Carbonyl 1,2-Transposition through Triflate-Mediated α-Amination

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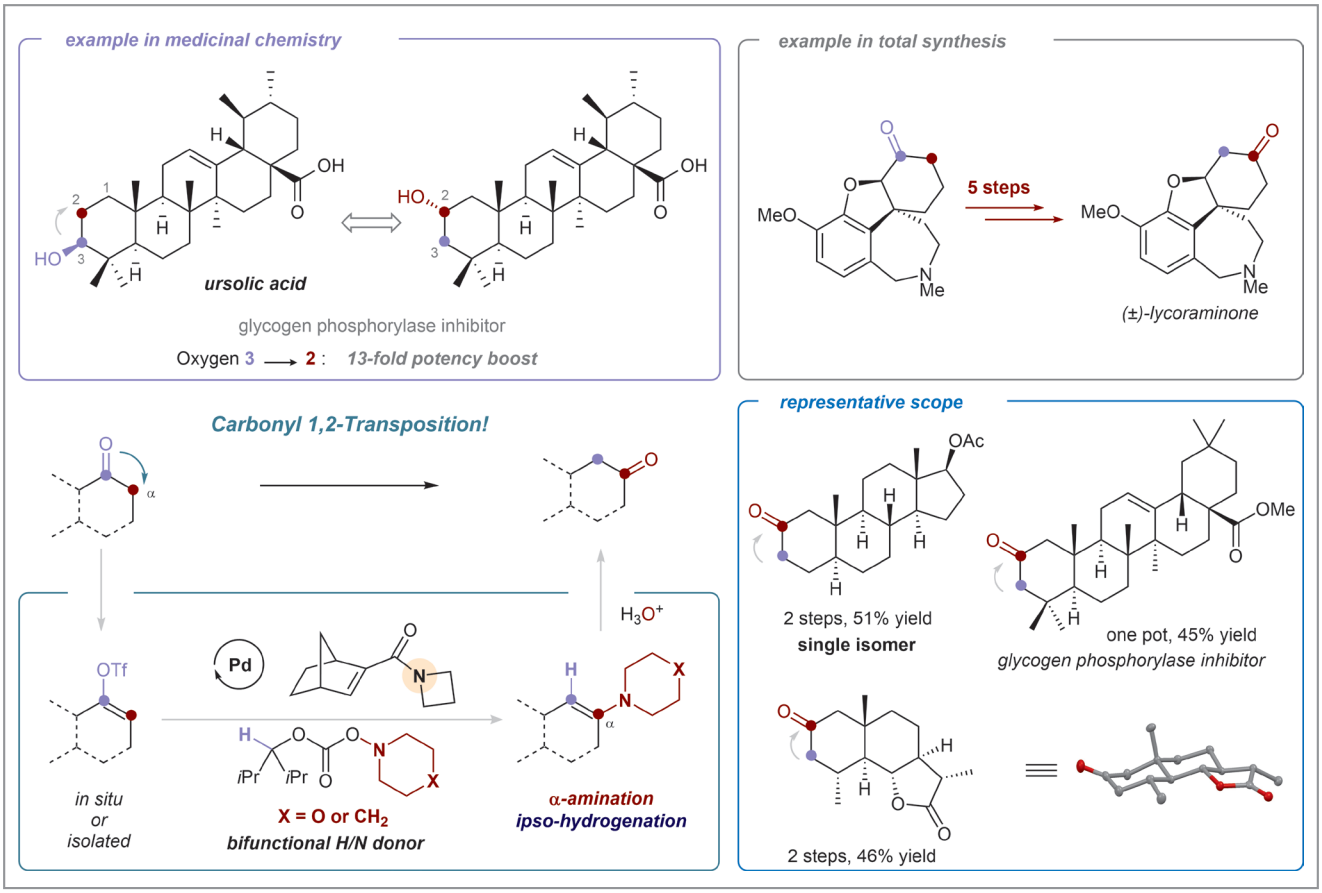
Carbonyl groups – and their carbinol reduction products – are widespread in natural products, pharmaceutical agents, and other bio-related molecules. The location of the C–O functionality within a specific molecule is a key factor in determining its biological properties. For example, the C2-hydroxy analogue of ursolic acid displays 13-fold potency boost for inhibiting glycogen phosphorylase, relative to the parent compound. The group of Professor Guangbin Dong at the University of Chicago (USA) was interested in developing a synthetic method for selectively migrating a carbonyl oxygen within a given molecular structure, particularly to an adjacent carbon. "A facile carbonyl 1,2-transposition strategy would enable alternative synthetic designs starting from more accessible materials," said Professor Dong. "Unfortunately, current state-of-the-art carbonyl migration methods suffer from low efficiency, multiple-step functional group manipulation, and poor selectivity. For example, a five-step synthetic sequence was required to migrate the carbonyl to the adjacent carbon in the total synthesis of lycoraminone (see Scheme 1). Therefore, a general and efficient carbonyl 1,2-transposition method could be quite valuable."

Professor Dong's group has a long-term interest in the palladium/norbornene (Pd/NBE) cooperative catalysis, the original reactivity of which was first reported by Catellani in 1997 (*Angew. Chem. Int. Ed.* **1997**, *36*, 119–122). Professor Dong said: "This powerful strategy has allowed for a highly efficient and regioselective difunctionalization of arenes. Twenty-two years after its original report, the Catellani reaction



Scheme 1 The novel 1,2-transposition reaction and selected examples of its scope

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was achieved in a non-aromatic system." Indeed, Professor Dong's group reported the first non-aromatic alkenyl Catellani reaction for simple alkenyl halides and triflates in 2019 (*Nat. Chem.* **2019**, *11*, 1106–1112), but at that time only C–C bond formation could be enabled at the *ortho* position with carbon-based electrophiles. "We envisioned that if an α-amination/*ipso*-hydrogenation of alkenyl triflates could be realized, i.e. using nitrogen-based electrophiles, the resulting 'transposed' enamine would give the carbonyl 1,2-shifted product upon hydrolysis," explained Professor Dong.

After Dr. Jianchun Wang (first author of the group's *Nat. Chem.* **2019** paper) finished the study on *ortho*-alkylation using alkenyl substrates, he had a discussion with Professor Dong on how to further extend this exciting reaction. Dr. Wang recalled: "*Ortho*-amination was at first thought as an unattractive transformation, because the enamine product would hydrolyze easily, but Professor Dong pointed out that this would be a special opportunity to migrate the carbonyl in ketone." Realizing the value of this transformation, Dr. Wang screened various conditions for this reaction. While the initial attempts were unfruitful, he was lucky to identify 5–10% of the desired ketone as a product of one reaction, just before his graduation from the University of Chicago.

Shortly afterwards, Dr. Zhao Wu and Dr. Xiaolong Xu further explored this transformation using morpholine benzoate as the electrophilic amine source and isopropanol as the exogenous hydride source. "However, the reactions suffered from low conversion even after screening a number of different catalysts, ligands, NBE co-catalysts, and solvents," remarked Professor Dong. He continued: "The design of difunctional H/N reagents was originally aimed at minimizing the premature hydrogenation side process. To our delight, however, this amino carbonate reagent not only reduced the side products, but substantially improved the reactivity. A hit with around 50% yield was obtained in a first try with isopropyl morpholino carbonate. Inspired by this exciting result, Dr. Wu synthesized a series of H/N reagents with various electronic and steric properties and eventually figured out the optimal one for this transformation."

Professor Dong concluded: "This reaction offers a simple, yet straightforward, carbonyl 1,2-transposition method that is not trivial to realize otherwise. We hope it will be beneficial for medicinal chemists for the late-stage functionalization of carbonyl compounds, especially in the synthesis of complex and/or high-value products, thus providing synthetic chemists with an alternative retrosynthetic strategy."

About the authors

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Zhao Wu was born in Fuzhou, P. R. China. He obtained his B.S. degree in chemistry from University of Science and Technology of China in 2013. In the same year, he moved to the University of Illinois at Urbana-Champaign (USA) where he studied rhodium-catalyzed asymmetric reactions to access chiral nitrogen-containing molecules in Prof. Kami Hull's research group. After earning his Ph.D. in 2018, he moved north to the University of Chicago (USA) where he joined Prof. Guangbin Dong's lab as a postdoctoral researcher. Since then, he has been working on the Pd/NBE cooperative catalysis.

Dr. X. Xu

Xiaolong Xu was born in Huaibei, P. R. China. He received a B.S. in chemistry from Jiangsu University and a Ph.D. in organic chemistry from Shanghai Institute of Organic Chemistry (P. R. China) in 2020 under the direction of Prof. Zhi Li. He systematically studied organometallic catalysis as an exchange student at the University of Chicago (USA) under the direction of Prof. Guangbin Dong from 2019–2020. Then he joined Bioduro-Sundia as a senior research chemist where he explored new chemical processes to pharmaceutical synthesis.

Dr. J. Wang

Jianchun Wang received his B.S. degree in chemistry from Peking University (P. R. China) in 2014. In the same year, he joined Prof. Guangbin Dong's research lab and he graduated from the University of Chicago (USA) in 2019. His research focused mainly on developing novel norbornene co-catalysts to solve long-standing limitations in Pd/NBE cooperative catalysis. He then began research with Prof. Robert H. Grubbs at California Institute of Technology (USA) as a postdoctoral researcher. In 2021, he joined the Shenzhen Grubbs Institute at the Southern University of Science and Technology (SUSTech, P. R. China) as an assistant professor.

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