1)	> 99
5	(*E*,*R*)-**4e** (78% *ee*)	(*E*,*S*)-**5e** (74% *ee*)	61	95

[a] Reaction condition: allylic alcohol (0.5 mmol), $[Pd(\text{-allyl})Cl]_2$ (0.5 mol%), BiPhePhos (1.1 mol%),AgOTf (5 mol%) toluene (2 mL) [b] Isolated yield [c] % e.s. is (% *ee* of product)/(% *ee* of substrate), % *ee* was determined by chiral HPLC.

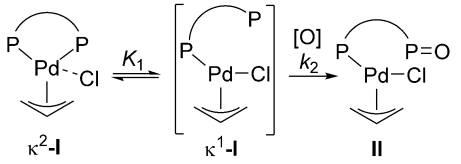
tures (Figure 3). At catalysis temperatures the broad signal in the ^{31}P NMR spectrum alludes to an equilibrium between κ^2-**I** and κ^1-**I**. Even though this equilibrium is strongly shifted to κ^2-**I** ($K_1 = < 1$), a low concentration of κ^1-**I** will be present in solution. The highly reactive κ^1-**I** undergoes a rapid and irreversible oxidation to the corresponding phosphate to generate complex **II**. In the case of the triflate complex **III**, there is no interaction between the triflate and the palladium. The crystal structure of complex **III** shows a distance of 3.75 Å between palladium and the triflate. By studying fluxional behavior of complex **III** by ^{31}P NMR, no interaction between triflate and metal were observed (Figure 3). Thereby, in the case of complex **III**, the X-ligand cannot promote the equilibrium to the corresponding κ^1-complex in analogy to complex **I** ($K_1 = \ll 1$). This prevents the irreversible oxidation of one of the phosphites and thereby explains the stability of complex **III**.

It is known that the stereospecificity in allylic substitution is dependent on a low concentration of free Pd^0 species present in solution. This is even more important in the case of allyl substrates with poor leaving groups, as in the present case with non-derivatized allylic alcohols. In this case, there will be a competition of the Pd^0 species to promote oxidative addition with either the allyl alcohol or a formed Pd π-allyl complex present in solution. The mechanism for the latter case is depicted in Scheme 6, where Pd^0 promotes an oxidative addition of the chiral palladium allyl species and thereby racemize the complex. The Pd[BiPhePhos] complex that is very reactive in the C–O bond cleavage of non-derivatized allylic alcohols will not promote the racemization in Scheme 6. This is supported by the fact that complex **III** gives high conversion and enantiospecificties and a low degree of catalyst degradation. However, in the case of complex **I**, degradation to monodentate species were observed at the same time as the reactions gave poorer and less reliable enantiospecificities. This can be explained by that a less reactive complex will lead to a higher concentration of Pd^0 species. These generated Pd^0 species are not reactive in the C–O bond cleavage in allylic alcohols. However, these less reactive species are reactive in the racemization reaction depicted in Scheme 5. This was supported by an experiment in which Pd^0 (1 equiv to **III**) was added to the reaction mixture of the reaction of **1a** and **2a** to generate **3a**. The addition of Pd^0 led to a decrease in the enantiospecificity from 98% to below 44%. This was further supported by the fact that starting the reaction using Pd^0 with the BiPhePhos ligand gave poorer enantiospecificity (Table 1, entry 5). An alternative explanation for the racemization is that the degradation species promote a hydrogen borrowing pathway in which the allylic alcohol would be dehydrogenated to the corresponding achiral ketone.[26] An experiment was performed in which **1a** and **2a** were reacted in the presence of complex **I** and benzoquinone. The formation of hydroquinone was observed however, no increase in enantiospecificity was observed. Thereby, the hydrogen borrowing pathway is not operating in the current reaction. We have recently studied the reaction mechanism of the related $Pd[P(OPh)_3]_3$-catalyzed reaction and based on rate order determination, kinetic isotope effect, and ESI-MS a reaction mechanism that proceeded through a palladium hydride intermediate was proposed.[18b]

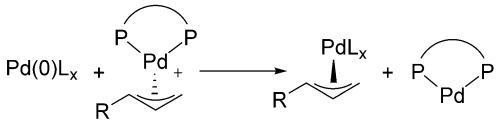
Ozawa and Yoshifuji proposed a similar reaction mechanism for their Pd[DPCB] catalyst, based on thorough studies on both Pd and Pt catalysts.[27] The palladium hydride intermediate is responsible for the C–O bond cleavage to generate the π-allyl palladium intermediate. With the Pd[BiPhePhos] we propose a similar reaction mechanism (Scheme 7). In this reaction mechanism, the Pd[BiPhePhos] promotes the generation of the reac-



Scheme 4. Total synthesis of (*S*)-cuspareine and (+)-lentiginosine using Pd[BiPhePhos]-catalyzed stereospecific allylic substitution in the key step.



Scheme 5. The chloride promotes oxidation to generate complex **II**.

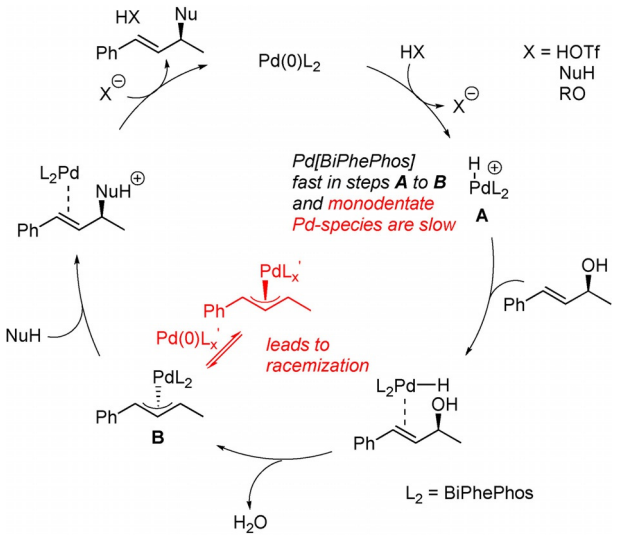


Scheme 6. Pd^0 promotes racemization of chiral palladium π-allyl complexes.

tive palladium hydride intermediate **A** that is responsible for the C–O bond cleavage reaction to generate the π-allyl palladium intermediate **B** (Scheme 7, black path). The Pd[BiPhePhos] is very reactive in the initial steps in the reaction mechanism and this leads to that this species will always be present at low concentration. However, the degradation products, such as complex **II** and $Pd[P(OPh)_3]_2$, are not reactive enough in these reaction steps and therefore the concentration of Pd^0 species may build up during the reaction. These less reactive Pd^0 species can promote the oxidative addition of a π-allyl palladium intermediate and this leads to the observed racemization (Scheme 7, red pathway). Finally, the nucleophile attacks from the outer sphere to generate a product with retention of configuration.

Conclusion

In conclusion, novel palladium BiPhePhos catalyst (**III**) has been synthesized and fully characterized. The stability and thereby also the efficiency of this catalyst in the C–O bond cleavage reaction of allylic alcohols are highly dependent on the counter anion. With less coordinating anions, such as the triflate, the coordination of the phosphites of the BiPhePhos ligand to palladium becomes stronger and this promotes the stability of the catalyst. With a more coordinating anion such as the chloride, an equilibrium between κ^2-**I** and κ^1-**I** occurs. The resulting decoordination of one of the phosphites of the BiPhePhos leads to an irreversible oxidation to the corresponding non-coordinating phosphate. This decomposition leads to palladium species in solution that are not reactive in the reaction steps leading to the palladium-π-allyl complex. However, these Pd^0 species are reactive in the oxidative addition of a palladium-π-allyl complex which leads to a racemization. Gratifyingly, suppressing this unwanted pathway is easily conducted using a non-coordinating anion. Highly reactive complex **III** is readily prepared in situ by mixing Pd precursor, BiPhePhos ligand and silver triflate. The resulting catalyst (**III**) is very reactive in a broad scope of both inter- and intramolecular stereospecific substitution of the OH group in enantioenriched allylic



Scheme 7. Proposed reaction mechanism for the Tsuji–Trost reaction of allylic alcohols.

alcohols by a variety of N-, S-, C-, and O-centered nucleophiles. The corresponding products were obtained in good to excellent yields and enantiospecificities with water as the only by product. The efficiency of this catalyst was further demonstrated in the total synthesis of (*S*)-cuspareine and (+)-lentiginosine where the methodology was used in key steps. We hope that this easily accessible catalyst will be used in the allylic substitution of non-derivatized alcohols in both academia and in industry.

Experimental Section

General information

All catalysts, reagents and solvent were purchase from Sigma–Aldrich Company. Solvents were dried by distillation from the appropriate drying reagents prior to use. Toluene and dichloromethane were distilled from calcium hydride under argon. Aniline was distilled under reduced pressure and stored under argon. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon using standard Schlenk techniques. Analytical thin-layer chromatography (TLC) was conducted using Merck analyticl TLC plates (silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1 M sulfuric acid in ethanol. Flash column chromatography was performed on silica gel (35–70 micron). Infrared (IR) spectra were recorded on a PerkinElmer FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using a Varian 400 MHz spectrometer, Bruker 400 MHz spectrometer and Bruker 500 MHz spectrometer. Chemical shifts were recorded as δ values in ppm. Coupling constants (J) are given in Hz, and multiplicity is defined as follows: br = broad, s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, dq = doublet of quintet, t = triplet, td = triplet of doublet, tt = triplet of triplet, q = quartet, quint = quintet, hep = heptet, m = multiplet. High resolution mass spectrometry was recorded on Bruker Daltonics MicrOTOF. Chiral separation was performed with HPLC (YL-Clarity HPLC instrument) using Daicel Chiralcel column AD, OD-H and OJ-H.

Procedure for preparation of the Pd[κ²-BiPhePhos][η³-C_3H_5]⁺ + [OTf]⁻: A flame-dried Schlenk tube was charged with $[Pd(allyl)Cl]_2$ (0.028 mmol), BiPhePhos (0.051 mmol), AgOTf (0.11 mmol) and CH_2Cl_2 (0.5 mL). The mixture was degassed by three freeze–pump–thaw cycles and stirred at room temperature for 30 min then AgCl was filtered off through syringe filter and the solvent was removed under vacuum.

General procedure for catalytic enantiospecific nucleophilic substitution of allylic alcohol: A solution of enantiopure allylic alcohol (0.50 mmol), NuH (0.75 mmol) in toluene or MTBE (0.5 mL, 1.0 M) was added to the Pd[κ²-BiPhePhos][η³-C_3H_5]⁺ + [OTf]⁻ (complex **III**) (1–5 mol%). The slurry was degassed by three freeze–pump–thaw cycles and stirred at 0 °C or room temperature. The reaction was monitor by ^{1}H NMR, when the reaction had reached full conversion it was purified by column chromatography on silica gel.

Experimental procedure for catalytic asymmetric synthesis of (*E*,*S*)-(3-(benzyloxy)but-1-en-1-yl)benzene, (*S*)-3 a: A flame-dried Schlenk tube containing a stir bar was charged with $[Pd(allyl)Cl]_2$ (0.9 mg, 0.5 mol%) and BiPhePhos (4.3 mg, 1.1 mol%) and AgOTf (6.3 mg, 5 mol%) and CH_2Cl_2 (0.5 mL). The mixture was degassed by three freeze–pump–thaw cycles and stirred at room temperature for 30 min, after which the AgCl was filtered off and solvent was removed under vacuum. A solution of allylic alcohol (*S*)-**1 a** (74 mg, 0.50 mmol), benzyl alcohol **2 a** (50 μL, 0.75 mmol) in toluene (0.5 mL, 1 M) was added to the [Pd-BiPhePhos]OTf complex. The slurry was degassed by three freeze-pump-thaw cycles and stirred at room temperature. The reaction was monitor by ^{1}H NMR, when the reaction had reached full conversion it was purified by column chromatography on silica gel eluting with pentane:EtOAc (50:1) to give the desired product (*S*)-**3 a** as colorless oil (108 mg, 0.45 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.21 (m, 10H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.17 (ddd, *J* = 1.3, 7.8, 16.0 Hz, 1H), 4.62 (dd, *J* = 1.3, 12.0 Hz, 1H), 4.44 (dd, *J* = 1.3, 12.0 Hz, 1H), 4.15–4.05 (m, 1H), 1.37 (dd, *J* = 1.3, 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.8, 136.6, 131.7, 131.4, 128.6 (2), 128.3 (2), 127.7 (3), 127.4, 126.5 (2), 75.8, 70.0, 21.7; IR (neat, cm^{-1}): 3027, 2970, 2861, 1493, 1450, 1229, 1217, 1068; HRMS (ESI) Calcd. for $C_{17}H_{18}NaO$, $[M+Na]^+$: 261.1250 Found 261.1244; HPLC condition for **3 a**: Daicel Chiralpak OJ-H, *n*-hexane/*i*PrOH (97:3), flow rate 1 mL min^{-1}, t_R = 9 min for *S*-isomer, t_R = 11 min for *R*-isomer.

Experimental procedure for the catalytic transformation of (*Z*,*S*)-4 a to (*E*,*S*)-5 a: A flame-dried Schlenk tube containing a stir bar was charged with $[Pd(allyl)Cl]_2$ (0.86 mg, 0.5 mol%) and BiPhePhos (4.1 mg, 1.1 mol%) AgOTf (6 mg, 5 mol%) and CH_2Cl_2 (0.5 mL). The mixture was degassed by three freeze–pump–thaw cycles and stirred at room temperature for 30 min, after which the AgCl was filtered off and solvent was removed under vacuum. A solution of allylic alcohol (*Z*,*S*)-**4 a** (103 mg, 0.47 mmol), in toluene (5 mL, 0.25 M) was added to the [Pd-BiPhePhos]OTf complex. The slurry was degassed by three freeze–pump–thaw cycles and stirred at room temperature. The reaction was monitor by ^{1}H NMR, when the reaction had reached full conversion it was purified by column chromatography on silica gel eluting with pentane:EtOAc (50:1) to give the piperidine (*E*)-**5 a** as a colorless oil (70 mg, 0.35 mmol, 75% yield with 10:1 *E*/*Z* mixture). (*E*,*S*)-**5 a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 7.4, 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.76 (t, *J* = 7.4 Hz, 1H), 5.47–5.42 (m, 2H), 4.22 (br, 1H), 3.30 (dt, *J* = 3.2, 9.0 Hz, 1H), 3.12–3.03 (m, 1H), 1.91–1.49 (m, 6H), 1.59 (d, *J* = 3.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.3, 129.9, 128.8 (2), 126.8, 118.6, 117.1 (2), 57.5, 45.6, 31.2, 25.9, 20.2, 17.9; IR (neat, cm^{-1}): 3023, 2932, 2854, 1596, 1479, 1447, 1377, 1246, 1166, 1023;

HRMS (ESI) Calcd. for $C_{14}H_{20}N$, $[M+H]^+$: 202.1590 Found 202.1589; HPLC condition for (*E*)-5a: Daicel Chiralpak OJ-H, *n*-hexane/*i*PrOH (98:2), flow rate 0.5 mL min^{-1}, t_R = 10.7 min for *S*-isomer, t_R = 12.1 min for *R*-isomer; (*Z*,*R*)-**5a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (td, J = 7.4, 1.7 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H), 6.81 (tt, J = 0.8, 7.2 Hz, 1H), 5.54–5.33 (m, 2H), 4.35–4.30 (m, 1H), 3.15 (t, J = 4.9 Hz, 2H), 1.80–1.56 (m, 6H), 1.60 (d, J = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.8, 130.5, 128.7 (2), 124.6, 120.0, 118.7 (2), 54.1, 48.5, 31.8, 26.2, 21.2, 13.2; IR (neat, cm^{-1}): 3016, 2928, 2856, 1598, 1500, 1369, 1216; HRMS (ESI) Calcd. for $C_{14}H_{20}N$, $[M+H]^+$: 202.1590 Found 202.1599; HPLC condition for (*Z*)-**5a**: Daicel Chiralpak OJ-H, *n*-hexane/*i*PrOH (98:2), flow rate 0.5 mL min^{-1}, t_R = 9.2 min for *R*-isomer, t_R = 12.6 min for *S*-isomer.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · cuspareine · OH activation · palladium · Tsuji–Trost reaction

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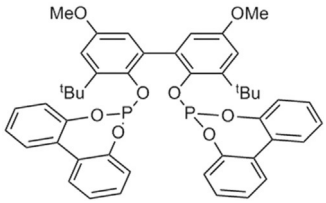

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