Catalytic Asymmetric Synthesis of Organofluorine Compounds for Drug Discovery

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The development of efficient methodology for the synthesis of fluoro-organic compounds has attracted considerable attention particularly in the field of medicinal chemistry. We will here focus on the catalytic enantioselective fluoromethylation reactions. We found 1-fluorobis(phenylsulfonyl)methane (FBSM) to be a synthetic equivalent of a fluoromethide species under the Tsuji-Trost allylic alkylation conditions, which provided the palladium-catalyzed asymmetric allylic monofluoromethylation reaction with high enantiocontrol. We also disclosed a catalytic enantioselective monofluoromethylation reaction of in situ-generated prochiral imines with FBSM in the presence of a chiral phase transfer catalyst (PTC) under the combination of Mannich-type reaction with reductive desulfonylation. In 2008, Michael-type enantioselective monofluoromethylation of enones by FBSM was also reported. In the second part, we will discuss the enantioselective trifluoromethylation reaction. Enantioselective trifluoromethylation using (trifluoromethyl)trimethylsilane, Me_3SiCF_3, has presented problems in fluoro-organic chemistry for more than 15 years ever since the first report on the trifluoromethylation of carbonyl compounds using tetrabutylammonium fluoride by Prakash and Olah. In 2007, we reported the highly enantioselective trifluoromethylation of ketones with Me_3SiCF_3 catalyzed by a combination of ammonium bromides of cinchona alkaloids and tetramethylammonium fluoride (TMAF). Our approach is especially attractive because non-fluorinated prochiral substrates can be directly transformed to chiral trifluoromethylated alcohols with quaternary carbon centers, with unprecedentedly high enantioselectivities (up to 94% ee), using readily available chiral ammonium bromides of cinchona alkaloids and TMAF. Enantioselective trifluoromethylation of imine derivatives was also achieved in 2009 by the use of cinchona alkaloids and KOH combination. Development of novel electrophilic trifluoromethylating agents will be also described in the lecture.