Division of Synthetic Chemistry
- Synthetic Organic Chemistry -

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Visitors

Prof ZIPSE, Hendrik — Ludwig-Maximilians-Universität in München, Germany, 9 September 2008
Prof WORTH, Thomas — Cardiff University, UK, 26 September 2008

Scope of Research

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.

Research Activities (Year 2008)

Publication

Kawabata T, Moriyama K, Kawakami S, Tsubaki K: Powdered KOH in DMSO: An Efficient Base for Asymmetric Cyclization via Memory of Chirality at Ambient Temperature, *J. Am. Chem. Soc*., **130**, 4153-4157 (2008).

Presentations

Asymmetric Reactions with Axially Chiral Compounds, Symposium on Molecular Chirality 2008, Kawabata T, 23 May 2008.

Asymmetric Synthesis *via* Planar Chiral Enolates, Third International Conference on Advanced Organic Synthesis Directed toward the Ultimate Efficiency and Practicability, Yoshimura T, 27 May 2008.

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.

Toward the Development of Intelligent Catalysts: Catalyst Design Based on Dynamic Molecular Recognition, Seminar of The Society of Synthetic Organic Chemistry, Japan, Tokai-Branch, Kawabata T, 12 July 2008.

Selective Acylation by Intelligent Nucleophilic Catalysis, UK/Japan Symposium on Asymmetric Catalysis, Kawabata T, 9 December 2008.

Acylation Catalysis via Fine Molecular Recognition, The Forth Symposium on Functional Molecules, Kawabata T, 20 December 2008.

Grants

Kawabata T, Fine Organic Synthesis by Nucleophilic Catalysis, Grant-in Aid for Scientific Research (A), 1 April 2006–31 March 2009.

Kawabata T, Advanced Molecular Transformation with Functional Carbanions, Grant-in Aid for Scientific Research on Priority Areas, 1 October 2005–31 March 2009.

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 **1** derived from readily available cheap lactic acid with a base gave chiral dihydrobenzofurans **2**. Effects of substituent R in **1** were critical on asymmetric induction. Treatment of **1** (R=Me) 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=^{i}Pr) gave **2** (R=Me) or **2** (R=^{i}Pr) in 84% ee or 99% ee, respectively. Racemization barrier of the planar chiral enolate (R=^{i}Pr) 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.

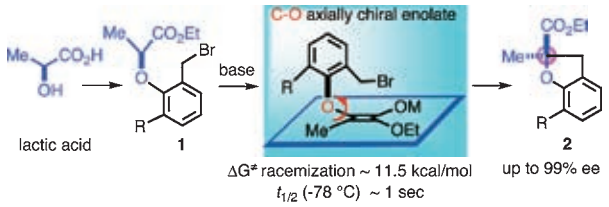

Figure 1.

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

Enolate chemistry has been extensively used for stereoselective 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.

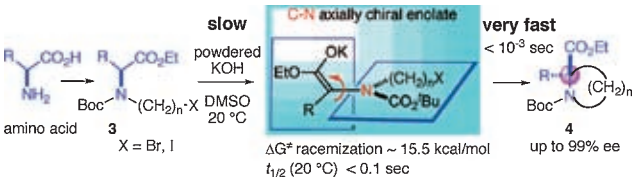

Figure 2.

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 $Pd_2(dba)_3$ without additional ligands to afford azahelicenes **5** 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.

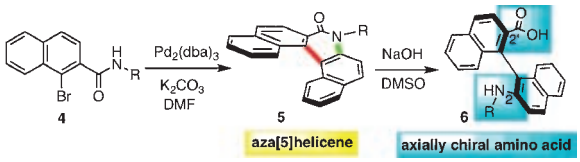

Figure 3.

1 April 2007–31 March 2009.

Furuta T, Synthesis of Functionalized Artificial Phospholipids for Investigation of Membrane Related Biosystems, Grant-in-Aid for Scientific Research (C), 1 April 2008–31 March 2011.

Yoshimura T, Syntheses of Natural Products via Memory of Chirality, Grant-in-aid for Young Scientists (B), 1 April 2007–31 March 2009.