論文の内容の要旨

題目：Enantioselective Synthesis of Aeruginosin 298-A and Direct Catalytic Asymmetric Aldol-Tishchenko Reaction of Methylene Ketones（アレギノシン２９８－A の不斉合成及びメチレンケトン類の直接的触媒的不斉アルドールーティシェンコ反応の開発）

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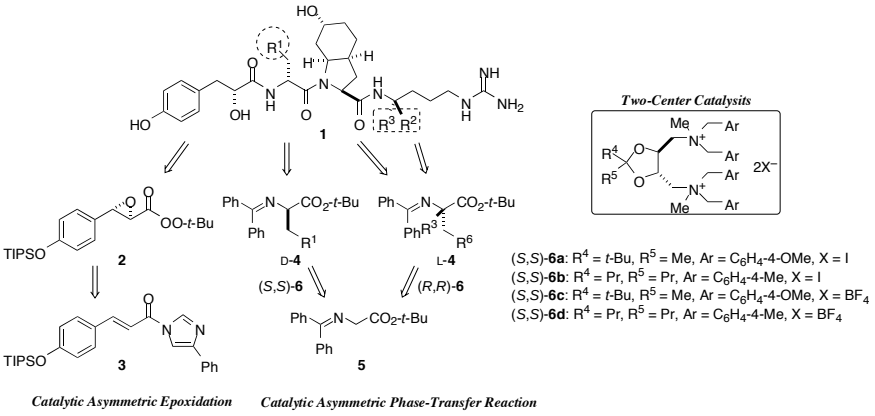
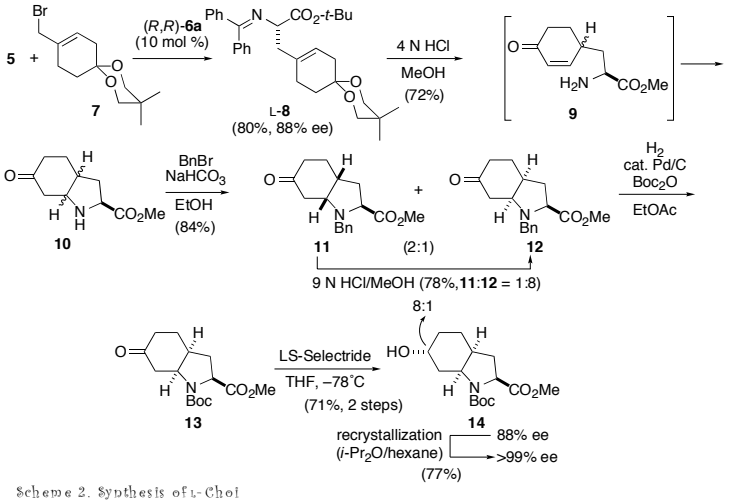
1) Enantioselective Syntheses of Aeruginosin 298-A and its Analogs.

The synthesis of both natural and unnatural organic compounds in opticaly pure form is a central challenge in chemistry, especially in relation to the study of biologically active compounds. Aeruginosin 298-A was isolated from the freshwater cyanobacterium Microcystis aeruginosa (NIES-298) is an equipotent thrombin and trypsin inhibitor. It has a tetrapeptide-like structure including nonstandard α-amino acids such as 3-(4-hydroxyphenyl)lactic acid (Hpla) and 2-carboxy-6-hydroxyoctahydroindole (Choi). I developed a versatile synthetic process focusing on the preparation of **14** for the synthesis of aeruginosin 298-A as well as their several attractive analogs, which were synthesized to gain insight into the structure–activity relations. In the process all stereo centers were controlled by catalytic asymmetric phase-transfer reaction promoted by two-center asymmetric catalysts and catalytic asymmetric epoxidation promoted by a lanthanide–BINOL complex.[1, 2]

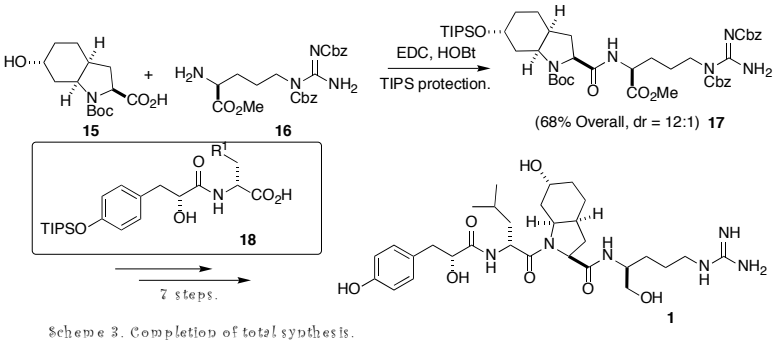


Scheme 1. Retrosynthetic Analysis.

Furthermore, serine protease inhibitory activities of aeruginosin 298-A and its analogs were also examined. 2-carboxy-6-hydroxyoctahydro indole (Choi) is a unnatural amino acid and most important key intermediate in the total synthesis of aeruginosin 298-A. I prepared **14** via phase-transfer alkylation of **5** with **7**, which was prepared from *p*-anisyl alcohol, as a electrophile. When using (*R*,*R*)-**6a** as a catalyst, the asymmetric PTC of **5** and **7** proceeded smoothly to afford the desired product L-**8** in 80% yield and 88% ee. Treatment of the product L-**8** with 4 N HCl in methanol promoted deprotection of the benzophenone imine and ketal, transesterification, migration of the C–C double bond, and then 1,4-addition of the resulting amine to enone, leading to the bicyclic compound **10** in 72% yield (one-pot, five reactions). After benzylation, the key intermediate was obtained in 84% yield as a diastereomixture (**11**:**12** = 2:1). The undesired isomer **11** was transformed to the desired **12** under acidic conditions (78%, **11**:**12** = 1:8) and **12** was successfully converted to the key intermediate **14** (71% in 2 steps) by following Bonjoch's procedure.[3] In addition, optically pure **14** was obtained by recrystallization (>99% ee, 77%).



Scheme 2. Synthesis of L-Choi



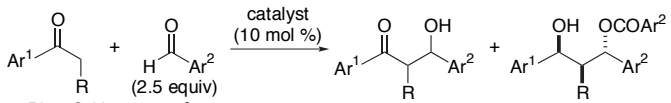
Scheme 3. Completion of total synthesis.

Furthermore this unnatural amino acid **15** was successfully used in the total synthesis of aeruginosin 298-A. As shown in Scheme 3, coupling reaction with **16** proceeded smoothly using EDC, HOBt condition to afford **17** with 68% overall yield (dr = 12:1). Compound **17** after Boc deprotection was coupled with compound **18** under HATU condition. Reduction using $LiBH_4$ in THF, subsequent deprotection of TIPS and Cbz groups provided aeruginosin 298-A **1**.[4] Moreover, six additional analogues were synthesized in a similar way and screened for inhibitory activities against serine protease trypsin.[5]

2) Direct Catalytic Asymmetric Aldol-Tishchenko Reaction of Methylene Ketones.[6]

Since the first successful intermolecular direct catalytic asymmetric aldol reaction of aldehydes with unmodified ketones using heterobimetallic asymmetric catalyst devoleped by Shibasaki's group, Shibasaki's and other groups have attempted this type of direct reaction with great success. In almost all of these direct asymmetric catalyses, however, only limited donors, such as methyl ketones, α-hydroxy ketones, and easily enolizable aliphatic aldehydes, are utilized. Thus, despite the high demand for the development of a direct aldol reaction of ethyl ketones, direct aldol reaction of ethyl ketones are viewed as a formidable synthetic challenge due to poor participation of the resulting aldolates in catalyst turnover and a strong tendency towards retro-aldol

reactions. I recently accomplished this elusive aldol reaction using the aldol-Tishchenko reaction.[6] By coupling an irreversible Tishchenko reaction to a reversible aldol reaction, the catalytic aldol-Tishchenko reaction provides high product yields and high enantioselectivities.



15a Ph = C_6H_5 **16** (Ar^2 = C_6H_4-4-Cl) **17** **18**
15b Ph = *p*-CF_3-C_6H_4

Table 1: Optimization studies.

entry	ketone	catalyst	conv. (%)	**17**:**18**	ee[a] (%)
1	**15a**	(*R*)-LLB	20	~1:1	64
2	**15a**	(*R*)-LLB+LiOTf (1:3)	60	~1:1	78
3	**15a**	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:6)	60	~1:1	86
4	**15b**	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:6)	75	2:>98	88
5	**15b**	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:5.6)	80	2:>98	93

a) ee of **18** after ester hydrolysis.

Preliminary studies using propiophenone (**15a**) with 4-chlorobenzaldehyde (**16**) in the presence of 10 mol % of LLB, afforded the anticipated sequential aldol-Tishchenko product with excellent diastereoselectivity and moderate enantiocontrol (>98/2 dr and 64% ee for **18**); however, the catalytic efficiency was unsatisfactory (Table 1, entry 1). I next examined the use of a metal salt additive. While a variety of lithium salts were productive in this context, 30 mol % LiOTf provided the optimal reaction efficiency and high selectivity (entry 2). Keeping the 1:3:3 ratio of lanthanum, BINOL, and LiOTf in mind, I investigated whether the same catalytic system would be accomplished by mixing 6 equiv of BuLi to the mixture of the 1:3 ratio of $La(OTf)_3$ and BINOL. The commercial availability of $La(OTf)_3$, high tolerance to air and water, and superior levels of asymmetric induction and efficiency (entry 3) exhibited by this modified procedure prompted me to further explore this catalytic condition. Switching to ketone **15b** had a significant effect on the reactivity and Tishchenko selectivity, while maintaining the similar enantiocontrol (entry 4). Superior levels of asymmetric induction were realized by decreasing the amount of BuLi. Thus, 1:3:5.6 $La(OTf)_3$:BINOL:BuLi was the appropriate ratio for a broad range of substrates (entry 5).

Experiments to probe the scope of the aldehyde substrates are summarized in Table 2. A variety of alkyl and heteroatom substituents can be incorporated on the phenyl ring at both the meta and para positions (Table 2, entries 1-7, 85-95% ee, 65-96% yield). The aryl framework can be successfully extended to naphthalene and heteroaromatic derived systems (entries 8-10, 88-94% ee, 67-82% yield). In addition, a number of aromatic ketones can also be used without loss of reaction efficiency or enantiocontrol (entries 11-15, 84-88% ee, 60-81% yield). I next examined the capacity of the present catalytic system to catalyze asymmetric aldol-Tishchenko reactions of propyl and butyl ketones. As highlighted, the catalyst exhibited similar efficiency without considerable deterioration of enantiocontrol (entries 16 and 17, 87-88% ee, 88-90% yield).

Table 2: Direct aldol-Tishchenko Reactions: Substrate Scope.

entry	ketone **15** Ar^1	aldehyde **16** Ar^2	time (h)	ee[a] (%)	yield (%)
1	4-F_3C-C_6H_4(R=Me)	4-Cl-C_6H_4	60	93	95
2	4-F_3C-C_6H_4(R=Me)	4-Br-C_6H_4	48	95	96
3	4-F_3C-C_6H_4(R=Me)	4-F-C_6H_4	72	92	85
4	4-F_3C-C_6H_4(R=Me)	4-Me-C_6H_4	94	92	67
5	4-F_3C-C_6H_4(R=Me)	C_6H_5	84	91	95
6	4-F_3C-C_6H_4(R=Me)	3-Br-C_6H_4	48	86	92
7	4-F_3C-C_6H_4(R=Me)	3-MeO-C_6H_4	72	85	65
8	4-F_3C-C_6H_4(R=Me)	2-naphthyl	80	88	67
9	4-F_3C-C_6H_4(R=Me)	3-furyl	84	93	77
10	4-F_3C-C_6H_4(R=Me)	3-thienyl	84	94	82
11	4-Br-C_6H_4(R=Me)	4-Br-C_6H_4	48	85	70
12	3-Cl-C_6H_4(R=Me)	4-Cl-C_6H_4	48	84	60
13	3,4-Cl2-C6H4(R=Me)	4-Cl-C_6H_4	48	88	81
14	3,5-Cl2-C6H4(R=Me)	4-Cl-C_6H_4	48	85	73
15	3,5-F_2-C_6H_4(R=Me)	4-Cl-C_6H_4	48	87	77
16	4-F_3C-C_6H_4(R=Et)	4-Br-C_6H_4	90	88	90
17	4-F_3C-C_6H_4(R=Pr)	4-Br-C_6H_4	90	87	88

a) ee of **18** after ester hydrolysis.

Preliminary mechanistic studies were performed to inspect the relation between the aldol product and the Tishchenko product, as well as their stereoselectivities. The aldol byproduct **17** was obtained by the reaction of **15a** and **16** was with no enantio- or diastereoselectivity. Attempted deliberate retro-aldolization of independently prepared racemic aldol adducts **17** (*syn*:*anti* = 7:3 or *syn*:*anti* = 3:7) under representative reaction conditions gave the same mixtures of **15a**, **17** (*syn*:*anti* = 4:6, racemic), and **18** (>98/2 dr, 70% ee) starting with either a 7:3 or a 3:7 *syn*:*anti* ratio of aldol adducts **17**. These results are consistent

with the rapid retro-aldol cleavage of metal aldolate and *confirm the essential role of the Tishchenko reaction in controlling the stereoselectivity.* In summary, aldol- Tishchenko reaction was established as one of the useful methods for overcoming the retro-aldol reaction problem for a variety of aromatic donors and acceptors.

In addition, I and one of my coworker observed a dynamic structural change of LLB to a novel binuclear La_2Li_4pentakis(binaphthoxide) complex by the addition of LiOTf.[7] Thus, I became interested in the role of LiOTf and the efficiency of these catalytic systems in other asymmetric reaction promoted by heterobimetalic bifunctional catalyst. In direct intermolecular aldol reaction of aldehydes and ketones, addition of LiOTf gradually decreased the enantioselectivity. On the other hand, in the case of nitro aldol reaction, LiOTf had no effect on the enantio or diastereoselectivities. In summary, heterobimetalic complex prepared from $La(OTf)_3$:BINOL:BuLi (1:3:6) was successfully used for nitro aldol reaction without decrease in enantio and diastreoselectivities. This novel catalyst system can be efficient alternative for conventional LLB, Which was prepared from rather expensive $La(O\textit{i}Pr)_3$.

References:

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