Asymmetric C–H Functionalization of Cyclopropanes Using an Isoleucine-NH_2 Bidentate Directing Group

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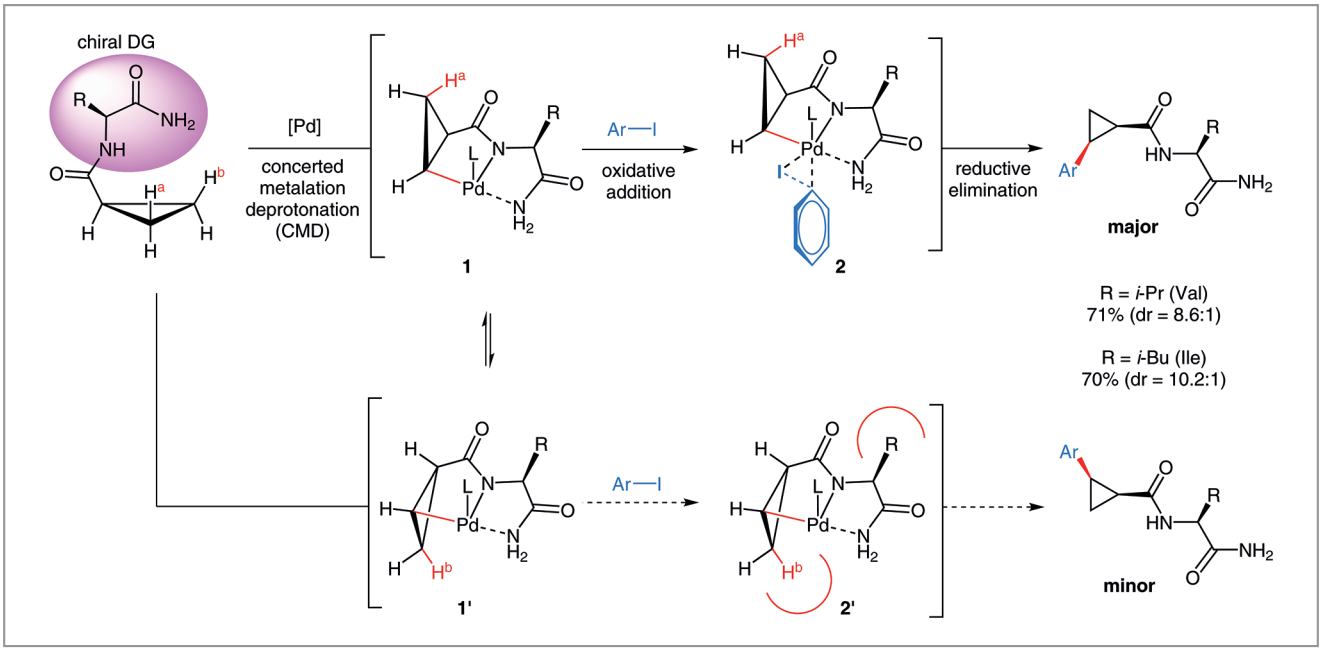
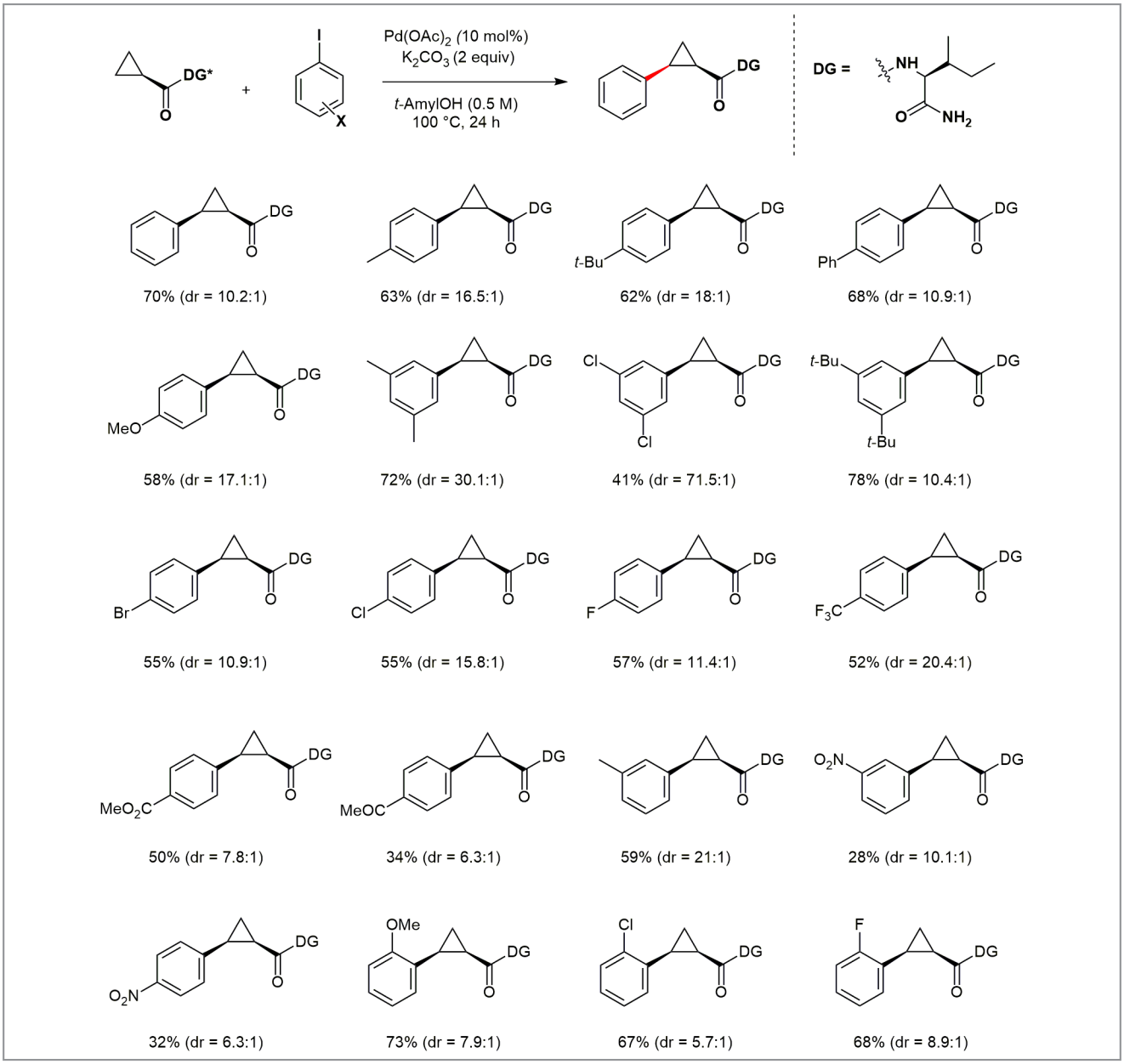
Since the original discovery by the Daugulis group (*J. Am. Chem. Soc.* **2005**, *127*, 13154), powerful bidentate directing groups such as 8-aminoquinoline and picolinamide auxiliaries have been widely used for the activation of both C(sp^2)–H and C(sp^3)–H bonds. In order to improve convenience and efficiency of the method, the development of new types of bidentate directing groups has been the subject of intensive research involving many research groups. Despite the impressive achievements in catalytic asymmetric C–H activation through installation of chiral auxiliaries, stereoselective functionalization of C(sp^3)–H bonds controlled by chiral bidentate directing groups still remains elusive. The laboratory of Professor Sungwoo Hong at the Korea Advanced Institute of Science and Technology (KAIST, Daejeon, Korea) has been particularly interested in selective C–H functionalization of medicinally important privileged structures. Professor Hong said: "We hypothesized that an appropriate chiral bidentate directing group embedded in the substrate could induce high levels of stereocontrol during C–H functionalization via a steric repulsion model. A range of chiral auxiliaries, such as ester, tetrazole, and amino acid amide groups, were investigated for feasibility as directing groups on C(sp^3)–H arylation." Intriguingly, revealed Professor Hong, the amino acid amide moiety was identified as the most efficient chiral bidentate directing group to achieve both high reactivity and diastereoselectivity. Systematic investigation of substrate-bound α-amino acid auxiliaries resulted in catalytic asymmetric C–H functionalization of cyclopropanes enabled by amino acid amide as chiral bidentate directing groups. Professor Hong explained: "Following the discovery that the N-unsubstituted $CONH_2$ moiety was crucial for achieving both high reactivity and diastereoselectivity, we further explored the effect of steric bulk at the α-position of amino acid amides on the selectivity of the process. The use of an Ile-NH_2 auxiliary embedded in the substrate was able to provide excellent levels of asymmetric induction (diastereomeric ratio of up to 72:1) in the Pd(II)-catalyzed β-methylene C(sp^3)–H bond activation of cyclopropanes and cross-coupling with aryl iodides. We proposed a plausible reaction mechanism in-

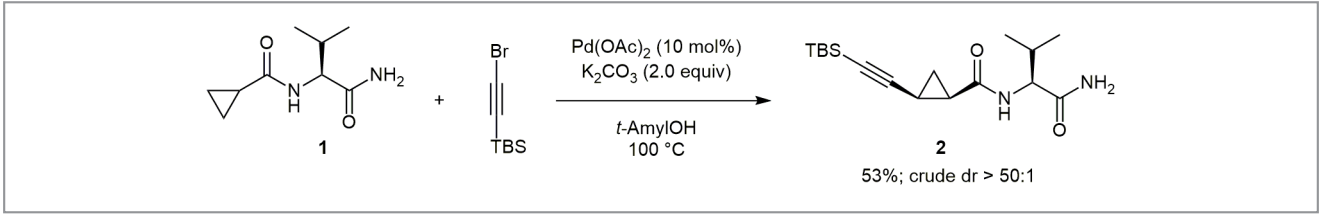


Scheme 1 Amino acid auxiliary controlled asymmetric C–H functionalization of cyclopropanes

volving Ile-NH_2 auxiliary-controlled asymmetric C–H functionalization in which a Pd(II)/Pd(IV) catalytic cycle is invoked (Scheme 1)." According to this mechanism, the cleavage of the C(sp^3)–H bond on the cyclopropane ring through a concerted metalation deprotonation (CMD) process produces the palladacycle complexes **1** and **1′** which may exist in equilibrium. The oxidative addition path that proceeds through transition state **2** is favored over the other pathways, thereby leading to the major stereoisomer. On the other hand, according to the authors, the oxidative addition process for insertion of aryl iodide into Pd complex **1′** appears to be less feasible because the R substituent and the methylene group of cyclopropane cause blocking of the top and bottom faces of **2′**. Therefore, high levels of asymmetric induction could be achieved in the Pd(II)-catalyzed C(sp^3)–H functionalization of cyclopropanes. "The directing group is removable and the hydrolysis of the



Scheme 2 Substrate scope



Scheme 3 Coupling with a bromoalkyne

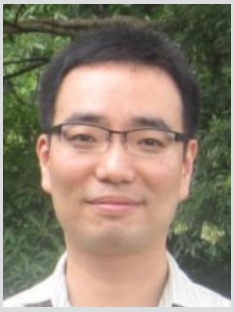
amino acid amide group occurred smoothly to afford arylated cyclopropanecarboxylic acid with conservation of the stereogenic centers," explained Professor Hong. "This study represents the first systematic investigation of substrate-bound α-amino acid amides as chiral bidentate directing groups in the asymmetric C(sp^3)–H functionalization of cyclopropanes."

"From a conceptual viewpoint, the ability of a substrate-bound α-amino acid auxiliary to promote asymmetric C–H functionalization is intriguing because the amino acid moiety derived from readily available chiral pools plays not only the role as a bidentate directing group, but also as a chiral auxiliary to provide efficient stereocontrol during C(sp^3)–H bond functionalization," said Professor Hong. The efficient protocol demonstrated a broad substrate scope and permitted for selective installation of a variety of substituted aryl groups on cyclopropanes (Scheme 2).

Professor Hong continued: "Furthermore, we preliminarily investigated the diastereoselective C–H alkynylation and observed that **1** reacted with a bromoalkyne under the same reaction conditions, resulting in the single diastereomer **2** (Scheme 3)."

This novel synthetic methodology has interesting potential applications since the cyclopropyl group is commonly found in many biologically active natural products. It is frequently used for structure–activity relationship studies in medicinal chemistry because of its unique steric and conformational properties. In particular, the rigidity of cyclopropane can be utilized as a conformationally restricting linker in medicinal chemistry to improve the binding activity in drug discovery. Professor Hong concluded: "Developing efficient catalytic methodologies for the functionalization of cyclopropane has received special attention in recent years. This convenient and powerful synthetic tool allows for the rapid and diastereoselective installation of the aryl groups into the cyclopropane scaffolds for delivery of potent biomolecules."

About the authors



Prof. S. Hong

Sungwoo Hong is an Associate Professor at the Department of Chemistry at Korea Advanced Institute of Science and Technology (KAIST, Korea) and a Group Leader of the Center for Catalytic Hydrocarbon Functionalizations at the Institute for Basic Science (IBS). He graduated from Seoul National University (Korea), where he gained his BS (1996) and MS degrees (1998). He then went on to Pennsylvania State University (USA) for his PhD program. After he had finished his postdoctoral course at Harvard University (USA, 2006), under the supervision of Professor E. J. Corey, he joined GlaxoSmithKline (GSK, USA) as a Principal Scientist. In 2009, he started independent work at KAIST and was promoted to Associate Professor in 2012. His research interests are in the field of development of new reactions and synthesis, advanced medicinal chemistry, and bioorganic chemistry.

J. Kim

Jinhee Kim graduated from Kyungpook National University (Korea) with a degree in applied chemistry in 2011. After graduation, she joined the Department of Chemistry at KAIST. She is currently in a PhD program under the supervision of Professor Sungwoo Hong. Her research is focused on transition-metal-catalyzed C–H activation and medicinal chemistry.

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M. Sim

Mikyung Sim earned her BS in pharmacology in 2011 and a MS in life & pharmaceutical science in 2013 from Ewha Womans University (Korea). She is currently doing her doctoral course at KAIST under the supervision of Professor Sungwoo Hong. Her research interests focus on developing catalytic methodologies for the preparation of biologically active compounds and their application to medicinal chemistry.

N. Kim

Namhoon Kim received his BS degree in chemical and biomolecular engineering in 2014 from Korea Advanced Institute of Science and Technology (KAIST). Currently he is in an integrated Master's & PhD program under the supervision of Professor Sungwoo Hong. His current research focus involves transition-metal-catalyzed C–H bond functionalizations.

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