Enantioselective Modular Approach to 3-Azabicyclohexanes

Significance: 3-Azabicyclo[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 cyclopropanes (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 R² = 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 (R¹ = Ar), to give dihydropyrroles 2. However, switching the ligand to Ph₃P 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.