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Enantioselective C–H Functionalization–Addition Sequence Delivers Densely Substituted 3-Azabicyclo[3.1.0]hexanes
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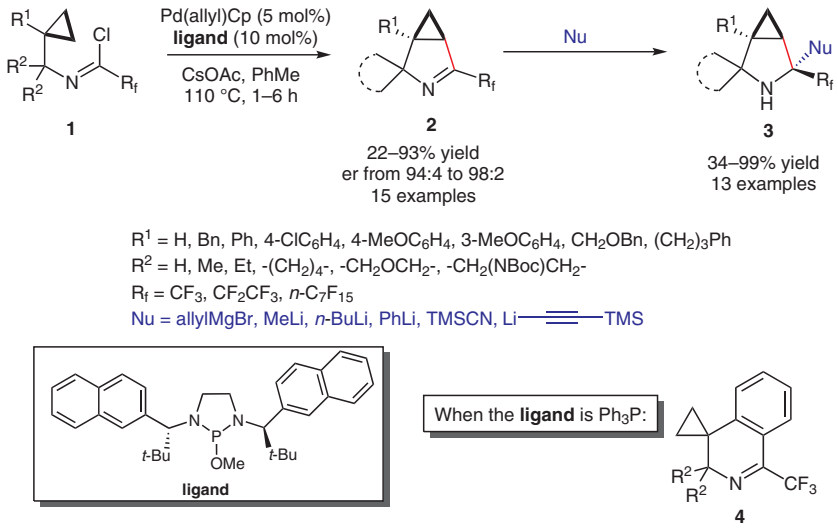
Enantioselective Modular Approach to 3-Azabicyclohexanes



Significance: 3-Azabicylo[3.1.0]hexanes are present in a wide range of bioactive compounds. Besides many common methods to access this scaffold, the 1,3-dipolar cycloaddition of azomethine ylides to cyclopropenes (A. S. Filatov et al. *J. Org. Chem.* **2017**, *82*, 959) and multicomponent reactions in water (M. Ghorbani et al. *Org. Lett.* **2016**, *18*, 4759) have recently been described. The present work takes advantage of the high electrophilic character of the intermediate alkylfluoro-substituted ketamine **2** to produce highly substituted 3-azabicyclo[3.1.0]hexanes **3** by addition of nucleophiles. The presence of the strained cyclopropane ring ensures the diastereoselective control of the addition.

Comment: Reported is the enantioselective palladium-catalyzed cyclization of imidoyl chlorides **1** to produce cyclopropane-fused dihydropyrrole **2**. The scope of this transformation is broad, and **1** with various substituents gave products **2** in high yields and high enantioselectivities. When R^2 = H, the reaction proceeded with low yield, although the er was unaffected. Cyclopropane C–H functionalization was observed exclusively in the presence of an aryl substituent (R^1 = Ar), to give dihydropyrroles **2**. However, switching the ligand to Ph_3P reversed the chemoselectivity to aryl C–H functionalization, producing spirocyclic dihydroisoquinolines **4**. The reaction of electrophilic ketimines **2** with various nucleophiles gave pyrrolidines **3** diastereoselectively. Moreover, **3** can be accessed directly from **1** in a one-pot manner without any significant loss in enantioselectivity.

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Synthesis of Heterocycles

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