Enantioselective Propargylic Amination and Related Tandem Sequences to α-Tertiary Ethynylamines and Azacycles

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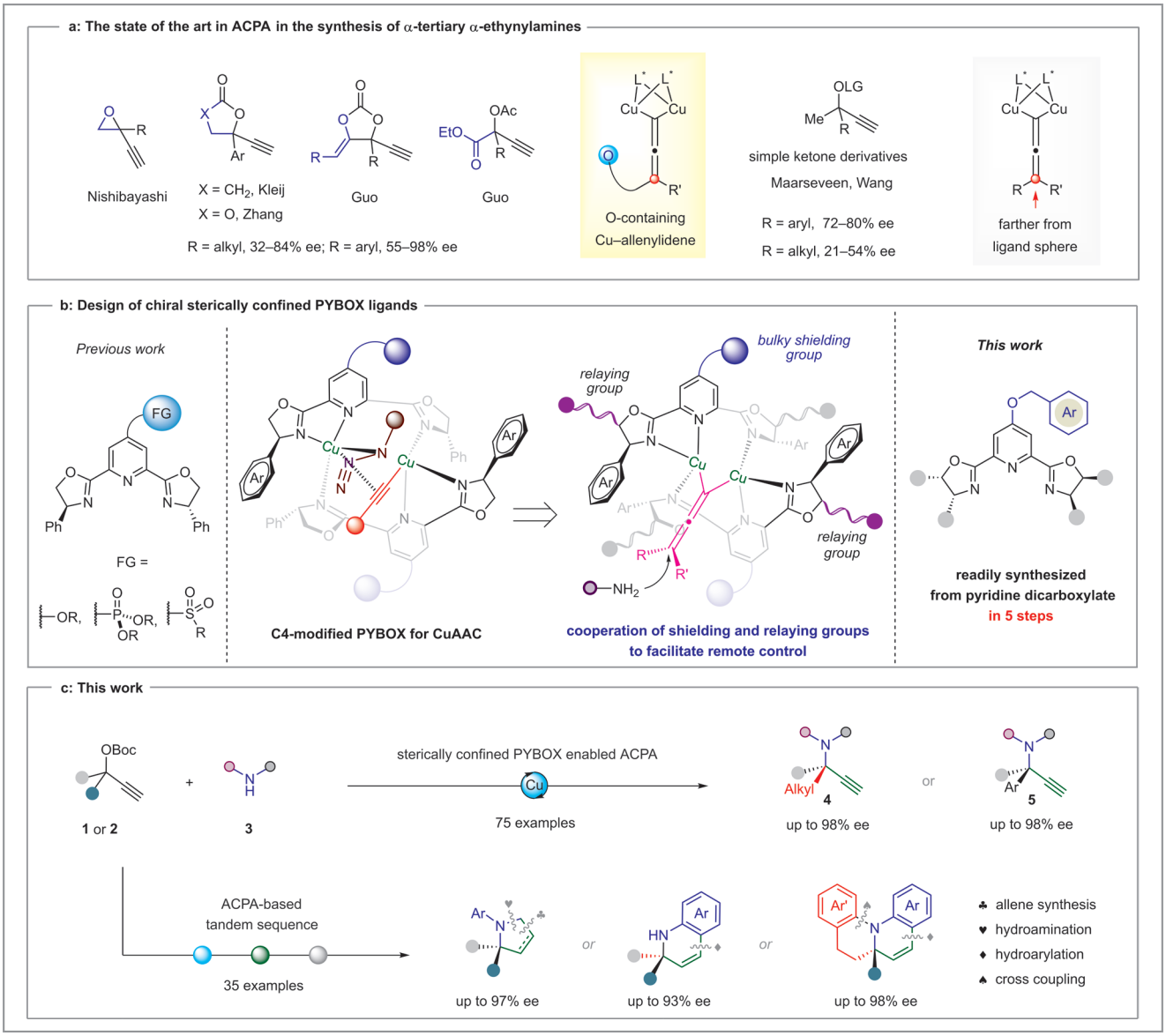
Optically active amines and azacycles are widely present in drugs, bioactive compounds and agrochemicals. The synthesis of chiral α-tertiary amines and related azacycles in sufficient structural diversity is important for drug development, but constitutes a long-term challenge confronting organic chemists. "Enantioenriched α-tertiary propargylamines featuring an α-ethynyl substituent are valuable platform molecules, because their sp C–H bonds and carbon–carbon triple bonds



Scheme 1 Working hypothesis

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permit versatile diversifying reactions," said Professor Jian Zhou [East China Normal University (ECNU), P. R. of China], adding: "Nevertheless, their facile access is undeveloped in terms of enantioselectivity, substrate scope and synthetic efficiency, as compared with internal proparygylamines."

According to Professor Zhou, asymmetric Cu(I)-catalysed propargylic amination (ACPA) is a promising strategy to access enantioenriched ethynylamines, following the seminal independent work of Maarseveen,[1a] Nishibayashi[1b] and colleagues. However, despite previous enlightening studies, there remains much to explore (Scheme 1a).[2] This is because only substrates leading to Cu–allenylidene intermediates with both an aryl and an oxygen-containing moiety could give satisfactory results, while aliphatic compounds and, especially, simple ketone-derived propargylic alcohol derivatives still represent problematic substrates.[3] Moreover, the modular combination of ACPA into tandem sequences for diverse synthesis of azacycles remains an untrodden path.

"As the prochiral carbon in the Cu–allenylidene intermediate is further away from the ligand sphere, how to achieve excellent remote enantiofacial control is the key to success," said Professor Zhou. He continued: "With our experience in asymmetric CuAAC reactions realized by PYBOX ligands featuring a bulky C4 shielding group, along with the fact that both reactions are proposed to involve di-copper catalysis, we wondered whether these C4-modified PYBOX ligands were effective for ACPA of challenging substrates." Professor Zhou further stated: "Initial trials using PYBOX ligands with a single C4 shielding group all failed, thus prompting us to exploit sterically more confined PYBOX ligands by installing relaying groups on the 5-position of both oxazoline rings, to form a sterically constrained microenvironment to relay stereochemical information from the ligand chirality through steric interactions (Scheme 1b)."

Indeed, sterically confined PYBOX ligands with both C4 shielding group and relaying groups can achieve excellent

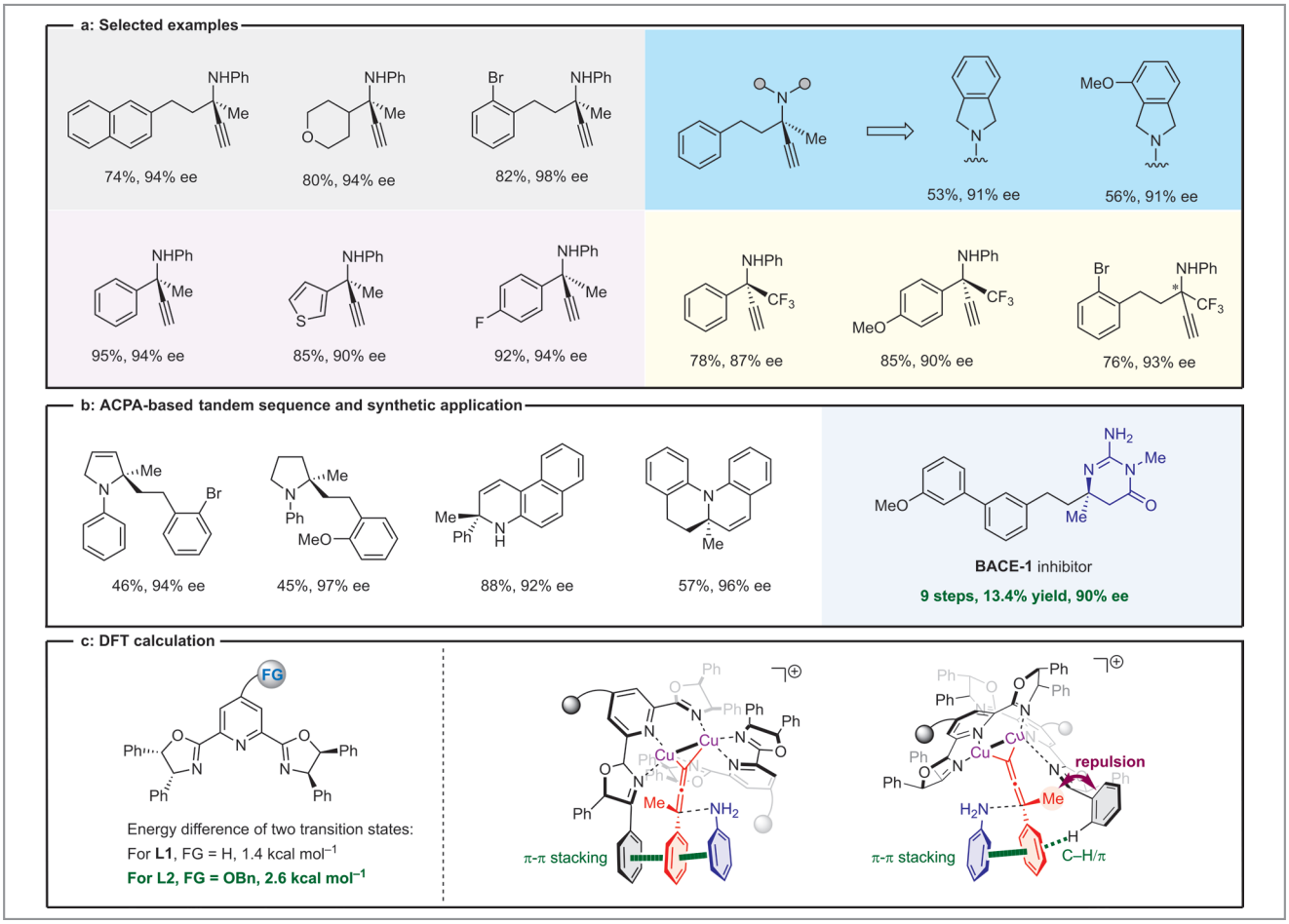

Figure 1 Substrate expansion in ACPA reaction and ACPA-based tandem sequence

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remote enantiofacial discrimination of the Cu–allenylidenes, thus allowing the highly enantioselective ACPA of aliphatic and alkyl aryl ketone-derived propargylic carbonates with a variety of primary and secondary amines (Scheme 1c). "The ACPA-based tandem sequences were also established as a new strategy to synthesize various chiral azacycles, such as dihydropyrroles, tetrahydropyrroles, dihydroquinines, or tetrahydroquinines with an aza-quaternary stereocenter (Figure 1a)," said Professor Zhou, adding: "The value of the thus-obtained chiral α-tertiary α-ethynylamines was demonstrated by various transformations and the enantioselective total synthesis of a selective multi-target β-secretase inhibitor (Figure 1b)." A collaboration with Prof. Xin Wang on theoretical calculations revealed that both the C4 bulky benzyloxy group and the phenyl relaying group on the oxazoline ring are responsible for the high enantioselectivity (Figure 1c). Professor Zhou explained: "With the combination of C4 benzyloxy and the phenyl relaying group, a more sterically confined chiral pocket should be formed, which enhances the favorable π–π stacking interactions and also the unfavorable repulsion interaction, thus resulting in a higher free energy gap of 2.6 kcal/mol."

Professor Zhou emphasized that the working model of sterically confined PYBOX ligands could also be extended to the asymmetric propargylic substitution of α-CF_3 propargylic carbonate with *O*- and *C*-centered nucleophiles. "This work provides a flexible solution to develop asymmetric propargylic substitutions involving metal–allenylidene intermediates," said Professor Zhou. He concluded: "Since the pioneering work of Nishibayashi, Hidai, Uemura and co-workers,[5] this field has grown exponentially, but the reaction of propargylic tertiary alcohol derivatives to α-ethynyl quaternary stereocenters is still in its infancy. Considering the good performance of sterically confined PYBOX, there are enormous opportunities for the asymmetric propargylic substitution reactions via the development of new PYBOX ligands."

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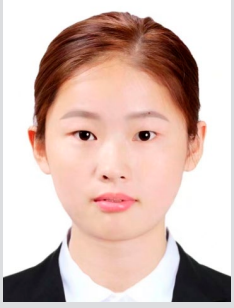

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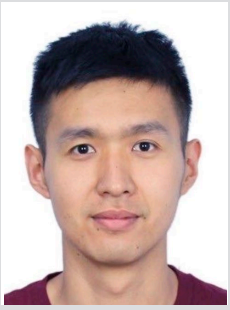

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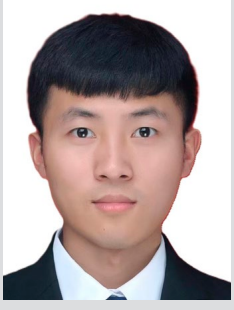

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