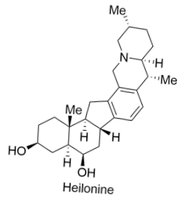
Homogeneous Catalysis Papers of the Month

January 2024

Total syntheses

Pd- and Ir-enabled total synthesis

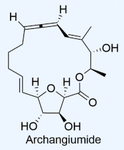


Challenge: Total synthesis of the steroidal alkaloid (+)-heilonine has only once been recorded, in 21 longest linear sequence steps (LLS).

Solution: (+)-Heilonine is achieved in 11 or 13 LLS steps, including Stille carbonylative cross-coupling with $Pd(PPh_3)_4$ and a CuCl additive, and $[Ir(cod)(OMe)]_2$-catalyzed C-H borylation.

Y. Jin et al., *J. Am. Chem. Soc.* **2024**, doi: 10.1021/jacs.3c13492

Au- and Mo-enabled total synthesis



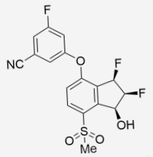
Challenge: (+)-Archangiumide is a complex macrocycle that contains cycloallene, two E-alkenes, and a tetrahydrofuran ring, making synthesis difficult due to ring strain.

Solution: The product was synthesized using a Mo-catalyzed macrocyclization and a propargyl benzyl ether rearrangement catalyzed by a gold complex.

J. Sutro et al., *J. Am. Chem. Soc.* **2024**, doi: 10.1021/jacs.3c13304

Process chemistry

Ni-catalyzed sulfonylation

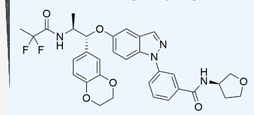


Challenge: Catalytic sulfonylation requires a safe and effective source of SO_2.

Solution: Use of $NiCl_2$dppe as a catalyst and $K_2S_2O_5$ as an SO_2 source, followed by methylation by TMP, provided the pharmaceutical product in 3kg scale.

J. C. Hethcox et al., *Org. Process Res. Dev.* **2024**, doi: 10.1021/acs.oprd.3c00410

Buchwald-Hartwig coupling



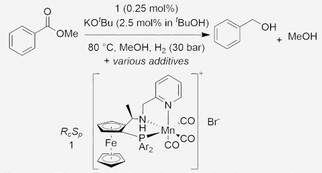
Challenge: Using CuI as the catalyst for a C-N coupling resulted in poor regioselectivity during scale-up, resulting in impurities that could not be purged.

Solution: Changing the reaction to a Buchwald-Hartwig coupling catalyzed by $Pd(dba)_2$, with *t*BuXPhos as the ligand, resulted in 100% conversion to the desired regioisomer.

G. Aydin et al., *Org. Process Res. Dev.* **2024**, doi: 10.1021/acs.oprd.3c00393

non-PGM catalysis

Mn-catalyzed hydrogenation

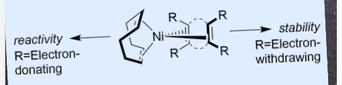


Challenge: The reactivity of amide hydrogenation reactions is generally lower than the hydrogenation of other substrates, such as esters.

Solution: Additive experiments with Mn-catalyzed hydrogenation show that primary alkyl amine substrates show a 4-fold inhibitory effect.

J. Luk et al., *Organometallics* **2024**, doi: 10.1021/acs.organomet.3c00399

Ni catalyst stability

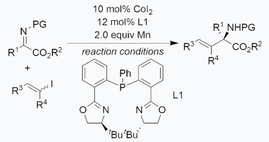


Challenge: The precatalyst $Ni(COD)_2$ is air- and room-temperature-sensitive, which complicates production of Ni(0).

Solution: An electron-deficient diene ligand was used to develop a class of Ni(COD)(EDD) precatalysts that are stable to air, moisture, room temperature, and silica gel.

C. Z. Rubel et al., *Acc. Chem. Res.* **2024**, DOI: 10.1021/acs.accounts.3c00638

Chiral cobalt catalysis



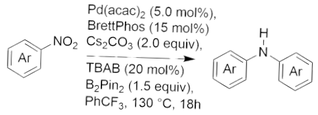
Challenge: The asymmetric Nozaki-Hiyama-Kishi (NHK) reaction creates chiral carbon-heteroatom bonds but has difficulty with construction of a tetrasubstituted stereocenter.

Solution: An enantioselective aza-NHK reaction, catalyzed by CoI_2 and NPN as a ligand, was able to create a range of α-tertiary allylic amino ester derivatives.

T. Xia et al., *Angew. Chem. Int. Ed.* **2024**, doi: 10.1002/anie.202316012

New methodology

Buchwald-Hartwig C-N coupling



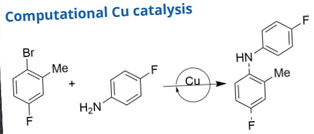
Challenge: Substrates for C-N cross-coupling include aryl halides and aryl borons, which are generally pre-synthesized and isolated from nitroarenes.

Solution: Nitroarenes can be used directly in Pd-catalyzed Buchwald-Hartwig couplings as the sole starting material, allowing one-pot synthesis of diverse di- and triarylamines.

Z. Lei et al., *Chem. Sci.* **2024**, doi: 10.1039/D3SC06618E

Computational predictions

Computational Cu catalysis

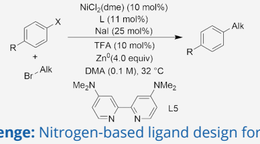


Challenge: Reaction optimization can be accelerated by the use of machine learning, including identification of ideal reaction conditions, substrates, and ligands.

Solution: A machine learning model based on the Cu-catalyzed Ullman C-N coupling reaction can predict reaction outcomes and identify effective ligands for a wide range of substrates.

M. H. Samha et al., *Sci. Adv.* **2024**, doi: 10.1126/sciadv.adn3478

Computational ligand design



Challenge: Nitrogen-based ligand design for Ni-catalyzed cross-electrophile coupling is challenging due to the lack of systematic molecular studies.

Solution: A computational ligand library led to the design of new N-substituted bipyridine ligands, and demonstrated the necessity of square planar intermediates and strongly donating ligands.

M. E. Akana et al., *J. Am. Chem. Soc.* **2024**, doi: 10.1021/jacs.3c09554

Selected papers from the catalysis literature published online in January 2024 (including pre-prints)