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Palladium Catalysis

Asymmetric Reductive and Alkynylative Heck Bicyclization of Enynes to Access Conformationally Restricted Aza[3.1.0]bicycles

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Abstract: *Conformationally restricted azabicycles are becoming increasingly important in medicinal research. Asymmetric Heck bicyclization of enynes proceeds to give medicinally useful aza[3.1.0] and aza[4.1.0] bicycles with excellent enantioselectivity. The key organopalladium species after bicyclization can be trapped by silanes and terminal alkynes.*

Saturated heterocycles such as pyrrolidines, piperidines, and piperazine are among the most frequently used motifs in medicines.[1] In particularly, saturated azacycles containing sp^3 stereocenters, instead of flat heteroarenes, confer unique 3D shapes and also improve druglike properties such as solubility and binding affinities to desired biological targets.[2] In recent years, azabicyclo[3.1.0]hexanes have emerged as a very useful scaffold in drug discovery.[3] These 3D azabicycles have rigid conformations with substituents pointing in specific directions, which helps to optimize selective binding to desired biological targets while minimizing unwanted promiscuous interactions. Some examples of drugs containing azabicyclo-[3.1.0]hexanes are shown in Figure 1, including a family of triple reuptake inhibitors (bicifadine, centanafadine and amitifadine),[4] the antibiotics trovafloxacin and indolizomycin,[5] a selective μ-opioid-receptor antagonist for the treatment of alcohol abuse,[6] a protease inhibitor to combat hepatitis C virus (boceprevir),[7] and others.[8] Examples of bioactive azabicyclo[4.1.0]heptanes include GSK 1360707, a triple uptake inhibitor for the treatment of depression (see Figure 1)[9] and orexin-receptor antagonists.[10]

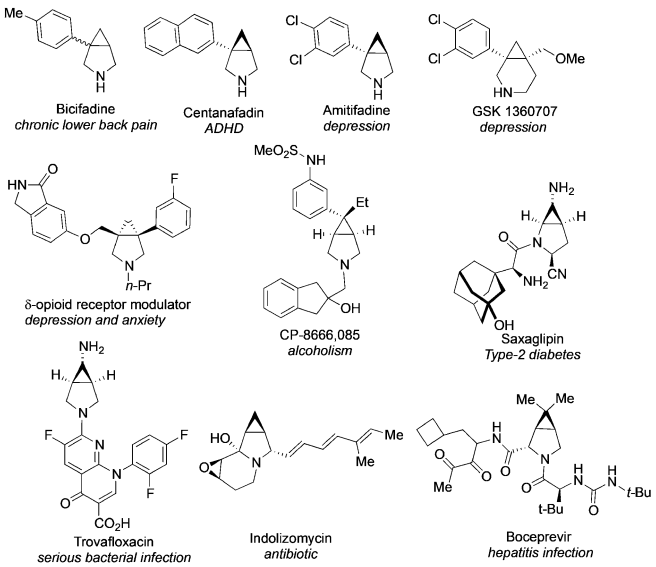

Figure 1. Examples of drugs containing [3.1.0] and [4.1.0] azabicycles.

To date, efficient enantioselective methods for the preparation of azabicyclo[3.1.0]hexanes still remain a challenge, unfortunately.[11] Arguably, asymmetric cyclopropanation is the most straightforward way to access these azabicycles, but a stereoselective variant still remains unavailable.[12] Another obvious choice of reaction is cyclization of 1,5-enynes catalyzed by carbophilic Au, Pt, and Pd,[13] but again the asymmetric version has not been reported yet.[14] Recently, Trost et al. reported an enantioselective isomerization of 1,6-enynes using a cationic cyclopentadienyl ruthenium catalyst (Figure 2a), which proceeded via hydride migration from the carbinol group to the alkyne to form alkenyl Ru species.[15] In the second example (Figure 2b), asymmetric annulation of strained cyclopropenes and N-allylamines was assisted by a cyclopentadienyl lanthanum catalyst.[16] In a recent report by Cramer et al. (Figure 2c), Pd-catalyzed desymmetrization of pendent cyclopropanes produced trifluoromethylated aza-[3.1.0]bicyclohexenes with excellent stereocontrol.[17] Finally, asymmetric intramolecular α-cyclopropanation of in situ generated α-iodoaldehydes proceeded with an amine catalyst.[18] Moreover, enantioselective synthesis of azabicyclo-[4.1.0]-heptanes also remains a challenge, for example, catalytic cyclopropanation did not provide good enantioselectivity under many conditions.[19]

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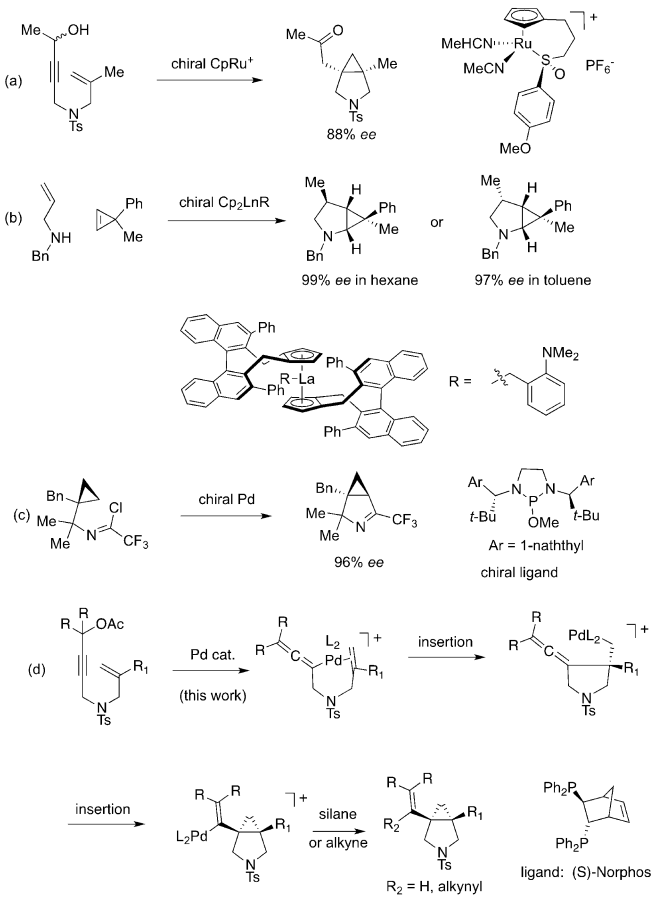
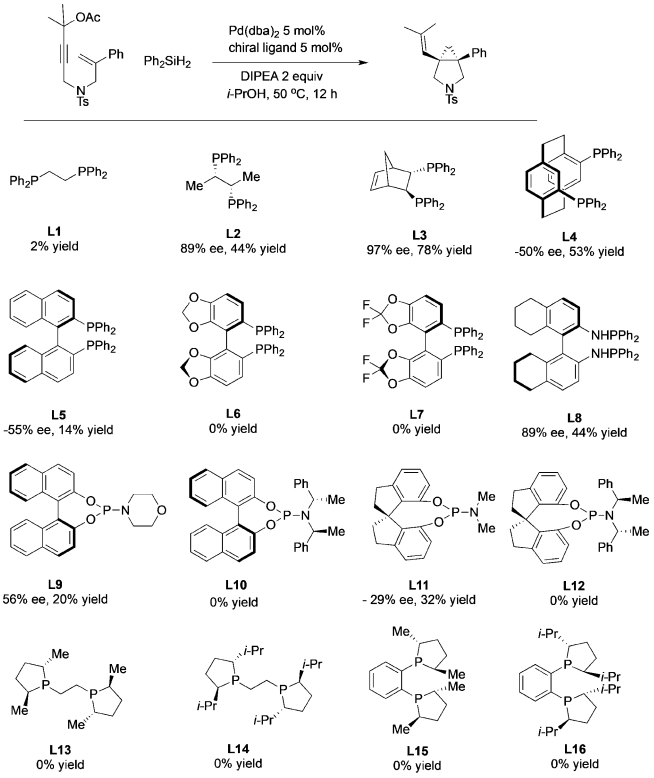


Figure 2. Examples of catalytic asymmetric synthesis of [3.1.0] azabicycles (Ts = *p*-toluenesulfonyl. Ac = acetyl, dba = dibenzylideneacetone, Cp = cyclopentadienyl).

In the late 1990s, Grigg and Oppolzer et al. separately reported reductive Heck cyclization of 1,6-enynes to prepare aza[3.1.0]bicycles,[20] using simple Pd catalysts of triphenylphosphine and trifurylphosphine. But an enantioselective version has remained elusive owing to a lack of suitable chiral ligands. A fine balance of steric factors around the chiral pocket must be struck to bias the formation of one enantiomer during alkene insertion, but also allow sequential allene cyclization to occur (see Figure 2d). Another issue is premature reduction of the allenyl Pd species by hydride donors. Furthermore, β-hydrogen elimination of the allenyl Pd species may also compete to give an enyne as a side product.[21]

In line with our interest in generating strained rings through asymmetric palladium catalysis,[22] we attempted Heck bicyclization to produce medicinally important azabicyclo[3.1.0]hexanes by intercepting the late-stage organopalladium species with hydride donors or carbon nucleophiles such as alkynes (Figure 2d). In recent years, enantioselective Pd-[23] and Ni[24]-catalyzed reductive Heck reactions have received renewed interest since they quickly provide useful chiral building blocks.[25] Furthermore, asymmetric Pd-[26] and Ni-catalyzed[27] alkene cyclizations have also been intercepted with coupling reagents.[28] For example, in 2017, Jia et al. reported that the intermediate of intramolecular Heck arylation of indoles can be successfully intercepted by alkynylation with good *ee* values.[26a] Very recently, Ge et al. also disclosed asymmetric Heck cyclization and subsequent alkynylation that produced α-CF_3-subsituted oxindoles.[29] It should be pointed out that all of the aforementioned processes only allowed construction of a new (benzo)fused ring. Asymmetric Heck-type bicyclization to generate the fused azabicycles as shown in Figure 2d has remained elusive.

In the Pd-catalyzed bicyclization of model enyne **1a**, we first examined a collection of chiral bisphosphines, including BINAP, Difluorophos, Segphos and Duphos, and monodendate phosphoramidites, but to no avail. Only Chiraphos and Phanephos afforded desired product **2a** in appreciable yields and in 89% *ee* and 50% *ee*, respectively (Scheme 1). To our gratification, Norphos on a norbonene skeleton[30] furnished **2a** in 78% yield and 97% *ee*. The main side product under most conditions was derived from premature reduction of the allenyl Pd species (see Figure 2d). Ph_2SiH_2 proved to be the optimal hydride donor, whereas $PhSiH_3$, Et_2SiH_2, and $NaHCO_2$ were less effective and offered moderate yields of product **2a**. Without any silane, **2a** was produced in 27% yield, thus suggesting that isopropanol can serve as a minor source of hydride. The reaction itself did not need a base, but addition of NaOAc or Hünig base slightly improved the yield of **2a**. Among the organic solvents we examined, we found that the *ee* was the highest in isopropanol. The model reaction on a 1 mmol scale using 1 mol% Pd catalyst also proceeded



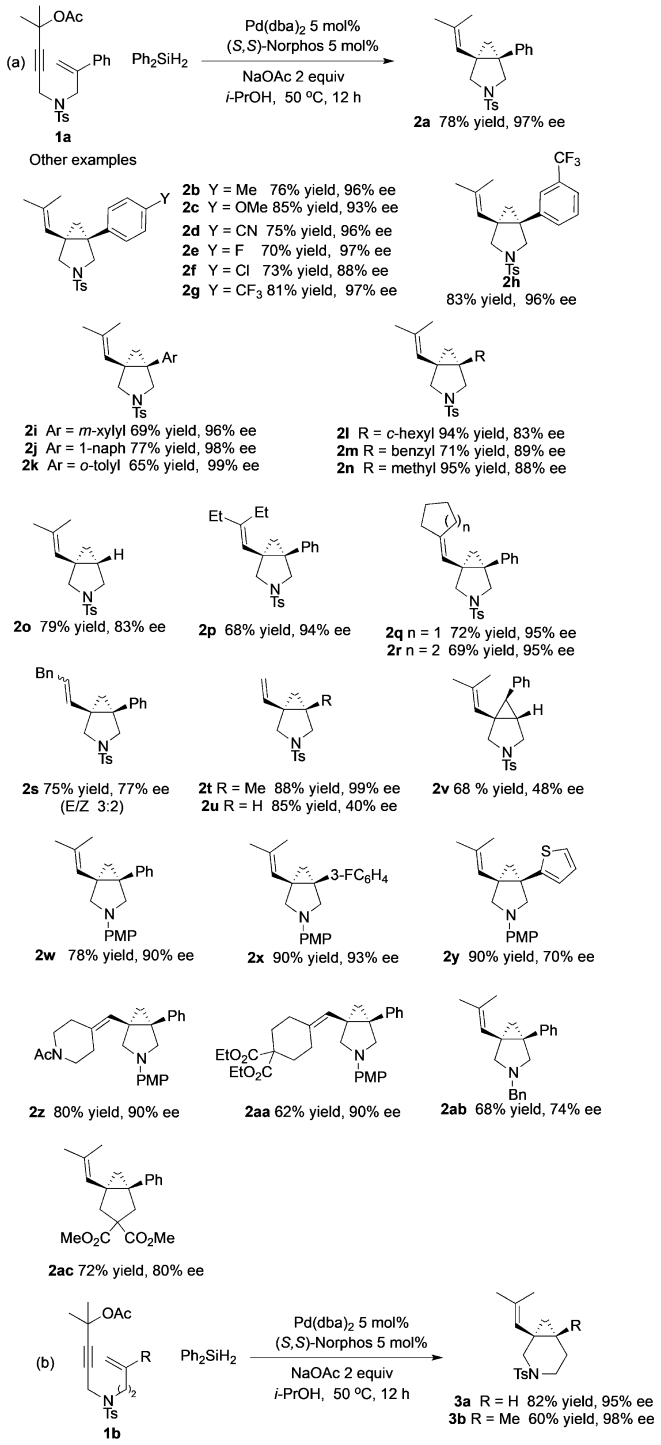
Scheme 1. The effects of chiral ligands on a model cyclization of model 1,6-enyne (calibrated GC yields and *ee* values determined by chiral HPLC). dba = dibenzylidene-acetone, DIPEA = diisopropylethylamine.

well to afford **2a** in 79% yield after 48 h. At 0.2 mol% Pd, the yield of **2a** was 67% along with 16% recovered **1a** after 48 h.

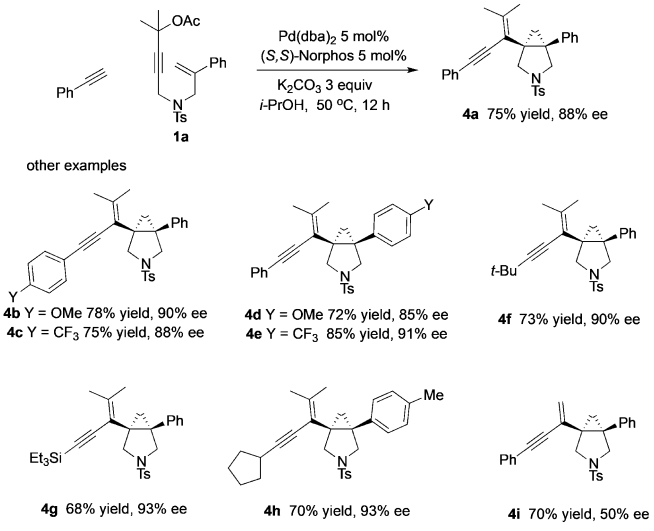
The Pd catalyst with Norphos was then successfully applied to various 1,6-enynes in reductive Heck bicyclization (Scheme 2). Aryl substituents carrying both electron-donating (**2b**,**c**) and electron-withdrawing (**2d**–**h**) groups can be present on the alkene fragment, as well as methyl, cyclohexyl, and benzyl groups (**2n**–**l**). Aryl nitrile, fluoride, chloride, amide, and ester groups were tolerated well. In an additive test using the model reaction of **1a**,[31] azacycles such as quinoline, isoquinoline, 2-phenylpyridine, and unprotected indole had almost no negative influence. Moreover, single-crystal X-ray diffraction of product **2g** helped to ascertain its absolute configuration.[32] When an enyne carrying a simple N-allyl group was used, **2o** was generated in 83% *ee*. This suggests that intramolecular insertion of the allene is faster than β-hydrogen elimination after the first insertion (see Figure 2).

Propargylic acetates carrying 1,1-disubstituents reacted smoothly (**2p**–**r**). A racemic sample bearing a benzyl group, however, led to two olefinic isomers **2s** in an *E*/*Z* ratio of 3:2. The enantiomers of two isomers overlapped on chiral HPLC traces. After catalytic hydrogenation of the two isomers over Pd/C, the *ee* was determined to be 77%. Without any C1 substituent on the propargyl fragments, the cyclization still proceeded in 99% *ee* (**2t**). The cyclization using an enyne carrying a cinnamyl group furnished *cis*-fused cyclopropane **2v** albeit in only 40% *ee*. Thus, C2-substituents on the alkene fragments are important for enantiofacial insertion. Furthermore, the enyne linker can be changed to arylamines, benzylamine, or a malonate (**2w**–**2ac**). However, we noticed that carbamates and benzamides as linkers inhibited the insertion process. Asymmetric cyclization of tosylamide-linked 1,7-enyne also proceeded smoothly to give azabicyclo-[4.1.0]heptanes in over 95% *ee* (**3a**,**b**).

We also attempted to intercept the alkenyl Pd species after bicyclization (see Figure 2) with carbon nucleophiles such as diphenylzinc, $PhB(OH)_2$ and $PhSi(OMe)_3$, but they all failed to deliver the desired arylation under many conditions. Later, cognizant of the congestion surrounding the alkenyl Pd center after bicyclization, we attempted to trap it with small nucleophiles, for example, terminal alkynes. Indeed, both aromatic and aliphatic alkynes of different electronic properties coupled efficiently to give alkynylation adducts (Scheme 3).[33] Premature propargylic alkynylation was detected as a side reaction.



Scheme 2. Asymmetric reductive Heck bicyclization of 1,6- and 1,7-enynes to access [3.1.0]azacycles (a) and [4.1.0]azacycles (b). Yields of isolated product are shown. PMP = *p*-methoxyphenyl.



Scheme 3. Asymmetric Heck bicyclization and alkynyl coupling of 1,6-enynes. Yield of isolated product are shown.

We next conducted DFT calculations for the initial alkene insertion step of **1a** at the SMD(2-propanol),M06L/Def2-TZVP//B3LYP-D3/6–31 g(d,p),SDD(Pd) level of theory, aiming to understand the origin of the enantioselectivity observed in the Heck bicyclization. Two transition states are shown in Figure 3. First, we found that electrostatic interaction of the sulfonamide group of **1a** with the electropositive Pd center significantly stabilized the insertion transition states, by around 2 kcal mol^{-1}.[34] The Pd···O distances were 3.14 Å in both transition states. Second, the energies of two transition states were 4.1 kcal mol^{-1} apart, which is consistent with experimental 97 % *ee* of **2a**. Third, careful examination of the disfavored transition structure (see the right of Figure 3) revealed that congestion between the dimethylallenyl fragment of **1a** and one of top P-phenyl rings of Norphos was the key factor contributing to destabilization of the transition state.

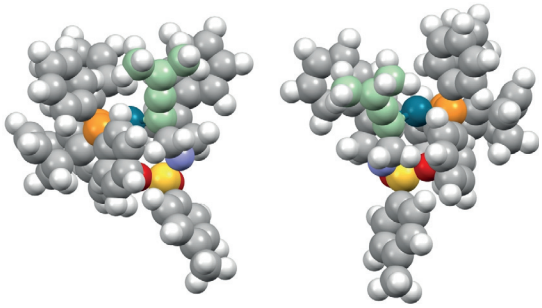


Figure 3. A favored transition state (left) and a disfavored transition state (right) for insertion of the allenyl-Pd on alkene fragment. N purple, O red, S yellow, and P orange, Pd blue. The 3,3-dimethylallenyl fragment connected to Pd is highlighted in light green.

In conclusion, we have developed an intramolecular reductive Heck cyclization of 1,6-enynes to generate medicinally important aza[3.1.0]bicycles with excellent *ee* values. Furthermore, the key alkenyl Pd species can also be trapped by terminal alkynes to give alkynylation adducts.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynylation · azabicycles · palladium · reductive Heck reaction · strained rings

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