

# Division of Synthetic Chemistry

## – Synthetic Organic Chemistry –

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## Scope of Research

The research interests of this laboratory include the development of advanced molecular transformation, total synthesis of biologically active products, and molecular recognition. Programs are active in the following areas: 1) organocatalytic site-selective transformation of multi-functionalized molecules, 2) dirhodium-catalyzed site-selective C-H functionalization, 3) asymmetric induction in transformation of compounds with molecular chirality, 4) total synthesis of glycoside-based natural product based on sequential site-selective functionalization.

### KEYWORDS

Site-Selective Functionalization  
Molecular Recognition  
Molecular Catalyst  
Sugar  
Natural Product

### Recent Selected Publications

- Shibayama, H.; Ueda, Y.; Tanaka, T.; Kawabata, T., Seven-Step Stereodivergent Total Synthesis of Punicafolin and Macaranganin, *J. Am. Chem. Soc.*, **143**, 1428-1434 (2021).
- Imayoshi, A.; Lakshmi, B.; Ueda, Y.; Yoshimura, T.; Matayoshi, A.; Furuta, T.; Kawabata, T., Enantioselective Preparation of Mechanically Planar Chiral Rotaxanes by Kinetic Resolution Strategy, *Nat. Commun.*, **12**, 404 (2021).
- Chen, G.; Arai, K.; Morisaki, K.; Kawabata, T.; Ueda, Y., Dirhodium-Catalyzed Chemo- and Site-Selective C-H Amination of *N,N*-Dialkylanilines, *Synlett*, **32**, 728-732 (2021).
- Takeuchi, H.; Fujimori, Y.; Ueda, Y.; Shibayama, H.; Nagaishi, M.; Yoshimura, T.; Sasamori, T.; Tokitoh, N.; Furuta, T.; Kawabata, T., Solvent-Dependent Mechanism and Stereochemistry of Mitsunobu Glycosylation with Unprotected Pyranoses, *Org. Lett.*, **22**, 4754-4759 (2020).
- Ninomiya, R.; Arai, K.; Chen, G.; Morisaki, K.; Kawabata, T.; Ueda, Y.,  $\beta$ -Silicon-Effect-Promoted Intermolecular Site-Selective C(sp<sup>3</sup>)-H Amination with Dirhodium Nitrenes, *Chem. Commun.*, **56**, 5759-5762 (2020).
- Yanagi, M.; Ueda, Y.; Ninomiya, R.; Imayoshi, A.; Furuta, T.; Mishihiro, K.; Kawabata, T., Synthesis of 4-Deoxy Pyranosides via Catalyst-Controlled Site-Selective Toluoylation of Abundant Sugars, *Org. Lett.*, **21**, 5006-5009 (2019).
- Arai, K.; Ueda, Y.; Morisaki, K.; Furuta, T.; Sasamori, T.; Tokitoh, N.; Kawabata, T., Intermolecular Chemo- and Regioselective Aromatic C-H Amination of Alkoxyarenes Promoted by Rhodium Nitrenoids, *Chem. Commun.*, **54**, 2264-2267 (2018).
- Yanagi, M.; Imayoshi, A.; Ueda, Y.; Furuta, T.; Kawabata, T., Carboxylate Anions Accelerate Pyrrolidinopyridine (PPy)-Catalyzed Acylation: Catalytic Site-Selective Acylation of a Carbohydrate in Situ Counteranion Exchange, *Org. Lett.*, **19**, 3099-3102 (2017).

## Seven-step Stereodivergent Total Syntheses of Punicafofin and Macaranganin

Ellagitannins constitute one of the major classes of hydrolysable tannins and more than 500 natural products have been structurally characterized. Punicafofin (**1**) and macaranganin (**2**), natural glycosides of an ellagitannins family, are characterized by a 3,6-hexahydroxydiphenoyl (HHDP) group bridged between C(3)-OH and C(6)-OH of the glucose core. (Figure 1). They are stereoisomeric to each other concerning the chiral axis of the HHDP moiety and show different biological activities depending on the chirality of the HHDP group. Although stereodivergent synthesis of the HHDP groups is desirable for their straightforward total syntheses, construction of the 3,6-HHDP group has been a synthetic challenge because a less stable axial-rich  ${}^1C_4$  conformer of the pyranose ring is required for the formation. We achieved the first total syntheses of **1** and **2** in 7 steps, respectively from D-glucose. The prominent features of the synthesis are; (1) sequential site-selective introduction of the adequate galloyl groups into unprotected D-glucose by a catalyst-controlled manner employing originally developed organocatalysts **C1** and **C2**, and (2) stereodivergent construction of the 3,6-HHDP bridge by oxidative phenol coupling of a common intermediate via a ring flipping process of the glucose core. Because no protective groups were used for glucose throughout the process, extremely short-step total syntheses were achieved.

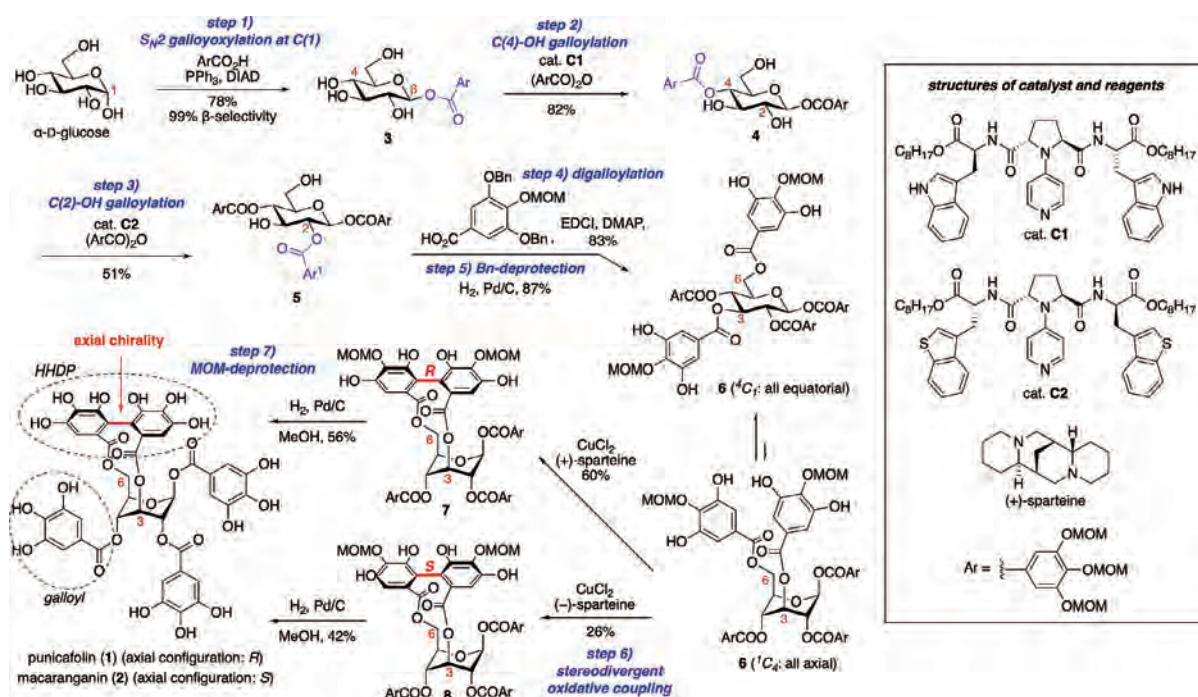


Figure 1. Total synthesis of punicafofin and macaranganin.

## Dirhodium-catalyzed Chemo- and Site-Selective C-H Amination of Dialkylanilines

Development of methods for the construction of C-N bonds is still of great synthetic importance in current synthetic organic chemistry because C-N bonds are ubiquitously involved in functional materials and bioactive molecules. Especially, direct C-N bond formation through C-H bond cleavage represents an attractive and efficient access to such functional molecules. We recently reported a method for dirhodium-catalyzed C(sp<sup>3</sup>)-H amidation of *N,N*-dimethylanilines (Figure 2). Chemo- and site-selective C(sp<sup>3</sup>)-H amidation of *N*-methyl group proceeded exclusively in the presence of C(sp<sup>2</sup>)-H bonds of the electron-rich aromatic ring and secondary, tertiary, and benzylic C(sp<sup>3</sup>)-H bonds  $\alpha$  to a nitrogen atom. The protocol was successfully applied to a two-step demethylation process of a *N*-methylaniline derivative.

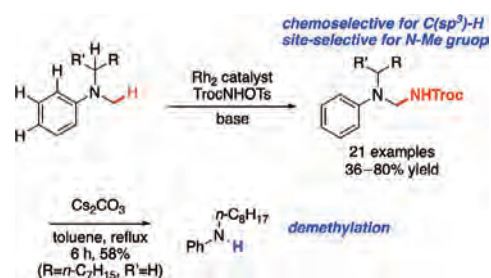


Figure 2. Chemo- and site-selective C-H amination and application to de-methylation.