

論文の内容の要旨

論文題目:

Development of Catalytic Asymmetric Reactions Based on Novel Concepts: Scale-up Studies of a Barium-Catalyzed Asymmetric Diels-Alder Reaction and Soft Metal-Catalyzed Asymmetric Tetrasubstituted Carbon Constructions

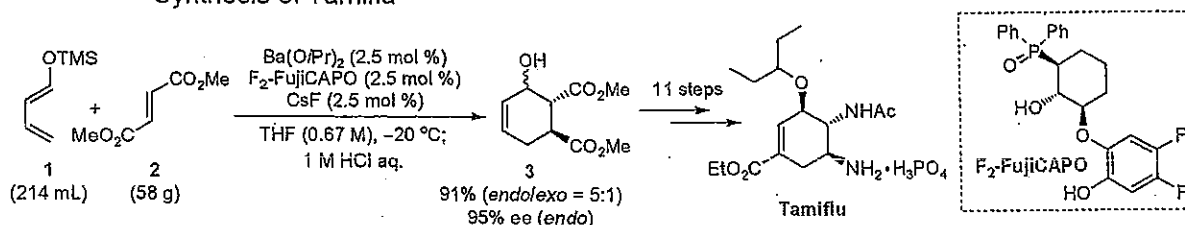
新規概念に基づく不斉触媒反応の開発:バリウム触媒による不斉 Diels-Alder 反応のスケールアップ研究とソフトメタル触媒を用いた不斉四置換炭素合成

氏名: 殷 亮

1. Scale-up Studies of a Barium-Catalyzed Asymmetric Diels-Alder Reaction for the Synthesis of Tamiflu¹

Our latest synthetic route of Tamiflu started from a novel barium-catalyzed asymmetric Diels-Alder reaction, which is conceptually distinct from classical Lewis acid catalysis. Labile diene **1**, which was easily polymerized in the presence of chiral Lewis acid catalysts, was successfully activated by chiral Ba-F₂-FujiCAPO complex and CsF to afford a reactive barium dienolate.² This reaction was initially problematic, however, with regard to reproducibility. After careful optimization, I established reliable conditions using degassed solvent. Finally, the reaction was successfully performed on 58-gram scale using 2.5 mol % catalyst, with high diastereoselectivity and excellent enantioselectivity (Scheme 1). Furthermore, the catalyst loading was reduced to 1 mol % of barium and 1 mol % of F₂-FujiCAPO affording constant results. In short, a practical catalytic asymmetric Diels-Alder reaction was established, which is the key methodology used for the Tamiflu synthesis.

Scheme 1. Scale-up Studies of the Catalytic Asymmetric Diels-Alder Reaction for a Practical Synthesis of Tamiflu



2. Nucleophile Generation via Decarboxylation: Asymmetric Construction of Contiguous Quaternary-Trisubstituted Stereocenters through a Cu(I)-Catalyzed Decarboxylative Mannich-Type Reaction³

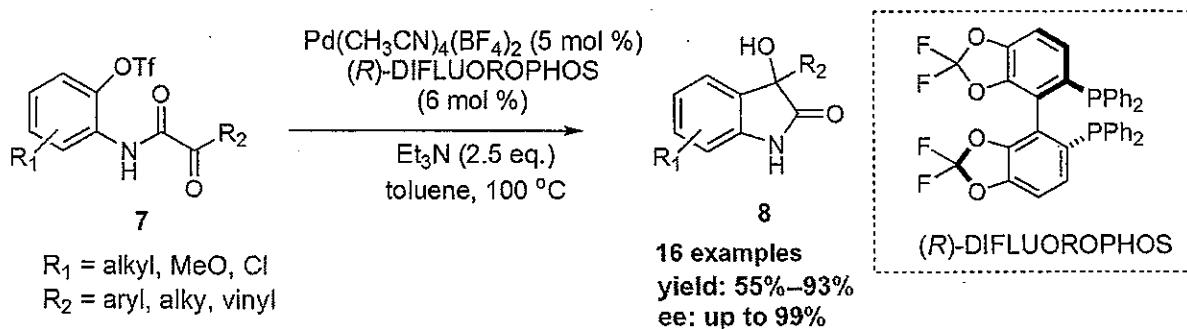
Catalytic asymmetric construction of contiguous trisubstituted and all-carbon quaternary stereocenters represents a particularly difficult challenge. There are two obvious obstacles involved in construction of such carbon centers, which lead to few successful examples available. The first is the enhanced steric hindrance. The second is the similarity between the nonhydrogen substituents on a prochiral carbon. The catalytic carbon-carbon bond-formation with high diastereo- and enantio-control using sterically congested substrates is prerequisite for the success of the targeted methodology. Aimed at expanding the scope of

developed system showed a superior effect in this Mannich-type reaction and complemented to the previous basic deprotonation system using Cu(I)-conjugated base.

3. Asymmetric Intramolecular Aryl-Transfer Reaction from Aryl Triflates to Ketones Catalyzed by a Palladium-DIFLUOROPHOS Complex⁴

The electrophilic nature of aryl and vinyl organopalladium intermediates, which are generated from aryl and vinyl halides or triflates via an oxidative addition process with a Pd(0) species, is widely employed in organic synthesis. However, its nucleophilic nature received much less attention. Palladium-catalyzed nucleophilic reactions of organic halides and triflates to ketones and aldehydes are not studied extensively, although such additions are frequently encountered in traditional main-group metal chemistry. Furthermore, asymmetric versions of such reactions have not been reported yet.

Scheme 4. Catalytic Asymmetric Intramolecular Aryl-Transfer Reaction from Aryl Triflates to Ketones Catalyzed by a Palladium-DIFLUOROPHOS Complex



Recently, I have successfully developed an asymmetric intramolecular aryl-transfer reaction from aryl triflates or iodides to ketones using a palladium-DIFLUOROPHOS complex as chiral catalyst with acceptable yields and excellent enantioselectivity. Optimized conditions were determined as shown in Scheme 4 by screening protecting groups on amide, Pd species, ligands (including phosphine ligands and BOX-type ligands), bases, temperature and the amount of Et_3N . The catalyst loading ($\text{R}_1 = \text{H}$, $\text{R}_2 = \text{phenyl}$) was decreased to 1.25 mol % with maintained yield, despite slightly decreased enantioselectivity and prolonged reaction time (120 h). In the presence of 5 mol % catalyst, a series of oxindoles containing tetrasubstituted carbon at 3-position were constructed. Substrates both with electron-donating and electron-withdrawing groups were competent. Furthermore, substrate with a heteroaromatic ($\text{R}_2 = \text{heteroaromatic}$) ring such as thiophene was a good substrate under the optimized conditions. Vinyl-contained substrate ($\text{R}_2 = \text{vinyl}$) showed excellent enantioselectivity with moderate yield. It was noteworthy that aliphatic ketones ($\text{R}_2 = \text{alkyl}$) afforded corresponding oxindoles in moderate yield and acceptable enantioselectivity. Expansion of current methodology to construct a six-member ring is now on going.

References:

- (1) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1070.
- (2) Yamatsugu, K. Ph. D. Thesis (March, 2010), The University of Tokyo.
- (3) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.
- (4) Yin, L.; Kanai, M.; Shibasaki, M. manuscript in preparation.