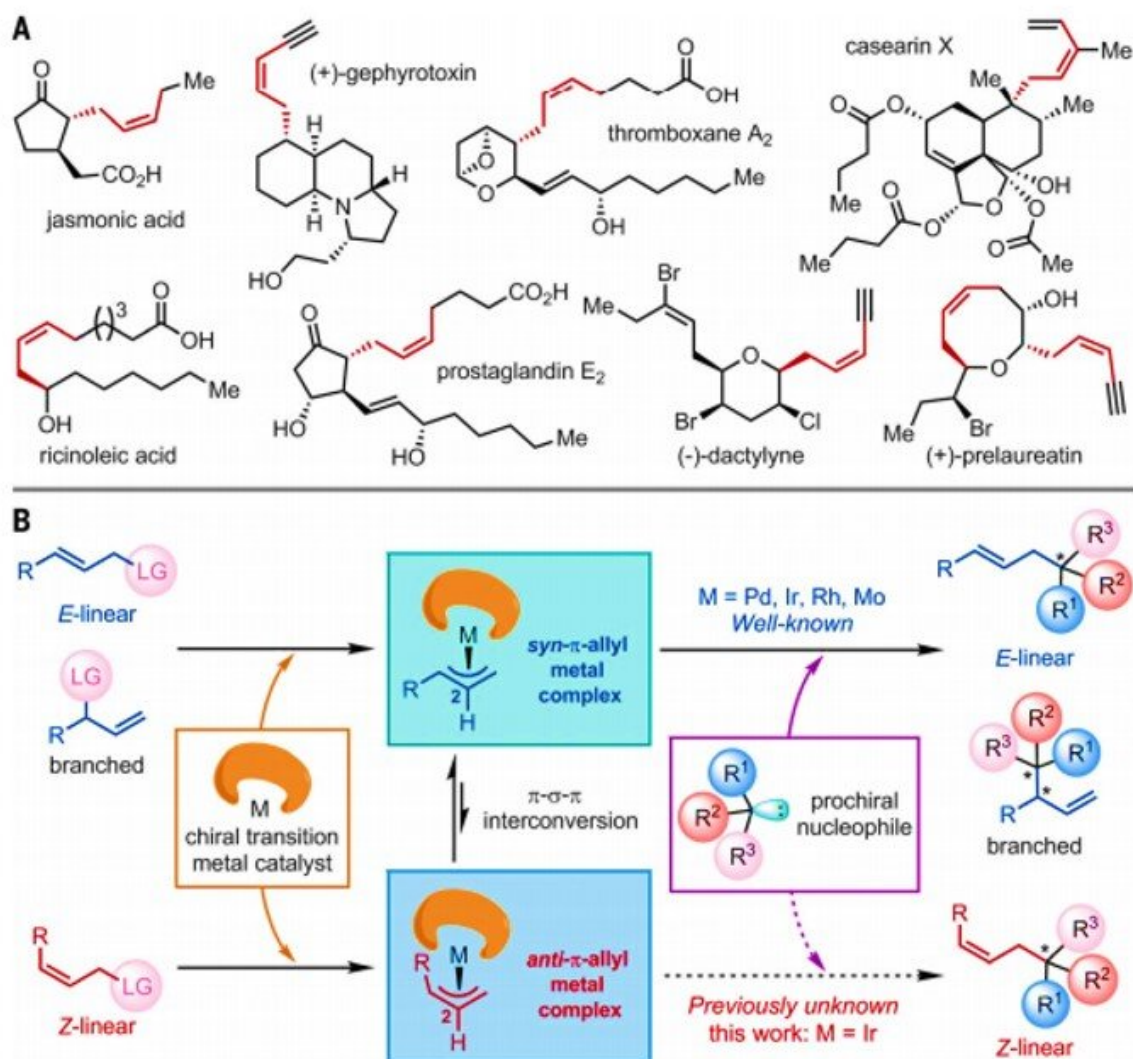


Iridium-catalyzed Z-retentive asymmetric allylic substitution reactions

February 11 2021, by Thamarasee Jeewandara



Strategy for the construction of Z-olefins via asymmetric allylic substitution

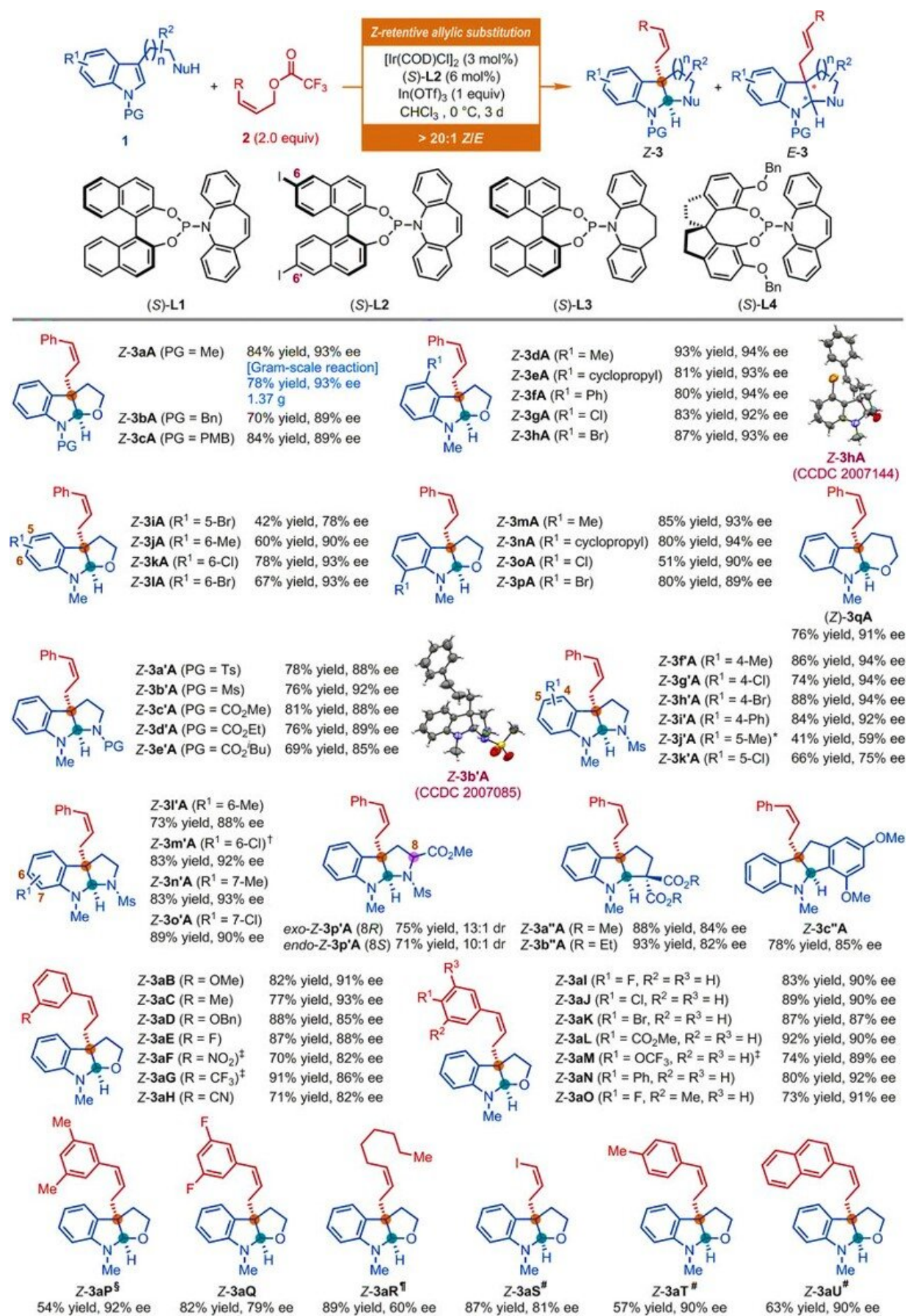
reactions catalyzed by transition metal catalysts. (A) Selected natural products containing Z-olefins with homoallylic stereocenters. Me, methyl. (B) Proposed general mechanism of transition metal-catalyzed asymmetric allylic substitution reactions involving E-linear, branched, or Z-linear olefin substrates, all of which include an atom or group of atoms denoted as a leaving group (LG). Credit: Science, doi:10.1126/science.abd6095

In synthetic organic chemistry, [Z-olefins](#) are a challenging synthetic target to produce in the lab due to their relative thermodynamic instability. The Z-olefins form an unsaturated compound with a C_nH_{2n} formula that can be [readily isomerized](#). Analogous reactions used to synthesize optically active Z-olefin products are rare. In a new report now published on *Science*, Ru Jiang and a research team at the University of Chinese Academy of Sciences in Shanghai, China, detailed an iridium-catalyzed asymmetric allylic substitution reaction to retain Z-olefin geometries while establishing an adjacent [quaternary stereocenter](#). The team observed the formation of transient [anti- \$\pi\$ -allyl-iridium](#) intermediates and their capture by external [nucleophiles](#) (electron donor) before [isomerization](#) to form thermodynamically more stable syn- π -allyl-iridium counterparts. The results provide a promising method to prepare chiral Z-olefin compounds in the lab.

Olefins

The Z-type geometric isomer of olefins are widely observed as basic structures in nature. Nevertheless, Z-olefins are comparatively less stable when compared with their E-type counterparts, and therefore, it is difficult to selectively [synthesize them in organic chemistry](#). Common methods to access Z-olefins include the [photoinduced isomerization of E-olefins](#), [Witting olefination](#), [Z-selective cross-metathesis](#), [Z-retentive cross-coupling](#) and the asymmetric addition of [Z-allylboron nucleophiles](#)

to ketones and imines. The Z-olefins with a homoallylic stereocenter are often embedded in diverse natural products and [bioactive molecules](#) to generate considerable interest in [synthetic organic chemistry](#). Researchers have shown the ability to conduct [asymmetric allylic substitution reactions](#) catalyzed by transition metals including molybdenum (Mo), palladium (Pd), iridium (Ir) and rhodium (Rh). Since its first report in 1997, Ir-catalyzed asymmetric allylic substitution reactions have garnered intense attention due to their exceptionally high regio- and enantioselective nature. In this work, Jiang et al. reported reactions of Z-linear allylic substrates with [tryptamines](#) and [tryptophol](#). During the comprehensive analysis of reaction mechanisms, they noted the formation of key anti- π -allyl-iridium complexes, prior to isomerization to form the thermodynamically stable syn- π -allyl-iridium counterparts.

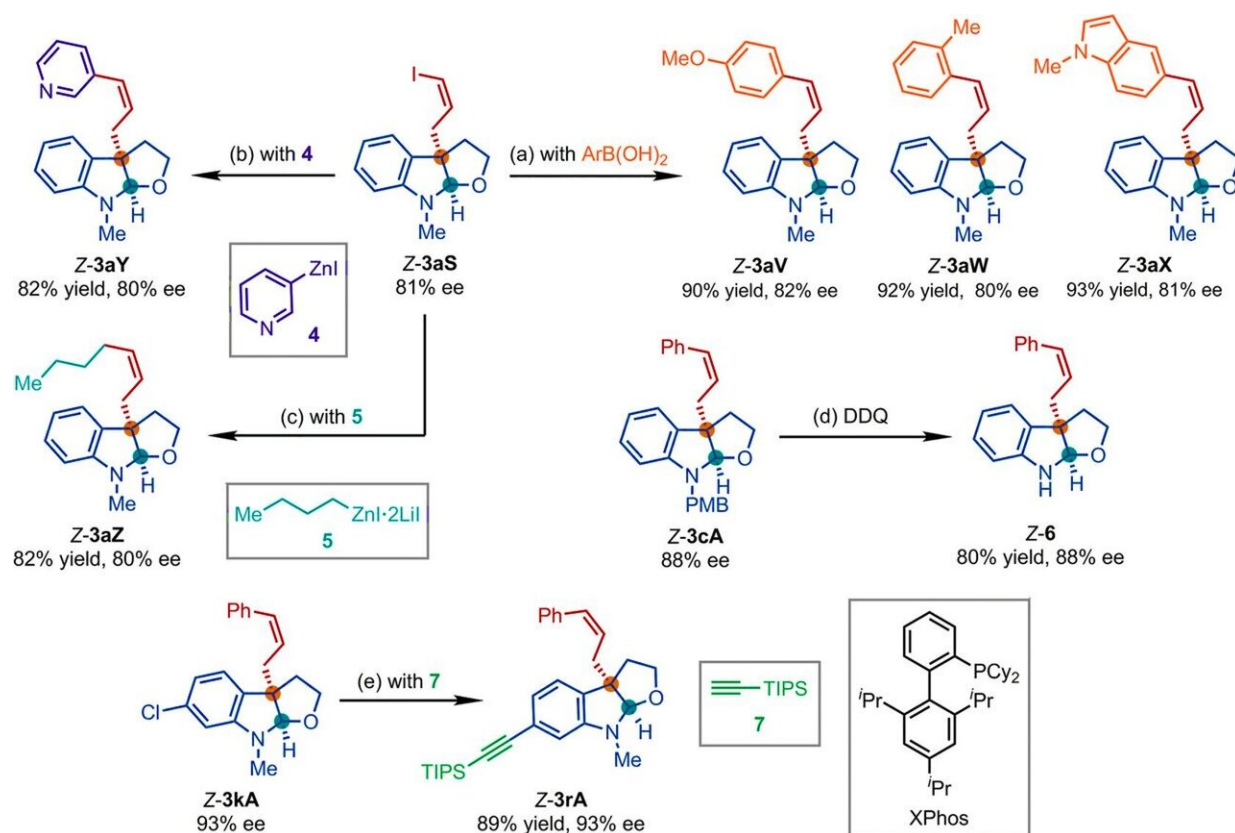


Substrate scope of Ir-catalyzed Z-retentive asymmetric allylic substitution reactions of indole derivatives. All reactions were conducted according to the conditions given here, unless otherwise indicated. The Z-type to E-type geometric ratio (Z/E) and diastereomeric ratio (dr) were determined by ¹H NMR analysis of the crude mixtures. The isolated yields of Z-3 are reported. The ee values were determined by high-performance liquid chromatography (HPLC) analysis with a chiral stationary phase. Asterisk indicates a Z/E ratio of 7:1. Single-dagger symbol indicates a Z/E ratio of 8:1. Double-dagger symbol indicates that the reactions were conducted for 1 day. Section symbol indicates a Z/E ratio of 11:1. Paragraph symbol indicates that the reactions were conducted using (Z)-non-2-en-1-yl acetate, [Ir(COD)Cl]₂ (3 mol %), (S)-L1 (6 mol %), InBr₃ (1.0 equiv), and tetrabutylammonium bromide (0.5 equiv) in CHCl₃ at 0°C. Pound symbol indicates that the reactions were conducted using the corresponding Z-allylic acetates, [Ir(COD)Cl]₂ (4.5 mol %), (S)-L2 (9 mol %), In(OTf)₃ (0.5 equiv for Z-3aS and Z-3aT; 1 equiv for Z-3aU) in CHCl₃ at -10°C for 2 days. Bn, benzyl; Bu, butyl; Et, ethyl; Ms, mesyl; Ph, phenyl; PMB, para-methoxybenzyl; p-Tol, para-tolyl; Ts, tosyl. Credit: Science, doi:10.1126/science.abd6095

Synthetic process

The researchers first investigated the asymmetric allylic de-aromatization reaction involving nucleophiles such as [N-methyl tryptophol](#) with Z-cinnamyl derivatives. By using [Z-cinnamyl acetate](#), they achieved the desired reaction with a catalyst derived from [iridium cyclooctadiene](#) (COD) chlorine dimer in the presence of other synthetic compounds. The scientists obtained the target product with moderate yield and enantioselectivity with a Z-type to E-type geometric ratio of 2:1. They then optimized the constituents to improve the quality and yield of the synthetic products. Based on the proposed Z-retentive

asymmetric allylic substitution reaction, Jiang et al. obtained diverse functional group compatibility that tolerated a broad substrate scope. The team successfully synthesized more than 50 examples of (homo)tryptophols, tryptamines and indole substrates bearing a pendant carbon-based nucleophile using Z-cinnamyl derivatives. Nearly all reactions provided a yield of Z-type to E-type ratios greater than 20:1. Examples include the corresponding Z-cinnamylated [furoindolines](#) (abbreviated Z-3aA to Z-3pA), [tetrahydropyranindoline](#) (abbreviated Z-3qA), [pyrroloindolines](#) (abbreviated Z-3a'A to Z-3o'A) and [hexahydrocyclopentaindoles](#) (abbreviated Z-3a''A to Z-3c''A) with good yields of up to 94 percent. Generally, the substitution of varied electronic and steric properties at available positions of the indole ring had no deleterious impact on the efficiency or enantioselectivity of the reaction. The researchers established the structures and absolute configuration of the products using [X-ray crystallographic analysis](#). They then also examined the performance of the D- and L-tryptophan derivatives.

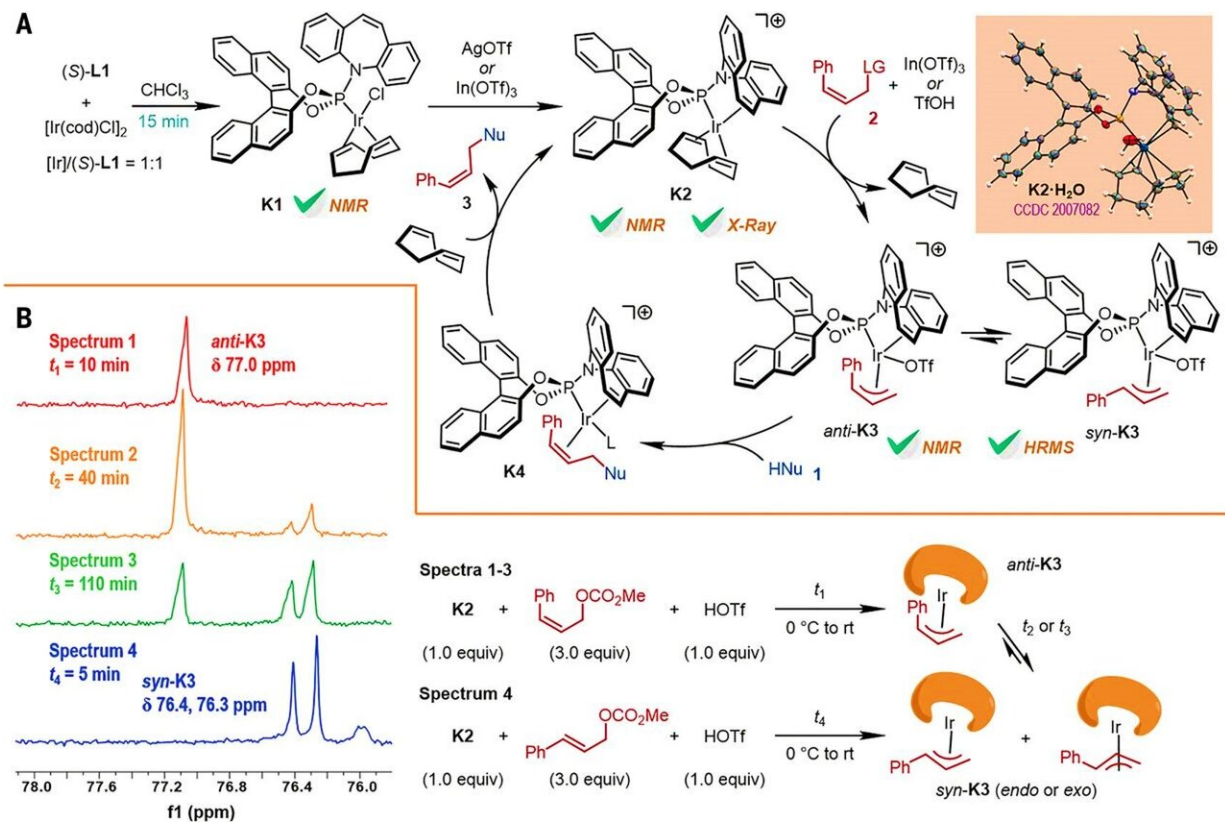


Representative products obtained in subsequent reactions with the products of Ir-catalyzed Z-retentive asymmetric allylic substitution reaction. Reaction conditions: (a) Pd(PPh₃)₄ (0.5 mol %), Cs₂CO₃ (2 equiv), ArB(OH)₂ (1.5 equiv), acetonitrile, 50°C; (b) 4 (2 equiv), THF/diglyme (1:1), 110°C, 24 hours; (c) 5 (2 equiv), LiCl (4 equiv), toluene/THF/TMU, 110°C, 24 hours; (d) DDQ (1.5 equiv), CH₂Cl₂, NaH₂PO₄ (aqueous 1 M); (e) 7 (2 equiv), PdCl₂(CH₃CN)₂ (5 mol %), XPhos (15 mol %), Cs₂CO₃ (2.5 equiv), acetonitrile, 80°C. Ar, aryl; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMU, 1,1,3,3-tetramethylurea. Credit: Science, doi:10.1126/science.abd6095

Downstream transformations

The researchers next studied how a number of products of the Z-retentive asymmetric allylic substitution reaction could be readily

investigated in diverse downstream transformations. For example, the Z-vinyl iodide of chiral furoindolines (abbreviated Z-3aS) was reactive towards aryl [boronic acids](#) and [organozinc reagents](#). This provided an alternative route to produce representative products with Ir-catalyzed, Z-retentive asymmetric allylic substitution reactions with high yields of up to 82 to 93%. The scientists evaluated the proposed Z-retentive asymmetric allylic substitution reactions by a series of analyses. They obtained the Z-cinnamylated furoindolines (Z-3aA) product with optimal results in the presence of iridium atoms in the catalyst in a molar ratio of 1:1. They then characterized the key intermediates in the catalytic cycle and elucidated their structures using [nuclear magnetic resonance](#) (NMR) spectroscopy alongside [X-ray crystallographic analysis](#). The team also monitored the reactions using [electrospray ionization mass spectrometry](#) and mechanistic studies. These results showed the isomerization of the complex from an anti- to the syn- π -allyl-iridium complex. Collectively, the analyses showed how the proposed Z-retentive asymmetric allylic substitution reaction successfully originated from the rapid and enantioselective capture of the transient anti- π -allyl-iridium complex by external nucleophiles, before converting it to more thermodynamically stable species.

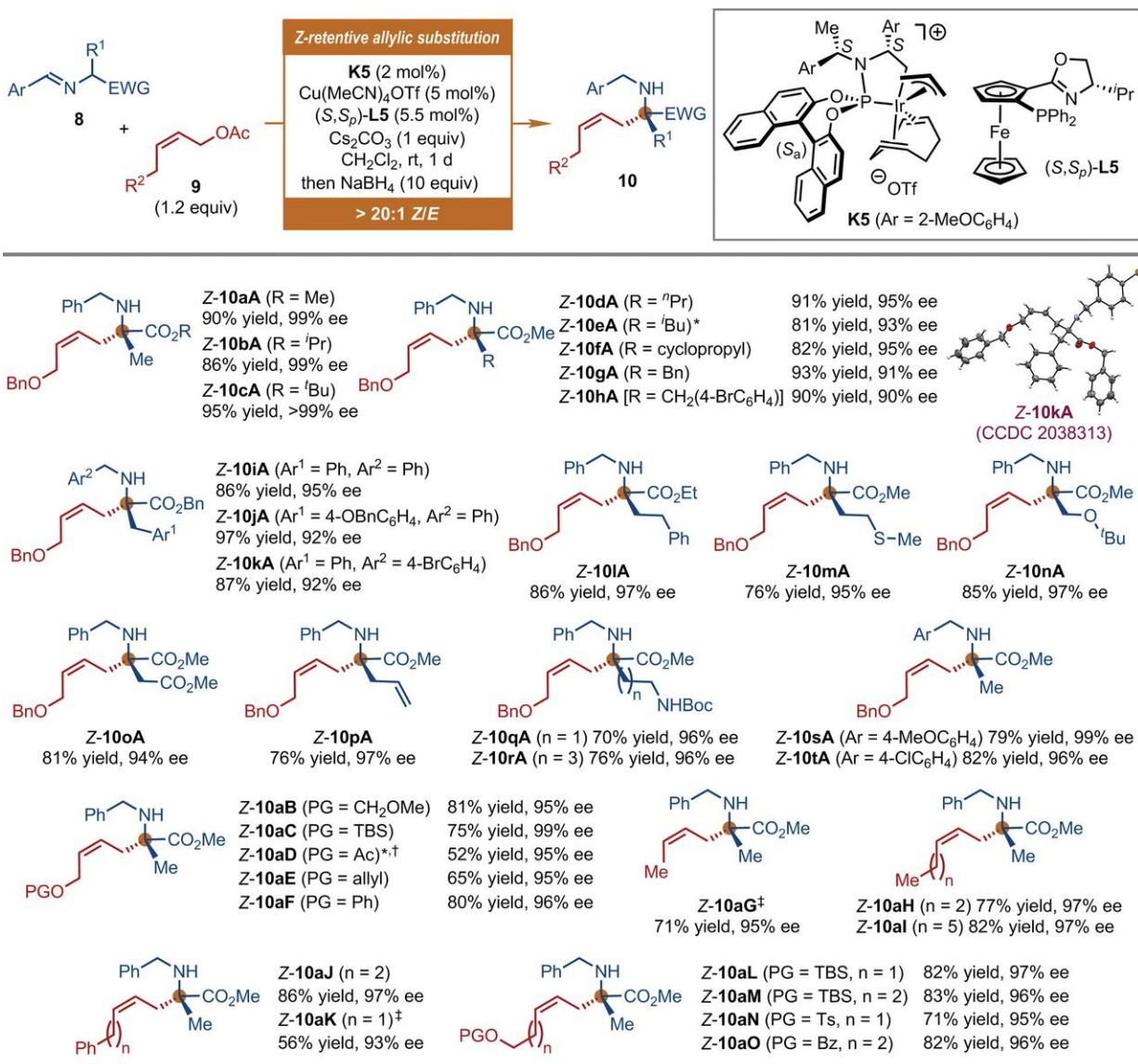


Reaction mechanism studies. (A) A proposed catalytic cycle. The key intermediates K1 and K2 were characterized by NMR spectroscopy, while K2·H₂O was characterized by x-ray crystallographic analysis. HRMS, high-resolution mass spectrometry. (B) The reactions of K2 with Z- or E-cinnamyl methyl carbonate demonstrated isomerization from anti-K3 to syn-K3 according to the results of monitoring by electrospray ionization mass spectrometry (ESI-MS) and ³¹P NMR spectroscopy, the results of which are shown at left, with the details given by the reaction process diagrams to the right. Credit: Science, doi:10.1126/science.abd6095

Exploring the synthetic spectrum

The scientists also explored the extension of this iridium-catalyzed Z-retentive asymmetric allylic substitution reaction to other nucleophiles.

Aside from the iridium catalysts containing [Carreira-type chiral ligands](#) that function under acidic conditions, they explored Ir catalysts derived from a [Feringa-type chiral phosphoramidite ligand](#) applied under basic conditions for this reaction mode. As a result, Jiang et al. used diverse nucleophiles beyond tryptophols and tryptamines. In this instance, they formed the prochiral nucleophiles from a copper (Cu) source. The independently prepared chiral cyclometallated Ir complex promoted the development of the transient anti- π -allyl-iridium complexes as well as their regio- and enantio-selective captures. The broad scope of the reaction presented more than 30 synthetic samples in good yields with excellent enantioselectivity. The scientists investigated the structure and absolute configuration of the products using X-ray crystallographic analyses. When the team used Z-cinnamyl acetate, they obtained a mixture of the desired Z-cinnamylated product and its branched isomer. The results highlighted the possibility of using the proposed protocol to accommodate diverse prochiral nucleophiles in asymmetric allylic substitution reactions. The researchers expect the work to evolve into a broadly practical method to synthesize chiral Z-olefins in the lab.



Substrate scope of Ir-catalyzed Z-retentive asymmetric allylic substitution reactions of α -amino acid derivatives. All reactions were conducted under the following conditions. Step 1: **8** (0.2 mmol, 1 equiv), **9** (1.2 equiv), **K5** (2 mol %), Cu(MeCN)₄OTf (5 mol %), (S,S_p)-L5 (5.5 mol %), and Cs₂CO₃ (1 equiv) in CH₂Cl₂ (2 ml) at room temperature. Step 2: Reaction residue of step 1, NaBH₄ (10 equiv) in CH₂Cl₂/MeOH (1:1, 4 ml) at room temperature. The Z-type to E-type geometric ratio (Z/E) values were determined by ¹H NMR analysis of the crude mixtures of step 1. The isolated yields of linear Z-10 are reported. The ee values were determined by HPLC analysis with a chiral stationary phase. The asterisk indicates that **9** (1.5 equiv) and **K5** (4 mol %) were used. The single-

dagger symbol indicates a Z/E ratio of 5.3:1. The double-dagger symbol indicates that 9 (2 equiv) was used. Ac, acetyl; Boc, tert-butoxycarbonyl; Bz, benzoyl; EWG, electron-withdrawing group; PG, protecting group; Pr, propyl; TBS, tert-butyldimethylsilyl. Credit: Science, doi:10.1126/science.abd6095

More information: Jiang R. et al. Iridium-catalyzed Z-retentive asymmetric allylic substitution reactions, *Science*, 10.1126/science.abd6095

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