論文の内容の要旨

論文題目　Direct Catalytic Asymmetric Reactions of α-Keto Anilides for the Synthesis of γ-Amino Amides and Azetidine Derivatives

(α-ケトアニリドの直接的触媒的不斉反応によるγ-アミノアミドおよびアゼチジン誘導体の合成)

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Chiral γ-amino acids and their derivatives are very important building blocks being the key structural motifs in natural products and pharmaceuticals. However, catalytic enantioselective methods leading to these compounds are still rare. Herein, I report direct catalytic asymmetric Mannich-type reactions and aldol-type reactions by utilizing the multifunctionality of α-keto anilides (Figure 1) toward the synthesis of chiral γ-amino amides and azetidine derivatives. In case of Mannich-type reactions, α-keto anilides functioned as the nucleophiles, providing either *syn*- or *anti*-Mannich adducts stereoselectively by using different types of bifunctional *Lewis acid-Brønsted base* catalysts.

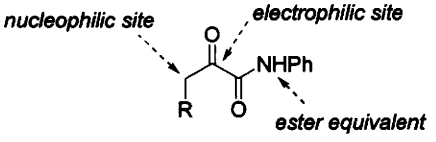


Figure 1. Multifunctionality of α-keto anilides

Transformations of Mannich adduct provided efficient accesses to chiral γ-amino amides and azetidine derivatives. On the other hand, α-keto anilides functioned as the electrophiles in catalytic asymmetric aldol-type reactions with a ketoimine as the nucleophile.

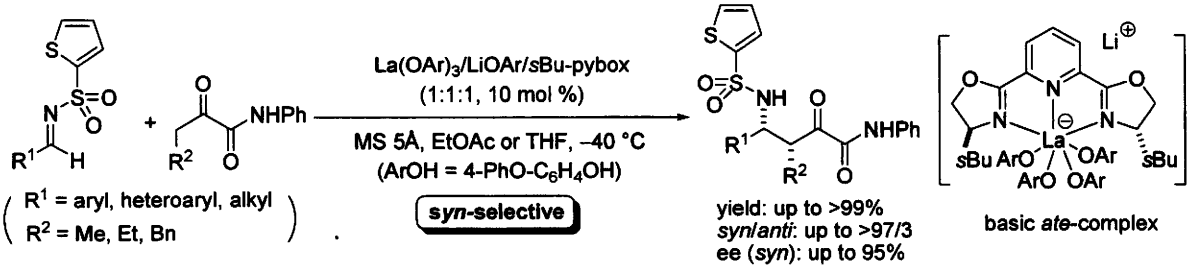
1. Direct Catalytic Asymmetric Mannich-Type Reactions Using α-Keto Anilides as Nucleophiles

(1) *syn*-Selective Mannich-Type Reactions[1]

Direct catalytic asymmetric Mannich-type reaction using α-keto esters as nucleophiles was reported by Jørgensen et al.[2] After diastereoselective reduction of α-keto unit in Mannich adduct, a highly functionalized γ-amino ester with three contiguous stereocenters was obtained with excellent enantio- and diastereoselectivity. However, the method was limited to the use of *N*-Ts α-imino ester as the only electrophile. Therefore, the development of other new method to enable the use of imines with various substituents for γ-amino acid derivative synthesis is in high demand.

Initially, I also examined the feasibility of using α-keto ester as nucleophile for Mannich-type reactions with imines activated by various protecting groups, and found that partial cyclization always occurred after C–C bond formation. Then, I turned my attention to using α-keto anilides as nucleophiles. The Mannich adducts were easily obtained in high yield. After screening several chiral catalysts developed in our group, I found heterobimetallic La-aryloxide/Li-aryloxide/pybox complex[3] to be the most effective for providing *syn*-form Mannich adducts when using *N*-2-thiophenesulfonyl imines as electrophiles. Finally, $La(OAr)_3$/LiOAr/*s*Bu-pybox catalyzed direct Mannich-type reactions of various aryl, heteroaryl and alkyl *N*-thiophenesulfonyl imines to give products in >99–66% yield, 95–70% ee, and >97:3–77:23 *syn*-selectivity (Scheme 1). Both La and Li were important in present system. The real catalyst was supposed to be a bifunctional basic *ate*-complex, in which one La-aryloxide moiety functioned as Brønsted base for deprotonating of α-keto anilide while La or Li functioned as Lewis acid for activating the substrate.

Scheme 1. Heterobimetallic La/Li/pybox-catalyzed direct asymmetric Mannich-type reactions of α-keto anilides

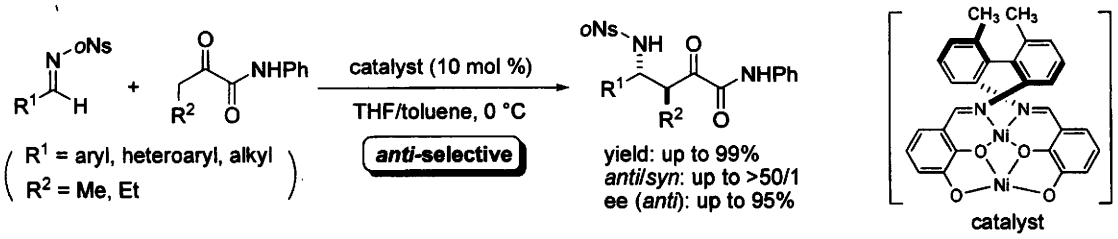


(2) *anti*-Selective Mannich-Type Reactions[4] (Co-worked with Yingjie Xu, M2 student)

Because the control of diastereoselectivity in asymmetric catalysis is a very important issue, therefore, after establishment of *syn*-selective Mannich-type reactions using α-keto anilides as nucleophiles, I considered how to achieve the *anti*-selectivity using the same substrates.

I examined the reactions using La(OAr)$_3$/phosphine dioxide as catalyst.[5] However, poor reactivity along with poor enantioselectivity was observed, albeit sometimes with high *anti*-selectivity. Then I found that bimetallic-Schiff base complex could promote the reaction of α-keto anilide and *N*-2-thiophenesulfonyl imine in *anti*-selectivity and with good yield. However, just by changing metals or the upper part of Schiff base ligand, both diastereo- and enantioselectivity would be affected greatly. A homodinuclear Ni_2-Schiff base complex was found to be the most promising candidate. However, the reproducibility was not so good. After that time, the optimal reaction conditions were successfully established by co-worker, Yingjie Xu, who found that careful washing of the complex without using water in catalyst preparation process is the key point for high enantioselectivity. Finally, Ni_2-Schiff base complex catalyzed direct Mannich-type reaction of α-keto anilides with various aryl, heteroaryl and alkyl imines which were activated by an *N-ortho*-nitrobenzenesulfonyl group, giving products in 99–76% yield, 95–91% ee, and >50:1–10:1 *anti*-selectivity (Scheme 2). In the homodinuclear Ni_2-Schiff base complex, one Ni-aryloxide moiety is supposed to function as Brønsted base for deprotonating of α-keto anilide, another Ni is supposed to function as Lewis acid for activating imine substrate.

Scheme 2. Homodinuclear Ni_2-Schiff base complex-catalyzed direct asymmetric Mannich-type reactions of α-keto anilides



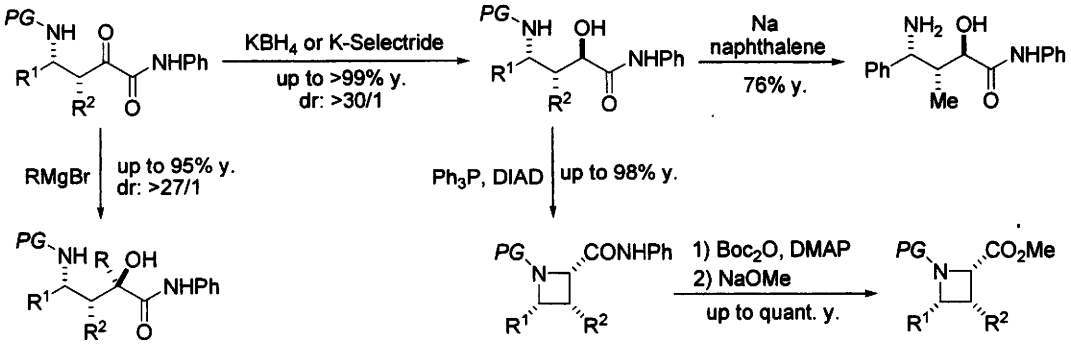
(3) Synthesis of Chiral γ-Amino Amides and Azetidine Derivatives[6]

To demonstrate the synthetic utility of *syn*- or *anti*-Mannich adducts obtained *via* above protocols, transformations of them into various chiral γ-amino amides and azetidine derivatives were investigated

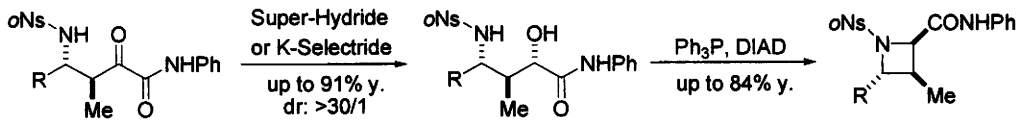
(Scheme 3). Various β-alkyl-γ-amino-α-hydroxy amides with three contiguous chiral centers were successfully obtained by diastereoselective reductions of α-keto moiety using K-Selectride, KBH_4, or Super-Hydride. γ-Amino amides containing one tetrasubstituted carbon unit were also synthesized by diastereoselective additions of various Grignard reagents to α-keto moiety. Finally, *N*-2-thiophenesulfonyl group was easily removed by Na/naphthalene for the first time. On the other hand, these γ-amino amides became good precursors for fully substituted azetidine-2-amides/esters, which are quite useful non-natural amino acid derivatives for medicinal chemistry but still rarely reported. As a result, intramolecular Mitsunobu cyclization proceeded and optically active azetidine-2-amides were obtained in high yield. As a potential ester equivalent, anilide moiety was easily converted into ester group under mild conditions without any epimerization.

Scheme 3. Transformations of Mannich adducts: chiral γ-amino amides and azetidine derivatives synthesis

***A)* from *syn*-Mannich adducts** (*PG* = 2-thienylSO$_2$-)



***B)* from *anti*-Mannich adducts**



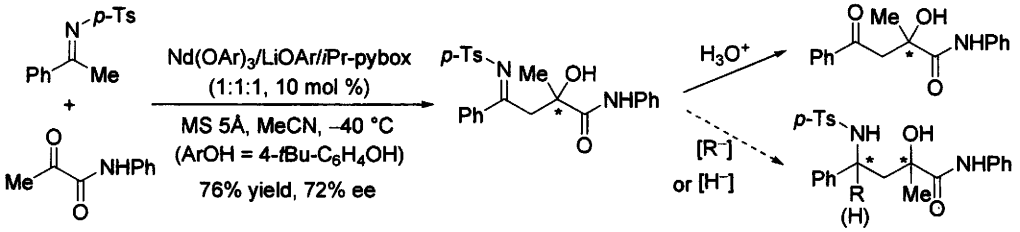
2. Direct Catalytic Asymmetric Aldol-Type Reactions Using α-Keto Anilides as Electrophiles

Chiral tertiary alcohols or α-tertiary amines are very important building blocks of naturally occurring and artificial biologically active molecules. Based on the results as described in above section, I envisaged the possibility of asymmetric Mannich-type addition of α-keto anilides to ketoimines, which would possibly construct γ-amino amides with a tetrasubstituted chiral carbon unit after reducing C=O bond. However, preliminary racemic reaction between α-keto anilide and ketoimine in the presence of LiOAr only afforded the product with a tertiary alcohol moiety quantitatively, which suggested an inversion

pathway—ketoimine worked as a nucleophile, while α-keto anilide worked as an electrophile. Upon treatment with H^-, R^- or H_3O^+, C=N bond in product would potentially present to be a reactive site for synthesizing γ-amino-α-hydroxy amide or α-hydroxy-γ-keto amide that contains one or two tetrasubstituted carbon centers. Therefore, I started to investigate direct catalytic asymmetric aldol-type reactions of ketoimines using α-keto anilides as electrophiles. Moreover, using achiral ketoimines as nucleophiles for the direct asymmetric C–C bond-forming reactions is still challenging now.

At present, one promising result has already been obtained by using heterobimetallic $Nd(OAr)_3$/LiOAr/*i*Pr-pybox complex (Scheme 4). The aldol adduct was hydrolyzed into α-hydroxy-γ-keto amide quantitatively. Further optimizations of reaction conditions to improve the reactivity and selectivity, as well as transformations of the aldol adducts into tetrasubstituted γ-amino-α-hydroxy amides are still under investigations.

Scheme 4. Heterobimetallic Nd/Li/pybox-catalyzed direct asymmetric aldol-type reaction of α-keto anilide



(further improvement is ongoing)

References

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4) Xu, Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3353.

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6) Lu, G.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *Manuscript in preparation.*