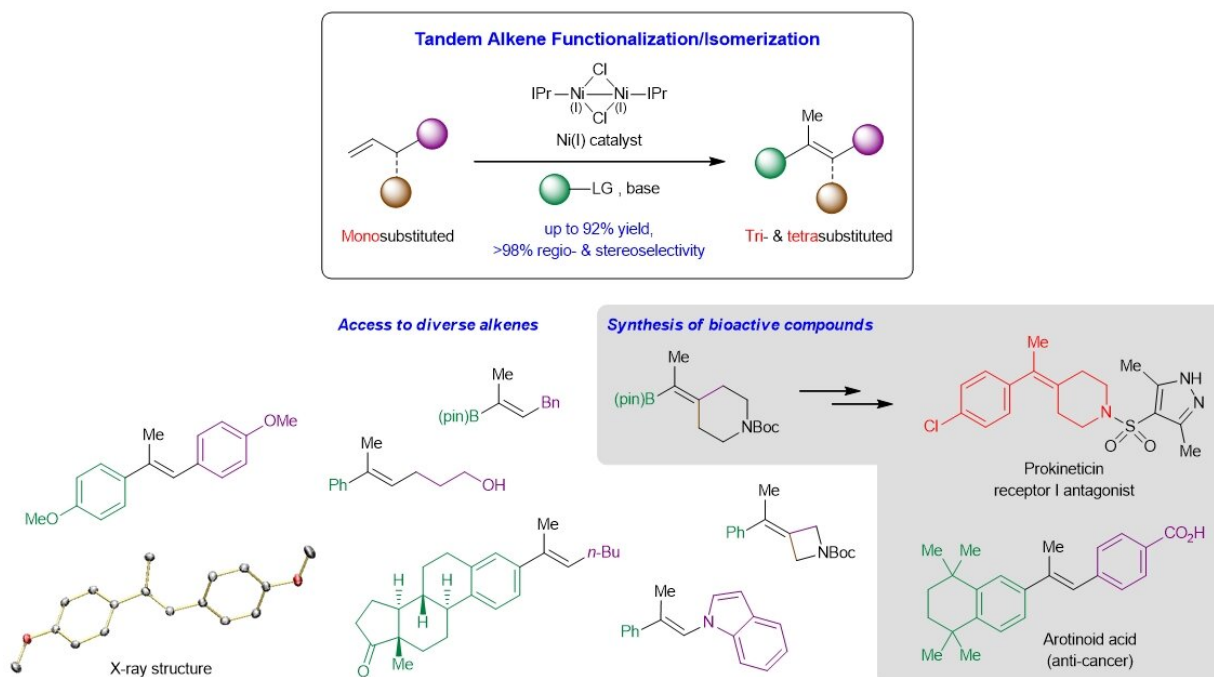


# Stereoselective alkene synthesis with non-precious nickel catalysis

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Schematic showing the development of a novel Ni-catalysed system that converts cheap and readily available monosubstituted olefins to high-value tri- and tetrasubstituted analogues, and its application to the synthesis of complex bioactive compounds. Credit: *Nature Catalysis*/ National University of Singapore

NUS chemists have developed a new way to access prized tri- and tetrasubstituted alkenes through a nickel-catalyzed tandem process involving a Heck reaction followed by carbon-carbon double bond

(C=C) migration.

The development of reliable methods that afford stereochemically defined acyclic tri- and tetrasubstituted alkenes is a longstanding goal in organic synthesis. These highly substituted C=C bonds commonly reside in countless molecules of interest including organic materials and biologically active entities, and are key intermediates for further derivatization to a broader spectrum of high-value products. Existing reactions that convert carbonyl compounds or unsaturated carbon-carbon bonds to tri- and tetrasubstituted olefins often involve lengthy synthetic routes, exhibit limited functional group compatibility, suffer from unsatisfactory regio- or stereoselectivity control, and/or are not sufficiently general. One complication arises from the small energy difference between the *cis* and *trans* isomers of these highly substituted alkenes, which increases the difficulty of generating these compounds in high stereoselectivity.

A research team led by Prof Koh Ming Joo, from the Department of Chemistry, National University of Singapore in collaboration with Prof Osvaldo Gutierrez, from the University of Maryland, has conceived a tandem strategy that merges regiocontrolled Heck reaction and stereocontrolled C=C bond migration in a single step (see Figure). Mechanistic and computational studies showed that the reaction proceeds through a non-radical pathway, and that both the sizeable alkoxide base and *N*-heterocyclic carbene (NHC) ligand are crucial for the catalytic process.

Prof Koh said, "Our initial foray into this research area was to hypothetically ask how can we transform monosubstituted  $\alpha$ -olefins, a highly abundant class of feedstock chemicals, to the more valuable but difficult-to-synthesize trisubstituted and tetrasubstituted analogs, in a single process. As it turns out, the solution to this was to design a tandem reaction that first reacts with the monosubstituted substrate, then

isomerizes it to the desired product. A well-orchestrated control of regio- and stereoselectivity was paramount, which led us to discover the unique effectiveness of the NHC-ligated nickel catalysts."

"We expect our new methodology to enhance the way in which many bioactive molecules are synthesized, and to serve as a blueprint for the design of catalytic tandem transformations to construct important building blocks from non-precious materials," added Prof Koh.

The research team plans to exploit the insights obtained from this work to develop new [tandem](#) transformations to facilitate fine chemical synthesis.

**More information:** Chen-Fei Liu et al, Olefin functionalization/isomerization enables stereoselective alkene synthesis, *Nature Catalysis* (2021). [DOI: 10.1038/s41929-021-00658-2](https://doi.org/10.1038/s41929-021-00658-2)

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