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<th>Division of Synthetic Chemistry</th>
<th>Synthetic Organic Chemistry</th>
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<td>Author(s)</td>
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<tr>
<td>Citation</td>
<td>ICR annual report (2011), 18: 8-9</td>
<td></td>
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<td>Issue Date</td>
<td>2011</td>
<td></td>
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<td>URL</td>
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<tr>
<td>Type</td>
<td>Departmental Bulletin Paper</td>
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<tr>
<td>Textversion</td>
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<td></td>
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<tr>
<td>Publisher</td>
<td>Kyoto University</td>
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TOPICS AND INTRODUCTORY COLUMNS OF LABORATORIES

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”, organocatalysis for regioselective and asymmetric syntheses, synthesis of novel amino acids and nitrogen heterocycles, regioselective functionalization of carbohydrates, and the structural and functional investigation of heterochiral oligomers.

KEYWORDS
Organocatalysis
Regioselective Functionalization
Dynamic Chirality
Unusual Amino Acid
Molecular Recognition

Selected Publications
Organocatalytic Chemoselective Monoacylation of 1,n-Linear Diol

Selective monoacylation of 1,n-linear diols seems simple molecular transformation, however, it is still a challenging subject in current organic synthesis because overacylation is usually unavoidable. Since the steric environments of the free OHs in diol 2 are similar to those of a free OH in mono 3 (Figure 1d), strategy for monoacylation based on conventional steric repulsive interaction is not effective, especially in the cases of long-chain diols. We describe here chemoselective monoacylation of 2 by organocatalytic discrimination of 2 from 3 via molecular recognition. In the presence of catalyst 1, exclusive or predominant monoacylation of 1,n-linear diols took place when the chain length of linear diols is equal to or shorter than five (Figure 1b). In sharp contrast to the acylation catalyzed by 1, random acylation of linear diols was observed in DMAP-catalysed acylation, independently from the chain length of linear diols (mono/diacylate=0.6~3.1, Figure 1c).

Monooacylation of 1,n-Linear Diol

Acylation catalyzed by 1 is diol-selective and chain-length-selective (Figures 1d,e). The relative rate of the acylation between 1,5-pentanediol (2) and its monoacylate (3) was found to be 113, while that of DMAP-catalyzed acylation was 1.0 (Figure 1d). The high diol-selectivity observed in the acylation catalyzed by 1 seems to be the origin of the high selectivity for monoacylation of linear diols. Catalyst 1 appears to discriminate the chain length of the diols on acylation. 1,5-Pentanediol (2) was found to be acylated 5.2 times faster than its one-carbon-longer analogue, 1,6-hexanediol (4) (Figure 1e).

Asymmetric Intermolecular Conjugate Addition of Axially Chiral Enolates: Total Synthesis of Manzacidin A

Unusual amino acids and their analogues have attracted considerable attention because of their potential utilities in the fields of natural product syntheses and medicinal chemistry. We developed a synthetic method of α,δ-diaminoglutaric acid derivatives via intermolecular conjugate addition of chiral enolates generated from readily available α-amino acids. In this reaction, asymmetric nucleophilic addition of chiral enolates A (blue thick arrow) competes racemization of axially chiral enolate A by C-N bond rotation (red arrow, half-life of racemization of A (R=Me)=1 h at −78°C). The highly enantioselective intermolecular conjugate addition of the enolates has been achieved by use of highly reactive Michael acceptor 6 as well as elaboration of the experimental procedure. Slow addition of potassium hexamethyldisilazide (KHMS) in THF to a mixture of 5 (R=Me) and 6 in DMF at −78°C gave a 1:1 diastereomeric mixture of 7 (R=Me) in a quantitative combined yield and in 97% ee and 97% ee, respectively. The conjugate addition of enolate A was found to proceed with a retention of configuration at the newly formed tetrasubstituted stereocenter. This method is well applicable for other α-amino acid derivatives such as phenylalanine derivative 5 (R=CH2Ph) and methionine derivative 5 (R=CH2CH2SMe). One of the diastereomers of 7 (R=Me, 97% ee) was successfully transformed to marine natural product manzacidin A. In this transformation, all of the carbon-nitrogen framework obtained by the asymmetric conjugate addition are incorporated in the structure of manzacidin A (shown in blue in Figure 2. The MOM group is utilized as a methylene unit between two nitrogen atoms).

Figure 1. (a) Acylation of 1,n-linear diols catalyzed by 1 or DMAP. Ratios of the mono-/diacylate in the acylation of catalyzed by 1 (b) and DMAP (c). The relative rate of acylation between 2 and 3 (d), and between 2 and 4 (e).

Figure 2. Asymmetric intermolecular conjugate addition of chiral enolates A derived from amino acid derivatives 5 and total synthesis of manzacidin A from the adduct 7.