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

Xiaolei Huang,‡ Minh Hieu Nguyen,‡ Maoping Pu,‖ Luoqiang Zhang,† Yonggui Robin Chi,‡ Yun-Dong Wu§ and Jianrong Steve Zhou†*

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 in 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 exquisite sp^3-stereocenters, instead of flat heteroarenes, confers unique 3D shapes and also improves druglike properties such as good solubility and affinities to biological targets.[2] In recent years, azabicyclo[3.1.0]hexanes emerge as a very useful scaffold in drug discovery.[3] These 3D-shaped azabicycles have rigid conformations with substituents pointing at specific directions, which help 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 Fig 1, including a family of triple reuptake inhibitors (e.g., bicifadine, centanafadine and amitifadine),[4] antibiotics trovafloxacin and indolizomycin,[5] a selective mu opioid receptor antagonist for the treatment of alcohol abuse,[6] boceprevir, a protease inhibitor to combat hepatitis C virus,[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 Fig 1)[9] and orexin receptor antagonists.[10]

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 such a stereoselective variant still remains unavailable.[12] Another obvious choice is cyclization of 1,5-enynes catalyzed by carbophilic Au, Pt and Pd,[13] but again its 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 (Scheme 1a), which proceeded via hydride migration from the carbinol to alkyne to form alkenyl Ru species.[15] In the second example (Scheme 1b), asymmetric annulation of strained cyclopropenes and *N*-allylamines was assisted by a moisture-sensitive cyclopentadienyl lanthanum catalyst.[16] In a recent report by Cramer *et al.* (Scheme 1c), Pd-catalyzed desymmetrization of pendent cyclopropanes produced trifluoromethylated aza[3.1.0]bicyclohexenes in excellent stereocontrol.[17] Lastly, asymmetric aminocatalysis resulted in intramolecular α-cyclopropanation of in situ generated α–iodoaldehydes.[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]

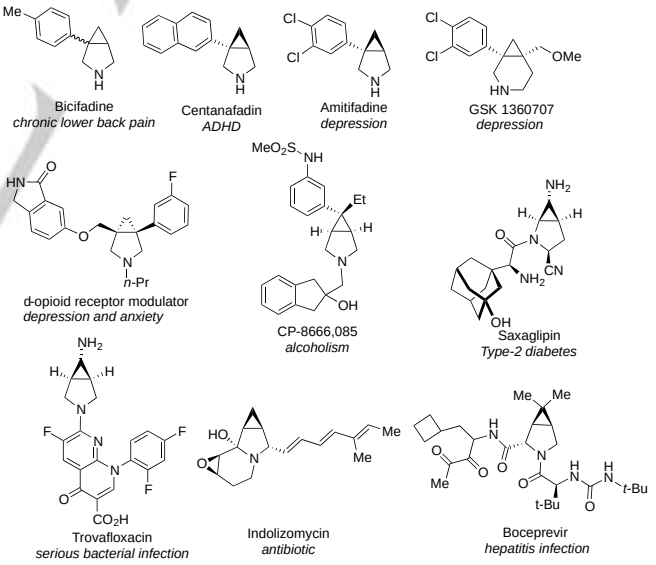

Figure 1. Examples of drugs containing [3.1.0] and [4.1.0] azabicycles

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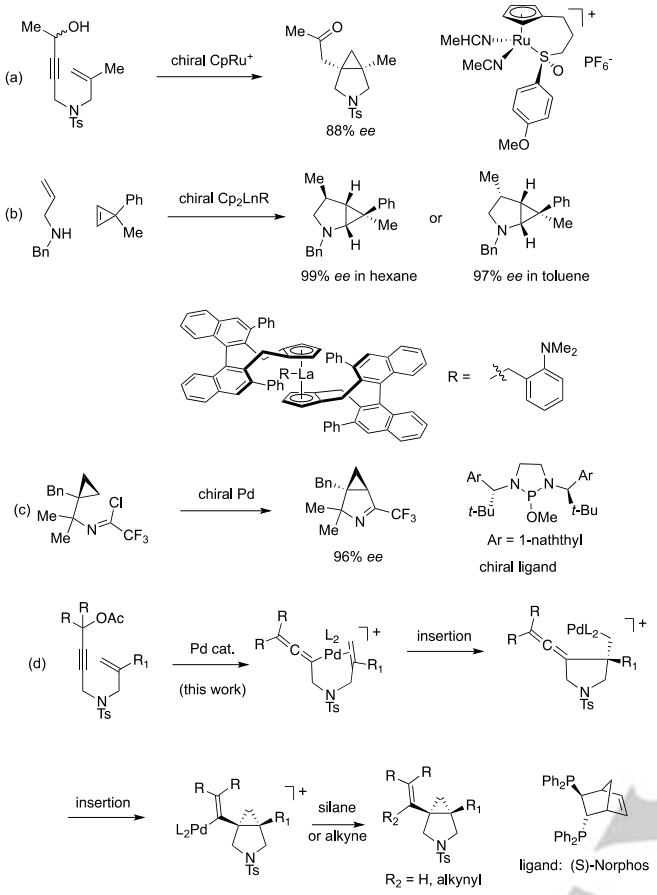
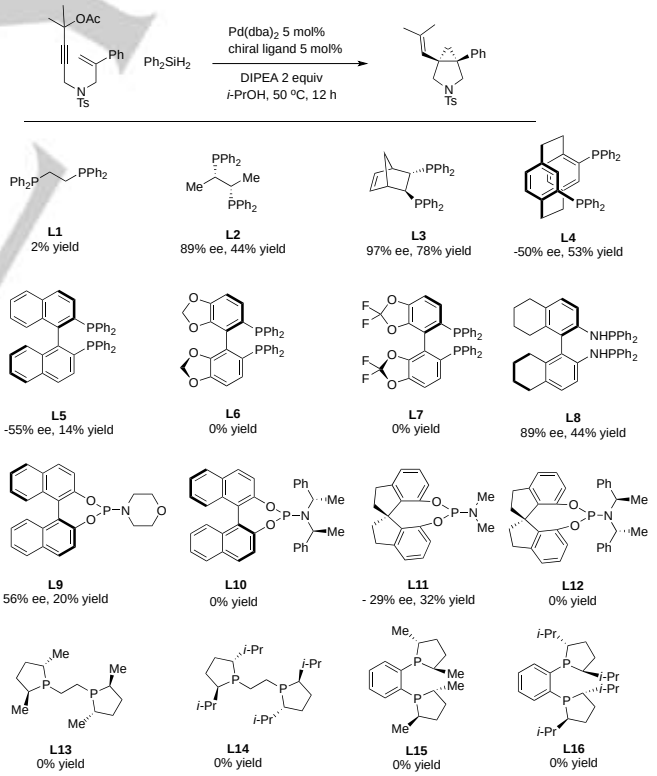


Figure 2. Examples of catalytic asymmetric synthesis of [3.1.0] azabicycles (Ts = *p*-toluenesulfonyl. Ac = acetyl. dba = dibenzylideneacetone. Cp = cyclopentadienyl)

In the 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. 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 remain relatively open for sequential allene cyclization to occur (see Fig 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 as a side reaction.[21]

In line with our interest in generating strained rings via 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 (Scheme 2d). In recent years, Pd-[23] and Ni[24]-catalyzed enantioselective reductive Heck reaction has received renewed interest which quickly provide useful chiral building blocks.[25] Furthermore, Pd-[26] and Ni-catalyzed[27] asymmetric alkene cyclization were also intercepted with coupling reagents.[28] For example, in 2017 Jia *et al.* reported that intramolecular Heck arylation of indoles was successfully trapped by alkynylation in 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 single (benzo)fused ring. Asymmetric Heck-type bicyclization to generate the rings as shown in Fig 2d has remained elusive.

In Pd-catalyzed bicyclization of a 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% and 50% *ee*s, respectively (Scheme 1). To our gratification, Norphos on a norbonene skeleton[30] furnished **2a** in 78% yield of 97% *ee*. The main side product under most conditions was derived from premature reduction of the allenyl Pd species (see Fig 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, 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 organic solvents we examined, we found that the *ee* was the highest in isopropanol. The model reaction on 1 mmol scale using 1 mol% Pd catalyst also proceeded 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**.



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

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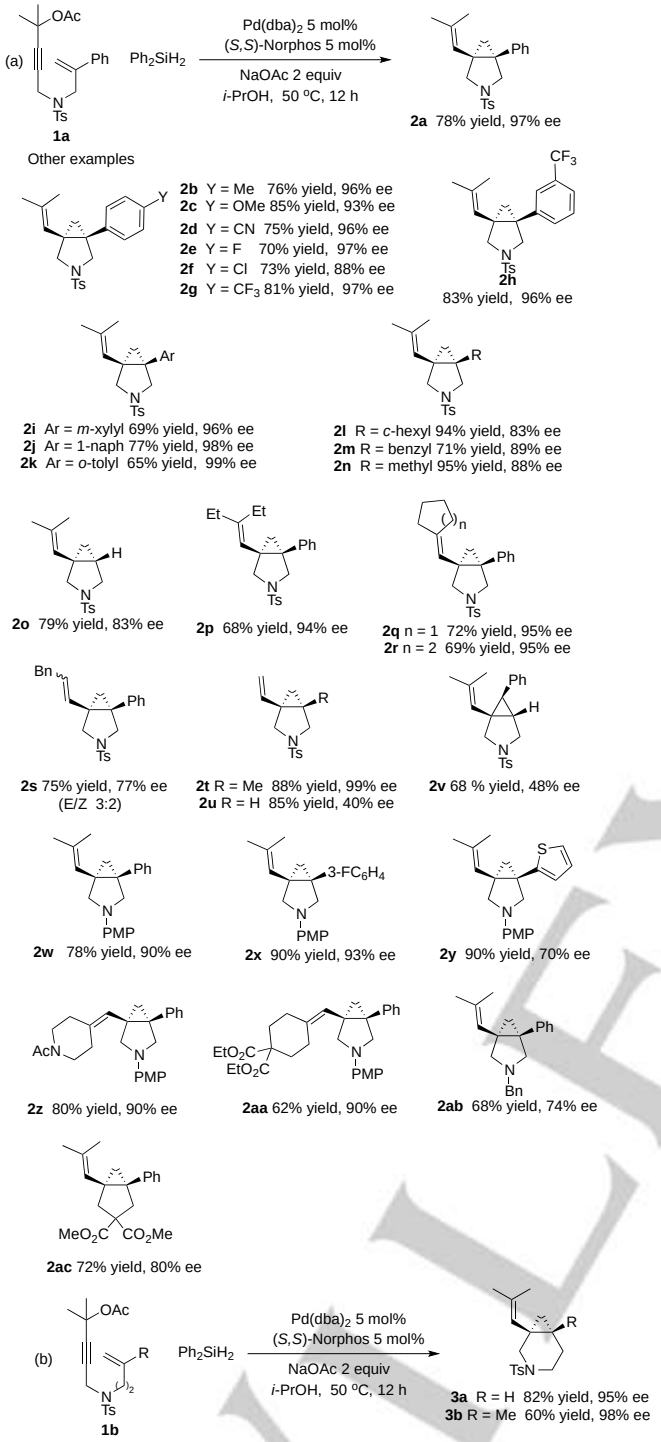
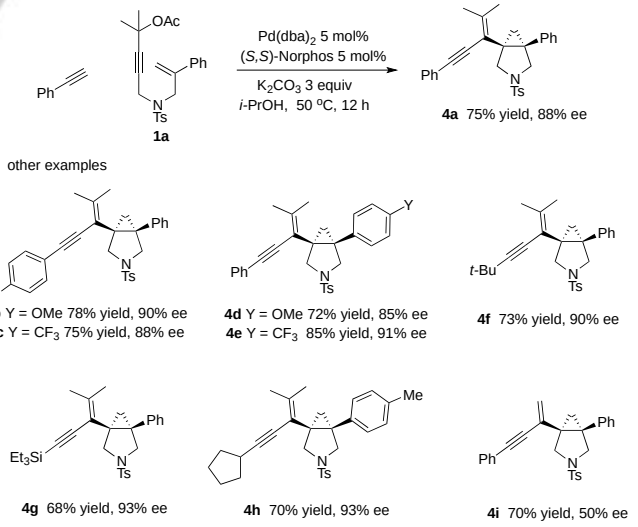


Scheme 2. Asymmetric reductive Heck bicyclization of 1,6- and 1,7-enynes to access [3.1.0]azacycles (a) and [4.1.0]azacycles (b) in isolated yields. PMP = *p*-methoxyphenyl.

The Pd catalyst of Norphos was then successfully applied to various 1,6-enynes in reductive Heck cyclization (Scheme 2). Both electron-donating (**2b-c**) and electron-withdrawing groups (**2d**–**h**) can be present on the aryl substituents of the alkene, as well as methyl, cyclohexyl and benzyl groups (**2n-l**). Aryl nitrile, fluoride and chloride, amides and esters were tolerated well. In an additive test in the model reaction of **1a**,[31] azacycles such as quinoline, isoquinoline, 2-phenylpyridine and unprotected indole had almost no influence. Moreover, single-crystal X-ray diffraction of product **2g** helped to ascertain the absolute configuration of products.[32] When an enyne carrying a simple *N*-allyl group was used, **2o** was generated in 83% *ee*. This suggested that intramolecular insertion of the allene is faster than β-hydrogen elimination (see Fig 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 two isomers overlapped on chiral HPLC traces. After catalytic hydrogenation of the two isomers over Pd/C, the ee was determined to 77%. Without any C1-substituent on the propargyl fragments, the cyclization still proceeded (**2t**). The cyclization using an enyne carrying a cinnamyl group furnished a cis-fused cyclopropane **2v** albeit in 40% *ee*. Thus, C2-substituents on the alkenes are important for enantiofacial insertion. Furthermore, the linker of enynes can be changed to arylamines, benzylamine and a malonate (**2w**-**2ac**). However, 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 Fig 2) with carbon nucleophiles such as diphenylzinc, $PhB(OH)_2$ and $PhSi(OMe)_3$, but they failed to deliver the desired alkynylation under many conditions. Later, cognizant of highly congested alkenyl Pd species after bicyclization, we attempted to trap with small nucleophiles, 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 minor side reaction.



Scheme 3. Asymmetric Heck bicyclization and alkynyl coupling of 1,6-enynes in isolated yields.

We next conducted DFT calculation of the initial Heck insertion step of **1a** at SMD(2-propanol), M06L/Def2-

TZVP//B3LYP-D3/6-31g(d,p), SDD(Pd) level of theory, aiming to understand the origin of enantioselectivity (Fig 3). Firstly, we determined that electrostatic interaction of the sulfonamide group of **1a** with the electropositive Pd center significantly stabilized the insertion transition states, by around 2 kcalmol^{-1}.[34] The Pd···O distances were 3.14 Å in both transition states. Secondly, the two transition states are 4.1 kcalmol^{-1} apart in energy, consistent with experimental 97% ee of **2a**. Thirdly, careful examination of the disfavored transition structure (see the right of Fig 3) revealed that congestion between dimethylallenyl fragment of **1a** and one of top *P*-phenyl rings of Norphos is the key factor contributing to destabilization of the transition state.

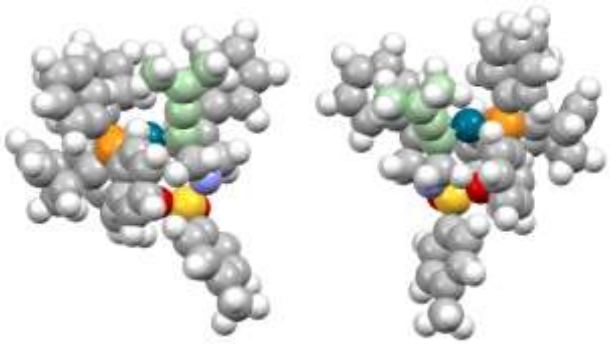


Fig 3. A favored transition state (left) and a disfavored transition state (right) for insertion of the allenyl-Pd on alkene fragment. Atoms are colored in purple (N), red (O), yellow (S) and orange (P) and blue (Pd), respectively. The 3,3-dimethylallenyl fragment on Pd is highlighted in neon green.

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

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Conflict of interest

The authors declare no conflict of interest

Keywords: palladium catalysis • reductive Heck reaction • alkynylation • privileged scaffold • azabicycles

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COMMUNICATION

Palladium catalysis

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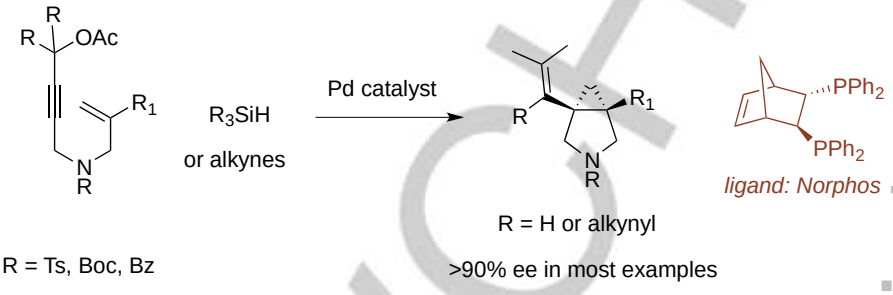
Asymmetric Reductive and Alkynylative Heck Bicyclization of Enynes to Access Conformationally Restricted Aza[3.1.0]bicycles



R = Ts, Boc, Bz

R = H or alkynyl

>90% ee in most examples

Heck bicyclization of enynes is intercepted by silanes and alkynes to give medicinally important azacycles with rigid conformations in good enantiomeric ratios.