As one of the most important transition-metal-catalyzed reactions, Pd-catalyzed allylic alkylation, usually proceeding via attack of nucleophiles on the carbon of π-allyl Pd complexes (outer-sphere mechanism), is a powerful tool for C–C bond and C–X bond formations. The adjacent two stereocenters are also constructed stereoselectively for both cyclic and acyclic compounds. Many different types of allyl reagents can be used in the reaction; however, control of the regioselectivity to afford branched allylic alkylated products from monosubstituted allyl reagents is still an important issue that has not been fully solved. To date several strategies have been developed to tackle the problem, such as ligand-control and cross-coupling strategies, which show their high efficiency (Scheme 1, a,b). However, efficient but simple protocols are still much in demand for the control of regioselectivity of the reaction with monosubstituted allyl reagents. The work of Professor Xue-Long Hou from the Shanghai Institute of Organic Chemistry (P. R. of China) on regioselectivity tuning by action of counterions of bases in the reaction of imines and allyl reagents under Pd catalysis with phosphines as ligands is one such example (Scheme 1, c).2e

Recently, an efficient and practical procedure was developed by Professor Hou and his colleagues. Professor Hou remarked: "We found that, with N-heterocyclic carbene (NHC) S-IPr as ligand, branched products were produced in high regioselectivity in the reaction of ketones with monosubstituted allyl substrates under Pd catalysis. A wide range of ketones and allyl reagents are suitable (Scheme 2)." Lower regioselectivity was observed with N,N′-phenyl or -trimethylphenyl-substituted NHCs, while linear products were afforded as the major component with phosphine as ligand despite of either Li+ or K+ as the counterion of the base. Professor Hou explained: "Like phosphine, NHCs are also strong σ-donors, but their stereochemistry is totally different in coordination chemistry. The substituents on the NHC nitrogen are toward the metal atom but those on phosphine are far away from the metal when they coordinate with it. This might be the reason for the observed regioselectivity of the reaction using NHC and phosphine as ligands." In addition to its unusual regioselectivity, the reaction exhibits another useful characteristic. "Acyclic ketones with three contiguous stereocenters were produced in excellent diastereoselectivity if β-substituted ketones were the pre-nucleophile," said Professor Hou. He continued: "Because of the easy availability of optically active β-substituted ketones, this methodology affords simple access to optically active acyclic ketones with three contiguous stereocenters, which should be useful in organic synthesis. We have shown some useful applications of the methodology in the Nat. Commun. paper (Scheme 3), and the reaction can also proceed on gram scale without loss of efficiency and stereoselectivity."

In collaboration with Dr. Bo Chen, a theoretical chemist at Cornell University (USA), transition states of the reaction were proposed to explain why anti-products were afforded predominantly in the reaction of ketones without substituents at the β-position, but syn-products were the major products.

Scheme 1 Some strategies in Pd-catalyzed allylic alkylation reaction using monosubstituted allyl reagents
Professor Hou said: “Mechanistic investigations by experiments using optically active deuterium-labeled allyl reagent and cis-disubstituted cyclohexene, as well as DFT calculations, revealed that the reaction proceeds via an inner-sphere mechanism, that is, through nucleophile attack on Pd followed by C–C bond-forming [3,3]-reductive elimination.”

According to Professor Hou and colleagues, these results demonstrate that, as NHCs are easily synthesized and also commercially available, Pd/NHC should be a simple and effective catalyst system to realize high regio- and diastereoselectivities in the reaction of ketones and monosubstituted allyl reagents, affording products with two or three contiguous stereocenters in excellent diastereoselectivity. “Because both

for those using ketones with substituents at the β-position. Professor Hou said: “Mechanistic investigations by experiments using optically active deuterium-labeled allyl reagent and cis-disubstituted cyclohexene, as well as DFT calculations, revealed that the reaction proceeds via an inner-sphere mechanism, that is, through nucleophile attack on Pd followed by C–C bond-forming [3,3]-reductive elimination.”

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Ketones and allyl reagents are easily available and the experimental protocol of the reaction is simple, this methodology should be useful in organic synthesis. More importantly, the results reveal that the reaction of ‘hard’ nucleophiles with allyl reagents under Pd catalysis, occurring in the intermolecular way through an inner-sphere mechanism, represents a new reaction mode,” said Professor Hou. He concluded: “There is much room to modify the structures of allyl reagents and nucleophiles to afford a variety of molecules with multiple stereocenters, which should further expand the scope of this method.”

REFERENCES


Xue-Long Hou graduated from Shanghai First Medical College (P. R. of China) in 1978. After working there for two years, he entered the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, P. R. of China) and obtained his Ph.D. in 1986 under the mentorship of Professors Wei Yuan Huang of SIOC and Henry N. C. Wong of the Chinese University of Hong Kong. Then, he did postdoctoral research with Professor Emanuel Vogel for about two years as Alexander von Humboldt Research Fellow at Cologne University (Germany). He returned to SIOC in 1989 and was promoted to full professor in 1997. His research interests are the design of chiral ligands and their applications in asymmetric catalysis as well as the development of efficient catalyst systems in organic synthesis.

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