

Towards α,α -disubstituted amino acids containing vicinal stereocenters via stereoselective transition-metal catalyzed allylation

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This review is dedicated to Peter A. Jacobi in honor of his accomplished career in organic chemistry

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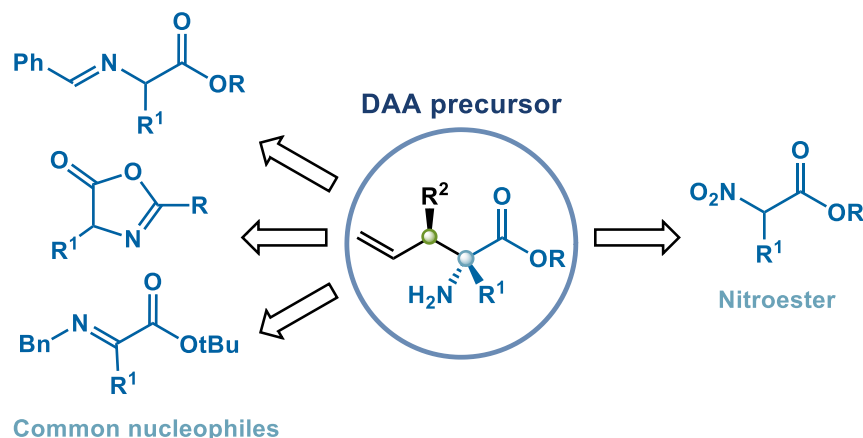
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Abstract

Designer amino acids find use across many scientific disciplines. The preparation of amino acids bearing acyclic vicinal stereocenters remains a challenge in synthesis. Herein, we highlight transition-metal catalyzed allylations for the stereoselective synthesis of disubstituted α -amino acid precursors bearing vicinal stereocenters. Allylation of azlactones, α -imino esters, and aldimine esters with dienes and allylic leaving groups are among the most common strategies. These developments provide context for our work featuring the asymmetric addition of α -nitroesters to alkynes.



Keywords: α,α -disubstituted α -amino acids, vicinal stereocenters, stereodivergent, enantioselective

Table of Contents

1. Introduction
2. Allylation of Azlactones
3. Synergistic Dual Catalysis
 - 3.1.1 Allylation of α -imino esters
 - 3.1.2 Allylation of aldimine esters
4. Alkynes as Atom Economical Metal-allyl Precursors
5. Conclusions

1. Introduction

Amino acids comprise the backbones of proteins and are fundamental building blocks of living organisms. Consequently, the ability to synthesize unnatural amino acids has enabled development of therapeutics development,¹ study of protein structure and function,²⁻⁴ and expansion of the genetic code.⁵⁻⁷ Additionally, amino acids have been used as intermediates in total synthesis^{8,9} and as chiral catalysts.^{10,11} More specifically, the incorporation of α,α -disubstituted amino acids (DAAs) improves metabolic stabilities and bioactivities for a number of structures (Figure 1).¹²⁻¹⁴ These amino acids can impart unique conformations for folded peptides.¹⁵

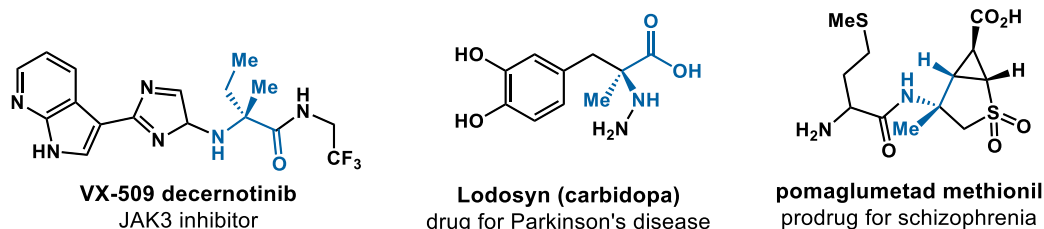


Figure 1. Examples of biologically active α,α -disubstituted α -AA and analogs¹²⁻¹⁴

Acyclic vicinal stereocenters are important yet challenging motifs to access. Nonetheless, chemists have accessed these scaffolds using strategies such as allylations, conjugate additions, sigmatropic rearrangements, and ring openings.¹⁶ For allylations, transition-metal catalysis generally offers excellent diastereocontrol, with high enantio- and regioselectivity.¹⁶ This approach uses allylic carbonates and acetates as surrogates to generate transition-metal- π -allyl complexes that can be intercepted by a nucleophile. A challenge of allylation involves the control of regioselectivity, determined by which side of the π -allyl complex is attacked by the nucleophile.¹⁷⁻²⁰ The “branched” isomer is defined by the attack of the nucleophile on the side with R^2 , resulting in a product where R^2 and the nucleophile are bonded to the same carbon atom (Figure 3). Contrarily, the “linear” isomer is a result of a nucleophilic attack on the π -allyl complex from the opposing side of R^2 .

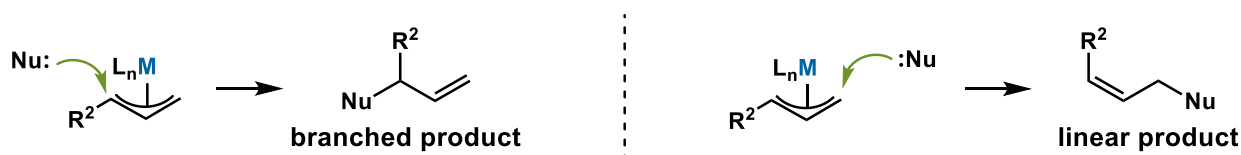
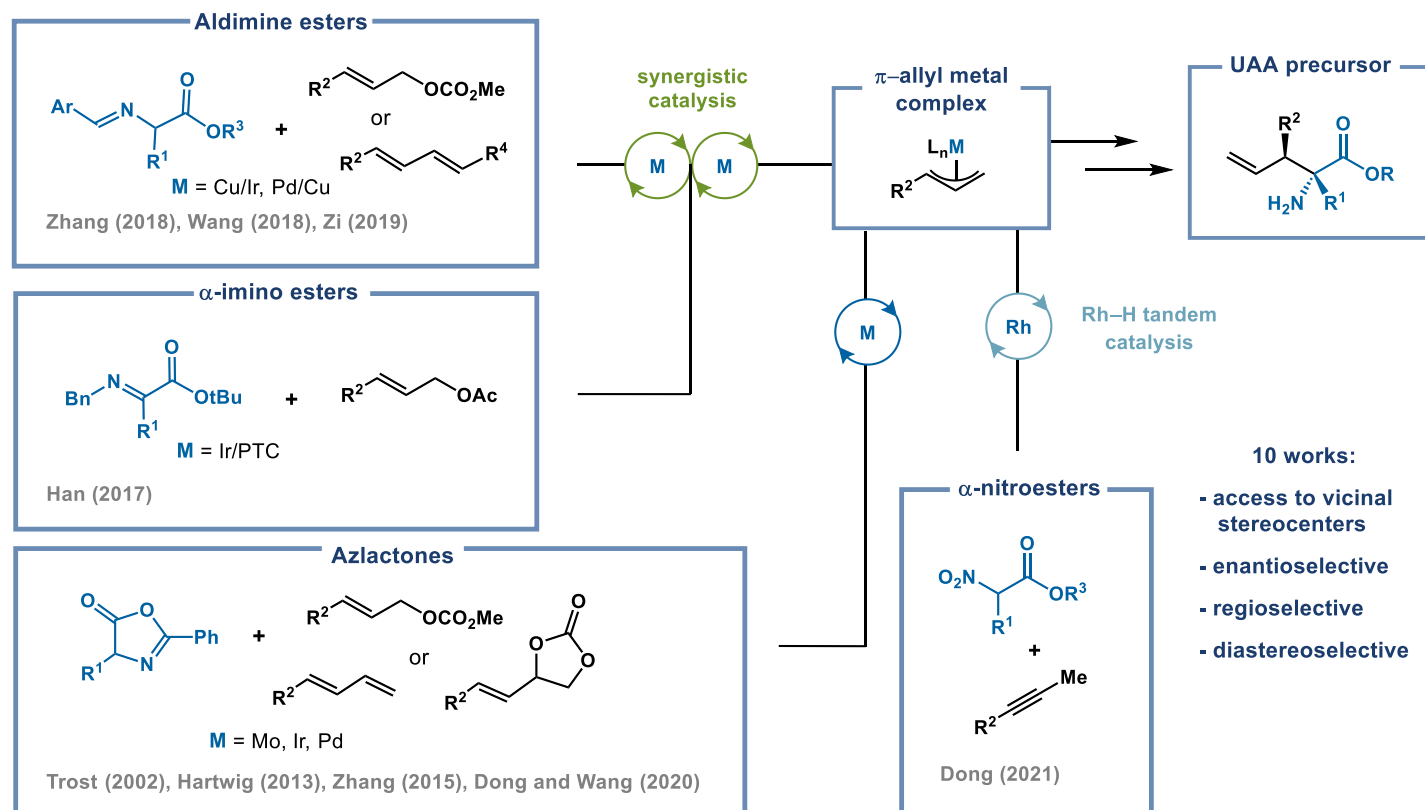


Figure 2. Formation of “branched” versus “linear” isomer

Herein, we discuss advancements in the use of transition-metal catalyzed allylation for the synthesis of acyclic DAA motifs bearing vicinal stereocenters. This review is organized by the amino acid derived coupling partners: azlactones, α -imino esters, and aldimine esters (Figure 2). These developments provide context for our work on the addition of α -nitroesters to alkynes to access DAA precursors.

**Figure 3.** Methods of preparing DAA precursors organized by coupling partner

2. Allylation of Azlactones

Azlactones are the earliest coupling partners used for the synthesis of DAA precursors using a transition-metal catalyzed allylation strategy. These acidic pronucleophiles readily tautomerize and react at the C4 carbon atom (Figure 4). The first example was reported by Trost which detailed an asymmetric Mo-catalyzed allylation of azlactones using ligand **L1**.¹⁷ This transformation was highly diastereoselective, and the strategic choice of base contributed to a regioselective preference for the branched product **1**. This is followed by *in situ* hydrolysis to give protected amino ester **2**. This one-pot protocol led to improved yields and diastereoselectivity compared to earlier multi-step procedures. The substrate scope explored numerous azlactones and aryl-substituted allylic carbonates. A selection of aryl substituents for R² were reported with good results (**2a**, **2b**). High branched selectivity was observed for methyl or benzyl R¹ substituents (**2a**, **2b**, **2c**). Substrates containing longer alkyl chains, however, suffered from lower regioselectivity (**2d**, **2e**). Altogether, high enantio- and diastereoselectivities were observed. Computational mechanistic studies provided a model

for understanding diastereoselectivity. Molecular Mechanics (MM2) calculations suggested that **TS1** is approximately 2–10 kcal mol⁻¹ lower in energy than **TS2** leading to the observed products.

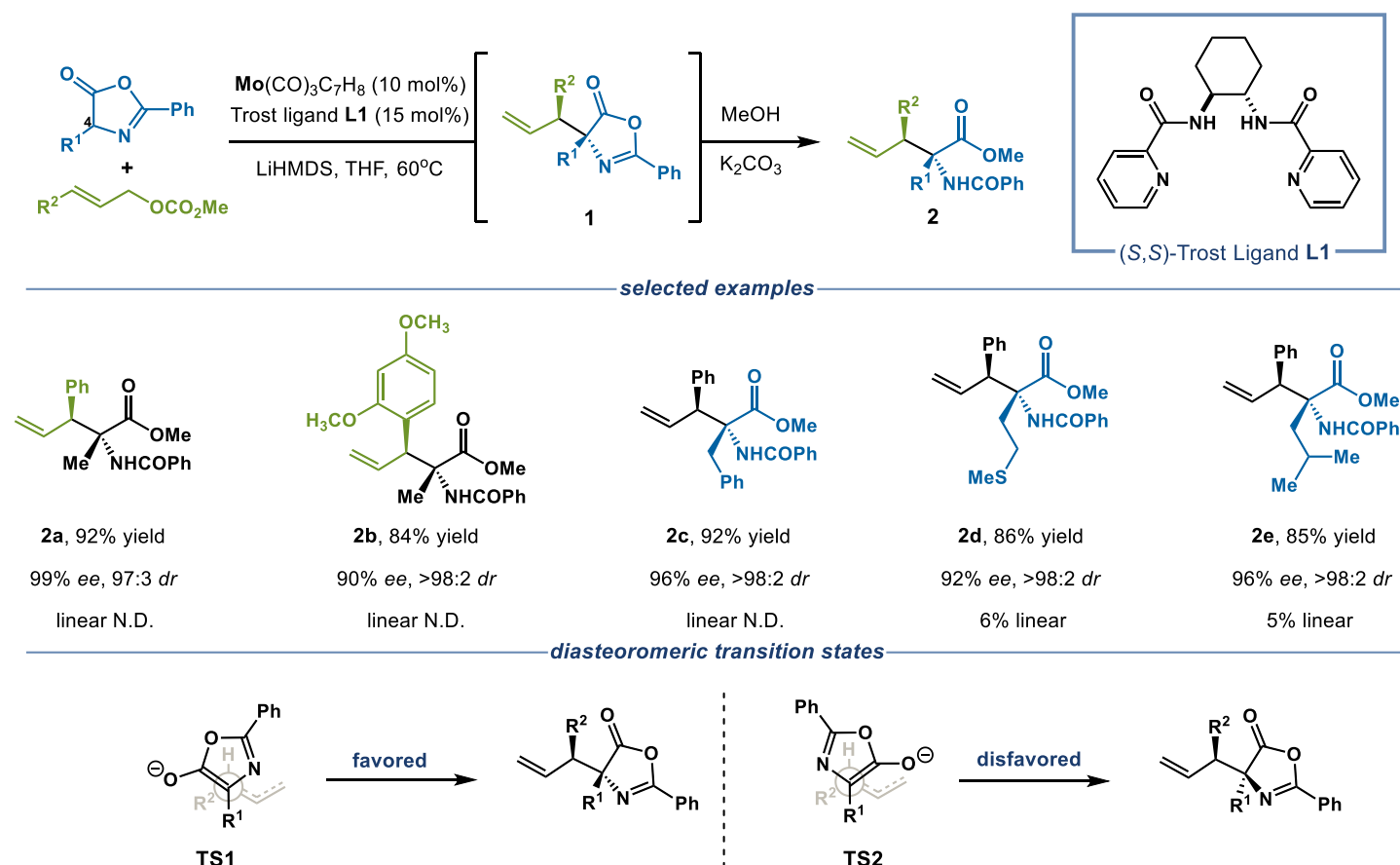


Figure 4. Trost¹⁷ and co-worker's Mo-catalyzed asymmetric allylic alkylation of azlactones. N.D. = not detected

Subsequently, Hartwig reported an Ir-catalyzed allylation of azlactones where high diastereo- and enantioselectivities were achieved using O,O,P,N-BINOL ligand **L2** for the synthesis of DAA precursors **3** (Figure 5).¹⁸ The transformation gave high regioselectivities for *meta*- and *para*-substituted phenyl R² groups (**3a–3d**). However, electron-donating substituents were less reactive (**3b**), and *ortho*-substituted aryl groups resulted in lower diastereo- and enantioselectivities (**3e**). This work expands upon the scope of Trost's Mo-catalyzed method by introducing heteroaromatic substituents and dienyl carbonates (**3f** and **3g**). Notably, aliphatic allylic carbonates resulted in low diastereoselectivity. As with Trost's method, Hartwig's Ir-catalyzed process favors the branched regioisomer. Furthermore, this method is applicable to azlactones derived from natural amino acids (**3h–3j**).

Further studies offer insight into the mechanism. Experiments replacing [Ag] with phosphoric acid **4** resulted in the same diastereoselectivity. Meanwhile, experiments without phosphate co-catalyst **4** resulted in diminished *dr*, suggesting that the phosphate anion, instead of the silver cation, is responsible for the high diastereoselectivity. These studies also confirm the counterion-assisted allylation via metalacyclic Ir complex **5**.

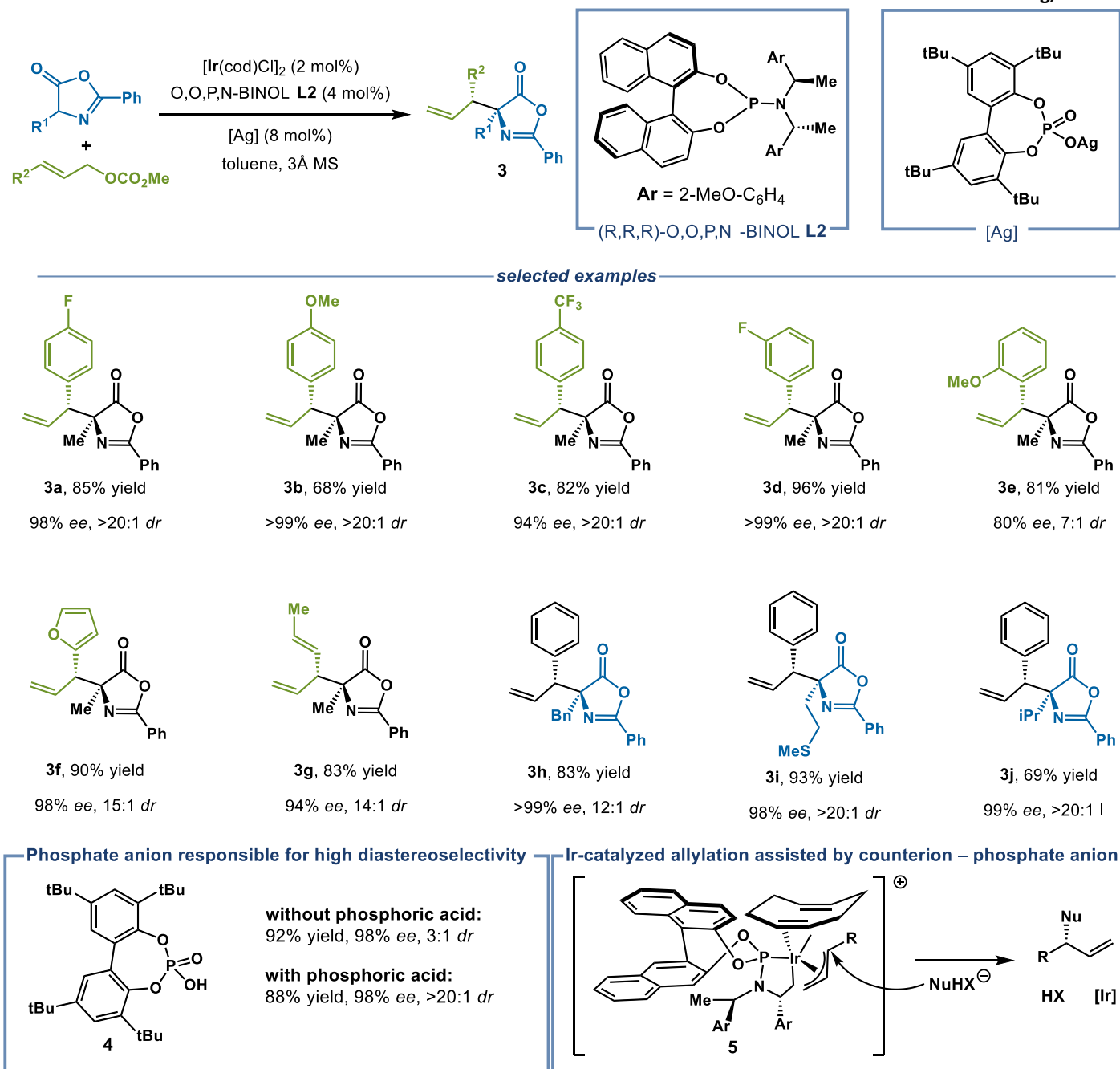


Figure 5. Hartwig¹⁸ and co-worker's Ir-catalyzed allylation of azlactones with a phosphate counterion

Zhang was the first to develop Pd-catalyzed allylation of azlactones. Similar to Hartwig,¹⁸ Zhang's method uses O,O,P,N-BINOL ligand **L3** to give protected amino acids **6** bearing tethered allylic alcohols (Figure 6).¹⁹ The enantioselectivity decreases as the sterics of the R¹ substituent increases (**6a** and **6b**). Aryl ethers with various *ortho*- or *para*-substituents at R² were well tolerated giving excellent enantioselectivities (**6c–6e**). Additionally, heteroaromatic substituents showed great reactivity but modest enantioselectivity (**6f**). The branched regioselectivity is dependent upon hydrogen-bonding between the incoming azlactone nucleophile and the hydroxyl group of the Pd- π -allyl complex (intermediate **7**). Removal of the hydroxyl coordinating group via allylic acetate **8** leads to a reversal of regioselectivity, as seen in **9**. Therefore, the strategic choice of a Pd- π -allyl precursor (cyclic carbonates or acetates) allows for complementary control of regioselectivity.

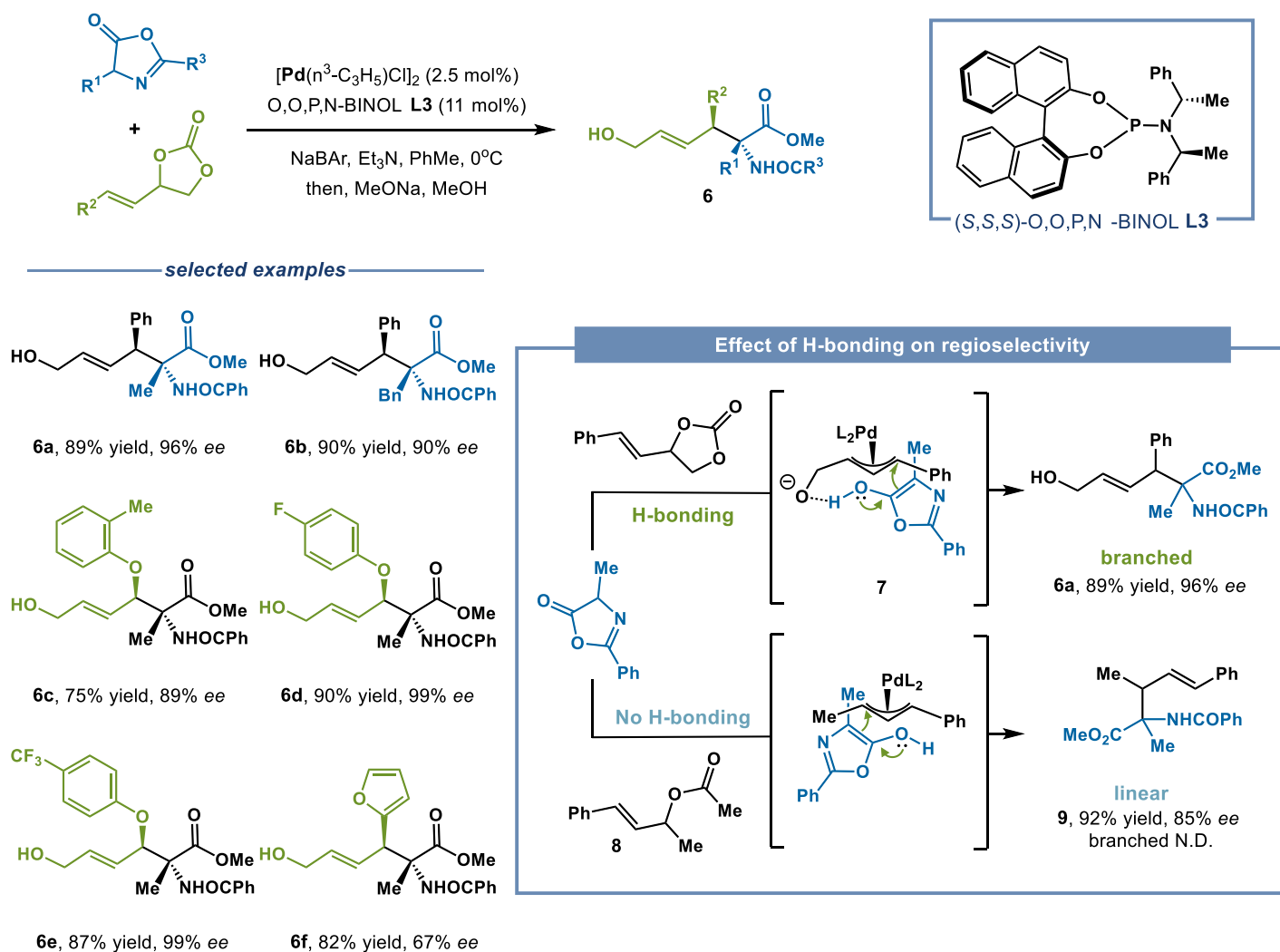


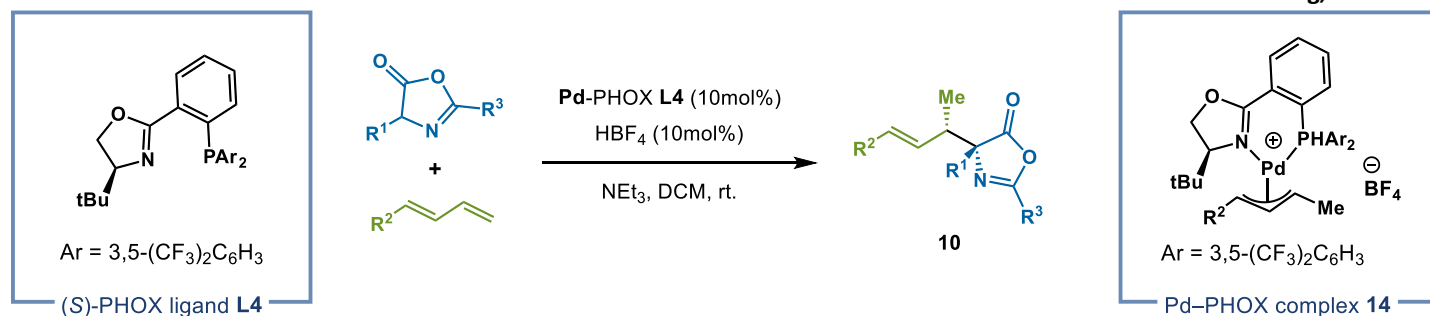
Figure 6. Zhang¹⁹ and co-workers' Pd-catalyzed asymmetric allylic alkylation of azlactones

Other transition-metal π -allyl precursors include 1,3-dienes. Meek and co-workers reported a Rh-catalyzed hydrofunctionalization of 1,3-dienes with azlactones for the preparation of DAA precursors.²¹ Afterwards, Wang and Dong developed an asymmetric Pd-catalyzed allylation of azlactones with 1,3-dienes using the phosphinoxazoline ligand **L4** (Figure 7).²⁰ A Pd-H is generated by oxidative addition to $\text{HBF}_4\text{-Et}_2\text{O}$ and undergoes migratory insertion with the 1,3-diene to generate the cationic Pd- π -allyl complex **14**. Intermediate **14** is then trapped by an azlactone pronucleophile to give DAA precursor **10**. Wang and Dong note that steric hindrance from the tert-butyl group in the ligand likely contributed to the selectivity.

The substrate scope tolerates a broad array of both aromatic and aliphatic substituents. Compared to methyl R^1 substituent (**10a**), more sterically hindered groups at R^1 maintained high enantioselectivities (>93% ee) and diastereoselectivities (>10:1 dr), albeit with lower yields (**10b**). This strategy tolerates olefin side chains giving access to handles for further functionalization (**10c**) (*vide infra*). *Para*-substituted aryl R^3 substituents with both electron-rich (**10d**) and electron-poor (**10e**) substituents showed high reactivity and diastereoselectivity; however, the diastereoselectivity is reduced when aryl R^1 substituents are introduced (**10f**). For the scope of 1,3-dienes, both electron-donating (**10g**) and withdrawing (**10h**) *para*-substituted phenyl groups gave higher diastereoselectivities compared to *ortho*- (**10i**) and *meta*-substituents (**10j**). Alkyl R^2

substituents (**10k**) were tolerated with high enantioselectivity but suffered from lower diastereoselectivity. Heteroaromatic furanyl (**10l**) and electron-withdrawing methyl ester substrates (**10m**) were reported to maintain good selectivity and yield. Although broad, the scope was limited to terminal 1,3-dienes.

Synthetic applications of these allylated azlactones were demonstrated. Reductive ring opening of **10a** gave the β -amino alcohol **11** with complete retention of stereochemistry. Hydrolysis of allyl-substituted allylation product **10c** with K_2CO_3 gave the protected amino ester **12**. A ring closing metathesis of **12** with Grubbs II gave cyclopentene **13**. These cyclic intermediates can be used for the synthesis of biologically relevant compounds such as metabotropic receptor antagonists.²²



selected examples

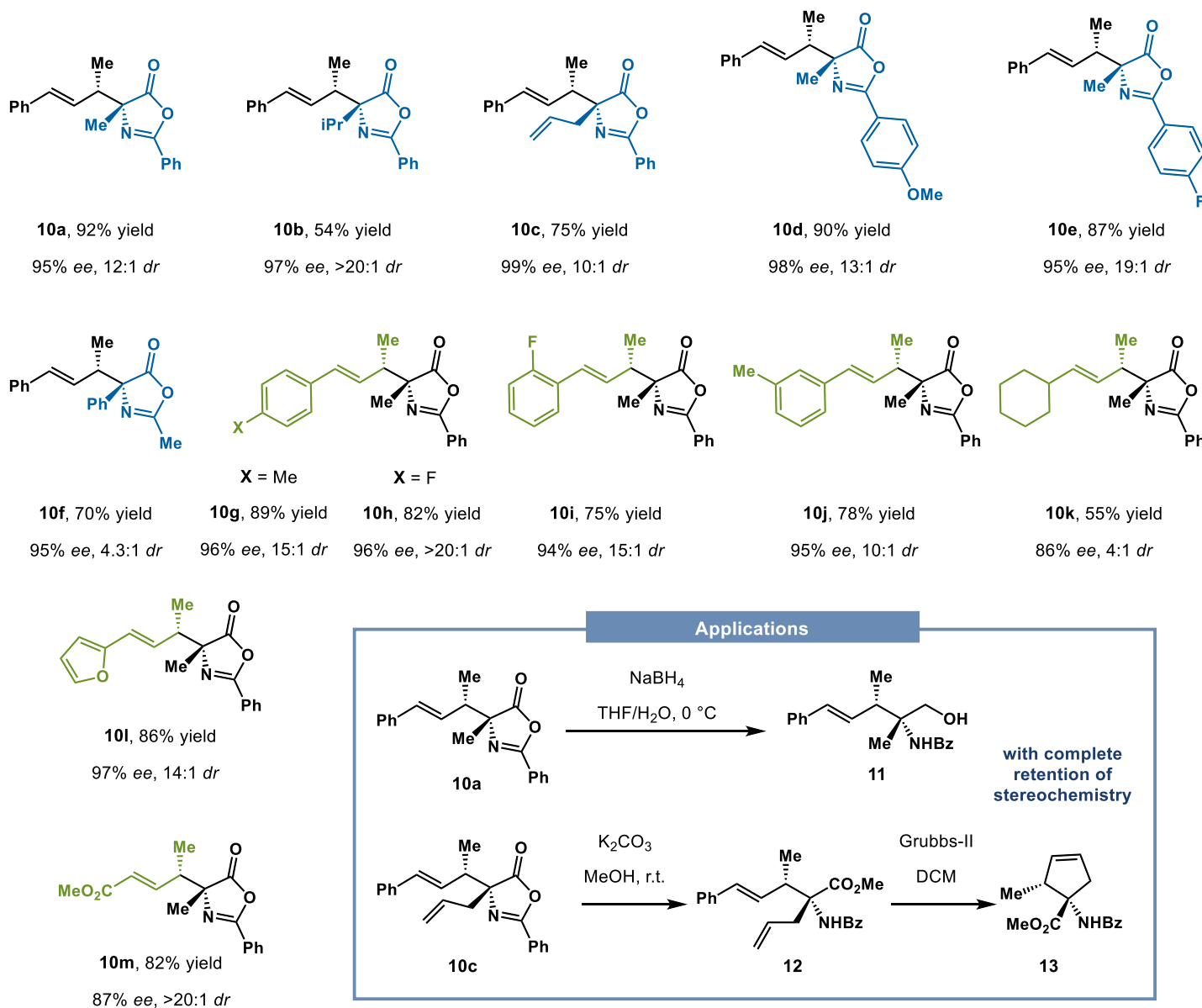


Figure 7. Wang, Dong,²⁰ and co-workers' Pd-catalyzed asymmetric hydroalkylation of 1,3-dienes with azlactones

3. Synergistic Dual Catalysis

The simultaneous activation of two coupling partners with two independent catalysts is known as synergistic catalysis.²³ This strategy has become a useful tool for the synthesis of complex molecular architectures,²⁴ and it has been especially useful in transition-metal catalyzed allylations. When each co-catalyst is chiral, synergistic catalysis can provide divergent control over the relative stereochemistry of two generated vicinal stereocenters. By the simple exchange of a catalyst with its enantiomer, one can access the opposite diastereomer. Herein, we highlight recent advancements in the use of synergistic transition-metal catalysis for the allylation of α -imino esters to access DAA motifs.

3.1. Allylation of α -imino esters

The earliest synergistic approach for the synthesis of DAA precursors was reported by Han.²⁵ Here, a chiral Ir catalyst was used along with a phase transfer ammonium co-catalyst to solubilize the *in situ* generated 2-aza-allyl anion **16** (Figure 8). The use of an ammonium co-catalyst was found to improve the reactivity. The solvated anion **16** then attacks the Ir- π -allyl complex **17** to generate the amino ester **15**. This method tolerates a range of aromatic substitutions. High enantio- and diastereoselectivity is achieved with *ortho*-substituted phenyl groups at the R² position (**15a**, **15b**). In addition, *para*- (**15c**, **15f**) and *meta*-substituted (**15d**) phenyl and naphthalene (**15e**) substituents are tolerated at the R¹ position. *Ortho*-substituted aryl nitroesters are not tolerated likely due to steric hindrance.

There are many notable advantages offered by Han's report. Contrary to the use of azlactones, dual catalysis provides single-step direct access to the acyclic amino ester motif. Additionally, a wide selection of aryl R¹ substituents, which were inaccessible by azlactone methods, are available using synergistic catalysis (*vide supra*). This expansion of scope allows for the preparation of biologically interesting compounds.²⁶ For instance, acylation of **15f** followed by cyclization with iodine provides the quaternary proline analogue **18**. These highly substituted proline derivatives are crucial for nucleating secondary structures in peptides.²⁶ In addition, deprotection of **15f** can be facilitated by TFA to provide the corresponding DAA **19**.

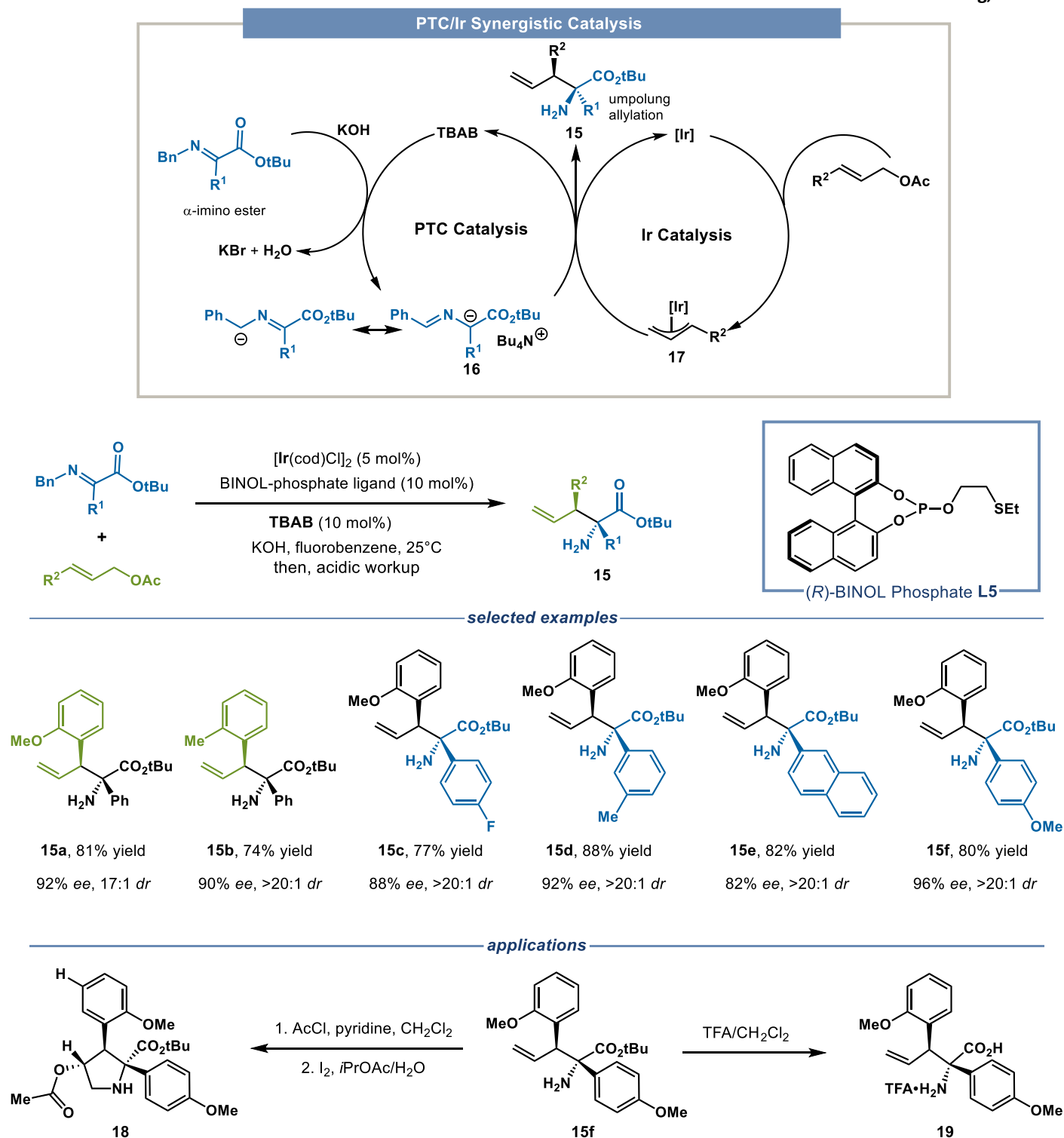


Figure 8. Han²⁵ and co-workers' Ir and PTC dual-catalyzed asymmetric umpolung allylation of α -imino esters

3.2. Allylation of aldimine esters

Zhang²⁷ and Wang²⁸ independently reported the first synergistic methods using two chiral transition-metal co-catalysts (Cu and Ir) to prepare α -AAs bearing vicinal stereocenters. By altering the ligand stereochemistry of either complex, all four stereoisomers could be accessed in similar yields and selectivity (Figure 9). A Cu catalyst bearing the chiral PHOX ligand **L6** activates the aldimine ester to form cyclic ylide **20**. Meanwhile, an Ir

catalyst containing the chiral O,O,P,N ligand **L3** coordinates to the allylic carbonate, generating the π -allyl complex **21**. Lastly, transition-metal complexes **20** and **21** are coupled to generate a new C–C bond forming amino ester **22**. Therefore, the Cu catalyst controls the α -carbon stereochemistry, and the Ir catalyst controls the β -carbon's stereochemistry.

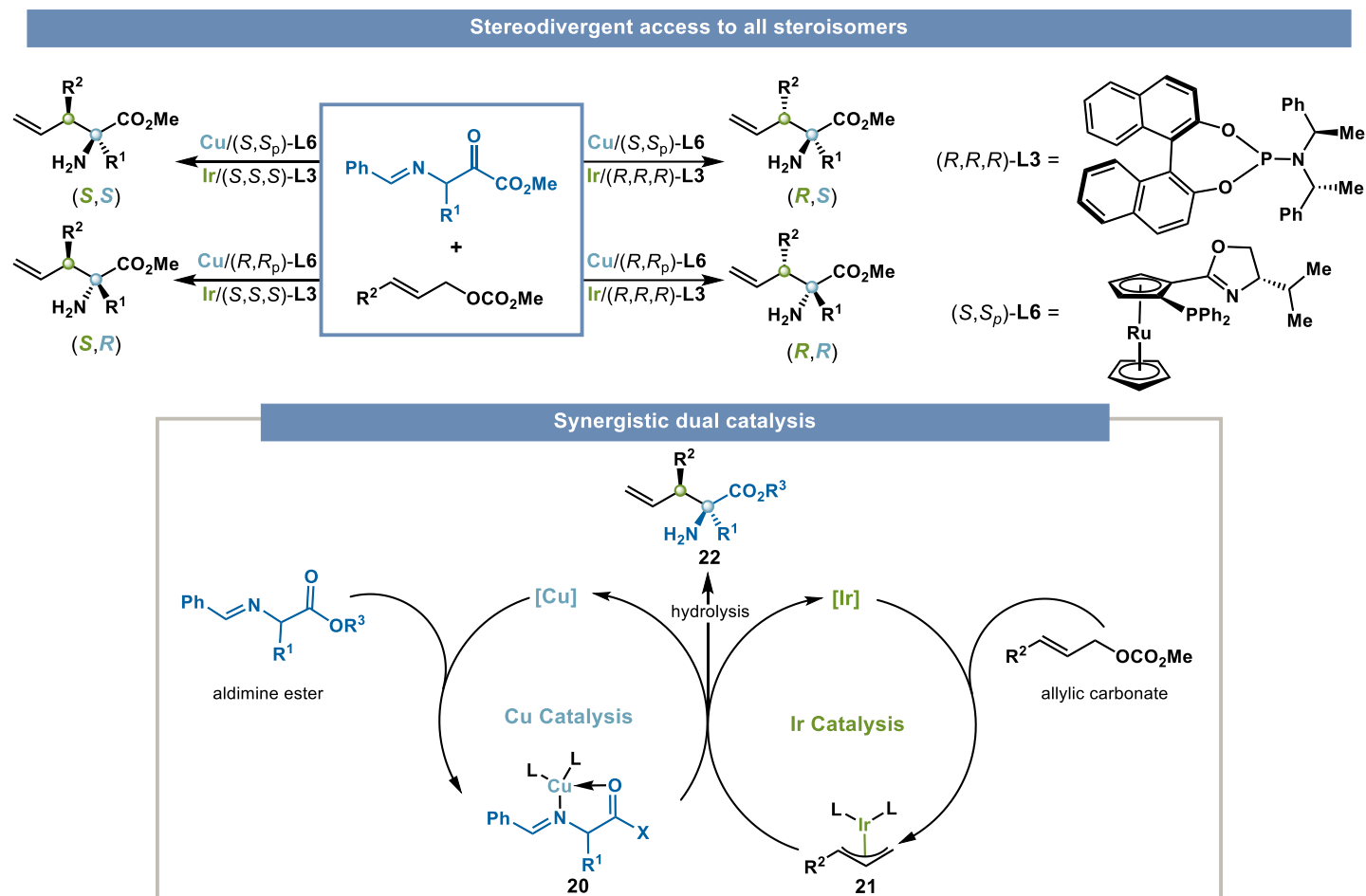


Figure 9. Synergistic dual catalysis allows controlled access to all four stereoisomers (top). Mechanism shows that each metal catalyst controls stereochemistry of one of the vicinal stereocenters (bottom).

The substrate scope of Zhang's study was quite broad.²⁷ All stereoisomers of model substrate **23a** were accessed in similar yields and selectivities by judicious combinations of the Cu and Ir catalysts (Figure 10). Electron-donating and electron withdrawing *ortho*-, *meta*-, and *para*-substituted phenyl rings at the R^2 position resulted in excellent enantioselectivity and good diastereoselectivity (**23b**, **23c**, **23d**, **23e**). Heteroaromatic substituents such as indolyl **23f** suffered from lower diastereoselectivity. When the aromatic substituent was replaced with a methyl group in R^2 , the enantioselectivity and diastereoselectivity remained high, but the yield dropped. A variety of aldimine esters were also well tolerated, particularly those with OMe as X. The allylation of α -AAs (**23g**) and dipeptides (**23h**) were also demonstrated. Stereo-divergent access to two stereoisomers of Gly-L-Leu derivative (**23h**) was achieved with high diastereoselectivity, while also retaining the configuration of the pre-existing stereocenter.

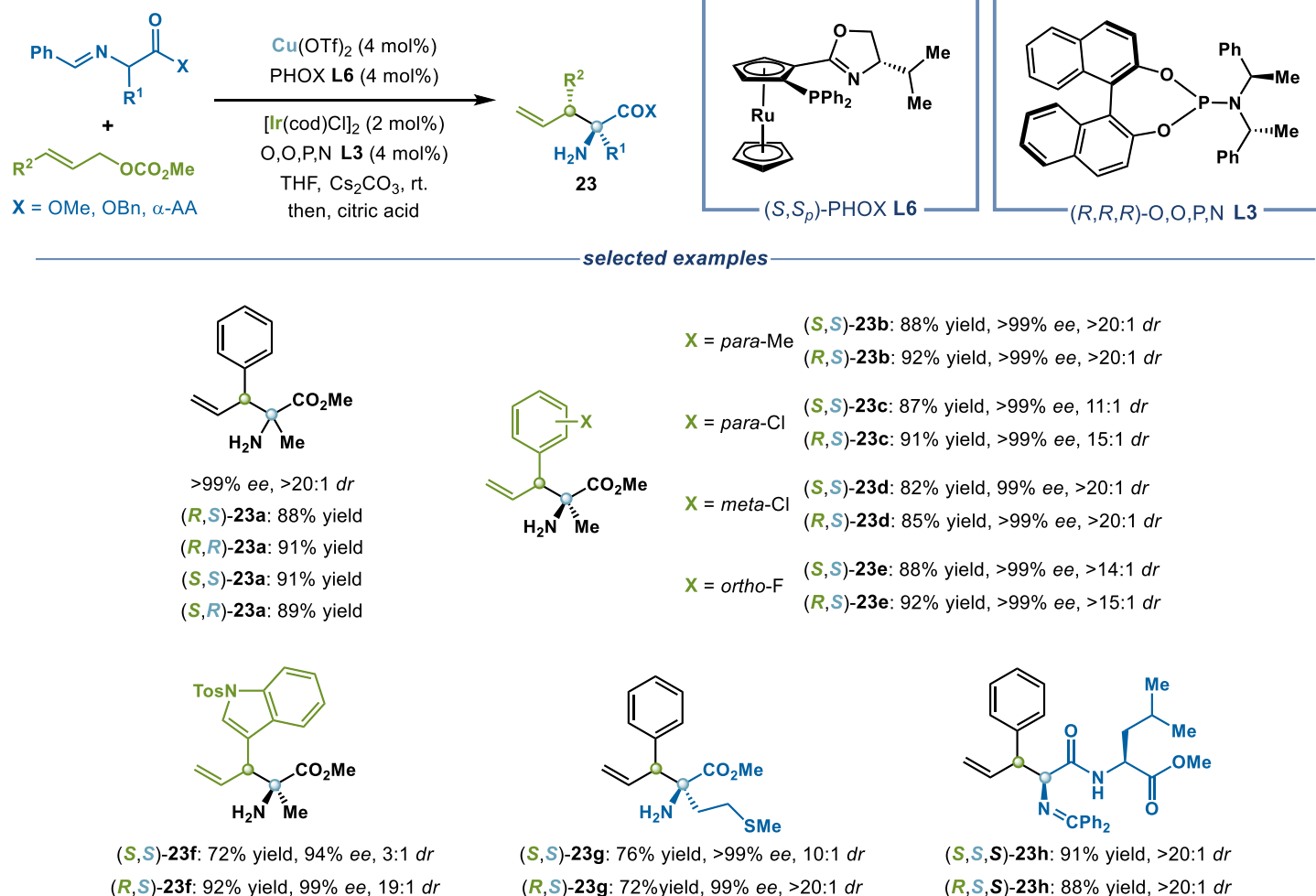


Figure 10. Zhang²⁷ and co-workers' Ir and Cu dual-catalyzed allylation of aldimine esters

Similarly, Wang reported an Ir and Cu dual catalyzed allylation of aldimine esters (Figure 11).²⁸ The results show improved scope with *para*-, *meta*-, and *ortho*-substituted phenyl allylic carbonates. Notably, *para*-fluoro substitutions gave higher diastereoselectivity but *meta*-halogenated rings gave lower selectivities compared to Zhang's work (**24b**). Observed diastereoselectivity was >20:1 for all reported allylic substrates, including aromatic, furyl, thienyl, and methyl (**24a**) for R². The only exceptions were 2-thiazolyl and *para*-Cl-C₆H₄, which gave 7:1 *dr* and 14:1 *dr*, respectively. In all cases, the enantioselectivity was at or above 98% *ee*. A variety of aldimine esters also provided excellent results, including alkyl, benzyl and aryl R¹ substituents (**24c–24e**). Additionally, all four stereoisomers of product **24e** were accessed with comparable yields and selectivities by altering the stereochemistry of the Ir and Cu co-catalysts.

Wang demonstrated applications of this method. For instance, the natural product and plant growth regulator (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid **26** was synthesized. Imino ester **24f** was first constructed using this highly selective synergistic coupling and was then converted to compound **25** via cyclopropanation in 99% yield. Lastly, cyclopropane **25** was hydrogenated to the carboxylic acid **26** in 99% yield and 10:1 *dr* with full retention of stereochemistry. These three steps offer highly efficient and selective access to **26** compared to previously reported 6-8 step syntheses.^{29,30}

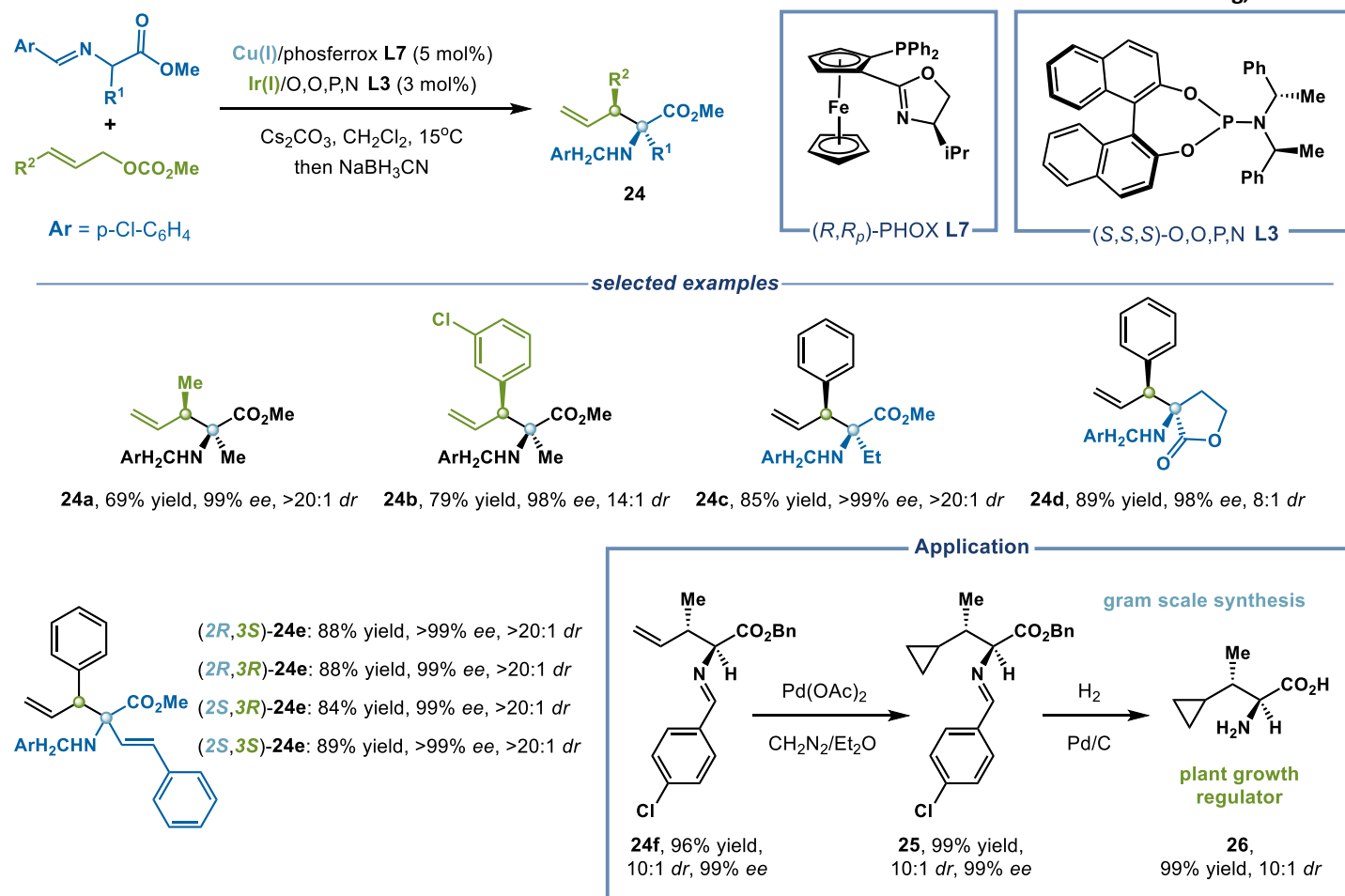
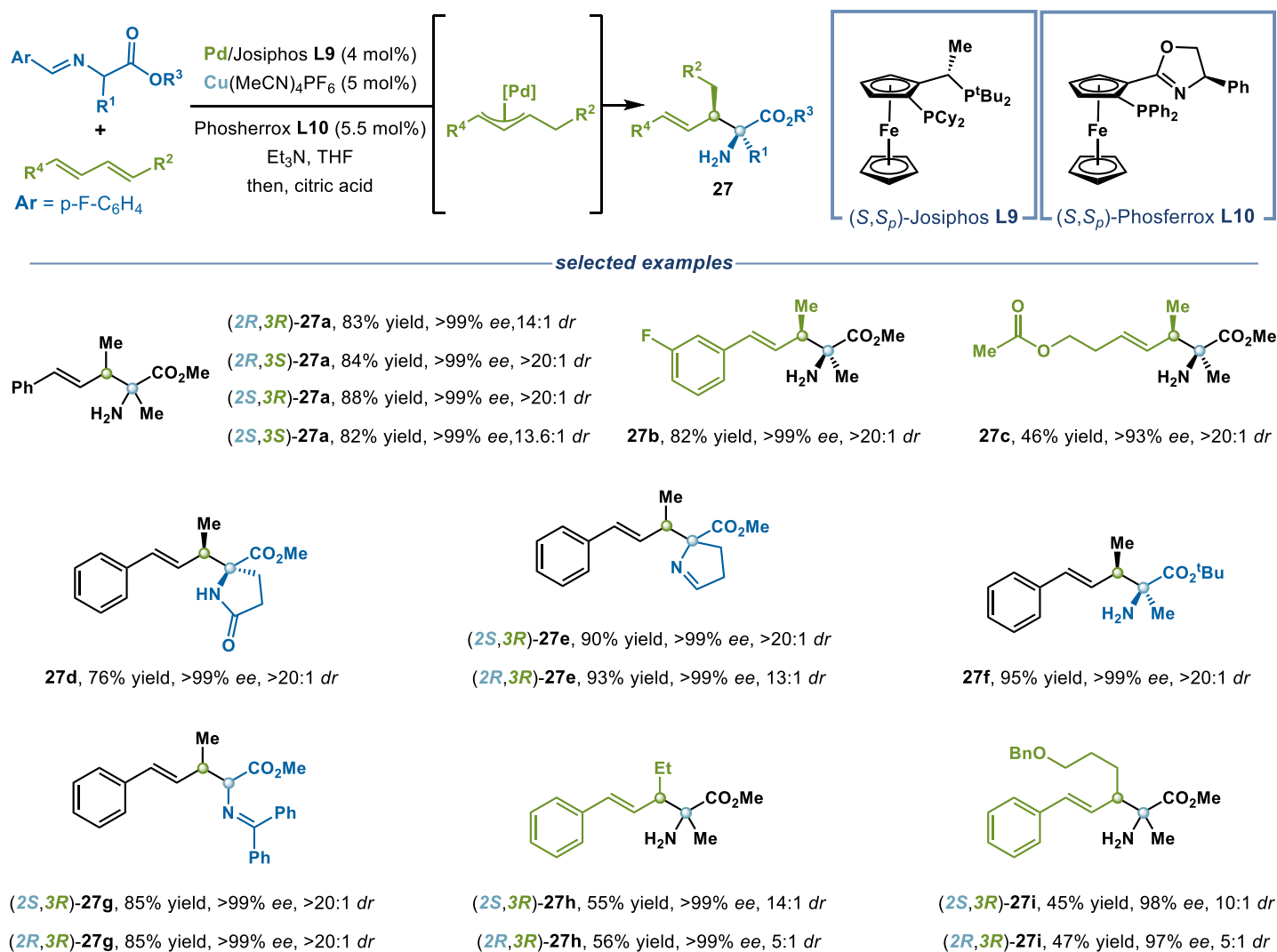


Figure 11. Wang²⁸ and co-workers' Ir and Cu dual-catalyzed allylation of aldimine esters

Next, Zi reported a variation of Zhang's and Wang's works using a Pd and Cu dual catalyst system and 1,3-dienes (Figure 12).³¹ In contrast to prior reports, however, a Pd- π -allyl complex bearing a chiral Josiphos ligand **L9** is formed by the insertion of a 1,3-diene into a Pd-H bond. The use of transition-metal hydrides has been effective for coupling of unsaturated motifs such as allenes, alkynes, and 1,3-dienes with various nucleophiles.³²⁻⁴⁴ This Pd- π -allyl complex then engages with the Cu-activated aldimine ester to generate the coupled product **27**.

The scope of this transformation builds upon the previously reported methods. Firstly, all four stereoisomers of **27a** were accessed in >99% ee; however, the diastereoselectivities varied for each case, which could be a result of matched-mismatched pairs. Halogen-substituted phenyl dienes (**27b**), lactams (**27d**), lactones, and cyclic imine-derived aldimine esters (**27e**) resulted in high reactivities and selectivities. Moreover, bulkier esters such as **27f** gave increased reactivities. Electron-withdrawing and electron-donating phenyl R⁴ substituents provided good yields as well as excellent diastereo- and enantioselectivities. A few other aromatic and heteroaromatic substituents (2-naphthyl, 2-furyl, and 2-thiophenyl) were also reported to give good yields and high selectivities. The scope was limited by alkyl substituted dienes which gave decreased yields **27c**. Additionally, the reaction performs well with the use of ketimine substrates (**27g**). In contrast to previous reports, this method allows for the addition of 1,4-disubstituted dienes enabling an expanded scope towards other alkyl-substituted β -stereocenters (**27h**, **27i**); however, accessing DAAs bearing aryl R² substituents with this method remains a challenge.

Figure 12. Zi³¹ and co-workers' Pd and Cu dual-catalyzed coupling of aldimine esters and dienes

4. Alkynes as Atom Economical Metal-Allyl Precursors

As an alternative to allylic carbonates and acetates, transition-metal π -allyl complexes can also be generated from alkynes.^{37,45-50} Similar atom economical⁵² isomerizations have been used in conjunction with nucleophiles to generate C–Heteroatom and C–C bonds with high enantioselectivities.³³⁻⁴³ Using this method, the branched regioisomer is preferred making this a complementary approach to previous reports by Ooi.^{44,51} This auto-tandem catalytic process begins with a migratory insertion of alkyne **28** into Rh–H **29** to generate intermediate **30**. This is followed by β -hydride elimination to generate allene **31** (Figure 13). The allene **31** then undergoes migratory insertion into Rh–H **29** to generate Rh– π -allyl complex **32**. As before, π -allyl complex **32** can be intercepted by a nucleophile to generate product **33**.

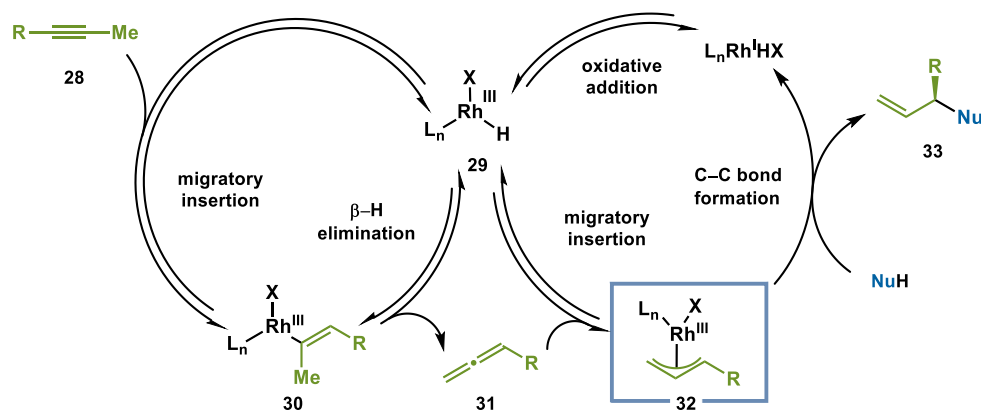


Figure 13. Catalytic cycle for Rh–H tandem catalysis

We envisioned employing this strategy for the asymmetric synthesis of DAA precursors.⁴⁴ An examination of α -nitrocarbonyl derivatives indicated α -nitroesters as the best coupling partners. These substrates provided high yields and diastereoselectivities as well as high enantioselectivities with the use of MeO-BIPHEP **L11** as a chiral ligand (Figure 14). The substrate scope was sensitive to both the sterics and elections of each coupling partner. In nearly all cases, high diastereo- and regioselectivities (>20:1 *dr* and *rr*) were observed. For α -nitroesters derived from the canonical amino acids, sterically hindered side chains such valine derivative **34a** gave no reactivity. Electron poor groups such as *para*-fluorophenylalanine derivative **34b** and tyrosine derivative **34c** gave moderate yields but high enantioselectivities. Interestingly, methionine derivative **34d** gave excellent enantioselectivity but showed a reduced diastereoselectivity of 6:1 *dr*. Heteroaromatic R^1 substituents such as the indole in tryptophan derivative **34e** performed well under the standard conditions. As with valine derivative **34a**, phenyl substitution at R^1 resulted in no reaction (**34g**). The reaction was more tolerant of steric hindrance for substitutions at R^3 (**34f**). For the scope of alkynes, electron-withdrawing **34h** and electron-donating **34i** *para*-substituted phenyl alkynes gave moderate to good yields (56% to 88%) and excellent enantioselectivities (90% *ee* to 94% *ee*). *Meta*-substituted electron-rich **34k** and electron-poor **34j** phenyl alkynes also resulted in good reactivity and selectivity (58% to 96% yield, 92% to 96% *ee*). Sterically hindered *ortho*-chloro-substituted phenyl alkyne **34l** as well as 2-naphthyl alkyne **34m** gave high enantioselectivities but only moderate yields. Unfortunately, alkyl substituents resulted in no reactivity. Nonetheless, product **34n** was efficiently reduced to the protected amino esters **35** with indium powder. This mild reduction can be performed in the presence of other reductively labile functional groups (i.e., esters and olefins).

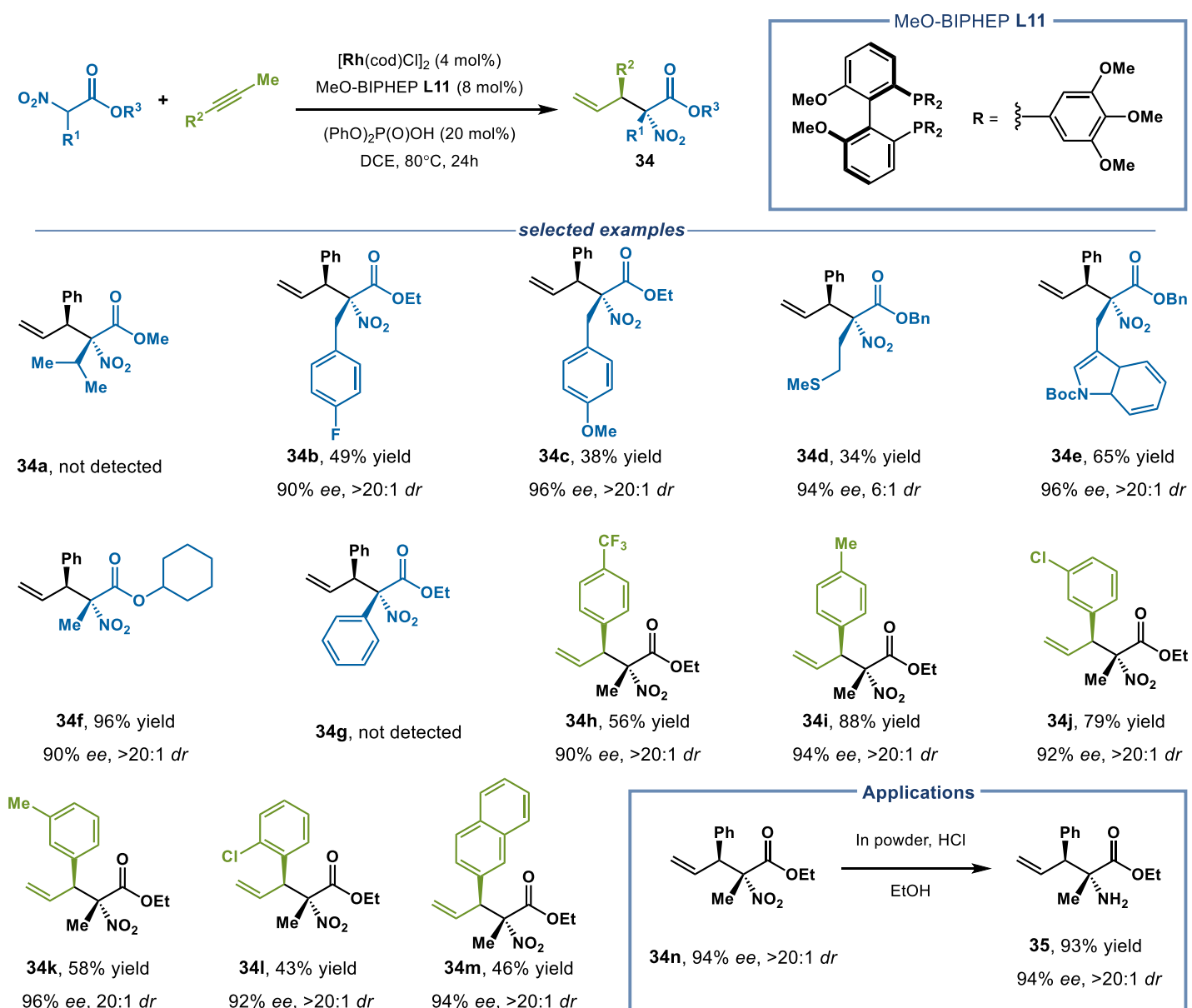


Figure 14. Selected examples from Dong⁴⁴ and co-workers, showing the substrate scope of nitroesters (**34a–34g**) and alkynes (**34h–34m**), and applications of the coupled product **34n**

We undertook mechanistic studies. Deuterated phenyl alkyne **36** was coupled with nitroester **37** to give product **38** (Figure 15). The presence of hydrogen atoms at the δ -position indicates a reversible β -hydride elimination step. A Rh–H complex was observed by ^1H NMR. Lastly, a proper balance between the rates of isomerization and allylation were found to be critical for the transformation's efficiency. When alkyne **28n** was replaced with allene **31n**, yields were significantly diminished with higher equivalencies of allene **31n**. At sub-stoichiometric amounts of allene, however, higher yields could be restored. These results indicated a possible allene intermediate that is likely generated at low concentrations.^{53–56} Moreover, allene **31n** polymerizes under the reaction conditions in the absence of nucleophile **37** indicating a decomposition pathway and supporting the need to control the relative rates of both the isomerization and allylation cycles to maintain high reaction efficiency.

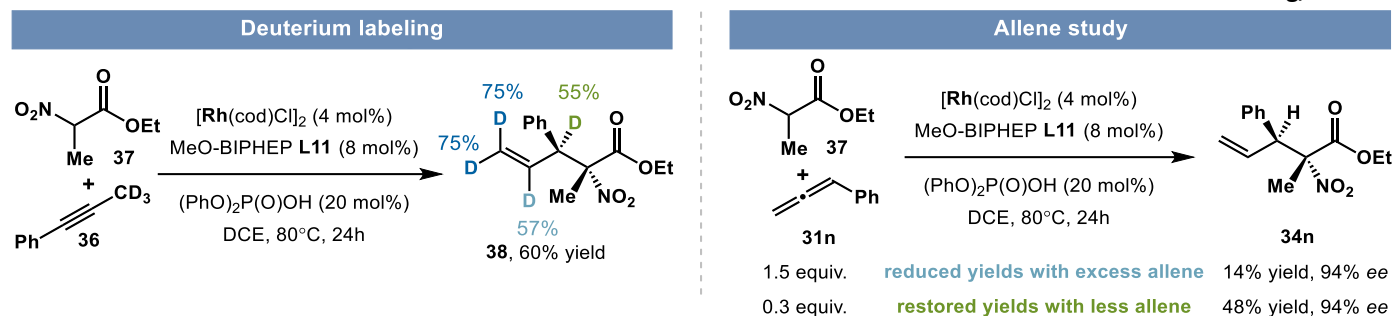


Figure 15. Mechanistic studies support the proposed catalytic cycle.

5. Conclusions

The highlighted works in this review offer insights into reaction mechanisms, scope, and versatility for the asymmetric preparation of DAA precursors with consecutive stereocenters. We recently added to this reaction toolbox by demonstrating the isomerization of alkynes with Rh–H tandem catalysis. This report provides an acyclic and atom-economical method to prepare these amino acid precursors, opening the door for further exploration to expand the scope and advance applications. Such future efforts could target other biologically relevant motifs such as β -amino acids.

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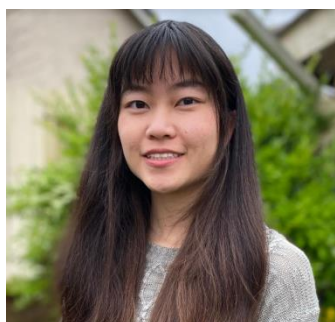
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