Division of Synthetic Chemistry
- Synthetic Organic Chemistry -

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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, synthesis and properties of homochiral oligonaphthalenes, and the structural and functional investigation of heterochiral oligomers.

Research Activities (Year 2009)

Publication

Kawabata T, Jiang C, Hayashi K, Tsubaki K, Yoshimura T, Majumdar S, Sasamori T, Tokitoh N: Axially Chiral Binaphthyl Surrogates with an Inner N-H-N Hydrogen Bond, *J. Am. Chem. Soc*., **131**, 54-55 (2009).

Presentations

Dynamic Molecular Recognition by an Organocatalyst: Glucose Specific Acylation, 11th International Kyoto Conference on New Aspects of Organic Chemistry, Kawabata T, 10 November 2009.

Practical Synthesis of Axially Chiral Amino Acid through Efficient Construction of Aza[5]helicenes, 22nd International Congress on Heterocyclic Chemistry (ICHC-22), Furuta T, 3 August 2009.

Synthesis of Chiral Cyclic Ethers with Tetrasubstited Carbon via C-O Axially Chiral Enolates, 7th Symposium on Organic Chemistry —The Next Generation—, Yoshimura T, 24 July 2009.

Catalytic Selective Acylation of Bifunctional Substrates, 96th Symposium on Organic Synthesis, Yoshida K, Kawabata T, 24 October 2009.

Binaphthyl Surrogates Possessing a Metal Center Directly Bound to the Chiral Axis, 34th Symposium on Progress in Organic Reactions and Syntheses —Applications in the Life Sciences—, Hayashi K, Kawabata T, 17 November 2009.

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, 1 April 2007–31 March, 2009.

Kawabata T, Fine Organic Synthesis Based on Catalytic Regioselective Functionalization, Grant-in-Aid for Scientific Research (A), 1 April 2009–31 March 2012.

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.

Discrimination of Distal Enantiotopic Hydroxy Groups by Organocatalysis

Asymmetric desymmetrization of *meso*-1,2-diols, *meso*-1,3-diols, and prochiral 1,3-diols have been well established. However, the corresponding reactions of 1,5-diols and the longer analogues have rarely been developed because of their extreme difficulty. We have developed organocatalytic asymmetric lactonization of σ-symmetric 1,9-diols via discrimination of distal enantiotopic hydroxy groups with ~12 Å distance in between. Treatment of **2** with 10 mol% of **1** in the presence of *t*-Bu(*i*-Pr)NMe followed by benzoyl chloride gave **3** in 92% ee and 91% yield.

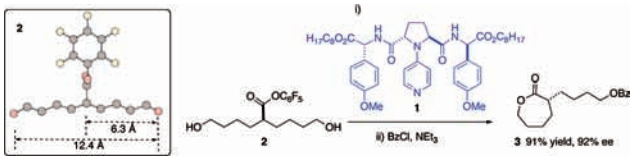

Figure 1.

Catalytic Kinetic Resolution of Axially Chiral Binaphthylamines

Nonenzymatic catalytic kinetic resolution of racemic amines has been extremely limited because uncatalyzed non-selective acylation competes significantly with catalyzed enantioselective acylation. We have developed the kinetic resolution of (±)-2,2'-disubstituted-1,1'-binaphthyl-8,8'-diamines with chiral C_2-symmetric organocatalyst **4**. Treatment of the racemic aromatic amines with isobutyric anhydride in the presence of 10 mol% of **4** gave recovered unacylated amines in 86~98% ee at 61~71% conversion, which corresponds to the selectivity factor (*s*), 15~24. Based on the temperature-dependence of the enantioselectivity of the kinetic resolution, $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ between the acylation reactions for the fast-reacting (*S*)-isomer and the slow-reacting (*R*)-isomer were determined to be –2.9 kcal/mol and –7.8 kcal/mol, respectively. We assume that the acylation of the fast-reacting (*S*)-isomer proceeds via intermolecular hydrogen bonding between the catalyst and the NH_2 group of the (*S*)-isomer, where the reacting amino group is located close to the carbonyl group of the acyl-pyridinium intermediate. On the other hand, the hydrogen bonding between the catalyst and the slow-reacting (*R*)-isomer does not make the reacting NH_2 group close to the carbonyl group, so that the (*R*)-isomer is expected to undergo direct acylation of the amino group without hydrogen-bonding interaction.

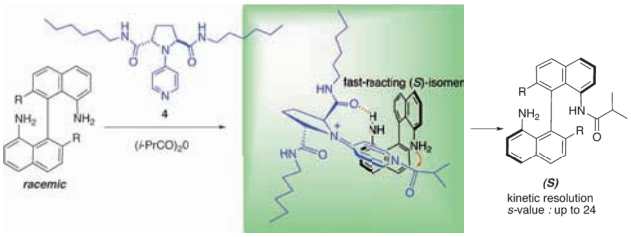

Figure 2.

Asymmetric Synthesis of Multisubstituted β-Lactams from α-Amino Acids

A method for asymmetric synthesis of multisubstituted β-lactams via intramolecular conjugate addition of the enolates derived from amino acid derivatives has been developed. Precursors **5** for β-lactam synthesis were readily prepared from α-amino acids via introduction of *p*-methoxyphenyl group into the nitrogen, acylation of the resulting amine with maleic anhydride, followed by esterification. Treatment of **5** (R=CH_2Ph) with cesium carbonate in ethanol at 0°C for 1 h gave a 1:1 mixture of *cis*- and *trans*-**6** in 95% and 96% ee, respectively, in a combined yield of 94%. Treatment of diastereomerically pure *trans*-**6a** (R=CH_2Ph, 96% ee) with cesium carbonate in ethanol at 20°C for 10 h gave a 12:1 mixture of *cis*- and *trans*-**6a** in 90% and 89% ee, respectively. Similarly, diastereomerically pure *cis*-**6a** (R=CH_2Ph, 92% ee) gave a 13:1 mixture of *cis*- and *trans*-**6a** in 84% and 77% ee, respectively, on treatment with cesium carbonate in ethanol at 20°C for 10 h. Thus, diastereoselectivity of the β-lactam formation was found to be thermodynamically controlled.

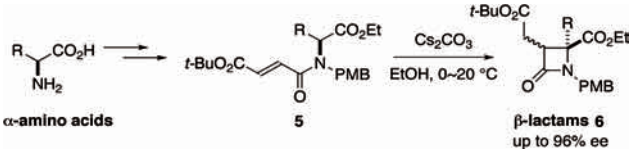

Figure 3.

Yoshimura T, Asymmetri Total Synthesis of Bioactive Natural Products via Planar Chiral Enolate, Grant-in-Aid for Young Scientists (B), 1 April 2009–31 March 2011.

Awards

Uruno Y, Best Poster Award, "The Creation of a Peptide[2]catenane and D,L-Peptide Catalysts Based on Alternating D,L-Peptide Architecture", The 29th Seminar on Synthetic Organic Chemistry for Young Scientists, Kobe, 24 November 2009.

Uruno Y, Impressive Oral Presentation Award, "Creation of a Peptide[2]catenane Based on Alternating D,L-Peptide Architecture", The 39th Congress of Heterocyclic Chemistry, Kashiwa, 16 October 2009.

Uruno Y, Impressive Poster Presentation Award, "Toward the Development of Unique Materials Based on Alternating D,L-Peptide Architecture", The 5th Host Guest Chemistry Symposium, Utsunomiya, 30 May 2009.