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ALLENE REDUCTION

Selectively stopping halfway

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Allenes are readily available and reactive polyunsaturated compounds in which one central carbon forms double bonds with two adjacent carbons. Selective reduction of just one of the double bonds can generate either an internal alkene or, as described by Zhiwei Chen and Vy Dong in *Nature Communications*, provide access to valuable chiral allylic compounds.

"One general theme of our research is the development of methods to couple together common functional groups," explains Dong. "An allene intermediate was implicated as a key intermediate in one such reaction — a ruthenium hydride mediated coupling of an aldehyde and an alkyne — and motivated our search for other reactions involving allene intermediates, such as alkyne hydroaminations."

Seeking a new project that could build upon the group's knowledge, graduate student Chen then proposed the allene semi-reduction that is described in their most recent work. "Despite the numerous catalysts and reagents available for reduction, this was an unsolved challenge because the few semi-reductions described tend to favour formation of the internal alkene," mentions Chen.

Dong and Chen knew that an allene would insert into a rhodium hydride catalyst. The key to effecting selective semi-reduction was to find a catalyst that would favour nucleophilic attack at the more substituted end of the resultant rhodium-allyl species while avoiding possible isomerization of the allene to a 1,3-diene. Chen tried typical reductants such as formic acid and hydrosilanes, but these resulted in poor selectivity for the desired terminal alkene product. They finally identified the Hantzsch ester — a dihydropyridine that readily undergoes oxidation to the pyridinium salt — as the best reductant. "The observed reactivity is really very interesting, and it would be hard to imagine traditional hydrogenations occurring with such selectivity," says Dong. Deuterium labelling studies indicated that the reaction proceeds by hydride attack, which also makes the method amenable to the synthesis of chiral, isotopically labelled stereogenic centres.

Chen and Dong then screened rhodium complexes bearing chiral phosphines as catalysts for the enantioselective production of the terminal alkene products. The well-known axially chiral ligand BINAP offered poor selectivity, leading to both isomerization of the allene starting material and poor selectivity between terminal and internal alkene products. The desired semi-reduction was promoted by phosphine ligands with point chirality, but the problem with regioselectivity remained. Ultimately, they found that Josiphos ligands — which feature a planar chiral ferrocene as the scaffold for two phosphines — were the most effective at suppressing isomerization while maximizing regio- and enantioselectivity.

At present, the reaction scope is limited to allenes bearing one aryl and one alkyl group: diaryl and dialkyl allenes were found to be unreactive under the conditions described here. The reaction does tolerate electron donating or electron-withdrawing aryl groups, as well as some heteroaryl groups. Alkenyl and alkynyl groups in the substrate were also left unperturbed by the reaction conditions.

Expanding the substrate scope of the reaction to encompass dialkyl and diaryl substituted allenes is a short term goal, but Chen and Dong are also keen to look at the possibility of using other nucleophiles. "Adding a carbon-centred nucleophile would give us access to compounds with quaternary stereocentres," says Dong, "and the ability to add fluoride would be of interest as well." Beyond these, the team plans to further explore the reactivity of allenes. "I think a method to transform a ketone directly into an allene — a sort of Wittig reaction analogue — would be immensely powerful," she says.

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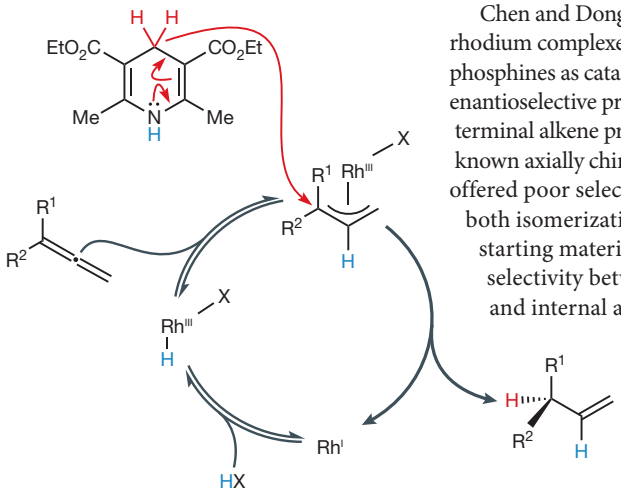

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ORIGINAL ARTICLE Chen, Z. & Dong, V. M. Enantioselective semireduction of allenes. *Nat. Comms* **8**, 784 (2017)

FURTHER READING Chen, Q.-A., Cruz, F. A. & Dong, V. M. Alkyne hydroacylation: switching regioselectivity by tandem ruthenium catalysis. *J. Am. Chem. Soc.* **137**, 3157–3160 (2015) | Chen, Q.-A., Chen, Z. & Dong, V. M. Rhodium-catalyzed enantioselective hydroamination of alkynes with indolines. *J. Am. Chem. Soc.* **137** 8392–8395 (2015)