

Regio- and Enantioselective Allylic Alkylation of Terminal Alkynes by Synergistic Rh/Cu Catalysis

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1,4-Enynes are important building blocks in organic synthesis, as they are endowed with a versatile combination of reactive double and triple bonds. Transition-metal-catalyzed asymmetric allylic substitutions represent the main method for accessing chiral 1,4-enynes in an enantioselective manner. “Alkynyl-aluminum/boron compounds and alkynyl carboxylic acids (Scheme 1a) were successfully utilized in 1,4-enynes synthesis (see the original paper for references). However, from the viewpoint of atom- and step-economy, direct asymmetric allylation of easily available terminal alkynes is attractive but challenging,” explained Professor Changkun Li at Shanghai Jiao Tong University (Shanghai, P. R. of China), who continued: “Sawamura and Ohmiya’s Cu-catalyzed asymmetric allylic alkylation of triisopropylsilylacetylene with (*Z*)-allylic phosphates (Scheme 1a) provides a nice solution to this challenge (*J. Am. Chem. Soc.* **2014**, *136*, 13932–13939). Tan and Lee previously developed a Cu/guanidine catalyst for enantioselective allylic alkynylation of cyclic allylic bromide, in which the regioselectivity aspect is not addressed (*J. Am. Chem. Soc.* **2018**, *140*, 8448–8455). Therefore, a new catalyst system that can control both the regioselectivity and the enantioselectivity in the coupling of general terminal alkynes and unsymmetrical allylic precursors is still in high demand.”

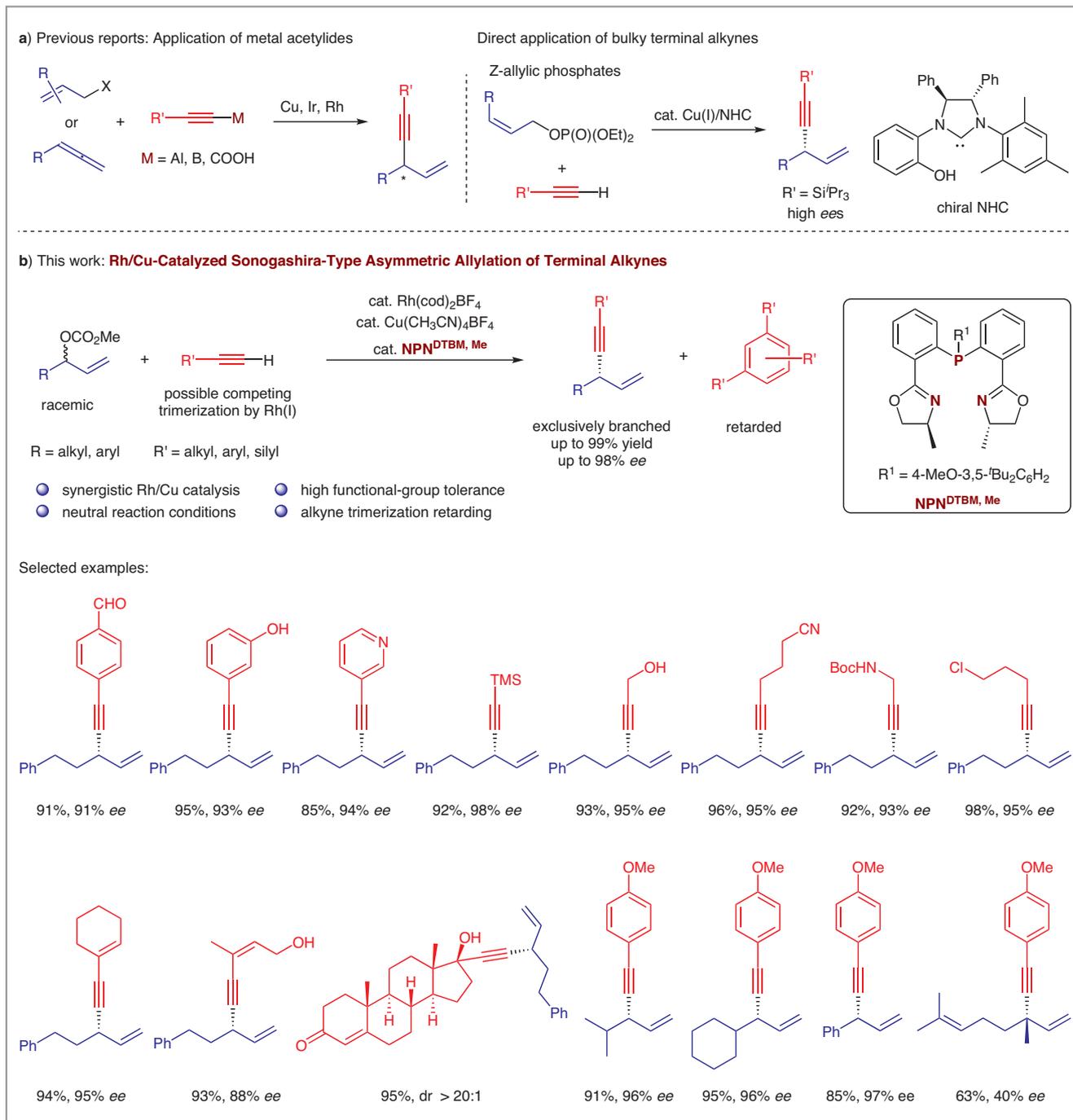
Previously, Professor Li’s group developed a new catalyst system based on rhodium and chiral bisoxazolinephosphine (NPN*) ligands (*ACS. Catal.* **2020**, *10*, 4491–4496) by following their reported cobalt/NPN*-catalyzed regioselective and enantioselective allylic amination (*J. Am. Chem. Soc.* **2019**, *141*, 11430–11434). “Rh and Co behave similarly in terms of regioselectivity and enantioselectivity, but rhodium catalysis is more generally applicable in terms of substrate scope, compared to cobalt,” said Professor Li. Under the catalysis of Rh/NPN*, both branched racemic and linear (*Z* and *E*) mono-substituted allylic carbonates could be converted into branched allylic products with branched/linear ratios over 20:1 and excellent enantioselectivities. Different nitrogen, carbon, oxygen and sulfur pro-nucleophiles could be used under neutral conditions, and – as explained by Professor Li – the problem of low regioselectivity for challenging alkyl-group-bearing allylic precursors could be solved.

“The Sonogashira coupling of aryl halides with terminal alkynes by synergistic Pd and Cu catalysis is one of the most

powerful methods to prepare internal alkynes. Some recent reports have extended the scope of aryl halides to aliphatic halides in the asymmetric Sonogashira coupling (*Nat. Chem.* **2019**, *11*, 1158–1166),” said Professor Li. “However, the Sonogashira-type reaction using allylic precursors is rarely reported. The main obstacle to extending the reaction to alkynes is that terminal alkynes exhibit various reactivities in the presence of transition metals such as Pd, Ir and Rh, which are normally used in asymmetric allylic substitutions.” In Professor Li’s latest work, a highly branch-selective and enantioselective allylic alkylation of a variety of functionalized aryl, aliphatic and silyl alkynes with challenging racemic allylic carbonates has been developed under neutral conditions by synergistic Rh and Cu catalysis (Scheme 1b).

Professor Li explained that terminal alkynes with different functional groups can successfully react under the optimized conditions: “Aldehyde, hydroxyl, pyridyl, trimethylsilyl, cyano, amide and chloride groups were tolerated. Dienynes could be prepared efficiently when enynes were used. The highly diastereoselective allylic alkylation of ethisterone indicates this method can be used in late-stage functionalization of complex molecules too. Sterically bulky allylic carbonates bearing isopropyl, cyclohexyl and phenyl groups were readily converted into the products in high yields. The formation of a quaternary carbon center was also realized under the same conditions, although the enantioselectivity was only moderate.” Professor Li revealed that an investigation on ligand development for highly enantioselective quaternary carbon construction is ongoing: “*N*-Benzyl-2-ethynylaniline reacts selectively at the sp C–H bond instead of the nitrogen atom, which allows the chiral 2-allyl indole preparation after gold-catalyzed cyclization.”

Single-crystal X-ray diffraction analysis and comparison with literature data confirmed that the absolute configuration of the allylic alkylation products of terminal alkynes is opposite to the configuration generated in reactions of nitrogen and other nucleophiles. “We believe that a mechanism involving the transmetalation of Cu-acetylide to rhodium complex and subsequent reductive elimination is the most likely scenario. Stoichiometric reaction of NPN/Rh-allyl complex with Cu-acetylide further supports the notion that the ligand for Cu is mandatory, probably because it breaks down the oligomers to



Scheme 1 (a) Previous examples of allylic alkynylations reported in the literature; (b) experimental conditions and scope of this work.

monomeric Cu-acetylide. The crystal structure of the tetrahedral CuI/NPN complex further supports this conclusion,” said Professor Li, who added: “Actually, this complex has been prepared and characterized by Mr. Bing Li over a very long time.

However, we did not find any good application of it until this reaction had been optimized.”

Professor Li thinks that the Rh-catalyzed trimerization of terminal alkynes to form trisubstituted benzenes could be

retarded by the fast reaction of rhodium complex with allylic carbonates. "The use of acetonitrile as the solvent is essential for the success of this reaction and other solvents lead to the fast consumption of terminal alkynes. The ligand with smaller methyl groups on the oxazoline ring is also important for achieving high yields." He then revealed: "Following a request by one of the reviewers, this ligand effect was identified to accelerate the transmetalation of Cu-acetylide to Rh complex. It is worth mentioning that a fast interconversion of diastereomeric π -allylrhodium/NPN complexes through rhodium(I)-catalyzed allyl exchange – other than the π - σ - π isomerization – was proposed when D-labeled allylic carbonates were tested for the reaction, which was requested by another reviewer."

Professor Li concluded: "A highly branch-selective and enantioselective allylic alkylation of terminal alkynes through synergistic Rh and Cu catalysis has been reported in our paper. Rh was used to control the regioselectivity and the enantioselectivity, while Cu was the key to activating the alkynes. The competing alkyne trimerization by the Rh(I) complex could be retarded using acetonitrile as solvent. Mechanistic studies support the inner-sphere reductive elimination C(sp)-C(sp³) bond formation process."

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About the authors



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Wen-Yu Huang was born and raised in Jilin Province, P. R. of China. He received his B.Sc. in organic chemistry from Nanchang University (P. R. of China) in 2010 and Ph.D. in organic chemistry from Nagoya University (Japan) in 2017 under the supervision of Professor Toshio Nishikawa and Associate Professor Atsuo Nakazaki. He is now working as a postdoctoral fellow with Professor Changkun Li at Shanghai Jiao Tong University (P. R. of

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Dr. S. Ghorai

Samir Ghorai was born and raised in India. He graduated with a B.Sc. in chemistry (H) (2009) and M.Sc. in inorganic chemistry (2011) from Vidyasagar University, India. Then he pursued his Ph.D. (2015) at the Indian Institute of Technology Guwahati (IITG; India). There, he worked under the supervision of Prof. Chandan Mukherjee in the inorganic and bioinorganic field of metal-radical complexes. In 2016, he moved to Daegu

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B. Li

Bing Li graduated from Qingdao Agricultural University (Qingdao, P. R. of China) with a B.Sc. (2011) in medicinal chemistry and from Nankai University (Tianjin, P. R. of China) with an M.Sc. (2014) in organic chemistry. In 2017, after a few years in pharmaceutical industry, he joined the research group of Changkun Li at Shanghai Jiao Tong University as a Ph.D. candidate. His work focuses on Rh-catalyzed regio- and enantioselective allylic substitution reactions with chiral NPN ligands.

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Changkun Li was born in Beijing, P. R. of China, in 1982. He received his B.Sc. (2004) and Ph.D. (2010) from Peking University (P. R. of China) with Professor Jianbo Wang and Yan Zhang. In 2010–2012, he worked as a postdoctoral fellow at Kyoto University (Japan) with Professor Masahiro Murakami. Then he moved to Freiburg (Germany) to work with Professor Bernhard Breit as a Humboldt Fellow. In 2016,

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