Heck Reaction

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# Palladium-Catalyzed Asymmetric Intermolecular Cyclization**

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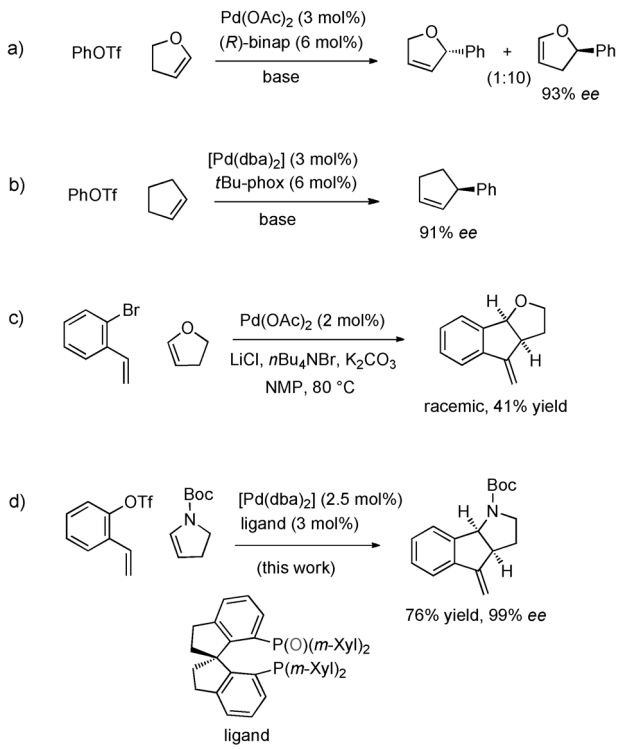
Asymmetric Heck reactions have been used to directly couple simple aryl electrophiles with carbocycles and heterocycles.[1] In 1991, Hayashi and co-workers described the first example of this kind using binap as a supporting ligand (Scheme 1 a).[2] Since then, many chiral ligands have been tested in the search for more active and stereoselective catalysts. Most of those fall into the categories of bisphosphanes, bisphosphites, and mixed phosphane–oxazoline ligands.[3] For example, the phosphanyldihydrooxazole (phox) catalysts developed by Pfaltz and co-workers can minimize double-bond migration in the Heck products, although the turnover was very slow (Scheme 1 b).[4] We envisioned that if a second alkene group was present in the vicinity, alkylpalladium species from the Heck reaction could undergo a second insertion. In this way, chiral compounds with rather complex structures could be accessed rapidly.

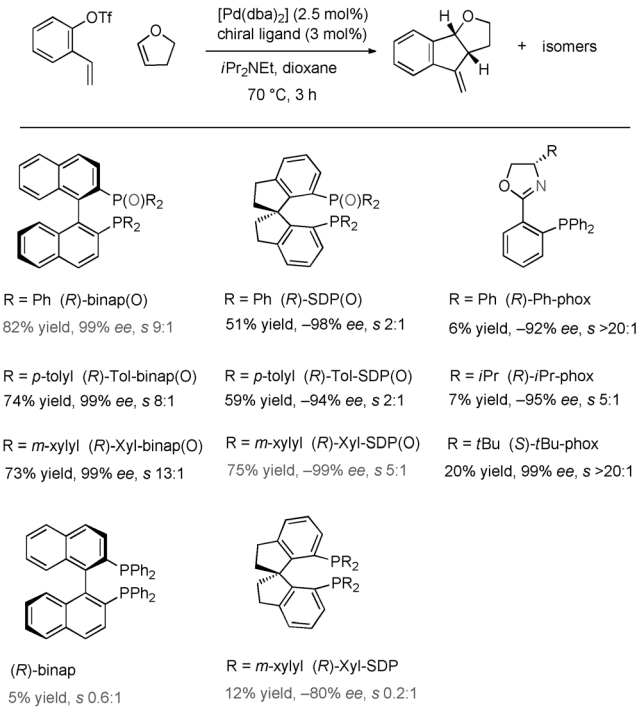
Numerous examples of palladium-catalyzed multiple insertions of alkenes and alkynes have been reported, but almost all were initiated by intramolecular insertion and provided racemic or achiral products.[5] In a rare example initiated by intermolecular insertion, de Meijere and co-workers reported a cyclization between *o*-vinylphenyl bromide and 2,3-dihydrofuran, albeit in moderate yield and with limited scope (Scheme 1 c).[6] In the presence of a phosphane ligand, however, noncyclized products became the major products.

Herein, we report an asymmetric domino cyclization that formed fused carbo- and heterocycles with excellent stereoselectivity (Scheme 1 d). The new method was used in a short synthesis of a chiral diamine en route to a primary ingredient in folk eye medicine in South America, (−)-martinellic acid.

Initially, we chose a model reaction between *o*-vinylphenyl triflate and 2,3-dihydrofuran to search for a suitable catalyst (Scheme 2). The ligand (*R*)-binap gave the desired product in only low yield and a significant amount of noncyclized isomers. In contrast, (*R*)-binap(O) gave the




***Scheme 1.*** Examples of asymmetric Heck reactions and domino Heck cyclization reactions. Boc = *tert*-butoxycarbonyl, dba = dibenzylideneacetone, NMP = *N*-methyl-2-pyrrolidinone, Tf = trifluoromethanesulfonyl, Xyl = xylyl.




***Scheme 2.*** Catalyst discovery.

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cyclized isomer in good yield with near-perfect enantioselectivity (99% *ee*). The selectivity *s*, which is the ratio between the amount of the cyclized isomer and the sum of the amounts of other isomers, was determined to be 9:1 by GC. The size of the *P*-aryl groups of the binap(O) ligand had little influence on the reaction. (*R*)-Binap dioxide was not an active ligand.

Previously, Oestreich et al. reported that the (*R*)-binap(O) ligand was much more active and stereoselective than (*R*)-binap in simple Heck reactions. For example, when the former was used as the supporting ligand, PhOTf and 2,3-dihydrofuran reacted to give the (2*R*)-isomer with 92% *ee*.[7] We assigned the absolute configuration of our tricyclic products by analogy with the simple Heck products described by Oestreich et al.

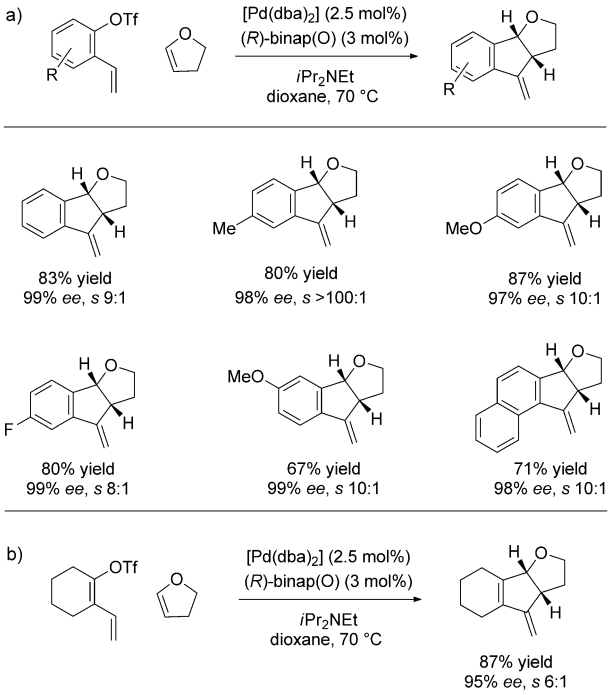
We also examined other bisphosphane oxides. When (*R*)-Xyl-SDP(O) was used, a good yield and almost perfect enantioselectivity were observed, although slightly more of the noncyclized isomers were observed (*s* value: 5:1).[8] Interestingly, the absolute configuration of the major product was opposite to that of the product formed with the (*R*)-binap(O) catalyst. In fact, (*R*)-binap(O) and (*R*)-SDP(O) are considered to be "pseudoenantiomers" owing to the difference in nomenclature. (*R*)-Segphos oxide also provided good results (74% yield, 99% *ee*, and *s* 11:1; segphos = 4,4′-bi-1,3-benzodioxole-5,5′-diylbis(diphenylphosphane)). With phox ligands, we observed very slow turnover, which mirrored the earlier observations by Pfaltz and co-workers for simple asymmetric Heck reaction.[4] Given a longer reaction time (2 days), the *t*Bu-phox catalyst gave almost exclusively the desired isomer (90% yield, 99% *ee*).

The less σ-donating bisphosphane oxides formed more active Heck catalysts than bisphosphanes. Alkene insertion into cationic aryl palladium(II) complexes may be faster with a more electron-deficient Pd center. Furthermore, base deprotonation of palladium hydride complexes is probably faster with more electron-poor palladium complexes. Fast deprotonation is essential to regenerate the Heck catalyst[9] and prevent double-bond migration in the Heck products.[10]

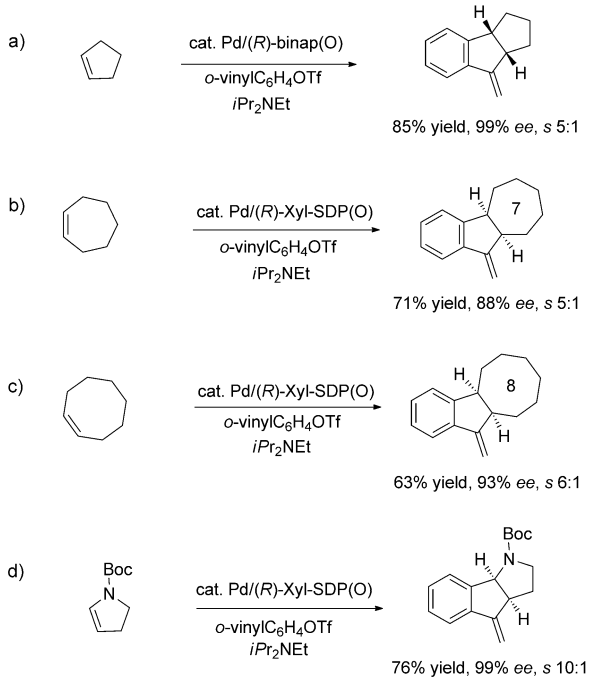
Next, we established that *o*-vinylaryl triflates bearing electron-donating and electron-withdrawing groups can be used in the cyclization with 2,3-dihydrofuran (Scheme 3a). The tricyclic products were obtained with excellent enantioselectivity. A 1,3-dienyl triflate also underwent this cyclization with 2,3-dihydrofuran (Scheme 3b).

Cyclic alkenes of five-, seven-, and eight-membered rings were also coupled efficiently with *o*-vinylphenyl triflate (Scheme 4). In the reactions of cycloheptene and cyclooctene (Scheme 4b,c), double-bond migration to the *endo* position in some products was observed if the (*R*)-binap(O) catalyst was used. Use of the (*R*)-Xyl-SDP(O) catalyst minimized this side reaction. *N*-Boc-2-pyrroline was also coupled very efficiently (Scheme 4d). Cyclohexene did not react, because its half-chair conformation interfered with its binding and insertion; neither did six-membered cyclic enol ethers or enecarbamates undergo the desired cyclization.

The cyclization was also applied successfully to norbornene and related bicyclic alkenes (Scheme 5). The strained olefin was known to readily insert into palladium–aryl bonds.[11] The resulting norbornylpalladium species lacked



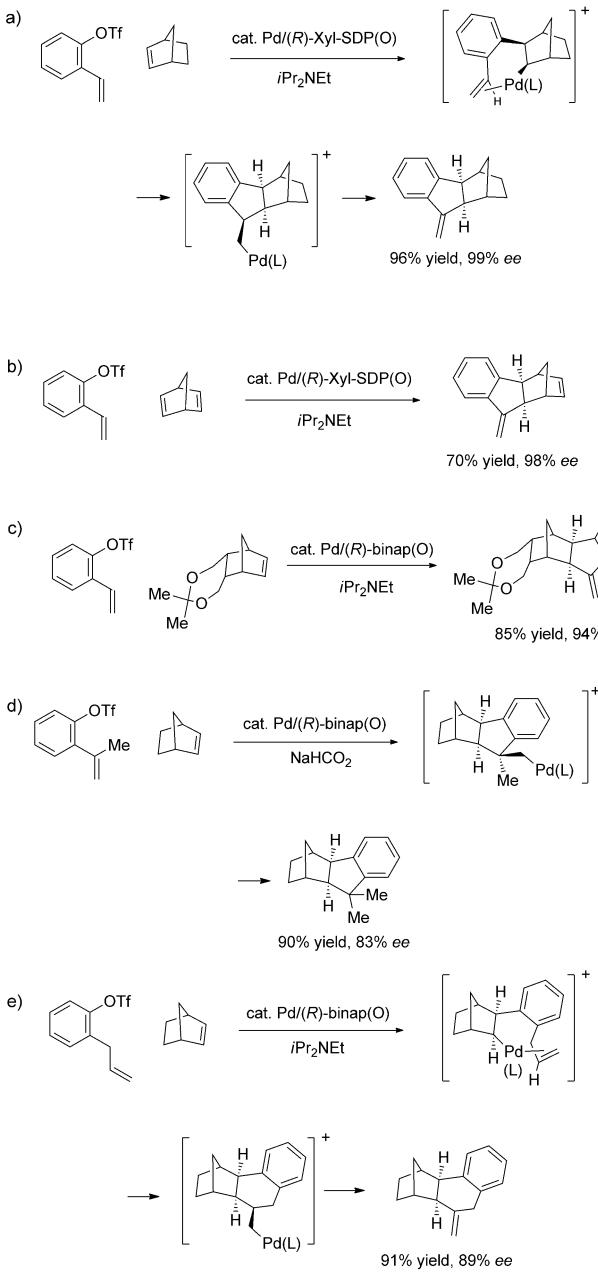

***Scheme 3.*** Cyclization of 2,3-dihydrofuran.




***Scheme 4.*** Cyclization of simple alkenes. (The reactions were carried out with 2.5 mol% of the Pd catalysts.)

β-hydrogen atoms for *syn* elimination, and hence the tricyclic products were produced as single stereoisomers. According to our conformational analysis, the preferred eclipsed insertion could not proceed unless the vinyl group was oriented towards the *exo* face of norbornane (Scheme 5a). Very little by-product was formed by insertion into the second alkene




***Scheme 5.*** Cyclization of bicyclic alkenes. (The reactions were carried out with 2.5–5 mol% of the Pd catalysts.)

group of norbornadiene after the first insertion (Scheme 5b). The key alkyl palladium intermediate could be reduced with sodium formate (Scheme 5d). Furthermore, the *ortho* vinyl group in the triflate substrate can be changed to an allyl group (Scheme 5e).

To probe the origin of the stereoselectivity observed with the (*R*)-binap(O) catalyst, we prepared a neutral oxidative-addition complex of *o*-vinylphenyl bromide (Figure 1). In the X-ray crystal structure of this complex, the *o*-vinylphenyl and diphenylphosphanyl groups were found to be *cis* to each other on the Pd center; thus, a so-called *cis* complex was formed.[12] In the crystal structure of [(*R*)-Xyl-SDP(O)]-(phenyl)(I)Pd$^{II}$[12] a *cis*-complex was also observed.

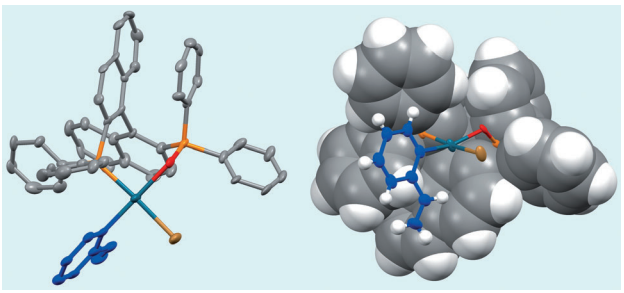


***Figure 1.*** Left: ORTEP diagram of [{(*R*)-binap(O)}(*o*-vinylphenyl)(Br)-Pd$^{II}$] with 50% thermal-ellipsoid probability and hydrogen atoms omitted for clarity. Right: front view with the ligand shown as a space-filling model. Important bond angles [°]: P-Pd-Br 172, O-Pd-C 174, Br-Pd-C 88, P-Pd-O 91.

We then conducted DFT calculations to investigate the first alkene-insertion step with (*R*)-binap(O) as the supporting ligand and 2,3-dihydrofuran as the cyclic alkene. The *cis* pathway was found to be preferred over the *trans* pathway. In cationic *trans*-[(*o*-vinylphenyl)(alkene)(L)Pd$^{II}$] complexes, the *trans* positioning of the strongly σ-donating aryl and triarylphosphane ligands at the Pd center destabilized these *trans* complexes by approximately 10 kcal mol$^{-1}$ as compared to the *cis* complexes. Furthermore, the *trans* pathway, if pperative, would produce the "wrong" enantiomers as the major products.

In the *cis* insertion pathway with the (*R*)-binap(O) ligand (Figure 2a), **TSa′** was higher in energy than **TSa** by $>3$ kcal mol$^{-1}$. In **TSa′**, close contacts were identified not only between the 2,3-dihydrofuran and phosphane oxide fragment, but also between the *ortho*-vinyl group and phosphane moiety (marked with arrows). The vinyl group was preferentially oriented *anti* to the cyclic olefin to avoid steric repulsion during insertion. Thus, our TS analysis offered a clear explanation as to why the presence of *ortho* substituents on aryl triflates improved the enantioselectivity of this process (99% *ee* in our cyclization versus 92% *ee* in the Heck reaction of PhOTf described by Oestreich).[7] Similar close contacts were also found in **TSb** for the complex of (*R*)-Xyl-SDP(O) (Figure 2b).

The new method was applied to an asymmetric synthesis toward (−)-martinellic acid. The natural product has been used in folk medicine to treat eye infections in South America, and it was found to be a potent bradykinin-receptor antagonist.[13] Several asymmetric syntheses of martinellic acid have appeared, but none of them used asymmetric catalytic methods to set the absolute configurations.[14] Our Heck reaction can quickly assemble a chiral diamine, by modifying Miyata's synthesis (Scheme 6).[15] The (*R*)-Xyl-SDP(O) catalyst gave the core tricycle in 99% *ee* with the right configuration. The olefin group was then oxidized to the ketone followed by condensation to form *O*-methyloxime. In comparison, 7 steps were used to arrive at a related *N*-benzylketone in Miyata's racemic synthesis. Selective reduction of the oxime C=N bond proved to be difficult, without cleaving the N–O bond. After trying many procedures, we found that *only* $NaBH_3CN$ in acetic acid can give satisfactory yield.[16] Subsequent treatment of the *N*-methoxyamine with

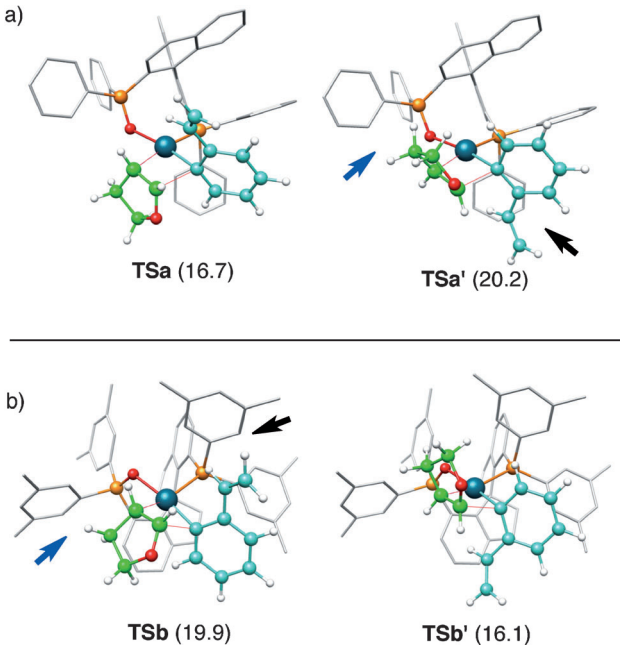
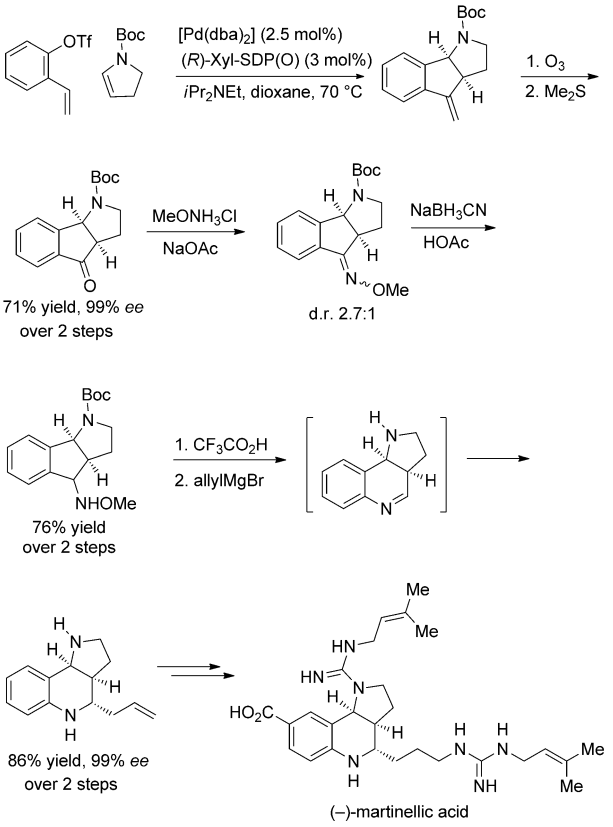



***Figure 2.*** Transition states and energies (kcal mol$^{-1}$) of 2,3-dihydrofuran insertion into cationic [(L)(alkene)(*o*-vinylphenyl)Pd$^{II}$] complexes. L is (*R*)-binap(O) in (a) and (*R*)-Xyl-SDP(O) in (b). Close contacts are indicated with arrows. To account for the dispersive effect in the cationic transition states, calculations were performed with a large basis set: M06-2X/[LANL2TZ(f)(Pd),6-31+G*(others)]//B3LYP/[LANL2DZ(Pd),6-31G*(O,P),6-31G(H,C)]. The solvent effect of 1,4-dioxane was taken into account by the polarizable continuum model (PCM) method.




***Scheme 6.*** Asymmetric synthesis towards (−)-martinellic acid.

allyl-MgBr reagent induced ring expansion followed by in situ trapping by Grignard addition to give exclusively the anti-isomer. Interestingly, the *N*-Boc group must be removed. Otherwise, the Beckmann-type ring expansion did not occur. Thus, our route provided the key diamine intermediate in 44% yield and 99% *ee* after three isolations. The secondary amine groups will not interfere with subsequent transformations towards (−)-martinellic acid.[14b,15]

In conclusion, we realized asymmetric domino cyclizations that can quickly assemble fused rings in excellent stereoselectivity.[17] The new method was applied to a short synthesis of the chiral diamine en route to (−)-martinellic acid.

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