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Acid-Base Catalysis of Chiral Palladium Complexes: Development of Novel Catalytic Asymmetric Reactions and Their Applications to Synthesis of Drug Candidates

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Using a unique character of cationic palladium aqua and m-hydroxo complexes, novel catalytic asymmetric reactions have been developed. In contrast to the conventional Pd(0)-catalyzed reactions, these complexes function as an acid-base catalyst under mild reaction conditions. Thus, active methine compounds such as b-ketoesters were activated to form configurationally stable chiral palladium enolates, which underwent the enantioselective Michael reaction and Mannich-type reaction with up to 99% ee. Interestingly, these palladium enolates acted cooperatively with a strong protic acid to activate the electrophiles, formed concomitantly during the formation of the enolates, thereby the C-C bond-forming reactions were promoted. This is characteristic reactivity of enolate formed under acidic conditions. Our palladium enolate chemistry was also applicable to catalytic asymmetric fluorination reactions with *N*-benzenesulfonimide (NFSI), and thus various carbonyl compounds including b-ketoesters, b-ketophosphonates, and oxindole derivatives were fluorinated in a highly enantioselective manner (up to 98% ee). It is advantageous that these reactions were carried out in environmentally friendly alcoholic solvents such as ethanol, and exclusion of air and moisture is not necessary. In addition, the direct enantioselective conjugate addition reaction of amines to ąb-unsaturated carbonyl compounds, which has been difficult with chiral Lewis acids, was successfully demonstrated (up to 98% ee). The combined use of the Pd m-hydroxo complex having the basic character and the amine salt was a key to success, allowing for the controlled generation of the nucleophilic free amine. Finally, to confirm the utility of these reactions, we demonstrated conversion of the products to fundamental chiral building blocks and catalytic asymmetric synthesis of important drug candidates such as BMS 204352 and Torcetrapib.