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The research interests of the laboratory include the development of advanced molecular transformation, total synthesis of biologically active products, and molecular recognition. Programs are active in the areas of asymmetric alkylation of carbonyl compounds based on “memory of chirality”, nucleophilic catalysis for fine organic syntheses, synthesis of unusual amino acids and nitrogen heterocycles, regioselective functionalization of carbohydrates, visualization of molecular information by functional phenolphthaleins, synthesis and properties of homochiral oligonaphthalenes, and the structural and functional investigation of heterochiral oligomers.

Scope of Research

Publication

Presentations

Convenient Synthesis of Axially Chiral Biaryls via a Pd-Catalyzed Domino Coupling Reaction, 17th International Conference on Organic Synthesis (ICOS-17), Furuta T, 24 June 2008.


Grants


Kawabata T, Creation of Novel Binaphthyls with Inner Hydrogen Bonding, Grant-in-Aid for Exploratory Research,
Asymmetric Synthesis via C-O Axially Chiral Enolates

Enantioselective construction of tetrasubstituted carbon has been the focus of current synthetic attention. We have developed a method for enantioselective construction of cyclic ethers with tetrasubstituted carbon via C-O axially chiral enolates for the first time. Treatment of chiral aryl alkyl ethers derived from readily available cheap lactic acid with a base gave chiral dihydrobenzofurans. Effects of substituent R in 1 were critical on asymmetric induction. Treatment of 1 (R=H) with sodium hexamethyldisilazide (NaHMDS) at −78 °C gave cyclization product 2 (R=H) as a racemate, while that of 1 (R=Me) or 1 (R=iPr) gave 2 (R=Me) or 2 (R=iPr) in 84% ee or 99% ee, respectively. Racemization barrier of the planar chiral enolate (R=iPr) was estimated to be ~11.5 kcal/mol by variable-temperature NMR measurement of the corresponding tert-butyldimethylsilyl ether. Based on the barrier, the half-life of racemization of the planar chiral enolate was roughly calculated to be ~1 second at −78 °C. Thus, asymmetric synthesis via intrinsically chiral enolates with very short half-lives of racemization has been achieved.

Powdered KOH in DMSO: An Efficient Base for Asymmetric Cyclization at Ambient Temperature

Enolate chemistry has been extensively used for stereo-selective C-C bond formation, in which metal amide bases are frequently employed in strictly anhydrous solvents at low temperatures. However, we found that asymmetric intramolecular C-C bond formation via axially chiral enolate intermediates proceeded in up to 99% ee at 20 °C by using powdered KOH in dry or wet DMSO as a base. The enantioselectivity was even higher than that of the corresponding reactions with potassium hexamethyldisilazide in DMF at −60 °C. The racemization barrier of the axially chiral enolate intermediate was experimentally estimated to be ~15.5 kcal/mol. Based on the barrier, the chiral enolate intermediate was supposed to undergo cyclization within ~10⁻³ sec at 20 °C after it is generated to give the product in ≥99% ee. The rate-determining step for the cyclization must be the enolate-formation step because the half-lives of racemization of the chiral enolate intermediates generated from 3 are supposed to be much shorter (< 0.1 sec) than the time required for the reactions to be complete (2~12 h). Thus, C-N axially chiral enolates would form gradually, and once formed, would immediately undergo asymmetric cyclization due to their extremely high reactivity.

Construction of Axially Chiral Amino Acids via Pd-Mediated Synthesis of Azahelicenes

Unnatural amino acids have attracted considerable attention in the field of asymmetric synthesis as well as medicinal chemistry. Although unnatural amino acids with central chirality have been well developed, axially chiral amino acids have not yet been well exploited. We have developed a straightforward method for the construction of axially chiral amino acids via Pd-mediated synthesis of azahelicenes. Domino coupling reactions of 4 proceeded in the presence of catalytic amount of Pd₂(dba)₃ without additional ligands to afford azahelicenes via successive C–C (red colored) and C–N (green colored) bond formations. The amide bond of 5 was cleaved under basic conditions to afford novel axially chiral amino acids 6, which possesses amino and carboxyl groups at C-2 and C-2' positions, respectively.